AR Baltic Medical

The clinical data were achieved with ELUTAX "3", Emperor or previously with ELUTAX SV a product, which was identically in construction or equivalent with the actual product.

This internal data serves for educational purpose only and is not intended to be distributed or published.

Index:

1) Comparison between sirolimus and paclitaxel-coated balloon for revascularization or coronary arteries. The SIRPAC (SIRolimus-PAClitaxel) study 3

2) Drug-Coated Balloon Versus Drug-Eluting Stent for Small Coronary Vessel Disease PICCOLETO II Randomized Clinical Trial 9

3) Treatment of coronary artery disease with a new-generation drug-coated balloon: final results of the Italian Elutax SV rEgistry-DCB-RISE 19

4) Clinical and Angiographlc outcomes With Drug-Coated Balloons for De Novo Coronary Lesions: A Meta-Analysis of Randomized Clinical Trials 25

5) Effect of Drug-Coated Balloons in Native Coronary Artery Disease Left With a Dissection 53

6) Effect of drug-coated balloons in native coronary artery disease left with a dissection. Subanalysis and comparison between Restore and ElutaxSV drug-coated balloons 60

7) Drug-coated balloon angioplasty: An intriguing alternative far the treatment of coronary chronic total occlusions 64

8) First experience of drug-coated balloons far treatment of bioresorbable vascular scaffold restenosis 66

9) PICC0LET0 II: More Supporl lor DCB Safety and Efficacy in Small Coronaries 71

10) Long-Term Outcome of Drug-CoatedBalloon vs Drug-Eluting Stent for Small Coronary Vessels PICCOLETO-II 3-Year Follow-Up 75

11) Balloon dilatation of pulmonary vein stenosis using PACLITAXEL eluting balloon: midterm result in an infant 83

Cardiovascular Revascularization Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Comparison between sirolimus and paclitaxel-coated balloon for revascularization of coronary arteries. The SIRPAC (SIRolimus-PAClitaxel) study

Bernardo Cortese [a,b,*,1], Gianluca Caiazzo [c,1], Gaetano Di Palma [a], Salvatore De Rosa [d]

[a] Cardiovascular Research Team, San Carlo Clinic, Milano, Italy
[b] Fondazione Ricerca e Innovazione Cardiovascolare, Milano, Italy
[c] ICCU, San Giuseppe Moscati Hospital, Aversa, Italy
[d] Division of Cardiology, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy

ARTICLE INFO

Article history:
Received 1 February 2021
Received in revised form 12 April 2021
Accepted 13 April 2021
Available online xxxx

Keywords:
Drug-coated balloon
Sirolimus
Paclitaxel
Percutaneous coronary intervention

ABSTRACT

Objective: Our study sought to compare the 12-month clinical outcome of patients treated with paclitaxel-coated balloons (PCB) vs. sirolimus-coated balloons (SCB) during coronary angioplasty.
Background: Drug-coated balloons represent an established therapeutic tool for percutaneous coronary interventions (PCI). A comparison between PCB and SCB is still lacking.
Methods: We performed an indirect comparison between two cohorts of patients previously included into two investigator-driven registries with clinical primary endpoints, 494 treated with the Elutax SV PCB (AR Baltic, Lithuania) from the DCB RISE registry, and 596 treated with the Magic Touch SCB (Concept Medical, India) from the EASTBOURNE registry. The primary endpoint was the rate of major adverse cardiovascular events (MACE) at 12-month clinical follow-up.
Results: After propensity score matching, a total of 580 patients were well matched for baseline clinical and procedural characteristics and were analyzed. At 12 months there was no significant difference between the matched DCB RISE and EASTBOURNE cohorts in terms of the primary endpoint MACE (10.3% DCB RISE vs. 10.7% EASTBOURNE, $p = 0.892$). No significant difference was observed also regarding the rate of TLR (7.9% DCB RISE vs. 8.3% EASTBOURNE; $p = 0.879$, respectively). By multivariate analysis, insulin-dependent diabetes was the only predictor of MACE.
Conclusions: In the SIRPAC study, the first indirect comparison between paclitaxel-coated and sirolimus coated balloons, no significant difference in clinical endpoints were found at 12-month follow-up. Randomized studies are necessary to confirm these findings.

© 2021 Elsevier Inc. All rights reserved.

1. Introduction

Despite an increasing use in the last decade and growing scientific evidences provided to date, drug coated balloons (DCB) are still underused by many interventional cardiologists. Their role for the treatment of in-stent restenosis (ISR) [1] is widely acknowledged and current European Revascularization Guidelines recommend their use in either bare metal stent (BMS) or drug eluting stent (DES) restenosis, with a Class I (LoE A) recommendation [2]. Although an official endorsement by clinical guidelines for their use in "de novo" lesions is still lacking, there are several studies suggesting their role in such context, especially in selected clinical and anatomical settings such as small vessel disease [3,4]. In addition, DCB represent an appealing alternative in high-bleeding risk patients, where DES implantation may result in a higher risk of complications [5].

Most of the currently available DCB are coated with paclitaxel (PCB), a highly lipophilic anti-proliferative drug, chemically stable after tissue delivery [6]. However, new debatable findings regarding the long-term safety of paclitaxel-eluting devices (either stents or balloons) for peripheral use have recently raised some concerns in the interventional cardiology field. In fact, a meta-analysis of patients with peripheral artery disease located in the femoro-popliteal vessels suggested a higher risk of mortality after 2 and 4–5 years associated to the use of such

Abbreviations: BMS, Bare-Metal Stent; DES, Drug-Eluting Stent; DCB, Drug-Coated Balloon; ISR, In-Stent Restenosis; MACE, Major Adverse Cardiovascular Event; MI, Myocardial Infarction; PCB, Paclitaxel-Coated Balloon; PCI, Percutaneous Coronary Intervention; SCB, Sirolimus-Coated Balloon; TLR, Target Lesion Revascularization.

* Corresponding author at: Cardiovascular Research Team, San Carlo Clinic, Fondazione Ricerca e Innovazione Cardiovascolare, Via Ospedale, 21, 20037, Paderno Dugnano, Milano, Italy.
E-mail address: bcortese@gmail.com (B. Cortese).
[1] Drs Cortese and Caiazzo are joint First Authors of this paper.

https://doi.org/10.1016/j.carrev.2021.04.013
1553-8389/© 2021 Elsevier Inc. All rights reserved.

Please cite this article as: B. Cortese, G. Caiazzo, G. Di Palma, et al., Comparison between sirolimus and paclitaxel-coated balloon for revascularization of coronary arterie..., Cardiovascular Revascularization Medicine, https://doi.org/10.1016/j.carrev.2021.04.013

devices [7]. Thereafter, many interventional cardiologists wondered if PCB could have undesirable long-term effects also in the coronary setting. As a consequence, the perception that other anti-proliferative drugs including -limus analogues could be safer than paclitaxel, led to a substantial boost of the research of newer devices in the field.

In 2016 Magic Touch (Concept Medical, India) was the first sirolimus DCB (SCB) being marketed in Europe and some Asian countries. Thenceforth, some small studies showed the short and mid-term safety and efficacy profile of this device in coronary artery disease [8–11]. Given the absence of any direct comparison between sirolimus and paclitaxel in an "all comer" population, the aim of the SIRPAC study was to compare a new generation paclitaxel-DCB to the Magic Touch SCB.

2. Methods

2.1. Study design

The SIRPAC study was designed to provide a propensity-score matched comparison of clinical outcomes at 12 months between patients enrolled in the DCB RISE and EASTBOURNE registries.

The DCB RISE [12] was an investigator-initiated registry with prospective data-entry of patients treated with Elutax SV (also marketed as Emperor in some European countries; Aachen Resonance, Germany, and AB Medica, Italy) DCB. The aim of this study was to assess the safety and efficacy of Elutax SV at the longest available clinical follow-up. DCB-RISE represented a real-world registry, enrolling 544 all-comer patients at nine Italian centers. A complex, real world population was enrolled, with 32% of diabetics and 51.3% of patients presenting with an acute coronary syndrome. The primary study endpoint was the occurrence of target-lesion revascularization (TLR) at the longest available follow-up. Secondary endpoints were procedural success and the occurrence of a device-oriented endpoint (DOCE), including cardiac death, target vessel myocardial infarction (MI), stroke, or TLR.

The EASTBOURNE [13] is an ongoing, prospective, multicenter, investigator-initiated, real-world clinical registry with external validation of quality of data input and centralized clinical event assessment, evaluating the performance Magic Touch SCB at 40 European and Asiatic centers. To date, EASTBOURNE represents one of the largest studies in this field, including 2000 consecutive patients with a broad spectrum of lesions, including native vessel disease and in-stent restenosis, and clinical presentations. Similar to DCB RISE, the primary endpoint of the study is TLR at 12 months. Secondary endpoints are: angiographic success, procedural success, MACE at 6, 12, 24 and 36 months. In both studies, patients enrolled underwent a clinical follow up, up to twelve months after the procedure. For the purpose of this analysis we compared the published 12 months clinical outcome of the DCB RISE [12] with the published 12 months "*ad interim*" analysis of the EASTBOURNE [13]. All the events reported in the 2 registries were centrally adjudicated by a dedicated committee. In both registries the manufacturer had no role on the study design, the analysis and interpretation of the data and the publication of the results. Both registries were approved from the Ethical Committee of each center involved.

Inclusion criteria for both studies were symptomatic coronary artery disease (including patients with chronic stable angina, silent ischemia, and acute coronary syndromes) with clinical indication to PCI. Exclusion criteria were the following:

- ☐ Patients with known (and untreatable) hypersensitivity or contraindication to aspirin, heparin, clopidogrel, prasugrel, ticagrelor, sirolimus or a sensitivity to contrast media which cannot be adequately pre-medicated.
- ☐ Patients participating in another clinical evaluation.
- ☐ Target lesion/vessel with any of the following characteristics:
  - o successful pre-dilatation not performed in the target lesion, or not efficacious (residual stenosis >50%);
  - o severe calcification of the target vessel, also proximal to the lesion;
  - o highly tortuous lesions which can impair access of device to treatment site.
- ☐ Visible thrombus at lesion which is not treatable with aspiration.

2.2. Devices description

The Elutax SV is a paclitaxel-coated balloon whose characteristics have been previously described [12]. Briefly, the device consists in a semi-compliant balloon coated with 2.2 μg paclitaxel/mm^2; the top coating is made of 0.7 μg dextran/mm^2, with a maximum amount of 1.89 μg dextran/mm^2, which acts as excipient (drug carrier). After the balloon inflation, the drug is released to the tissue of the vessel wall; the highest uptake of paclitaxel occurs after 1 h and decreases slowly over days and weeks, allowing a successful inhibition of proliferation and migration of smooth muscle cells over time.

Magic Touch is a non-compliant balloon coated with sirolimus through the use of a spray coating on inflated balloon with a technology specifically designed (Nanolutè®); in order to exert its effects, sirolimus is encapsulated in a protective lipophilic package, which allows drug diffusion and transfer into the arterial wall during balloon inflation, overcoming the drug inherent low lipophilia. This package consists of nanospheres of 100–300 nm diameter. The total dosage of the drug corresponds to 1.25 mg/mm^2 of the balloon surface, well within the therapeutic window of the drug. The blood concentration reaches its peak in 30 min, and then disappears within 24 h, while the drug is still detectable within the tissue after 14 days [14].

2.3. Endpoints definition

Primary endpoint of the SIRPAC study was major adverse cardiovascular events (MACE) at 12 months, a composite endpoint including target lesion revascularization (TLR), non-fatal myocardial infarction (MI) and total death. Secondary endpoints were the single components of MACE and a safety endpoint, type 2–4 bleedings according to the BARC classification [15]. TLR was defined as repeated percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the target segment including 5 mm proximal and distal to the previously treated lesion. MI was defined according to the third universal definition of myocardial infarction [16].

2.4. Statistical analysis

Continuous variables are reported as mean ± SD and were compared using ANOVA or Man-Whitney *U* tests. Categorical variables are reported as counts and percentages, and were compared using chi-square or Fisher exact tests. In order to control for confounders between the DCB RISE and EASTBOURNE, a propensity score matching was applied. A propensity (likelihood to undergo major adverse cardiovascular events) score was calculated by means of a multivariate logistic regression model encompassing baseline demographics, clinical, angiographic, and procedural risk factors (age, type 2 diabetes, hypercholesterolemia, smoke, chronic kidney disease, acute coronary syndrome, in-stent restenosis, small target vessel). Patients with similar propensity scores in the two treatment groups were matched using a greedy nearest neighbor matching within specified caliper widths without replacement. Patients without matched observations were excluded. We used C-index and Hosmer Lemeshow goodness of fit test to assess the appropriateness of the model.

All reported *p* values are 2-sided, and p values <0.05 were considered to indicate statistical significance. Univariate analysis was conducted to identify factors associated with MACE at 12 months. Significant factors from univariate analyses were entered into a multivariate logistic regression model. All data were processed using the

Table 1
Patients characteristics and procedural details (before PSM).

	DCB RISE ($n = 494$)	EASTBOURNE ($n = 596$)	p value
Age (mean ± SD)	68 ± 11	65 ± 11	0,001
Male n (%)	349 (71)	479 (80)	<0,001
Hypertension n (%)	340 (69)	441 (74)	0,004
Hypercholesterolemia n (%)	299 (60)	423 (71)	0,008
Smoke n (%)	177 (36)	164 (27)	0,003
Diabetes n (%)	158 (32)	244 (41)	0,012
Family history n (%)	128 (26)	149 (25)	0,203
Previous MI n (%)	181 (37)	263 (44)	0,252
Previous PCI n (%)	324 (66)	408 (68)	0,159
Previous CABG n (%)	61 (12)	76 (13)	0,662
CKD n (%)	54 (11)	61 (10)	0,360
LVEF (%) (mean ± SD)	53 ± 9	52 ± 11	0,322
ACS	243 (49)	267 (45)	0,088
Small vessels (≤ 2,5 mm)	204 (41)	330 (55)	<0,001
In-stent restenosis n (%)	281 (57)	274 (46)	<0,001
Lesion length (mm) (mean ± SD)	17 ± 7	19 ± 9	<0,001
Pre-dilation n (%)	399 (81)	543 (91)	<0,001
DCB diameter (mm) (mean ± SD)	2,8 ± 0,5	2,7 ± 0,6	<0,001
DCB length (mm) (mean ± SD)	20 ± 6	22 ± 7	<0,001
DCB inflation time (*sec*) (mean ± SD)	56 ± 26	60 ± 26	0,007
DCB inflation pressure (atm) (mean ± SD)	11 ± 4	10 ± 4	0,039
Angiographic success n (%)	481 (97)	576 (97)	0,304

PSM = Propensity Score Matching; SD = Standard Deviation; IDDM = insulin—dependent diabetes mellitus; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery By-pass Grafting; CKD = chronic kidney disease; ACS = Acute Coronary Syndrome; DCB=Drug coated balloon.

Table 2
Patients characteristics and procedural details (after PSM).

	DCB RISE ($n = 290$)	EASTBOURNE (n = 290)	p value
Age (mean ± SD)	67 ± 11	66 ± 12	0,507
Male n (%)	219 (75)	224 (77)	0,625
Hypertension n (%)	200 (69)	216 (74)	0,153
Hypercholesterolemia n (%)	177 (61)	194 (67)	0,141
Smoke n (%)	90 (31)	84 (29)	0,587
Diabetes n (%)	103 (35)	131 (45)	0,018
Family history n (%)	86 (30)	86 (30)	0,978
Previous MI n (%)	124 (43)	139 (48)	0,254
Previous PCI n (%)	212 (73)	215 (74)	0,885
Previous CABG n (%)	45 (15)	46 (16)	0,938
CKD n (%)	46 (16)	36 (12)	0,233
LVEF (%) (mean ± SD)	53 ± 9	51 ± 11	0,296
ACS	150 (52)	155 (53)	0,678
Small vessels (≤ 2,5 mm)	117 (40)	134 (46)	0,154
In-stent restenosis n (%)	175 (60)	184 (63)	0,442
Lesion length (mm) (mean ± SD)	16 ± 7	18 ± 9	0,001
Pre-dilation n (%)	263 (91)	261 (90)	0,779
DCB diameter (mm) (mean ± SD)	2,8 ± 0,5	2,8 ± 0,6	0,984
DCB length (mm) (mean ± SD)	19 ± 5	22 ± 7	0,001
DCB inflation time (sec) (mean ± SD)	56 ± 30	58 ± 13	0,188
DCB inflation pressure (atm) (mean ± SD)	11 ± 4	11 ± 4	0,400
Angiographic success n (%)	282 (97)	283 (98)	0,794

PSM = Propensity Score Matching; SD = Standard Deviation; IDDM = insulin—dependent diabetes mellitus; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery By-pass Grafting; CKD = chronic kidney disease; ACS = Acute Coronary Syndrome.

Statistical Package for Social Sciences, version 23 (SPSS, IBM, Chicago, Illinois).

3. Results

3.1. Characteristics of the broad study population

Briefly, a total of 1090 patients were enrolled in the SIRPAC study, 494 from DCB RISE and 596 from EASTBOURNE. The two groups of patients differed significantly for several clinical and procedural characteristics (Table 1). In particular, diabetes was present in 158 patients (32%) in the DCB RISE, while in the EASTBOURNE it was present in 244 (41%) while the number of smokers was higher in the DCB RISE registry compared to the EASTBOURNE ($n = 177$, 36% vs $n = 164$,27%; p 0.003). Also, lesions located in small vessels were more frequent in the EASTBOURNE ($n = 204$, 41% in DCB RISE vs $n = 330$, 55% in EASTBOURNE; $p < 0.001$) whereas in-stent restenosis was more frequent in the DCB RISE ($n = 281$, 57% vs $n = 274$, 46%; $p < 0.001$). In line with these differences, the mean Propensity Score was significantly lower ($p = 0.007$) in the EASTBOURNE compared to the DCB RISE cohort (Fig. 1).

3.2. Characteristics of patients matched for propensity score

The matched cohort consisted in a total of 580 patients, 290 for each group.

The mean age was 67 ± 11 years and men accounted for 443 (76%) of patients. Diabetes mellitus was present in 234 patients (40%). A total of 305 patients (53%) presented with an ACS, and the culprit lesion occurred in an ISR segment in 359 cases (62%). The mean lesion length was 17.3 ± 8.1 mm. In the matched cohorts there was no significant difference for any covariate, except for diabetes ($n = 103$, 35% vs. $n = 131$, 45%; $p = 0.018$), lesion length and DCB length (Table 2). Accordingly, no significant difference in the mean Propensity Score ($p = 0.98$) was present between the matched cohorts (Fig. 1).

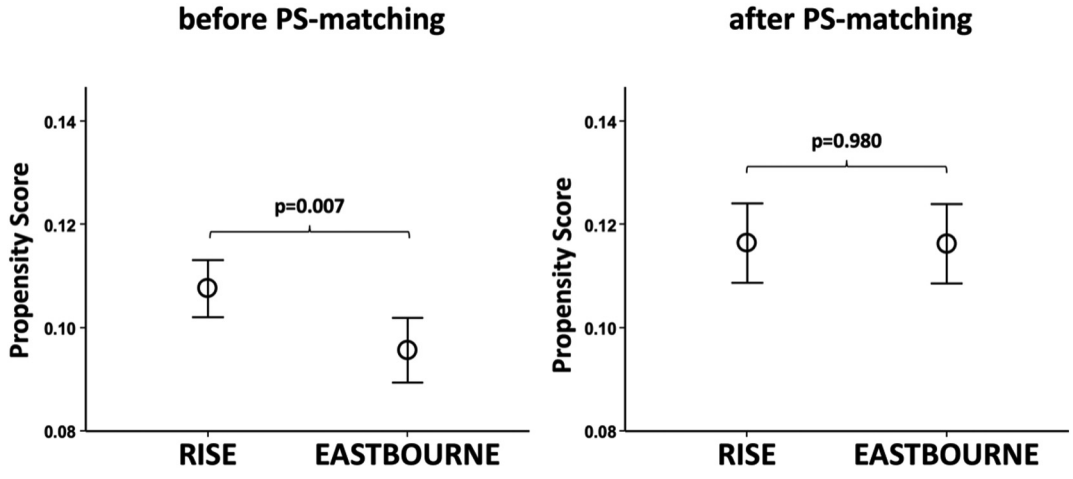


Fig. 1. Propensity score between registries before and after matching.

Table 3
Incidence of clinical endpoints at 12 months (matched cohorts).

	DCB RISE (n = 290)	EASTBOURNE (n = 290)	p value
MACE	30 (10,3)	31 (10,7)	0,892
TLR	23 (7,9)	24 (8,3)	0,879
MI	6 (2,1)	8 (2,7)	0,588
Death	5 (1,7)	4 (1,4)	0,737
Bleeding	2 (0,7)	0	0,157

MACE = Major Cardiovascular Events; TLR = Target Lesion Revascularization; MI = Myocardial Infarction.

3.3. Clinical outcomes of the matched cohorts

At 12 months there was no significant difference between the matched DCB RISE and EASTBOURNE cohorts in terms of the primary endpoint MACE with 30 events (10.3%) in the DCB RISE vs. 31 (10.7%) in the EASTBOURNE (RR = 0.96; 95% CI, 0.60–1.55; $p = 0.892$). No statistical difference was found in the rate of non-fatal acute MI with 6 cases (2.1%) in the DCB RISE vs. 8 (2.7%) in the EASTBOURNE (RR = 0.75; 95% CI, 0.26–2.13; $p = 0.588$) or in the rate of TLR with 23 events (7.9%) in the DCB RISE vs. 24 (8.3%) in the EASTBOURNE (RR = 0.95; 95% CI, 0.55–1.65; $p = 0.879$, respectively). Finally, the rate of BARC 2–4 major bleedings during the follow-up was negligible, without significant differences between the treatment groups (RR = 5.0; 95% CI, 0.24–103.70; $p = 0.157$) (Table 3, Fig. 2). Fig. 3 shows the Kaplan-Meier curves of the primary endpoint and total death rate at 12 months follow-up, again with no significant differences.

3.4. Predictors of adverse clinical outcome

Univariate analysis showed that diabetes, previous MI, ISR and DCB diameter were significant predictors for the occurrence of MACE. At multivariable analysis, diabetes remained the only independent predictor of MACE (Exp B = 2.13; 95% CI, 1.06–4.30; $p = 0.034$) (Table 4).

4. Discussion

SIRPAC is the first study which indirectly compares a SCB with a second-generation PCB in a real-world population of coronary artery disease patients. The main finding of the current study is the absence of significant differences between these 2 devices in terms of clinical endpoints at 1 year. Of note, such findings were confirmed also by the multivariate analysis, where the type of DCB used had no predictive impact on the outcome.

The results of this study are of particular interest, considering the recent warning about a supposed increased risk in late mortality with paclitaxel-eluting devices (DCB or DES) in patients undergoing femoro-popliteal angioplasty, issued after the publication of a meta-analysis by Katsanos et al. [7]; in addition to these unexpected results, last year the U.S. Food and Drug Administration issued a warning on the potential risk of paclitaxel-eluting devices [17]. The lack of biological plausibility for the supposed increased mortality determined by paclitaxel, and the fact that only first-generation devices were investigated with adequate follow up, did not stop the storm against paclitaxel [18–21].

Bittl et al. [22], in a new analysis done applying Bayes factors to the available studies, showed the results by the former meta-analysis to be inconclusive in terms of hard adverse events. Despite these results, such controversial messages led to a decrease in the use of paclitaxel-eluting devices for both peripheral and coronary interventions. Although a signal of late increased mortality cannot be ignored, it is important to point out that:

- Single trials included in the meta-analysis by Katsanos were not powered enough for mortality;
- Paclitaxel systemic exposure after peripheral or coronary interventions is small and self-limited in time, and drug tissue levels are undetectable at 1 year, making it hard to explain how mortality could increase when the drug may not be present anymore [19];
- Much higher dosages of paclitaxel were proven to be safe [23].

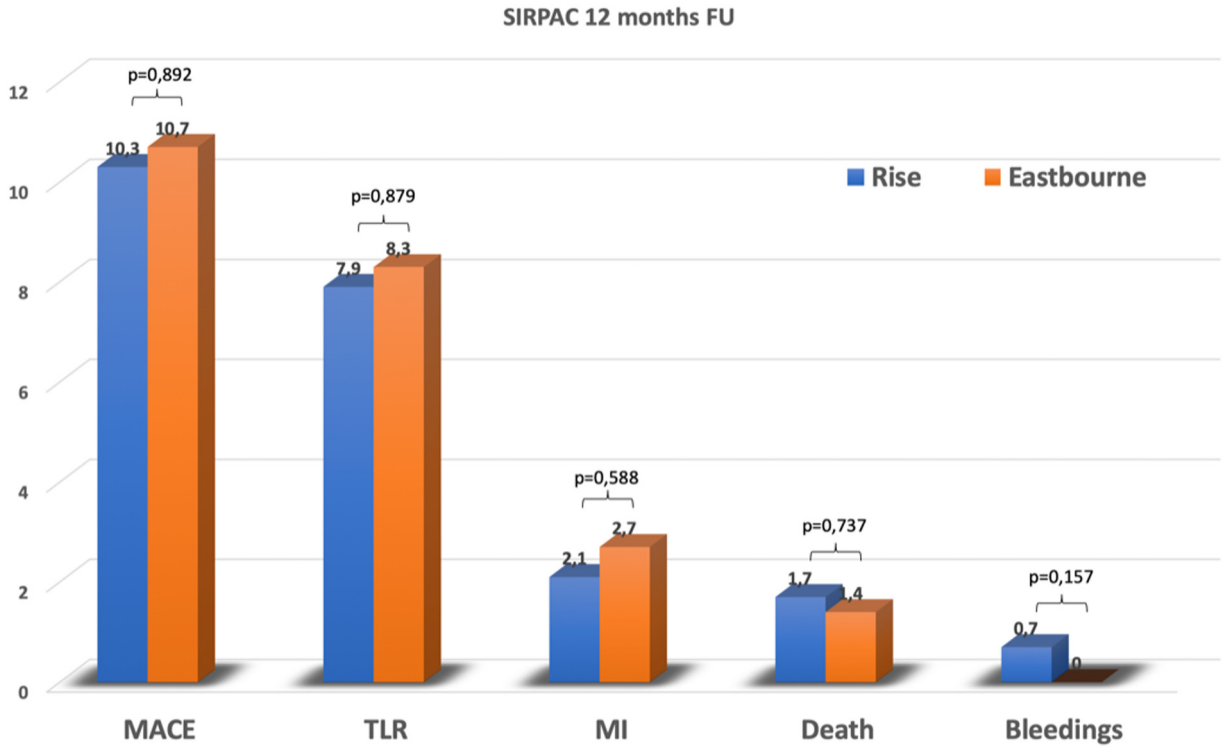


Fig. 2. 12-months clinical outcomes of the SIRPAC study.

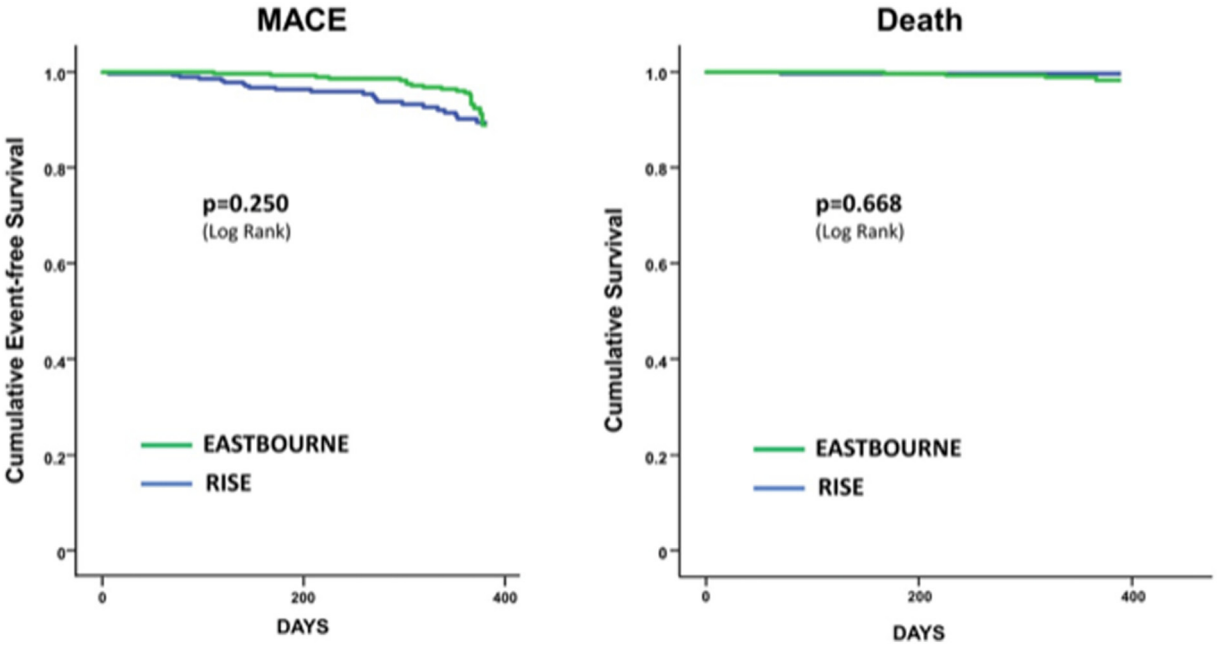


Fig. 3. Kaplan-Meier curves of MACE and total death rate at 12 months follow-up.

Regarding coronary interventions a recently published meta-analysis [24] helped to clear the fog. In this work all available RCTs comparing PCBs with non-PCB devices, for the treatment of both coronary ISR or "de novo" lesions, were included. A clinical follow-up of at least 6 months was required. Interesting, there was no difference in all-cause mortality after 12 months, but a significant reduction after 3 years in DCB-treated patients.

One of the main arguments on this topic is the concept that not all PCBs are equal and there is not a class effect. The meta-analysis of Katsanos takes into consideration only 2 types of the first generation DCB, with devices reporting a high percent of drug loss during manipulation and before reaching the lesion. Afterwards, newer technologies developed drug carriers with higher performances, with the aim of protecting the delivery of the drug to the culprit site, and also a correct distribution during the upcoming weeks in order to exert an effective inhibition of restenosis. This should happen with a limitation of drug loss. It should be noted that we are well aware that the results of SIRPAC do not clarify if the results of the aforementioned meta-analysis should be emphasized or downgraded, taking into consideration the different clinical setting, methodology and the limited follow up duration of our study.

All currently available DES elute a "-limus" drug, which exerts an antiproliferative effect by inhibiting the mTOR chinase. The therapeutic window of this class of drugs is wider than paclitaxel's. The possibility to add sirolimus to a DCB has been extensively studied over the years, with the main difficulties related to the low lipophilia of the drug thence its reduced ability to be retained into the vessel wall upon balloon inflation.

Table 4
Univariate and Multivariate analysis.

	Univariate (p value)	Multivariate Exp B (95% C.I.)	Multivariate (p value)
Diabetes	0,023	2,13 (1,06-4,30)	0,034
Previous myocardial infarction	0,050	1,36 (0,77-2,39)	0,285
ISR	0,010	1,72 (0,85-3,48)	0,128
DCB diameter	0,025	1,33 (0,77-2,31)	0,305

The first DCB eluting sirolimus to be marketed in Europe in 2016 was Magic Touch. A specific protective lipophilic package allows encapsulating the drug into nanospheres, overcoming the low drug lipophilia and allowing a sustained diffusion to the vessel wall. Despite the high expectations on this device, available data in the literature are limited to mid-term follow up. The first experiences and registries showed however promising results [8,9,13,25].

Recently El-Mokdad et al. [11] reported the final result of the Nanolutè study [10], an Indian real world, prospective study, which enrolled 408 patients with ISR or "de novo" lesions and a 24 months follow-up. Magic Touch proved its safety and efficacy in both settings with an overall MACE rate of 4.2%.

Until the results of SIRPAC however, a comparison between DCB eluting sirolimus or paclitaxel was still lacking.

Our analysis contains some limitations that should be acknowledged.

First, this is an indirect comparison between 2 different studies. However we performed an adequate statistical analysis with propensity score matching to overcome such differences, a direct comparison is highly advocated to confirm our results. Data for the SCB have been extracted from the "ad interim" 12 months analysis of the EASTBOURNE registry: the enrollment of this study is expected to finish by Q3 2020. Finally, the follow-up of the current study is limited to 12 months.

5. Conclusions

The SIRPAC study is a non-randomized comparison which shows clinical equivalence between a novel sirolimus-coated balloon and one of the latest generation paclitaxel-coated balloons at 12 months clinical follow up in coronary artery disease patients. Randomized studies are necessary to confirm these findings.

CRediT authorship contribution statement

We state that these were the contributions of each Author to the SIRPAC manuscript:

B. Cortese: conceptualization; data curation; supervision; validation; review & editing.

G. Caiazzo: formal analysis; investigation; methodology; writing.

G. Di Palma: investigation; methodology; data curation; writing.

S. De Rosa: formal analysis, project administration; resources; Bernardo Cortese MD (corresponding author).

Declaration of competing interest

Authors have no competing interest for this manuscript and no relationship with industry.

References

[1] Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med. 2006;355:2113–24. https://doi.org/10.1056/nejmoa061254.

[2] Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87–165. https://doi.org/10.1093/eurheartj/ehy394.

[3] Yerasi C, Case BC, Forrestal BJ, Torguson R, Weintraub WS, Garcia-Garcia HM, et al. Drug-coated balloon for De novo coronary artery disease. JACC State-of-the-Art Review J Am Coll Cardiol. 2020;75:1061–73. https://doi.org/10.1016/j.jacc.2019.12.046.

[4] Alfonso F, García-Guimaraes M, Navarrete G, Cuesta J, Bastante T, Benedicto A, et al. Drug-eluting balloons in coronary interventions: the quiet revolution? Expert Opin Drug Del. 2016;14:841–50. https://doi.org/10.1080/17425247.2017.1245291.

[5] Rissanen TT, Uskela S, Eränen J, Mäntylä P, Olli A, Romppanen H, et al. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. Lancet. 2019;394:230–9. https://doi.org/10.1016/s0140-6736(19)31126-2.

[6] Alfonso F, Scheller B. State of the art: balloon catheter technologies – drug-coated balloon. Eurointervention. 2017;13:680–95. https://doi.org/10.4244/eij-d-17-00494.

[7] Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2018;7:e011245. https://doi.org/10.1161/jaha.118.011245.

[8] Cortese B, di Palma G, Latini RA, Elwany M, Orrego PS, Seregni RG. Immediate and short-term performance of a novel sirolimus-coated balloon during complex percutaneous coronary interventions. The FAtebenefratelli SIrolimus COated-balloon (FASICO) registry. Cardiovasc Revascularization Med. 2017;18:487–91. https://doi.org/10.1016/j.carrev.2017.03.025.

[9] Cortese B, Pellegrini D, Latini RA, Palma GD, Perotto A, Orrego PS. Angiographic performance of a novel sirolimus-coated balloon in native coronary lesions: the FAtebenefratelli SIrolimus COated NATIVES prospective registry. J Cardiovasc Medicine Hagerstown Md. 2019;20:471–6. https://doi.org/10.2459/jcm.0000000000000806.

[10] Dani S, Shah D, Sojitra P, Parikh K, Shetty R, di Palma G, et al. A novel nanocarrier sirolimus-coated balloon for coronary interventions: 12-month data from the Nanoluté registry. Cardiovasc Revascularization Med Incl Mol Interv. 2018;20:235–40. https://doi.org/10.1016/j.carrev.2018.06.003.

[11] El-Mokdad R, Palma G, Cortese B. Long-term follow-up after sirolimus-coated balloon use for coronary artery disease. Final results of the Nanolutè study. Catheter Cardiovasc Interv. 2020. https://doi.org/10.1002/ccd.28863.

[12] Cortese B, D'Ascenzo F, Fetiveau R, Balian V, Blengino S, Fineschi M, et al. Treatment of coronary artery disease with a new-generation drug-coated balloon. J Cardiovasc Med. 2018;19:247–52. https://doi.org/10.2459/jcm.0000000000000632.

[13] Cortese B, Testa L, Palma GD, Heang TM, Bossi I, Nuruddin AA, et al. Clinical performance of a novel sirolimus-coated balloon in coronary artery disease: EASTBOURNE registry. J Cardiovasc medicine Hagerstown md; 2020. https://doi.org/10.2459/jcm.0000000000001070 Publish Ahead of Print.

[14] Lemos PA, Farooq V, Takimura CK, Gutierrez PS, Virmani R, Kolodgie F, et al. Emerging technologies: polymer-free phospholipid encapsulated sirolimus nanocarriers for the controlled release of drug from a stent-plus-balloon or a stand-alone balloon catheter. Eurointervention. 2013;9:148–56. https://doi.org/10.4244/eijv9i1a21.

[15] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials. Circulation. 2011;123:2736–47. https://doi.org/10.1161/circulationaha.110.009449.

[16] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012;33:2551–67. https://doi.org/10.1093/eurheartj/ehs184.

[17] Dan K, Shlofmitz E, Khalid N, Hideo-Kajita A, Wermers JP, Torguson R, et al. Paclitaxel-related balloons and stents for the treatment of peripheral artery disease: insights from the Food and Drug Administration 2019 circulatory system devices panel meeting on late mortality. Am Heart J. 2019;222:112–20. https://doi.org/10.1016/j.ahj.2019.12.012.

[18] Fanelli F, Cortese B, Zeller T. Use of paclitaxel-eluting technologies in the femoropopliteal segment under scrutiny over possible link to late all-cause mortality: time to panic or an opportunity to resurge? J Endovasc Ther. 2019;26:41–3. https://doi.org/10.1177/1526602818824682.

[19] Cortese B, Granada JF. Mortality increase and paclitaxel-coated device use: a plausible but inconclusive hypothesis. JACC Cardiovasc Interv. 2019;12:2538–40. https://doi.org/10.1016/j.jcin.2019.10.044.

[20] Cortese B, Alfonso F, Pellegrini D, Sing KR, Granada JF. The hypothesis of an increased mortality following paclitaxel coated device use in peripheral vascular interventions (and the emerging era of meta-analysis based evidence). Catheter Cardiovasc Interv. 2019;95:329–31. https://doi.org/10.1002/ccd.28600.

[21] Cortese B, Pellegrini D. Paclitaxel drug-coated balloons in peripheral artery disease: who's trying to shoot the football star? Cardiovasc Revascularization Med. 2019;20:285–6. https://doi.org/10.1016/j.carrev.2019.02.006.

[22] Bittl JA, He Y, Baber U, Feldman RL, von Mering GO, Kaul S. Bayes factor meta-analysis of the mortality claim for peripheral paclitaxel-eluting devices. JACC Cardiovasc Interv. 2019;12:2528–37. https://doi.org/10.1016/j.jcin.2019.09.028.

[23] Alfonso F, Rivero F, Granada JF. Safety of paclitaxel-coated balloons in the coronary arteries. J Am Coll Cardiol. 2020;75:1029–32. https://doi.org/10.1016/j.jacc.2019.12.051.

[24] Scheller B, Vukadinovic D, Jeger R, Rissanen TT, Scholz SS, Byrne R, et al. Survival after coronary revascularization with paclitaxel-coated balloons. J Am Coll Cardiol. 2020;75:1017–28. https://doi.org/10.1016/j.jacc.2019.11.065.

[25] Cortese B, Palma GD, Latini R. Magic touch®: preliminary clinical evidence with a novel sirolimus drug coated balloon. Minerva Cardioangiol. 2018;66:508–17. https://doi.org/10.23736/s0026-4725.18.04641-8.

JACC: CARDIOVASCULAR INTERVENTIONS
© 2020 PUBLISHED BY ELSEVIER ON BEHALF OF THE
AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. ■, NO. ■, 2020

Drug-Coated Balloon Versus Drug-Eluting Stent for Small Coronary Vessel Disease

PICCOLETO II Randomized Clinical Trial

Bernardo Cortese, MD,[a] Gaetano Di Palma, MD,[a] Marcos Garcia Guimaraes, MD,[b] Davide Piraino, MD,[c] Pedro Silva Orrego, MD,[d] Dario Buccheri, MD,[e] Fernando Rivero, MD,[b] Anna Perotto, RN,[d] Giulia Zambelli, MD,[c] Fernando Alfonso, MD[b]

ABSTRACT

OBJECTIVES This study sought to compare the performance of a novel drug-coated balloon (DCB) (Elutax SV, Aachen Resonance, Germany), with an everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California) in patients with de novo lesions.

BACKGROUND Small vessel coronary artery disease (SVD) represents one of the most attractive fields of application for DCB. To date, several devices have been compared with drug-eluting stents in this setting, with different outcomes.

METHODS The PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) trial was an international, investigator-driven, multicenter, open-label, prospective randomized controlled trial where patients with de novo SVD lesions were randomized to DCB or EES. Primary study endpoint was in-lesion late lumen loss (LLL) at 6 months (independent core laboratory), with the noninferiority between the 2 arms hypothesized. Secondary endpoints were minimal lumen diameter, percent diameter stenosis at angiographic follow-up, and the occurrence of major adverse cardiac events at 12 months.

RESULTS Between May 2015 and May 2018, a total of 232 patients were enrolled at 5 centers. After a median of 189 (interquartile range: 160 to 202) days, in-lesion LLL was significantly lower in the DCB group (0.04 vs. 0.17 mm; $p = 0.001$ for noninferiority; $p = 0.03$ for superiority). Percent diameter stenosis and minimal lumen diameter were not significantly different. At 12-month clinical follow-up, major adverse cardiac events occurred in 7.5% of the DES group and in 5.6% of the DCB group ($p = 0.55$). There was a numerically higher incidence of spontaneous myocardial infarction (4.7% vs. 1.9%; $p = 0.23$) and vessel thrombosis (1.8% vs. 0%; $p = 0.15$) in the DES arm.

CONCLUSIONS In this multicenter randomized clinical trial in patients with de novo SVD lesions, a new-generation DCB was found superior to EES in terms of LLL as the angiographic pattern and comparable in terms of clinical outcome. (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment [PICCOLETO II]; NCT03899818) (J Am Coll Cardiol Intv 2020;■:■–■) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

From the [a]Cardiovascular Research Team, San Carlo Clinic, Milano, Italy; [b]Cardiology Department, Hospital de la Princesa, Madrid, Spain; [c]Interventional Cardiology, Giaccone Hospital, University of Palermo, Palermo, Italy; [d]Interventional Cardiology, ASST Fatebenefratelli-Sacco, Milano, Italy; and the [e]Interventional Cardiology, San Giovanni di Dio Hospital, Trapani, Italy. This is an investigator-driven study with the Italian Society of Interventional Cardiology GISE as a sponsor. The role of GISE was to coordinate the centers and submit the protocol to the ethics committees.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

Manuscript received May 20, 2020; revised manuscript received July 28, 2020, accepted August 19, 2020.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2020.08.035

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DCB = drug-coated balloon

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

HR = hazard ratio

LLL = late lumen loss

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

MLD = minimal lumen diameter

PCI = percutaneous coronary intervention

SVD = small vessel disease

TLR = target lesion revascularization

The overall complexity of interventions for coronary artery disease has progressively increased during the last 2 decades, due to epidemiological reasons and to the availability of devices with superior performance and long-term clinical efficacy (1,2). Drug-eluting stents (DES) especially experienced a dramatic improvement from the technological point of view, leading to the possibility to treat virtually any coronary lesion (3). However, despite the improved clinical outcome obtained with latest-generation DES, the total amount of stent length remains associated with an increase in late adverse events (4). This is 1 of the reasons why newer devices are required as potential alternatives to DES. Among them, drug-coated balloons (DCB) have been widely adopted in some specific settings, including in-stent restenosis and de novo lesions, particularly in small vessel disease (SVD). SVD is associated with a higher risk of restenosis and stent thrombosis after the use of DES (5–7). Accordingly, the possibility to treat SVD without the implantation of a permanent prosthesis by means of direct delivery of an antirestenotic drug with DCB has been considered appealing since the first results of this strategy were published 10 years ago (8,9).

However, it rapidly became evident how the addition of a drug to a balloon was not sufficient to produce an efficacious and homogeneous delivery of the drug to the vessel wall, and an effective and persistent antirestenotic effect. In fact, several DCB have been investigated so far, with mixed results, explaining why recent revascularization guidelines emphasize that there is not a class effect for DCB (10). The Elutax SV/Emperor (AR Baltic Medical, Vilnius, Lithuania) is a new-generation DCB eluting paclitaxel thanks to dextran as the drug carrier.

The aim of the PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) study was to assess the angiographic efficacy of this DCB as compared with Xience everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California) in patients with SVD.

METHODS

STUDY DESIGN. The PICCOLETO II trial (NCT03899818) is an investigator-driven, prospective, randomized, multicenter, open-label clinical trial performed at 5 European centers. The study protocol was presented and accepted at the coordinating center (Fatebenefratelli Hospital, Milano, Italy) ethics committee in February 2015, and thereafter by the ethics committees of all the participating centers. First patient inclusion occurred in May 2015, and the last patient was enrolled in May 2018. The protocol was designed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All participants provided prior oral and written informed consent to be enrolled into the study.

PATIENT POPULATION. In order to be enrolled, the patient had to be hospitalized for stable coronary artery disease or an acute coronary syndrome, with an indication for percutaneous coronary intervention (PCI). The angiographic characteristics to enroll the patient were the following: coronary artery disease in a vessel with a diameter between 2.00 and 2.75 mm with a target lesion ≥70% (by investigator's judgment by visual estimation). The clinical exclusion criteria were as follows: inability to provide oral and written informed consent or unwillingness to come back for systematic angiographic follow-up; age <18 years; life expectancy <1 year; recent ST-segment elevation myocardial infarction (MI) (<72 h); left ventricular ejection fraction <30%; and creatinine clearance <30 ml/min. We also applied the following angiographic exclusion criteria: index lesion at left main stem; aorto-ostial lesion; presence of stent at target vessel; target lesion previously treated by means of any device; chronic total occlusion; severe calcification or tortuosity of the target vessel; untreatable thrombus at the target lesion; target lesion involving a major bifurcation; and lesion length >25 mm.

Periprocedural MI was defined according to the Third Universal Definition as type IV (11). All patients underwent electrocardiogram and cytonecrosis biomarker analyses the day following the intervention. Renal failure was defined as creatinine clearance between 30 and 50 ml/min calculated with the Cockroft and Gault formula.

INTERVENTION. Patients were enrolled just after diagnostic angiography but before the PCI procedure, and underwent open label randomization. Randomization was generated through randomly permuted blocks and randomization list was independently generated for each center and automatically integrated into an e-CRF website. Patients were randomized between Xience EES and Elutax SV/Emperor (experimental group) in a 1:1 fashion. In order to

reduce the confusion in event allocation, we decided to keep a maximum of 1 lesion per patient treated with any study device. If any additional lesion required treatment, the choice of intervention was left to the discretion of the operator.

In case of allocation to the DES arm, the investigator was left free to pre-dilate and prepare the lesion and post-dilate as required to ensure an optimal angiographic result. If the patient was randomized to the DCB arm, lesion preparation was strongly recommended, and in case of major dissection after predilatation, the investigator could decide to convert the intervention into a DES-based one. DCB inflation time had to be at least 30 s. In case of major, flow-limiting dissection or residual stenosis >50% after DCB use, the patient could be treated with DES; in this case, the stent length had to be inferior to the DCB (avoiding "geographic mismatch"), and the group allocation of the patient did not change (intention-to-treat analysis).

The PCI procedure was then performed according to current European Society of Cardiology guidelines (10). including the periprocedural and subsequent antithrombotic regimen. After DCB use, a minimum of 30 days of dual antiplatelet treatment was required (stable patients). In case of DES implantation, a minimum of 6 months was required. All patients with acute coronary syndrome received a 12-month prescription of 2 antiplatelet agents. All patients were discharged with a scheduled 6-month angiographic assessment and with 12-month and 24-month clinical visits.

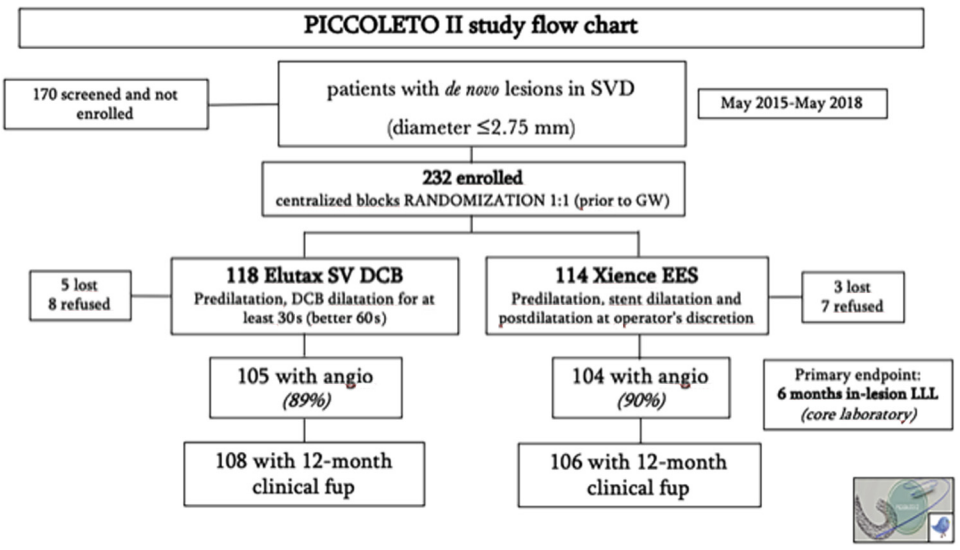
STUDY DEVICE. The technical characteristics of Elutax SV (also marketed as Emperor in some European countries) have been described previously (12). Briefly, this DCB elutes paclitaxel that is loaded on a folded balloon at dosage of ≅2.2 μg/mm^2 (tolerance of 1.4 to 3.00 μg/mm^2). The drug is added with dextran, which acts as an excipient to modulate paclitaxel diffusion in the vessel wall upon balloon inflation and to allow its persistence for the first 3 to 4 weeks. The drug uptake measured in different animal models is highest after 1 h and decreases slowly over days and weeks, with values at the beginning of around 250 μg/ml decreasing to around 100 μg/ml after 1 week to 10 μg/ml after 4 weeks, allowing a successful inhibition of proliferation and migration of smooth muscle cells over time, within the therapeutic window of paclitaxel; in a preclinical study by Lamichhane, only 10% to 20% of the total drug loaded was lost during transit, whereas ~80% was delivered during balloon inflation time.

STUDY ENDPOINTS. For the primary objective of PICCOLETO II, we hypothesized the noninferiority of the DCB arm versus the DES arm in terms of in-lesion late lumen loss (LLL). Angiographic success was defined as final stenosis <30% in the DCB arm and <20% in the DES arm, without major, flow-limiting dissections and Thrombolysis In Myocardial Infarction flow grade 3. This was caused by the intrinsic difference between a stent and a DCB, which is more prone to acute recoil due to the absence of scaffolding properties, especially for some types of de novo lesions. Procedural success was defined as angiographic success and the absence of in-hospital cardiovascular complications. Secondary angiographic endpoints were post-intervention minimal lumen diameter (MLD) and 6-month percent diameter stenosis, MLD, and binary restenosis. Clinical endpoints were major adverse cardiovascular events (MACE, a composite of cardiac death, MI, target lesion revascularization [TLR]) and the single components of MACE at 1 and 2 years.

ANGIOGRAPHIC ANALYSIS. Baseline and follow-up angiographies were assessed in an independent core lab (University of Ferrara, Ferrara, Italy). Study investigators were committed to perform at least 2 orthogonal views pre-procedurally, after the intervention, and during follow-up angiography, maintaining similar angulations. Additional views were requested for the correct localization of DCB and stent. Quantitative coronary artery analysis was performed using the Q-Angio XA system version 7.2 (Medis Medical Imaging Systems, Leiden, the Netherlands) by experienced operators.

STATISTICAL ANALYSIS. The study hypothesis was that PCI with Elutax SV was noninferior to PCI with the latest-generation DES for the treatment of native small coronary vessels, in terms of in-lesion LLL. Accordingly, the power calculation of the PICCOLETO II trial included the assumption of a LLL of 0.20 mm in the EES arm, with a delta of 0.35, alpha of 5%, power of 90%, and a noninferiority margin of 0.25 mm (5). The estimation of 0.20 mm of LLL in the control group was derived by previous studies with the same device, in a similar lesion setting. Therefore, we calculated a population of 99 patients per group. With an attrition rate for the angiographic follow-up of 10%, we decided to include a total population of 230 patients. In case the primary analysis confirmed the noninferiority hypothesis, a secondary analysis assessing superiority was predefined. We used Cox proportional hazards models

FIGURE 1 Study Flow Chart and Follow-Up of the PICCOLETO II Trial



angio = angiography; DCB = drug-coated balloon; EES = everolimus-eluting stent(s); fup = follow-up; GW = guidewire; LL = late lumen loss; PICCOLETO II = Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment trial; SVD = small vessel disease.

and Kaplan-Meier curves to analyze time-related events. Hazard ratios (HRs) were presented with 95% confidence interval (CI). For baseline characteristics, continuous variables were reported as mean ± SD (Mann-Whitney *U* test), and categorical variables as frequency with percentage, with 95% CI determined by the Wilson score method. A prespecified subgroup analysis was done for sex, age, renal failure, diabetes, MI at presentation, SYNTAX score >20, hemoglobin <10 g/dl, severe coronary calcification, and lesion length >20 mm. Adjusted odds ratios were calculated with a logistic regression model, and HR with a Cox model. All p values of <0.05 were considered statistically significant. Results were analyzed by intention to treat for primary and secondary endpoints. All statistical analyses were performed with SPSS software (version 24, IBM, Chicago, Illinois).

TABLE 1 Demographic Characteristics and Comorbidities of the Study Population at Baseline

	DES (n = 114)	DCB (n = 118)	p Value
Male	87 (76.9)	83 (70.3)	0.25
Age, yrs	66 (50-82)	64 (48-80)	0.32
Hypertension	76 (67.2)	77 (65.2)	0.74
Diabetes	40 (35.4)	45 (38)	0.65
Insulin-dependent diabetes	15 (13.3)	21 (17.8)	0.66
Smoking	19 (16.7)	23 (19.5)	0.84
Dyslipidemia	63 (55)	72 (61)	0.66
Renal failure	12 (10.6)	4 (3.3)	0.03
Previous MI	34 (30)	45 (38)	0.19
Previous CABG	4 (3.5)	4 (3.3)	0.95
Previous PCI	60 (53)	59 (50)	0.33
LVEF	58 (51-65)	58 (48-68)	0.89
Clinical presentation			
Stable angina	63 (55.7)	64 (54.2)	0.81
Unstable angina	18 (16)	17 (14.4)	0.74
NSTEMI	23 (20.3)	25 (21.1)	0.87
STEMI, late comers	9 (8)	12 (10.3)	0.34

Values are n (%) or median (interquartile range).

CABG = coronary artery bypass grafting; DCB = drug-coated balloons; DES = drug-eluting stent(s); LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

RESULTS

A total of 402 consecutive patients were screened at study centers between May 2015 and May 2018 (Figure 1). A total pf 232 patients were finally randomized after the exclusion of 170 patients due to the presence of at least 1 exclusion criterion, or the unwillingness to participate in the study. After randomization, 114 patients were allocated to the DES group, and 118 to the DCB group by intention to treat. Table 1 describes the baseline characteristics, which were well matched, except for a higher rate of renal failure in the DES group. Overall, 127 patients had stable coronary disease and 105 an acute coronary syndrome at hospital admission.

Table 2 describes baseline angiographic and procedural characteristics. Of note, the percentage of patients with lesion pre-dilatation (84% vs. 69%; p = 0.007), length of device used (21.8 ± 8.2 mm vs. 18.3 ± 6.9 mm; p = 0.04), and mean duration of study device inflation (49 vs. 21 s; p = 0.003) were higher in the DCB group. By contrast, patients in the DES group more often received balloon post-dilatation (59.4% vs. 3.3%; p = 0.001). Interestingly, the rate of bailout stenting in the DCB arm was particularly low (6.8%). As expected, the in-lesion acute gain rate was higher in the EES arm (1.47 ± 0.3 mm vs. 0.99 ± 0.4 mm; p = 0.03), and percent diameter stenosis at the end of PCI was numerically, but not statistically, higher in the DES arm (13 ± 18% vs. 21 ± 22%; p = 0.2). Angiographic and procedural success were not different between the groups. The rate of in-hospital complications related to the intervention was not significantly different as well. However, we observed a not statistically significant increase in periprocedural MI in the DES group (8% vs. 4%; p = 0.07).

After a median of 189 (interquartile range: 160 to 202) days, 105 patients (89%) in the DCB arm, and 104 (90%) in the DES arm underwent the scheduled angiographic control. Of the 23 patients who did not receive control angiography, 18 refused to undergo the planned invasive assessment, and 5 were lost at follow-up.

In-lesion LLL, the primary study endpoint, was significantly lower in the DCB arm (0.04 ± 0.28 mm vs. 0.17 ± 0.39 mm) and showed the hypothesized noninferiority (p = 0.001), but also the superiority (p = 0.03) as compared with DES (Central Illustration). Table 3 describes the angiographic performance of the 2 study groups after the intervention and at angiographic follow-up. Notably, in-lesion binary restenosis (6.5% vs. 6.3%; p = 0.98) and percent diameter stenosis (21.6 ± 13% vs. 25.1 ± 11%; p = 0.37) were similar in both arms.

Twelve-month clinical follow-up (median 348, interquartile range: 292 to 390 days) was obtained in 108 DCB and 106 DES patients (92.2% of the enrolled population). MACE occurred in 7.5% of the DES group and in 5.6% of the DCB group (p = 0.55) (Table 4). There was a numerically, but not significantly, higher incidence of spontaneous MI (4.7% vs. 1.9%; p = 0.23) and vessel thrombosis (1.8% vs. 0%; p = 0.15) in the DES arm. Death, cardiac death, TLR, and target vessel revascularization were not significantly different in the 2 groups. The risk of MACE at 12 months was also not different across the prespecified study groups, and no interaction was found after formal testing (Central Illustration). A Kaplan-Meier analysis of the secondary endpoint MACE is presented in Figure 2.

TABLE 2 Lesion Characteristics and Procedural Aspects

	DES (n = 114)	DCB (n = 118)	p Value
SYNTAX score	17 ± 12	16 ± 11	0.36
Bifurcation lesion	14 (12.3)	15 (12.7)	0.94
Multivessel disease	86 (76)	86 (72.8)	0.5
Target vessel LAD	44 (39)	47 (40)	0.31
Target vessel LCx	35(31)	44 (37.2)	0.12
Target vessel RCA	34 (30.2)	27 (22.8)	0.19
Total contrast use, ml	155 (67-289)	152 (75-301)	0.37
Total fluoroscopy time, min	11 (4 to 67)	13 (5 to 59)	0.22
Pre-dilatation	78 (69)	99 (84)	0.007
Post-dilatation	66 (59.4)	4 (3.3)	0.001
Scoring balloon use for lesion preparation	18 (15.8)	26 (22)	0.13
Number of devices used, mean	1.12	1.03	0.004
Length of device used, mm	18.3 ± 6.9	21.8 ± 8.2	0.006
Inflation pressure, atm	13.7 ± 2.5	11.4 ± 3.3	0.03
Duration of inflation, s	21.4 ± 11.8	49.2 ± 14.5	0.002
Bailout stenting	–	8 (6.7)	–
Angiographic success	113 (99.1)	116 (98.3)	0.88
Procedural success	112 (98.2)	116 (98.3)	0.92
Peak troponin I after the intervention, ng/ml	6.14 ± 5.80	3.6 ± 3.21	0.09

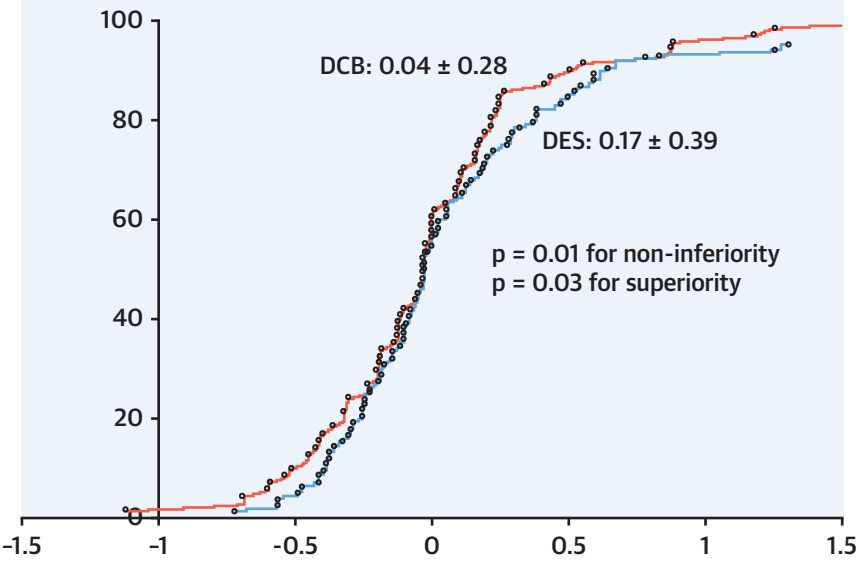
Values are mean ± SD, n (%), or median (interquartile range).
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; other abbreviations as in Table 1.

A specific sensitivity post hoc analysis regarding a comparison between patients with DES implanted after DCB (8 patients, 6.8%) and patients allocated to the control group and the sole-DCB group did not show differences in terms of MACE (respectively, 12.5% vs. 7.5%; p = 0.21, and 12.5% vs. 4.9%; p = 0.08). Likewise, pre-dilatation in the DCB arm did not affect either the angiographic or the clinical outcome (LLL 0.07 ± 0.16 mm in patients without pre-dilatation vs. 0.02 ± 0.31 mm; p = 0.31).

DISCUSSION

SUMMARY OF THE STUDY RESULTS. The PICCOLETO II trial was a multicenter, multinational randomized clinical trial meeting the primary endpoint of non-inferiority and showing the superiority of a new-generation DCB versus a current-generation DES regarding LLL in patients with de novo SVD. Both strategies provide equivalent efficacy in other important surrogate angiographic endpoints including MLD and percent diameter stenosis at follow-up. Although underpowered for clinical events, our study suggests similar mid-term efficacy

CENTRAL ILLUSTRATION **Primary Measure of Outcome, In-Lesion Late Lumen Loss**



Cortese, B. et al. J Am Coll Cardiol Intv. 2020;■(■):■–■.

Primary measure of outcome, in-lesion late lumen loss (LLL), showing both noninferiority and superiority of DCB **(blue)** versus DES **(red)**. DCB = drug-coated balloon; DES = drug-eluting stent(s).

TABLE 3 **Outcomes at 6-Month Angiographic Follow-Up**

	DES (n = 104)	DCB (n = 105)	p Value
Pre-procedure			
RVD, mm	2.18 ± 0.4	2.23 ± 0.4	0.46
MLD, mm	0.83 ± 0.4	0.82 ± 0.5	0.98
Stenosis, % of lumen diameter	76 ± 15	75 ± 17	0.83
Lesion length, mm	14.0 ± 6.9	13.5 ± 7.3	0.75
Post-procedure, in-lesion			
MLD, mm	2.29 ± 0.4	1.89 ± 0.3	0.02
Stenosis, % of lumen diameter	13.1 ± 18	21.4 ± 22	0.20
Acute gain, mm	1.47 ± 0.3	0.99 ± 0.4	0.03
Post-procedure, in-segment			
MLD, mm	1.93 ± 0.3	1.73 ± 0.3	0.04
Stenosis, % of lumen diameter	26.8 ± 12	29.6 ± 16	0.55
Acute gain, mm	1.10 ± 0.2	0.85 ± 0.2	0.05
At follow-up, in-lesion			
MLD, mm	2.12 ± 0.53	1.85 ± 0.49	0.14
Stenosis, % of lumen diameter	21.6 ± 13	25.1 ± 11	0.37
Binary restenosis	7 (6.5)	7 (6.3)	0.98
Late loss, mm	**0.17**	**0.04**	**0.03 for superiority**
At follow-up, in-segment			
MLD, mm	1.79 ± 0.48	1.74 ± 0.46	0.69
Stenosis, % of lumen diameter	32.2 ± 19	36.6 ± 21	0.78
Binary restenosis	10 (9.6)	11 (10.5)	0.94
Late loss, mm	0.14 ± 0.38	0.01 ± 0.25	**0.03 for superiority**
Net luminal gain*	0.96 ± 0.23	0.84 ± 0.19	0.49

Values are mean ± SD or n (%). *Acute gain − late lumen loss. **Bold** indicates a primary endpoint.
MLD = minimal lumen diameter; RVD = reference vessel diameter; other abbreviations as in Table 1.

with both strategies, with a trend suggesting a safer profile of DCB in this challenging anatomic scenario.

NATIVE SVD TREATMENT OPTIONS. We would like to stress the importance of finding an optimal treatment strategy for these lesions accounting for 30% to 50% of all coronary interventions in the Western world, with percentages even higher in some Eastern countries. The general DES strategy in native coronary vessel disease seems weaker here, because the mid-term angiographic performance of DES is reduced and the restenosis rates higher. In the SVD setting, the prospective Spirit SV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System Small Vessel) study accounts for a target lesion failure rate of 10.8% after 13 months with Xience DES (5). The cumulative data analysis of the SPIRIT and COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice) studies shows a 2-fold risk of MACE versus larger vessels (10.4% vs. 5.6%; $p < 0.001$) (13), with a significantly higher risk of MI and TLR. The TWENTE II (DUTCH PEERS [DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity]) study showed similar data, with a target lesion failure rate of 9.5% versus

TABLE 4 Outcome After 12 Months

	DES (n = 106)	DCB (n = 108)	p Value
MACE	8 (7.5)	6 (5.6)	0.55
Total death	1 (0.9)	0 (0)	0.78
Cardiac death	0 (0)	0 (0)	–
Myocardial infarction,	4 (4.7)	2 (1.9)	0.23
TLR	6 (5.6)	6 (5.6)	0.80
BARC bleeds type 3 or 5	0 (0)	0 (0)	–
Vessel thrombosis	2 (1.9)	0 (0)	0.15

Values are n (%).

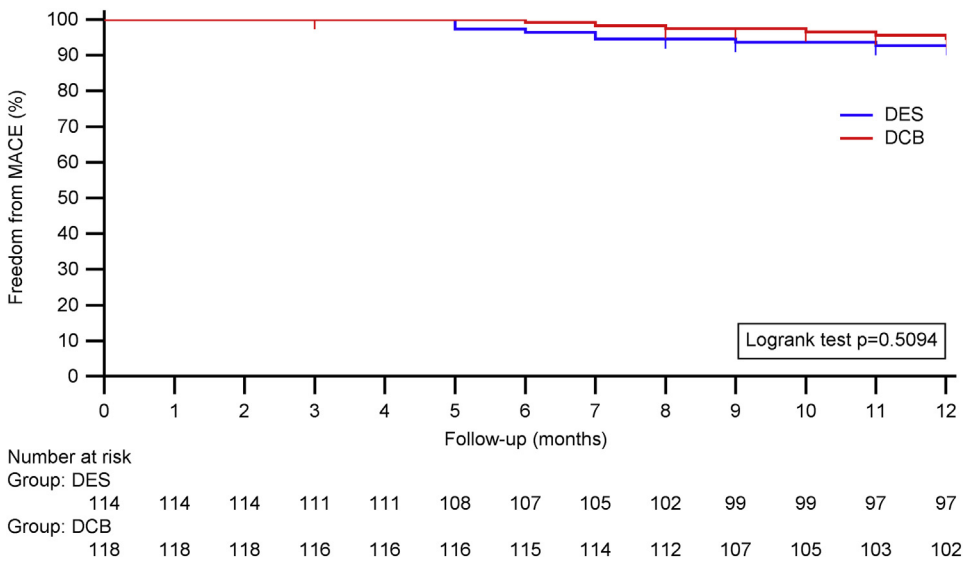
BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiac event(s); TLR = target lesion revascularization; other abbreviations as in Table 1.

5.4% in larger vessels after 2 years (HR: 1.60, 95% CI: 1.09 to 2.34), and a significantly higher risk of MI and TLR in the SVD setting (3.1% vs. 1.3%, 4.8% vs. 2.8%. respectively) (7).

The use of DCB may have some potential advantages in this setting (14): it may theoretically overcome the risk of negative vessel remodeling obtained with plain balloon angioplasty, and both the immediate encumbrance and the subsequent neointimal proliferation after stent implantation may be reduced. DCB share dedicated technologies that allow the delivery and persistence of the drug released upon inflation (either paclitaxel or sirolimus are available in the European market). An effective DCB may also exert a positive remodeling effect, which can be perceived to be particularly advantageous in small coronary lumens; this has been already demonstrated with at least 2 different brands of paclitaxel-coated balloons, including the device tested in the PICCOLETO II trial (15,16). Another potential advantage of DCB over stents in native vessel disease is related to the perpetual yearly risk of ≅2% of adverse events with current-generation DES (17), as compared with the theoretical absence of such risk with DCB after the first year in de novo lesions (18,19).

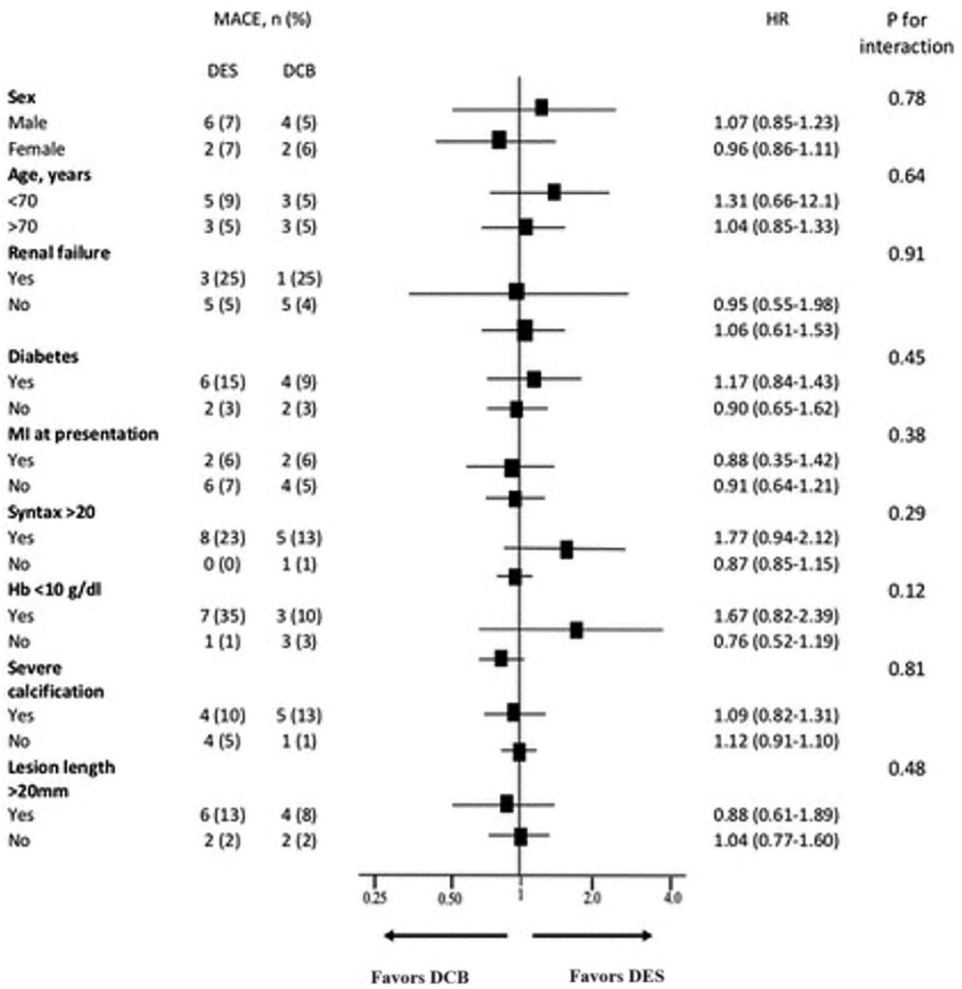
PREVIOUS STUDIES. To date, randomized studies on the use of DCB in small vessels brought variable results. The first-generation Dior DCB (Eurocor, Bonn, Germany) failed to show the angiographic noninferiority versus Taxus DES (Boston Scientific, Marlborough, Massachusetts) in the prematurely interrupted PICCOLETO study, where the rate of MACE after 9 months was higher in the DCB arm (20). The limited effectiveness of this preliminary DCB was blamed for the results (21). On the other hand, newer-generation DCB showed the potential advantages of this technology in native vessel disease. The BELLO study (Balloon Elution and Late Loss Optimization Study) was able to show the angiographic superiority of the In-Pact Falcon DCB (Invatec-Medtronic, Frauenfeld, Switzerland) versus the Taxus

FIGURE 2 Kaplan-Meier Analysis of the Secondary Endpoint MACE at 1 Year



MACE = major adverse cardiac event(s); other abbreviations as in Figure 1.

FIGURE 3 **Risk of MACE at 12 Months**



Risk of MACE at 12 months was not different across the pre-specified study groups, and no interaction was found after formal testing. HR = hazard ratio; other abbreviations as in Figures 1 and 2.

stent, and the 3-year data also showed a significant reduction in the rate of MACE (14% vs. 30%; p = 0.015) (18). More recently, the RESTORE SVD (Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease) study compared Restore DCB (Cardionovum, Bonn, Germany) to DES and showed the noninferiority of DCB in terms of percent diameter stenosis during angiographic follow-up (11% vs. 7.5%; p for noninferiority <0.001), with no significant differences in terms of LLL (0.25 ± 0.42 vs. 0.27 ± 0.36; p = 0.41) and 12-month MACE (4.4% vs. 2.6%; p = 0.72) (22). The largest study (powered for clinical endpoints) assessing the role of DCB in a SVD setting (reference vessel diameter <3 mm) after successful lesion pre-dilatation was the BASKET SMALL II (Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions) study. In this study, Sequent Please DCB (B. Braun, Melsungen, Germany) was compared with DES (72% Xience, 28% Taxus). The primary endpoint of MACE at 12 months was 7.3% in the DCB group and 7.5% in the DES group (HR: 0.97, CI: 0.58 to 1.64; p = 0.92) (23).

PRESENT STUDY. The PICCOLETO II study for the first time to our knowledge showed the angiographic superiority, as per the LLL endpoint, of a new-generation DCB versus 1 of the latest-generation DES in a native vessel disease setting, with comparable clinical outcome at 1 year. This finding was

confirmed in all pre-specified subgroups (**Figure 3**). These data seem particularly appealing, taking into consideration the direct correlation between measures of angiographic outcome such as LLL and percent diameter stenosis and late clinical events, and might reflect a favorable effect of paclitaxel delivery by means of DCB leading to late lumen enlargement (15,16). To note, the most important difference between our study and the 2 most recent ones (the BASKET SMALL II and RESTORE SVD trials [22,23]) is that whereas in the latter studies randomization was performed after successful lesion predilatation, in the PICCOLETO II trial, it was performed before lesion preparation, reflecting a real intention-to-treat strategy, of special value for the "real-world" patients seen in routine clinical practice. Despite this, the rate of crossover to stenting from the DCB group or reverse (e.g., a patient assigned to DCB treated instead with DES) was negligible (4.4%). We chose this randomization strategy because the presence of a non-flow-limiting dissection before or after DCB use has not been correlated with worse outcomes in 1 of our previous studies (16).

MORTALITY AFTER DCB USE. A specific mention should be made regarding the hypothetical increase in mortality after paclitaxel application for femoropopliteal interventions (24-26). A recent meta-analysis of randomized controlled trials in the coronary territory showed no increase in mortality after DCB application during PCI as compared with other options including simple angioplasty and bare-metal stent or DES implantation, with a significant reduction in mortality after 3 years with DCB (relative risk: 0.73; 95% CI: 0.53 to 1.00; p = 0.047) (19). The results of the PICCOLETO II trial did not show any safety signal at mid-term follow-up and go in the same direction of the data provided by the latter meta-analysis.

STUDY LIMITATIONS. First of all, due to the open-label nature of the study, some ascertainment bias cannot be completely excluded. However, all clinical data were analyzed by an independent blinded clinical event committee, and an independent core laboratory analyzed the angiographic outcome measures. Second, this study is not powered for hard clinical endpoints. Third, these results have been obtained in centers that had to certify a strong leadership in the use of DCB, therefore it is possible that the results are not reproducible in a different scenario. Finally, the primary endpoint chosen, LLL, could favor the DCB in consideration of the better post-procedural MLD after DES implantation.

CONCLUSIONS

The PICCOLETO II trial for the first time shows the angiographic superiority in terms of LLL, and the equivalence in terms of MLD and percent diameter stenosis, of a novel DCB over 1 of the best-in-class DES for the treatment of de novo coronary lesions in small vessels. This trial also shows the clinical noninferiority of the DCB strategy after 12 months.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Bernardo Cortese, Cardiovascular Research Team, San Carlo Clinic, Via Ospedale, 21, 20037 Paderno Dugnano, Milano, Italy. E-mail: bcortese@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? Small vessel coronary artery disease still represents a challenging subset for DES.

WHAT IS NEW? This is the first randomized study to show an improved angiographic outcome of "new generation" DCB versus DES in small coronary vessel disease.

WHAT IS NEXT? A larger study adequately powered for hard clinical endpoints is needed in order to confirm these findings.

REFERENCES

1. Werner N, Nickenig G, Sinning J-M. Complex PCI procedures: challenges for the interventional cardiologist. Clin Res Cardiol 2018;107:64-73.

2. Bricker RS, Glorioso TJ, Jawaid O, et al. Temporal trends and site variation in high-risk coronary intervention and the use of mechanical circulatory support: insights from the Veterans Affairs Clinical Assessment Reporting and Tracking (CART) program. J Am Heart Assoc 2019;8:e014906.

3. Chichareon P, Katagiri Y, Asano T, et al. Mechanical properties and performances of contemporary drug-eluting stent: focus on the metallic backbone. Expert Rev Med Devices 2019;16:211-28.

4. Konigstein M, Madhavan MV, Ben-Yehuda O, et al. Incidence and predictors of target lesion failure in patients undergoing contemporary DES implantation-Individual patient data pooled analysis from 6 randomized controlled trials. Am Heart J 2019;213:105-11.

5. Cannon LA, Simon DI, Kereiakes D, et al. The XIENCE nano everolimus eluting coronary stent system for the treatment of small coronary arteries: the SPIRIT Small Vessel trial. Catheter Cardiovasc Interv 2012;80:546-53.

6. Claessen BE, Smits PC, Kereiakes DJ, et al. Impact of lesion length and vessel size on clinical

outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) randomized trials. J Am Coll Cardiol Intv 2011;4:1209–15.

7. van der Heijden LC, Kok MM, Danse PW, et al. Small-vessel treatment with contemporary newer-generation drug-eluting coronary stents in all-comers: insights from 2-year DUTCH PEERS (TWENTE II) randomized trial. Am Heart J 2016; 176:28–35.

8. Cortese B, Bertoletti A. Paclitaxel coated balloons for coronary artery interventions: a comprehensive review of preclinical and clinical data. Int J Cardiol 2012;161:4–12.

9. Unverdorben M, Kleber FX, Heuer H, et al. Treatment of small coronary arteries with a paclitaxel-coated balloon catheter in the PEPCAD I study: are lesions clinically stable from 12 to 36 months? EuroIntervention 2013;9:620–8.

10. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165.

11. Thygesen K, Alpert JS, Jaffe AS, et al. Third Universal Definition of Myocardial Infarction. J Am Coll Cardiol 2012;60:1581–98.

12. Cortese B, D'Ascenzo F, Fetiveau R, et al. Treatment of coronary artery disease with a new-generation drug-coated balloon: final results of the Italian Elutax SV rEgistry-DCB-RISE. J Cardiovasc Med (Hagerstown) 2018;19:247–52.

13. Kereiakes DJ, Smits PC, Kedhi E, et al. Predictors of death or myocardial infarction, ischaemic-driven revascularisation, and major adverse cardiovascular events following everolimus-eluting or paclitaxel-eluting stent deployment: pooled analysis from the SPIRIT II, III, IV and COMPARE trials. EuroIntervention 2011;7:74–83.

14. Yerasi C, Case BC, Forrestal BJ, et al. Drug-coated balloon for de novo coronary artery disease: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:1061–73.

15. Kleber FX, Schulz A, Waliszewski M, et al. Local paclitaxel induces late lumen enlargement in coronary arteries after balloon angioplasty. Clin Res Cardiol 2014;104:217–25.

16. Cortese B, Orrego PS, Agostoni P, et al. Effect of drug-coated balloons in native coronary artery disease left with a dissection. J Am Coll Cardiol Intv 2015;8:2003–9.

17. Madhavan MV, Kirtane AJ, Redfors B, et al. Stent-related adverse events >1 year after percutaneous coronary intervention. J Am Coll Cardiol 2020;75:590–604.

18. Latib A, Ruparelia N, Menozzi A, et al. 3-Year follow-up of the Balloon Elution and Late Loss Optimization Study (BELLO). J Am Coll Cardiol Intv 2015;8:1132–4.

19. Scheller B, Vukadinovic D, Jeger R, et al. Survival after coronary revascularization with paclitaxel-coated balloons. J Am Coll Cardiol 2020;75:1017–28.

20. Cortese B, Micheli A, Picchi A, et al. Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. Heart 2010;96:1291–6.

21. Cortese B. The PICCOLETO study and beyond. EuroIntervention 2011;7:K53–6.

22. Tang Y, Qiao S, Su X, et al. Drug-coated balloon versus drug-eluting stent for small-vessel disease: the RESTORE SVD China randomized trial. J Am Coll Cardiol Intv 2018;11: 2381–92.

23. Jeger RV, Farah A, Ohlow M-A, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. Lancet 2018;392:849–56.

24. Cortese B, Granada JF. Mortality increase and paclitaxel-coated device use: a plausible but inconclusive hypothesis. J Am Coll Cardiol Intv 2019;12:2538–40.

25. Cortese B, Alfonso F, Pellegrini D, Sing KR, Granada JF. The hypothesis of an increased mortality following paclitaxel coated device use in peripheral vascular interventions (and the emerging era of meta-analysis based evidence). Catheter Cardiovasc Interv 2019;95:329–31.

26. Fanelli F, Cortese B, Zeller T. Use of paclitaxel-eluting technologies in the femoropopliteal segment under scrutiny over possible link to late all-cause mortality: time to panic or an opportunity to resurge? J Endovasc Ther 2019;26:41–3.

KEY WORDS drug-coated balloon, everolimus-eluting stent(s), small coronary vessel disease, native vessel disease

Original article

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Treatment of coronary artery disease with a new-generation drug-coated balloon: final results of the Italian Elutax SV rEgistry-DCB-RISE

Bernardo Cortese[a,b], Fabrizio D'Ascenzo[c], Raffaela Fetiveau[d], Vruyr Balian[e], Simonetta Blengino[f], Massimo Fineschi[g], Renata Rogacka[h], Corrado Lettieri[i], Andrea Pavei[j], Maurizio D'Amico[c], Arnaldo Poli[h], Gaetano Di Palma[a], Roberto A. Latini[a], Pedro S. Orrego[a] and Romano Seregni[a]

Aims **Drug-coated balloons (DCBs) are a recognized alternative to stents for the treatment of in-stent restenosis (ISR), and there is some initial clinical evidence about their efficacy for the treatment of small coronary vessels. Newer-generation DCBs were developed to overcome the reduced deliverability of the previous generation, also warranting a more effective drug delivery to vessel wall. However, the vast majority of new-generation DCBs still lack of reliability due to paucity of clinical data.**

Methods **Between 2012 and 2015, all patients treated with Elutax SV DCB (Aachen Resonance, Germany) at nine Italian centers were enrolled in this retrospective registry. Primary outcome was the occurrence of target-lesion revascularization (TLR) at the longest available follow-up. Secondary endpoints were procedural success and occurrence of device-oriented adverse cardiovascular events including cardiac death, target-vessel myocardial infarction, stroke, and TLR. A minimum 6-month clinical follow-up was required.**

Results **We enrolled 544 consecutive patients treated at 583 sites. Fifty-three per cent of the patients had ISR, and the rest native vessel coronary artery disease. Procedural success occurred in 97.5%. At the longest available clinical follow-up (average 13.3 ± 7.4 months), 5.9% of the patients suffered a TLR and 7.1% a device-oriented adverse cardiovascular event. We did not register cases of target-vessel abrupt occlusion. At multivariate analysis, severe calcification at the lesion site was the first determinant for the occurrence of TLR.**

Conclusion **This registry on the performance of a new-generation DCB shows an adequate profile of safety and efficacy at mid-term clinical follow-up.**

J Cardiovasc Med 2018, **19**:000–000

Keywords: clinical registry, drug-coated balloon, target-lesion revascularization

[a]Interventional Cardiology, ASST Fatebenefratelli-Sacco, Milan, [b]Fondazione Monasterio CNR-Regione Toscana, [c]Division of Cardiology, University of Turin, Torino, [d]Division of Cardiology, Ospedale di Legnano, [e]Division of Cardiology, Busto Arsizio Hospital (MI), [f]Interventional Cardiology, Ist. Auxologico, Milan, [g]Division of Cardiology, Policlinico Le Scotte, Siena, [h]Interventional Cardiology, Ospedale di Desio, (MI), [i]Interventional Cardiology, ASST 'Carlo Poma', Mantova and [j]Interventional Cardiology, Ospedale S.M. dei Battuti Conegliano (TV), Italy

Correspondence to Bernardo Cortese, MD, FESC, Interventional Cardiology, A.S.S.T. Fatebenefratelli-Sacco Milano, Bastioni di Porta Nuova 21, 20100 Milan, Italy
Tel/fax: +39 0263632210; e-mail: bcortese@gmail.com

Received 12 September 2017 **Revised** 10 January 2018
Accepted 21 January 2018

Introduction

In recent years, drug-coated balloons (DCBs) have emerged as a therapeutic option in the interventional field.[1,2] Preliminary data showed how DCBs were a valuable treatment strategy in case of in-stent restenosis (ISR), either of bare-metal stent (BMS) or drug-eluting stent (DES).[3–6] Later, DCBs have also been used for the treatment of native coronary vessel disease as an alternative to DES in selected cases.[7] Several paclitaxel-coated balloons were released and obtained the european community mark, with different behavior and outcome, so that a 'class effect' does not exist for this technology. Recent advances, both in terms of device deliverability and effective drug release, and retention led to the creation of the arbitrary names 'second-' or 'latest-generation' DCBs. To this day, the clinical outcome of any of this newer 'generation' of DCBs is not available yet. With the drug-coated balloon- Results of the Italian elutax SV registry (DCB-RISE), we aim to investigate the clinical performance of one of these devices.

Methods

We here report the main results of the DCB-RISE registry, an investigator-initiated, retrospective, all-comer real-world registry of patients who were treated with the Elutax SV (Aachen Resonance, Germany) DCBs. The aim of this registry was to assess the safety and efficacy of Elutax SV at the longest available clinical follow-up. This study was not funded and ethically approved.

Study procedure

All patients underwent percutaneous coronary intervention (PCI) following international guidelines[8,9] and according to local practice. Antithrombotic treatment

1558-2027 © 2018 Italian Federation of Cardiology. All rights reserved.
DOI:10.2459/JCM.0000000000000632

© 2018 Italian Federation of Cardiology. All rights reserved.

was left at the operator's discretion, with a minimum of 30-day dual antiplatelet therapy (DAPT), that was increased to a minimum of 3 months in case of additional stent implantation, or more based on the clinical indication (e.g. acute coronary syndrome).

Stent implantation after DCB use was discouraged, unless a major dissection (>type B) or vessel recoil was discovered after PCI. In this case, DES use was suggested unless contraindicated. Avoidance of geographical mismatch was also recommended (in case of stenting the prosthesis had to be placed within and not exceeding the area previously treated with DCBs). Finally, in order to avoid acute recoil, we also suggested to wait for at least 10 min after DCB inflation before ending the intervention.[9]

After the procedure patients were clinically followed, according to the local practice.

Device

The device tested in this study is a rapid exchange percutaneous transluminal coronary angioplasty balloon catheter. Once inflated, it delivers the drug it is coated with to the vessel wall. The balloon is coated with an active pharmaceutical agent for preventing restenosis: 2.2 μg paclitaxel mm^{-2} with a tolerance of 1.4–3.00 μg paclitaxel mm^{-2} and has a 0.7 μg dextran mm^{-2} top coating with a maximum amount of 1.89 μg dextran mm^{-2}, which acts as excipient (drug carrier). The functional characteristic of the formulation is to release paclitaxel to the tissue of the vascular wall during inflation and to maintain it during the first days. The uptake of paclitaxel is controlled by the interaction with dextran and the vessel wall. The drug uptake measured in different animal models is highest after 1 h and decreases slowly over days and weeks, with values of around 250 μg ml^{-1} decreasing to around 100 μg ml^{-1} after 1 week to 10 μg ml^{-1} after 4 weeks, allowing a successful inhibition of proliferation and migration of smooth muscle cells over time.

Study endpoints

The primary endpoint was the occurrence of target-lesion revascularization (TLR) at the longest available follow-up. Secondary endpoints were procedural success, defined as angiographic success in the absence of in-hospital complications, and the occurrence of a device-oriented endpoint [device-oriented adverse cardiovascular event (DOCE)], which included cardiac death, target-vessel myocardial infarction (MI), stroke, or TLR.

Angiographic success was defined as Thrombolysis in Myocardial Infarction 3 flow with <50% final stenosis at the end of intervention. MI was defined according to the universal definition[10] and was considered only in case it was spontaneous. TLR was defined as repeat PCI or coronary artery bypass grafting for the target segment or within 5 mm proximally or distally.

Table 1 Baseline patient characteristics

Variable	$n = 544$
Demographic characteristics	
Age years, mean ± SD	67.25 ± 10.7
Male sex	388 (71%)
Cardiovascular risk factors	
Hypertension	413 (76%)
Diabetes	177 (32%)
Smoking history	217 (40%)
Previous myocardial infarction	228 (42%)
Previous bypass surgery	70 (13%)
Clinical characteristics	
LV ejection fraction, mean ± SD	53.3 ± 9.6
Chronic kidney disease (eGFR <30 ml min^{-1})	72 (13%)
Clinical presentation	
UA (troponine negative)	53 (9.7%)
NSTEMI	202 (37%)
STEMI	24 (4.4)
Stable CAD	265 (48.7)

Data are mean ± SD or *n* (%). ACS, acute coronary syndrome; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; LV, left ventricle; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Statistical analysis

Categorical variables are reported as count and percentage, whereas continuous variables as mean and standard deviations or interquartile range (IQR). Gaussian or not Gaussian distribution was evaluated by Kolmogorov–Smirnoff test. The *t* test has been used to assess differences between parametric continuous variables, Mann–Whitney *U* test for nonparametric variables, the chi-square test for categorical variables, and Fisher's exact test for 2×2 tables. Cox multivariate analysis was performed to assess the independent predictors of TLR, including all variables, which differ at univariate analysis or with significant association with TLR.

Proportional hazards assumption was not violated in statistical analysis. A two-sided *P* value less than 0.05 was considered statistically significant; all analyses were performed with SPSS 21.0 (IBM, Armonk, New York, USA).

Results

All consecutive patients treated with Elutax SV at nine Italian centers between December 2012 and December 2015, and with at least 6 months clinical follow-up available, were included in the DCB-RISE registry. In all, 544 patients (age 67 ± 12 years) with 583 lesions were included. One hundred and seventy-seven (32.6%) patients had diabetes mellitus, and 13% had chronic kidney disease with estimated glomerular filtration rate below 30 ml min^{-1}. In 49% of the patients, the clinical indication for PCI was stable coronary artery disease, and 4% of the population had a ST-elevation MI caused by ISR. Table 1 describes the clinical characteristics of the population.

© 2018 Italian Federation of Cardiology. All rights reserved.

Table 2 Angiographic and procedural characteristics, discharge

Variable (lesions treated with DCB)	583
Target vessel	
Left anterior descending artery	274 (47%)
Left circumflex artery	102 (17%)
Right coronary artery	190 (33%)
Saphenous vein graft	23 (4%)
Arterial graft	5 (0.9%)
Number of diseased vessels	
One-vessel	281 (48%)
Two-vessels	169 (29%)
Three-vessels	124 (21%)
Graft disease	9 (1.5%)
In-stent restenosis	
ISR after BMS	114 (19%)
ISR after DES	189 (32%)
Native vessel disease	280 (48%)
Lesion involving bifurcation with SB >2 m	96 (16.5%)
CTO	20 (3.4%)
Severe calcifications	19 (3.3%)
Moderate calcifications	62 (11%)
QCA analysis	
Lesion length, mm ± SD	16.9 ± 7.2
Long lesions (>24 mm)	88 (15%)
RVD, mm ± SD	2.84 ± 1.18
Preprocedural MLD, mm ± SD	0.43 ± 0.31
Percentage diameter stenosis pre, % ± SD	85.0 ± 11.4
Lesion preparation	
Absence of lesion predilatation	49 (8.4%)
Predilatation with semicompliant balloon	380 (65%)
Predilatation with noncompliant balloon	189 (32%)
Predilatation with scoring balloon	14 (2.4%)
Diameter of predilatation balloon, mm ± SD	2.9 ± 0.67
Number of DCB used/lesion, *n* ± SD	1.3 ± 0.63
DCB diameter, mm ± SD	2.9 ± 0.49
DCB length, mm ± SD	20.5 ± 6.47
DCB inflation, atmospheres ± SD	11.0 ± 3.9
DCB inflation length, s ± SD	55.6 ± 26.4
Stent implantation after DCB PCI	
DES implantation	62 (11%)
BVS implantation	1 (0.2%)
BMS implantation	4 (0.7%)
Final MLD, in segment, mm ± SD	1.57 ± 0.39
Final percentage diameter stenosis, % ± SD	17 ± 11.5
Angiographic success	576 (98.7)
Procedural failure	7 (1.3%)
IVUS/OCT use	60 (10%)
GP IIb/IIIa Inhibitors	21 (3.6%)
Bivalirudin use	2 (0.3%)
Aspirin at discharge	536 (98%)
Clopidogrel at discharge	410 (75%)
Ticagrelor at discharge	39 (7.2%)
Prasugrel at discharge	14 (2.6%)

ACS, acute coronary syndrome; BMS, bare-metal stent(s); BVS, bioresorbable vascular scaffold; CAD, coronary artery disease; DCB, drug-coated balloon; DES, drug-eluting stent(s); FFR, fractional flow reserve; GP, glycoprotein; IVUS, intravascular ultrasound; MLD, minimal lumen diameter; OCT, optical coherence tomography; TIMI, Thrombolysis in Myocardial Infarction.

Drug-coated balloon was used predominantly to treat ISR, either DES (32.4%) or BMS (19.5%) restenosis. On the contrary, treatment of de-novo coronary artery disease occurred in 48.1% of the patients, including 16.5% of patients with bifurcation with greater than 2 mm side branch diameter.

Average lesion length was 16.9 ± 7.2 mm and reference vessel diameter 2.84 ± 1.18 mm. According to study and consensus paper recommendations,[9] only less than 10% of the lesions were directly treated with DCBs, whereas the vast majority was pretreated either with semicompliant or noncompliant balloons. The average DCB length was 20.5 ± 6.47 mm, with an average diameter of 2.9 ± 0.49 mm. Stenting after DCB was required in 12.3% of the patients. In seven cases (1.3%), the procedure failed because it was impossible to reach the target lesion with the device, and the procedure was converted to DES-PCI (two cases) or plain-old balloon angioplasty (five cases). Procedural success occurred in 97.5% of the cases.

Table 3 Clinical endpoints at the longest follow-up available

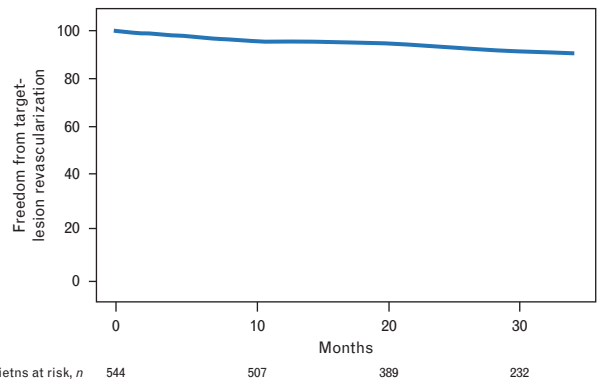
Variable	*n* = 507
Duration of follow-up, months, average (SD)	13.3 (7.4%)
TLR	30 (5.9%)
TLR managed with CABG	4 (0.8%)
TLR managed with PCI	26 (5.1%)
Acute vessel occlusion	0
Target vessel MI	3 (0.6%)
Stroke	2 (0.4%)
All-cause death	12 (2.4%)
Cardiac death	3 (0.6%)
DOCE	36 (7.1%)
TVR (non-TLR)	12 (2.4%)

CABG, coronary artery bypass graft; DOCEs, device oriented cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; TVR, target vessel revascularization.

Dual antiplatelet therapy was prescribed in 452 patients (83.1%) at discharge, and was prolonged for 1 month in 432 of them (79.4%); at final follow-up, only 39 patients (6.4%) were still on DAPT. Table 2 describes the angiographic and procedural characteristics of the population.

Average clinical follow-up was 13.3 ± 7.4 months and was available for 507 (93.2%) patients. Table 3 describes the main study results. The primary outcome measure, TLR, was observed in 30 (5.9%) patients. TLR was managed with coronary artery bypass graft in four patients (0.8%) and with re-PCI in 26 patients (5.1%) (Fig. 1). DOCE, secondary study endpoint, occurred in 36 (7.1%) patients. Cardiac death or MI occurred in 3 patients (0.6%),

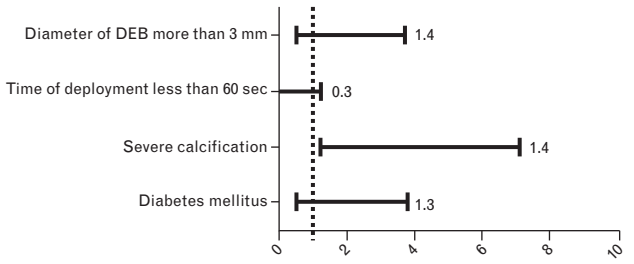
Fig. 1



Kaplan–Meier curve of survival from the primary study endpoint, TLR, at the longest available follow-up. TLR, target-lesion revascularization.

© 2018 Italian Federation of Cardiology. All rights reserved.

Fig. 2



Multivariate analysis with independent predictors for TLR. TLR, target-lesion revascularization.

whereas all-cause death occurred in 12 patients (2.4%). Cerebrovascular stroke occurred in two patients (0.4%).

Multivariate analysis showed that only severe calcifications at lesion site were an independent predictor of TLR (Figs 2 and 3).

We undertook a subanalysis of the data comparing patients treated for ISR and patients treated for de-novo lesions, and observed a significant difference in the TLR rate that occurred in 9 vs. 2.6% ($P = 0.006$), respectively; DOCEs were significantly higher in the ISR group (11 vs. 2.6%; $P = 0.001$), whereas no significant statistical difference was observed in terms of cardiac death, target vessel myocardial infarction, and stroke (Table 4). TLR rate was not different between patients with BMS or DES-ISR.

Table 4 Clinical endpoints at the longest available follow-up

	$n = 507$		
	13.3 (7.4)		
Average duration of follow-up, months (SD)	ISR ($n = 269$)	*de novo* ($n = 238$)	*P*
TLR, *n* (%)	24 (9%)	6 (2.6%)	0.006
TLR managed with CABG, *n* (%)	3 (1%)	1 (0.4%)	0.64
TLR managed with PCI, *n* (%)	21 (7.8%)	5 (2.1%)	0.003
Target-vessel MI, *n* (%)	3 (1.1%)	0	0.14
Stroke, *n* (%)	1 (0.3%)	1 (0.4%)	1
All-cause death	6 (2.2%)	6 (2.5%)	0.36
Cardiac death	3 (1.1%)	0	0.27
DOCE	30 (11%)	6 (2.6%)	0.001

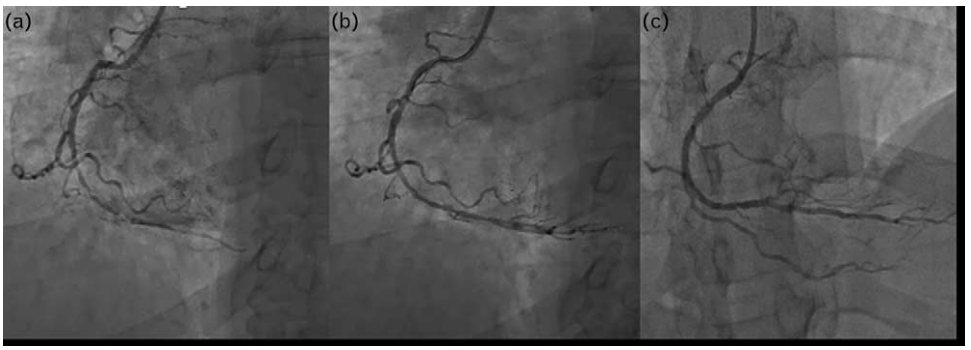
CABG, coronary artery bypass graft; DOCE, device-oriented cardiovascular events; ISR, in-stent restenosis; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target-lesion revascularization.

Discussion

The study shows how a PCI performed with one of the latest-generation DCBs is feasible and well tolerated at mid-term follow-up, with a low rate of TLR, also taking into consideration the medium/high-risk profile of the population (half of the patients had ISR as indication for PCI). This endpoint is also similar to the one observed in a registry with one of the most widely used DCB, at a shorter follow-up.[11] In another registry, a different DCB showed similar results in terms of safety and efficacy after 12 months.[12] In the international, multicenter, prospective, all-comers SeQuent Please World Registry,[13] a real-world registry which included both patients treated for ISR and de-novo lesions, the TLR rate was 5.2%, similar to the one observed in our registry; moreover, also analyzing the outcomes in native coronary lesions, TLR rates were comparable in the twio registries (respectively, 2.4 and 2.6%).

The main potential advantages of DCBs are as follows: a quick and homogeneous release of the antiproliferative drug to the vessel wall, which is absorbed and has a prolonged effect, attenuating the process of neointimal hyperplasia; the absence of polymer, which can reduce or eliminate the vascular inflammatory response, which is directly linked to late thrombotic events; the absence of a metal platform; the need for shorter DAPT. The role of DCB has recently gained a precise role in interventional cardiology, being the first choice for the treatment of DES or BMS restenosis in many centers. The DCB role

Fig. 3



(a) Chronic total occlusion of the right coronary artery (RCA). (b) Final angiographic result after angioplasty with a 2.5/30 mm Elutax SV drug-coated balloon, with persisting 30–40% stenosis. (c) Six-month angiographic follow-up, showing good persisting patency of the RCA and visible vessel lumen gain.

© 2018 Italian Federation of Cardiology. All rights reserved.

for the treatment of native coronary vessels is less recognized and these devices are less widely used in this setting, but some preliminary studies show interesting data in terms of vessel dissection healing and late coronary lumen gain, although prospective studies on the matter are still lacking.[7,14,15] Current patients treated in the cath laboratories of western countries represent a highly complex population with frequent involvement of two or three coronary vessels, diffuse disease, and small vessels. These anatomical settings seem appropriate for a hybrid strategy that can reduce the total stent length, thus may potentially reduce the risk for late adverse events. Our study also confirms how DCBs may constitute a reasonable addendum to DES in diffuse coronary disease, as some preliminary data have previously shown. In this study, 38% of the entire population underwent an all-in-one (21%) or staged (17%) hybrid procedure,[16] and the outcome between hybrid or solo-DCB PCI did not differ.

On the contrary, one potential advantage of a solo-DCB PCI is the possibility to reduce the duration of DAPT. The recently published european society of cardiology 2017 update document on DAPT[17] acknowledges the lack of dedicated clinical trials investigating the optimal duration of DAPT in patients treated with DCBs and recommends a DAPT duration of 6 months (class IIa, B); it must be noted, though, that in the largest randomized trials,[18,19] a 3–12-month DAPT duration was recommended, whereas real-world registries[13] suggest a duration of at least 1 month. In our clinical practice, we follow the recommendations of current consensus documents that suggest 30 days after DCB use for native vessels, and 3–6 months in case of stent implantation.[9] However, the possibility to reduce it further, or even discharge the patient with one single antiplatelet, seems intriguing. In the registry, 17% of the patients did not receive the second antiplatelet at discharge, the main reasons being the need for elective/urgent surgery (6%) or recent bleeding or high risk of bleeding (9%). To note, a subanalysis of the cohort of patients discharged with one single antiplatelet showed clinical results similar to the rest of the population, theoretically suggesting a role for this strategy in a highly selected patient population.

A specific mention should be made on the device used in this study. Preliminary results with the first generation of DCBs showed how these devices are different in terms of efficacy, and underlined the importance of a drug carrier, firstly with the role of targeting paclitaxel to the lesion site (a sort of protection from proximal tortuosities and disease), and then, after balloon inflation, to help the drug to reach the vessel wall and persist there. In the recent years, all new generations of DCBs were developed with dedicated carriers, and both randomized controlled studies and real-world registries showed their good efficacy and no specific safety issue. The Elutax SV DCB tested in this registry has already shown to warrant adequate late lumen loss at 6-month angiographic follow-up.

There are several limitations that need to be acknowledged for the current registry. There was not data monitoring, and clinical event assessment was performed by the single investigators. The absence of a prospective enrollment is another major limitation, for example, it was not possible to know the reasons why operators preferred a DCB over a DES at index procedure, and device selection might have suffered of unknown confounders. Also, there was not a direct comparison with 'old-generation' DCBs. Periprocedural MI was not an endpoint, and only spontaneous MIs were collected.

In conclusion, the DCB-RISE registry shows how the use of the new-generation DCB Elutax SV in an all-comer population is associated with good mid-term clinical outcome, which is comparable with other similar devices present in the market.

References

1 Cortese B, Bertoletti A. Paclitaxel coated balloons for coronary artery interventions: a comprehensive review of preclinical and clinical data. *Int J Cardiol* 2012; **161**:4–12.
2 Byrne RA, Joner M, Alfonso F, Kastrati A. Drug-coated balloon therapy in coronary and peripheral artery disease. *Nat Rev Cardiol* 2014; **11**:13–23.
3 Scheller B, Clever YP, Kelsch B, *et al.* Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *JACC Cardiovasc Interv* 2012; **5**:323–330.
4 Unverdorben M, Vallbracht C, Cremers B, *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* 2015; **11**:926–934.
5 Alfonso F, Pérez-Vizcayno MJ, García Del Blanco B, *et al.* Everolimus-eluting stents in patients with bare-metal and drug-eluting in-stent restenosis: results from a patient-level pooled analysis of the RIBS IV and V trials. *Circ Cardiovasc Interv* 2016; **9**:e003479.
6 Kawamoto H, Ruparelia N, Latib A, *et al.* Drug-coated balloons versus second-generation drug-eluting stents for the management of recurrent multimetal-layered in-stent restenosis. *JACC Cardiovasc Interv* 2015; **8**:1586–1594.
7 Cortese B, Silva Orrego P, Agostoni P, *et al.* Effect of drug-coated balloons in native coronary artery disease left with a dissection. *JACC Cardiovasc Interv* 2015; **8**:2003–2009.
8 Cortese B, Sgueglia GA, Berti S, *et al.* [SICI-GISE position paper on drug-coated balloon use in the coronary district]. *G Ital Cardiol* 2013; **14**: 681–689.
9 Cortese B, Berti S, Biondi-Zoccai G, *et al.* Drug-coated balloon treatment of coronary artery disease: a position paper of the Italian Society of Interventional Cardiology. *Catheter Cardiovasc Interv* 2014; **83**:427–435.
10 Thygesen K, Chaitman BR, White HD, *et al.* Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; **60**:1581–1598.
11 Mahmood Zuhdi AS, Zeymer U, Waliszewski M, *et al.* The use of paclitaxel coated balloon (PCB) in acute coronary syndrome of small vessel de novo lesions: an analysis of a prospective 'real world' registry. *Springerplus* 2016; **5**:373.
12 Toelg R, Merkely B, Erglis A, *et al.* Coronary artery treatment with paclitaxel-coated balloon using a BTHC excipient: clinical results of the international real-world DELUX registry. *EuroIntervention* 2014; **10**:591–599.
13 Wöhrle J, Zadura M, Möbius-Winkler S, *et al.* SeQuentPlease World Wide Registry: clinical results of SeQuent please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. *J Am Coll Cardiol* 2012; **60**:1733–1738.
14 Kleber FX, Schulz A, Waliszewski M, *et al.* Local paclitaxel induces late lumen enlargement in coronary arteries after balloon angioplasty. *Clin Res Cardiol* 2015; **104**:217–225.
15 Cortese B, Alfonso F. DCB and dissections: in search of a good balance between enthusiasm and scientific strictness. *JACC Cardiovasc Interv* 2016; **9**:506–507.

© 2018 Italian Federation of Cardiology. All rights reserved.

16 Costopoulos C, Latib A, Naganuma T, *et al.* The role of drug-eluting balloons alone or in combination with drug-eluting stents in the treatment of de novo diffuse coronary disease. *JACC Cardiovasc Interv* 2013; **6**:1153–1159.
17 Valgimigli M, Bueno H, Byrne RA, *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018; **39**:213–260.
18 Byrne RA, Neumann F-J, Mehilli J, *et al.* Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet* 2013; **381**:461–467.
19 Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, *et al.* A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the RIBS IV Randomized Clinical Trial. *J Am Coll Cardiol* 2015; **66**:23–33.

© 2018 Italian Federation of Cardiology. All rights reserved.

Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Clinical and Angiographic Outcomes With Drug-Coated Balloons for De Novo Coronary Lesions: A Meta-Analysis of Randomized Clinical Trials

Islam Y. Elgendy, MD; Mohamed M. Gad, MD; Akram Y. Elgendy, MD; Ahmad Mahmoud, MD; Ahmed N. Mahmoud, MD; Javier Cuesta, MD; Fernando Rivero, MD; Fernando Alfonso, MD, PhD

BACKGROUND: The role of drug-coated balloons (DCBs) in the treatment of de novo coronary lesions is not well established.

METHODS AND RESULTS: Electronic databases and major conference proceedings were searched for randomized controlled trials that compared DCBs with stents or angioplasty for de novo coronary lesions. The primary outcome was target lesion revascularization. Summary estimates were conducted using random-effects analysis complemented by several subgroup and sensitivity analyses. A total of 14 randomized controlled trials with 2483 patients were included. At a mean follow up of 12 months, DCBs were associated with no difference in the incidence of target lesion revascularization as compared with alternative strategies (risk ratio [RR], 0.79; 95% CI, 0.35–1.76). There was no difference in treatment effect based on the indication (ie, small-vessel disease, myocardial infarction, bifurcation, or high bleeding risk) ($P_{interaction}$=0.22). DCBs were associated with lower target lesion revascularization compared with bare metal stents and similar target lesion revascularization compared with drug-eluting stents ($P_{interaction}$=0.03). There was no difference between DCBs and control in terms of major adverse cardiac events, vessel thrombosis, or cardiovascular mortality. However, DCBs were associated with a lower incidence of myocardial infarction (RR, 0.48; 95% CI, 0.25–0.90) and all-cause mortality (RR, 0.45; 95% CI, 0.22–0.94).

CONCLUSIONS: In patients with de novo coronary lesions, use of DCBs was associated with comparable clinical outcomes irrespective of the indication or comparator device. DCBs had a similar rate of target lesion revascularization compared with drug-eluting stents. A randomized trial powered for clinical outcomes and evaluating the role of DCBs for all-comers is warranted.

Key Words: coronary artery disease ■ de novo lesions ■ drug-eluting stent ■ drug-coated balloon ■ meta-analysis ■ mortality ■ small vessels

Downloaded from http://ahajournals.org by on November 17, 2020

Drug-eluting stents (DESs), particularly second-generation, remain the cornerstone management during percutaneous coronary intervention.[1] Coronary restenosis as a result of the persistence of the metallic struts within the vessel as well as the need for dual antiplatelet therapy remain major limitations even with the current generation of DESs.[2,3] In this context, drug-coated balloons (DCBs) offer an attractive therapeutic modality because these devices allow for local delivery of the antiproliferative agent directly into the artery wall with a single balloon inflation without the need for the metallic implant.[4] Several randomized trials have established the role of DCBs in treatment of in-stent restenosis of both DESs and bare metal stents (BMSs),[5–8] and the use of DCBs is currently endorsed by the 2018 European Society of Cardiology guidelines for myocardial revascularization as a class I recommendation for this indication.[9]

Correspondence to: Fernando Alfonso, MD, PhD, Cardiology Department, Hospital Universitario de La Princesa, IIS-IP, CIBER-CV, Universidad Autónoma de Madrid, c/Diego de León 62, Madrid 28006, Spain. E-mail: falf@hotmail.com

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.016224

For Sources of Funding and Disclosures, see page 10.

© 2020 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In patients with de novo coronary lesions, drug-coated balloons were associated with comparable clinical outcomes irrespective of the indication or comparator device.
- Drug-coated balloons had a similar rate of target lesion revascularization compared with drug-eluting stents.

What Are the Clinical Implications?

- These findings suggest the value of drug-coated balloons as an attractive "leave-nothing-behind strategy" for selected patients with de novo coronary lesions provided a satisfactory result is obtained after lesion predilation.
- A randomized trial powered for clinical outcomes and evaluating the role of drug-coated balloons for all-comers is warranted.

Nonstandard Abbreviations and Acronyms

BMS	bare metal stent
DCB	drug-coated balloon
DES	drug-eluting stents
MLD	minimum lumen diameter
MI	myocardial infarction
TLR	target lesion revascularization

However, the role of DCBs is not as established for de novo coronary lesions.[4] Recently, several small-to-moderate–sized, randomized trials have evaluated the merits of DCBs for patients with small-vessel disease,[10,11] high risk of bleeding,[12] and myocardial infarction (MI).[13,14] However, most of these individual trials were not powered to assess the differences in clinical outcomes.[10,13,14] Moreover, the trials that were powered for clinical outcomes were noninferiority trials and did not routinely evaluate angiographic outcomes.[11–13] To address this knowledge gap, we performed a comprehensive systematic review and meta-analysis of randomized trials to evaluate the impact of DCBs for de novo coronary lesions on angiographic and clinical outcomes.

METHODS

The authors declare that all supporting data are available within the article (and in the accompanying supplementary material online).

Data Sources and Search Strategy

Electronic databases, including MEDLINE, Embase, and the Cochrane Register of Controlled Trials, as well as major scientific sessions, were searched without language restriction from inception through November 2019 using the search algorithm in Table S1. The bibliography of the retrieved articles was reviewed. The search was independently performed by 2 authors (I.Y.E., F.A.). The protocol for this meta-analysis was prospectively registered at the PROSPERO international prospective register of systematic reviews (CRD42019143329),[15] and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16]

Selection Criteria and Data Extraction

Trials that randomized patients with obstructive de novo coronary lesions to DCBs versus any comparator were included (ie, DES, BMS, angioplasty only). We excluded trials that electively performed routine BMS placement after DCBs, but included trials that permitted bailout stent placement after DCBs. Clinical and angiographic data from the longest available reported follow-up time were preferentially used. Observational studies were excluded for inherent risk of bias. Two independent authors (I.Y.E., A.Y.E.) extracted data on study design, sample size, intervention strategies, outcomes, and other study characteristics from the included studies. Discrepancies were resolved by consensus.

Assessment of Quality of Included Studies

The Cochrane Collaboration's tool was used for the assessment of the risk of bias. This consists of 7 points that test for selection, performance, detection, attrition, reporting, and other biases.[17] Performance bias (ie, blinding of participants and physicians) was found to be irrelevant due to the interventional nature in both arms. The overall risk of bias for each trial was classified as low, unclear, or high risk, based on whether level of bias in each domain could have resulted in biases in risk estimation.

Outcomes

The primary clinical outcome was target lesion revascularization (TLR). The secondary clinical outcomes included: major adverse cardiac events, as defined by the individual trials (Table S2); target vessel revascularization; MI; vessel thrombosis; cardiovascular mortality; and all-cause mortality. The following angiographic outcomes were assessed: minimum lumen diameter (MLD); diameter stenosis; late lumen loss; and binary restenosis.

Downloaded from http://ahajournals.org by on November 17, 2020

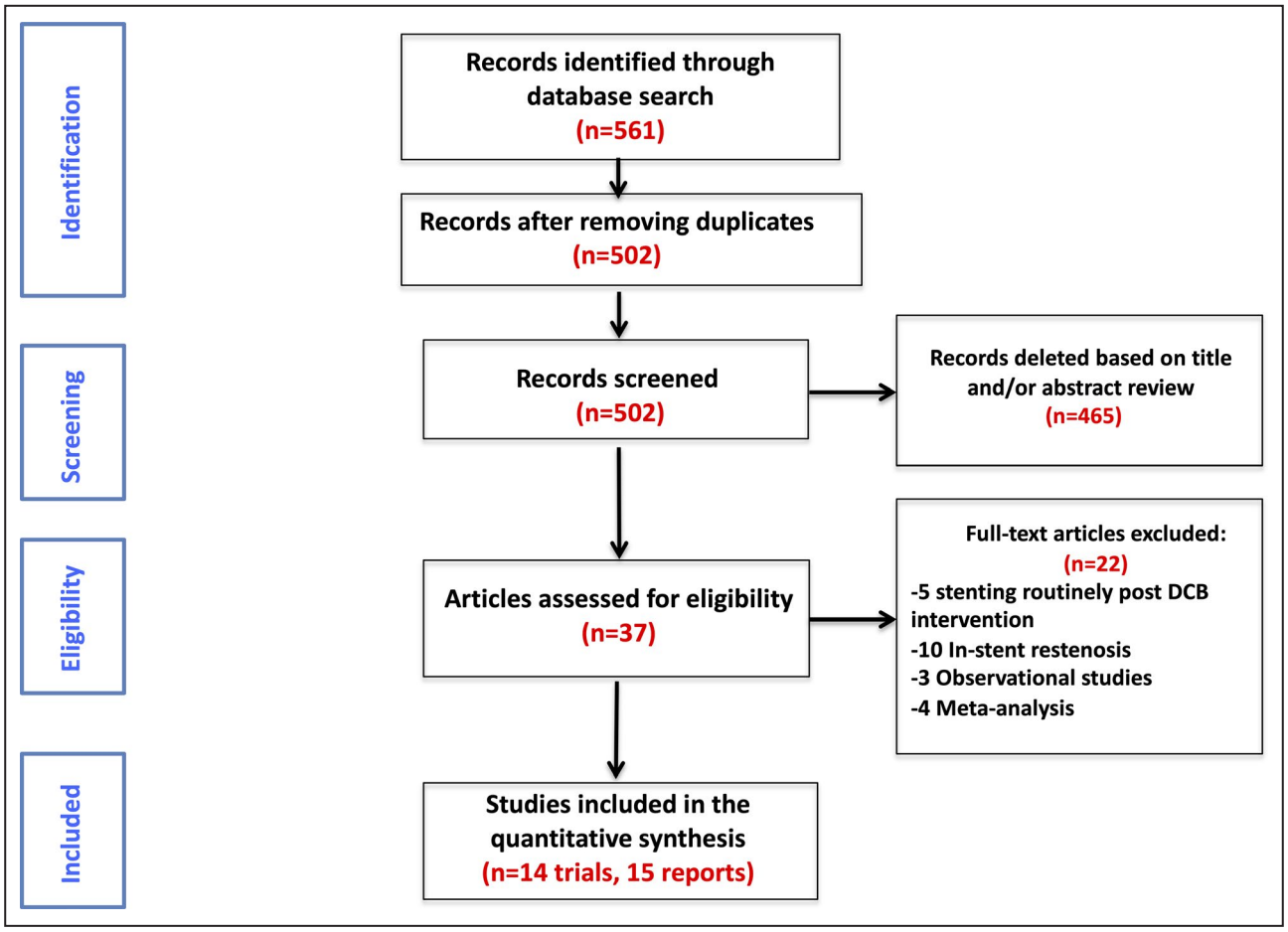


Figure 1. Study search diagram.
Summary of how the systematic search was conducted and eligible studies were identified. DCB indicates drug-coated balloon.

Statistical Analysis

Outcomes were evaluated by an intention-to-treat analysis. Random-effects summary risk ratios were primarily estimated with the DerSimonian and Laird model, because we anticipated a high degree of statistical heterogeneity.[18] Summary odds ratios were also estimated with a Peto model as a secondary analysis due to the low incidence of events.[19] Statistical heterogeneity was assessed using the Cochrane Q and I^2 statistics.[20] Egger's method was used to calculate publication bias.[21] Standardized mean differences were used for continuous variables. All P-values were 2-tailed, with statistical significance set at 0.05, and CIs were calculated at the 95% level for the overall estimates effect. All analyses were performed using the RStudio software meta package (RStudio, Inc, Boston, MA).

The following prespecified subgroup analyses were performed for the primary outcome (TLR): (1) according to indication; and (2) by comparing DESs versus BMSs. In addition, the following prespecified sensitivity analyses for TLR were also conducted by: (1) excluding trials using the first-generation DCB, which is no longer available[22]; (2) excluding trials using angioplasty alone in the control arm; (3) limiting to trials utilizing second-generation DESs as the control; and (4) excluding trials with high risk of bias. Random-effects meta-regression analyses for the primary outcome were prespecified in relation to baseline reference vessel diameter, diabetes mellitus, and proportion of bailout stent placement in the DCBs arm.[23] Finally, a sensitivity analysis limited to trials using second-generation DESs as the control was performed for the angiographic outcomes, and a sensitivity analysis limited to trials that defined MI as spontaneous (ie, not procedure-related) was also conducted.

RESULTS

Included Studies

The systematic search identified 502 studies after removal of the duplicates, among which 37 were reviewed for eligibility. The final number of records included in this meta-analysis was 14 trials from 15

Downloaded from http://ahajournals.org by on November 17, 2020

Table. Characteristics, Interventional Strategies, and Follow-Up of the Included Trials

Trial (Reference No.)	Year	Indication	Drug-Coated Balloon Type	Control Group	Patients (n)	Clinical Follow-Up (months)	Angiographic Follow-Up (months)	Primary Outcome	Reference Vessel Diameter (mm)	Bailout Stenting in DCB Arm (%)
PICCOLETO II[24]	2019	Small-vessel disease	Elutax SV/Emperor	Second-generation DES	118/114	6	6	Late lumen loss	2.2/2.2	6.8
RESTORE CVD[10]	2019	Small-vessel disease	Restore	Second-generation DES	116/114	12	9	Diameter stenosis	2.4/2.4	5.2
BASKET-SMALL 2[11]	2019	Small-vessel disease	SeQuent Please	Second-generation DES	382/376	12	NR	MACE	NR	NR
Funatsu et al[25]	2017	Small-vessel disease	SeQuent Please	POBA	92/41	6	6	TVF	2.0/2.0	2.9
BELLO[26,27]	2012/2015	Small-vessel disease	IN.PACT Falcon	First-generation DES	90/92	36	6	Late lumen loss	2.4/2.4	20.2
PICCOLETO[22]	2010	Small-vessel disease	Dior	First-generation DES	29/31	9	6	Diameter stenosis	2.4/2.4	NR
PEPCAD NSTEMI[13]	2019	Myocardial infarction	SeQuent Please SeQuent Please Neo	BMS/second-generation DES	104/106	9	NR	Target lesion failure	NR	7.3
REVELATION[14]	2019	Myocardial infarction	Pantera Lux	Second-generation DES	60/60	9	9	FFR value	3.3/3.2	18.0
Gobic et al[28]	2017	Myocardial infarction	SeQuent Please	Second-generation DES	41/37	6	6	Late lumen loss	2.6/3.0	7.3
Shin et al[29]	2019	High bleeding risk	SeQuent Please	BMS	20/20	12	9	Late lumen loss	3.0/3.2	NR
DEBUT[12]	2019	High bleeding risk	SeQuent Please	BMS	102/106	9	NR	MACE	NR	2.0
PEPCAD-BIF[30]	2016	Bifurcational lesion	SeQuent Please	POBA	32/32	9	9	Late lumen loss	2.4/2.4	0
BABILON[31]	2014	Bifurcational lesion	SeQuent Please	POBA	52/56	24	9	Late lumen loss	2.3/2.3	7.8
Nishiyama et al[32]	2016	Unspecified	SeQuent Please	Second-generation DES	30/30	8	8	Not specified	2.9/2.7	10.0

Results are presented as drug-coated balloon/control. ACS indicates acute coronary syndrome; BABILON, The Paclitaxel-Coated Balloon in Bifurcated Lesions Trial; BASKET-SMALL 2, The Basel Kosten Effektivitäts Trial–Drug-Coated Balloons versus Drug-eluting Stents in Small Vessel Interventions; BELLO, Balloon Elution and Late Loss Optimization; BMS, bare metal stent; DCB, drug-coated balloon; DEBUT, Drug-Eluting Balloon in Stable and Unstable Angina: A Randomized Controlled Non-Inferiority Trial; DES, drug-eluting stent; FFR, fractional flow reserve; MACE, major adverse cardiac events; NR, not reported; PEPCAD-BIF, Drug eluting balloons as stand alone procedure for coronary bifurcational lesions; PEPCAD NSTEMI, Bare Metal Stent Versus Drug Coated Balloon With Provisional Stenting in Non-ST–Elevation Myocardial Infarction; PICCOLETO, Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels; PICCOLETO II, Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment; POBA, "plain old" balloon angioplasty; RESTORE SVD, Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease; REVELATION, Revascularization With Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stenting in Acute Myocardial Infarction; and TVF, target vessel failure.

Downloaded from http://ahajournals.org by on November 17, 2020

reports (Figure 1).[10–14,22,24–32] One trial reported angiographic and clinical outcomes at 6 months[26] and reported an extended follow-up for the clinical outcomes at 36 months.[27] A total of 2483 patients were included: 1268 in the DCBs group and 1215 in the control group. The indication for DCBs was small-vessel disease in 5 trials,[10,11,22,24–27] MI in 3 studies,[13,14,28] high bleeding risk in 2 trials,[12,29] bifurcational lesions in 2 studies,[30,31] and unspecified de novo lesions in 1 study.[32] In the bifurcational lesion trials, 1 trial compared "plain old" balloon angioplasty followed by DCB versus plain old balloon angioplasty alone to the main or side branch,[30] whereas the other trial randomized patients with bifurcational lesions to a strategy of side-branch dilation with DCB versus plain old balloon angioplasty.[31] The SeQuent Please paclitaxel-coated balloon was used by most of the included studies (9 of 14). Only 1 trial tested the Dior paclitaxel-coated balloon, which is no longer available.[22] The control group was exclusively second-generation DES in 6 trials,[10,11,14,24,28,32] first-generation DESs in 2 trials,[22,26] BMSs in 2 trials,[12,29] and plain old balloon angioplasty alone in 3 trials.[25,30,31] In 1 trial, the control was second-generation DESs or BMSs, and a subgroup analysis was reported for the outcomes based on the stent type.[13] The weighted mean reference vessel diameter was 2.5 mm. Table shows the baseline trial characteristics, follow-up duration, and interventional strategies. Table S3 summarizes the pertinent patient demographics and trial information. Performance bias was unclear in all the trials. One trial was at high risk for detection bias and unclear for allocation bias,[32] otherwise the remainder of the trials were considered to be of high quality (Table S4).

Angiographic Outcomes

Routine angiographic follow-up was performed at a weighted mean of 7 (range, 6–9) months. There was no difference between DCBs and control in terms of MLD (1.9 mm versus 2.0 mm; standardized mean difference, −0.13; 95% CI, −0.32 to 0.06; *P*=0.17), diameter stenosis (28.0% versus 28.1%; standardized mean difference, 0.22, 95% CI, −6.92 to 7.36; *P*=0.95), and binary restenosis (13.9% versus 16.3%; RR, 0.83; 95% CI, 0.40–1.71; *P*=0.61). However, DCBs were associated with lower late lumen loss (0.08 mm versus 0.24 mm; standardized mean difference, −0.17; 95% CI, −0.24 to −0.10; *P*<0.0001) (Figure 2). There was a significant degree of statistical heterogeneity observed for the angiographic outcomes (I^2 ranged from 60% to 94%), which was explained on the sensitivity analysis limited to trials comparing DCBs with second-generation DESs (I^2=0% for all the outcomes, except for diameter stenosis where I^2=56%). The findings of the sensitivity analysis were consistent with the main analysis for all angiographic outcomes except for a lower MLD with DCBs (Figure S1).

Target Lesion Revascularization

The weighted mean follow up for the clinical outcomes was 12 (range, 6–36) months. There was

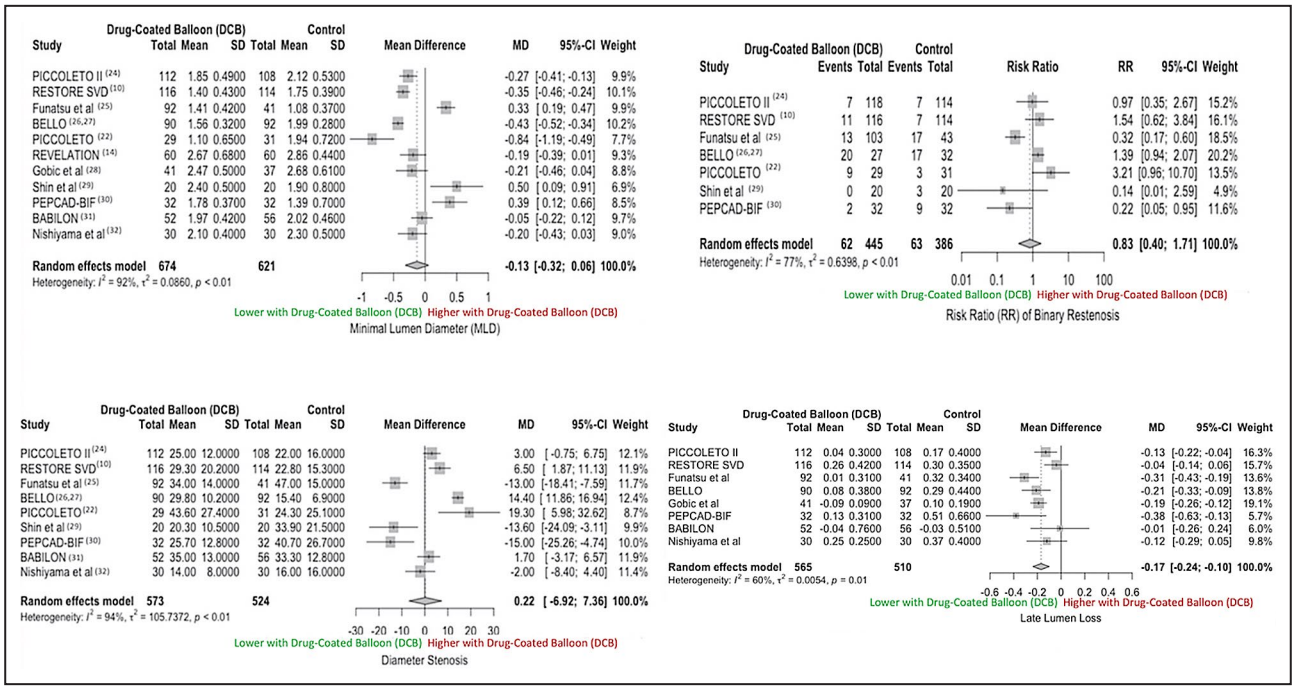


Figure 2. Summary plots for the angiographic outcomes.
The relative size of the data markers indicates weight of sample size from each study. DCB indicates drug-coated balloon; MD, mean difference; MLD, minimal lumen diameter; and RR, risk ratio.

Downloaded from http://ahajournals.org by on November 17, 2020

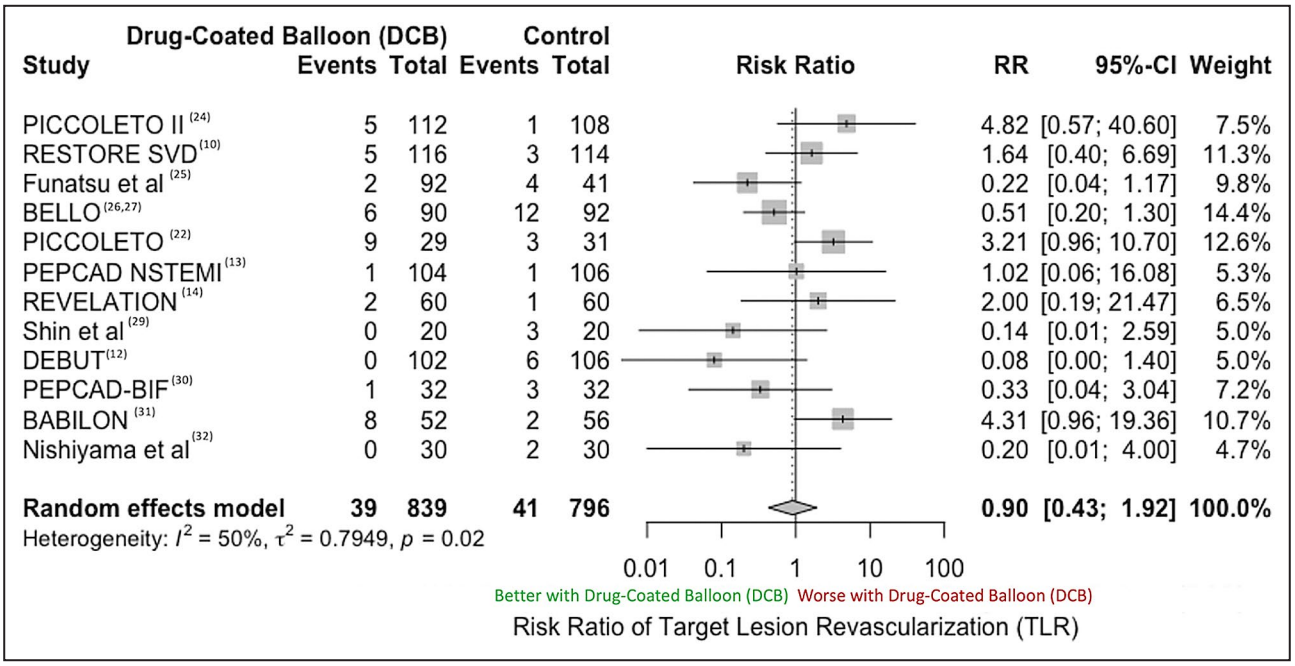


Figure 3. Summary plot for target lesion revascularization.
The relative size of the data markers indicates weight of sample size from each study. DCB indicates drug-coated balloon; and TLR, target lesion revascularization.

no difference in the incidence of TLR with DCBs compared with control (random effects: 4.6% versus 5.1%; RR, 0.79; 95% CI, 0.35–1.76; P=0.56; fixed effects: OR, 0.91; 95% CI, 0.58–1.44; P=0.69) (Figure 3). There was no evidence of publication bias using Egger's test (P=0.45). The outcome was characterized by moderate heterogeneity (I^2=50%; χ^2=22.1; $P_{heterogeneity}$=0.02). DCBs showed similar TLR compared with control, irrespective of the indication ($P_{interaction}$=0.22) (Figure 4). The incidence of TLR was similar when DCBs compared with DESs (RR, 1.37; 95% CI, 0.62–3.05; I^2=34%), but DCBs were associated with a lower incidence of TLR compared with BMSs (RR, 0.19; 95% CI, 0.04–1.00; I^2=0%) ($P_{interaction}$=0.03) (Figure 5). The findings of the prespecified sensitivity analyses for TLR were consistent with the overall analysis: (1) excluding trials that utilized the older generation DCBs (RR, 0.76; 95% CI, 0.35–1.65; I^2=43%; χ^2=17.6; $P_{heterogeneity}$=0.06) (Figure S2); (2) excluding trials using angioplasty alone in the control arm (RR, 0.97; 95% CI, 0.42–2.27; I^2=45%; χ^2=14.5; $P_{heterogeneity}$=0.07) (Figure S3); (3) limited to trials utilizing second-generation DESs as control (RR, 1.65; 95% CI, 0.65–4.34; I^2=0%; χ^2=2.9; $P_{heterogeneity}$=0.57) (Figure S4); and (4) excluding the trial with high risk of bias (RR, 0.97; 95% CI, 0.45–2.12; I^2=52%; χ^2=21.0; $P_{heterogeneity}$=0.02) (Figure S5). Meta-regression analysis did not identify a difference in the treatment effect based on baseline reference vessel diameter (P=0.81), diabetes mellitus (P=0.37), and proportion of bailout stent placement (P=0.63).

Secondary Clinical Outcomes

Compared with control, DCBs were associated with no difference in the incidence of target vessel revascularization (6.0% versus 5.3%; RR, 1.21; 95% CI, 0.60–2.44; P=0.59; I^2=52%; χ^2=8.3; $P_{heterogeneity}$=0.08), major adverse cardiac events (6.9% versus 9.1%; RR, 0.83; 95% CI, 0.50–1.36; P=0.46; I^2=53%; χ^2=23.3; $P_{heterogeneity}$=0.02), vessel thrombosis (0.3% versus 1.1%; RR, 0.38; 95% CI, 0.13–1.13; P=0.08; I^2=0%; χ^2=0.5; $P_{heterogeneity}$=0.91), and cardiovascular mortality (1.5% versus 1.5%; RR, 0.90; 95% CI, 0.27–3.00; P=0.86; I^2=56%; χ^2=6.8; $P_{heterogeneity}$=0.08). Importantly, DCBs were associated with a lower incidence of all-cause mortality (1.2% versus 2.9%; RR, 0.45; 95% CI, 0.22–0.94; P=0.03; I^2=0%; χ^2=0.78; $P_{heterogeneity}$=0.85), and MI (1.1% versus 2.9%; RR, 0.48; 95% CI, 0.25–0.90; P=0.02; I^2=0%; χ^2=6.2; $P_{heterogeneity}$=0.62) (Figures 6 and S6 through S11). In the sensitivity analysis limited to trials that defined MI as spontaneous MI, DCBs were associated with lower incidence of spontaneous MI (RR, 0.49; 95% CI, 0.25–0.96; P=0.04; I^2=0%) (Figure S12). There was no evidence of publication bias for any of the secondary clinical outcomes using Egger's test (all P>0.05).

DISCUSSION

In this meta-analysis of 14 randomized trials including 2483 patients with de novo coronary lesions undergoing percutaneous coronary intervention irrespective of

Downloaded from http://ahajournals.org by on November 17, 2020

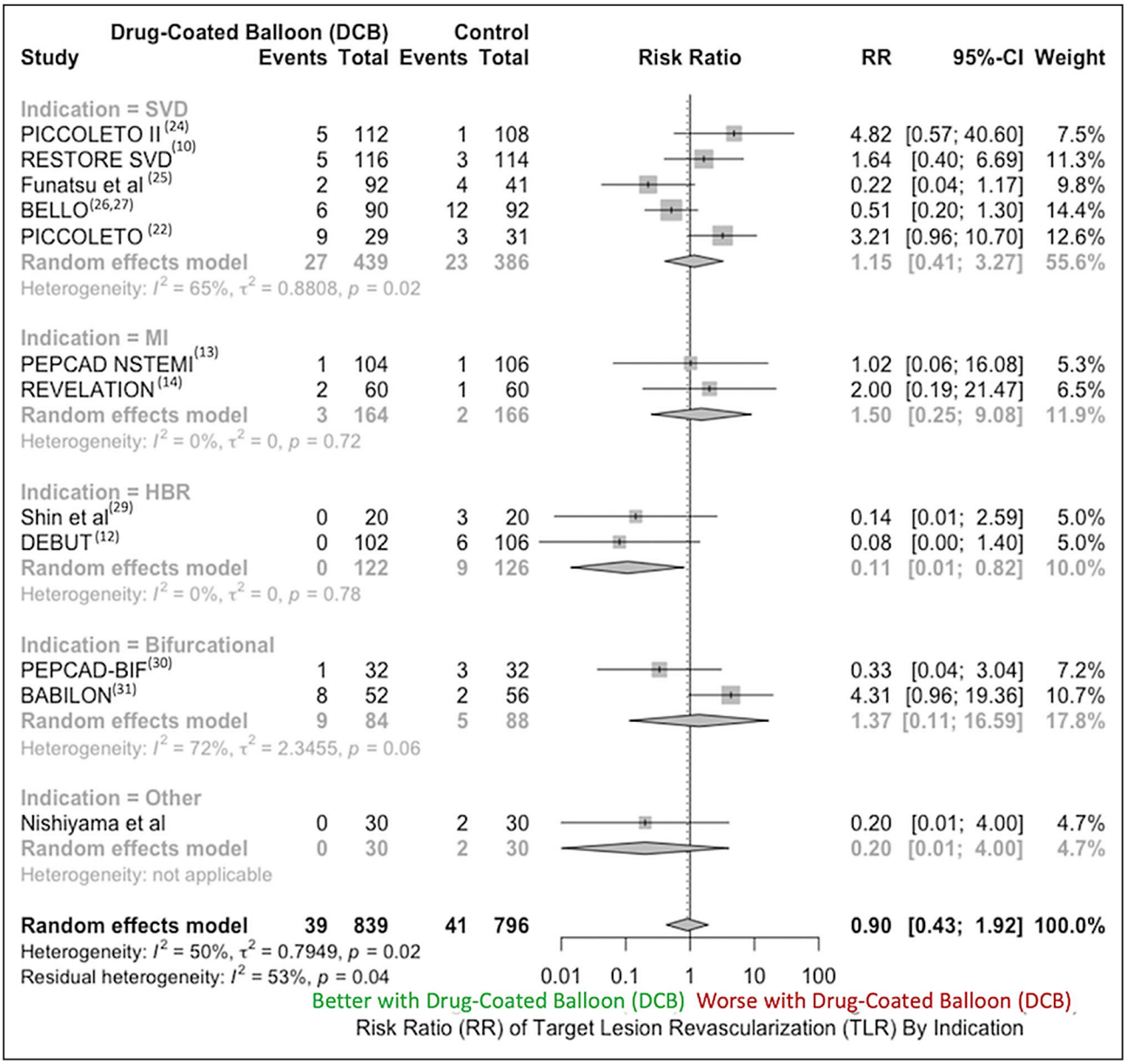


Figure 4. Subgroup analysis for target lesion revascularization according to indication.
The relative size of the data markers indicates weight of sample size from each study. There was no difference in treatment effect according to the different indications ($P_{interaction}$=0.22). DCB indicates drug-coated balloon; and TLR, target lesion revascularization.

indication, we documented that DCBs were associated with similar MLD, diameter stenosis, binary restenosis, and lower late lumen loss compared with control on routine angiographic follow up at a mean of 7 months. These findings were similar when DCBs were only compared with second-generation DESs (except that DCBs were associated with lower MLD). At a mean of 12 months, DCBs were associated with no difference in the incidence of TLR compared with control. This effect was consistent, regardless of indication (ie, small-vessel disease, high bleeding risk, MI, or bifurcational lesions), and on multiple sensitivity analyses, including comparing DCBs with second-generation DESs. DCBs were associated with lower risk of TLR compared with BMS. There was a moderate degree of statistical heterogeneity for TLR, which was partly explained by our subgroup analysis comparing DCBs with DESs versus BMSs, and on the sensitivity analysis limited to second-generation DESs. DCBs were also associated with no difference in the incidence of target vessel revascularization, major adverse cardiac events, vessel thrombosis, and cardiovascular mortality. Importantly, the incidence of all-cause mortality and MI (even when spontaneous MI was analyzed separately)

Downloaded from http://ahajournals.org by on November 17, 2020

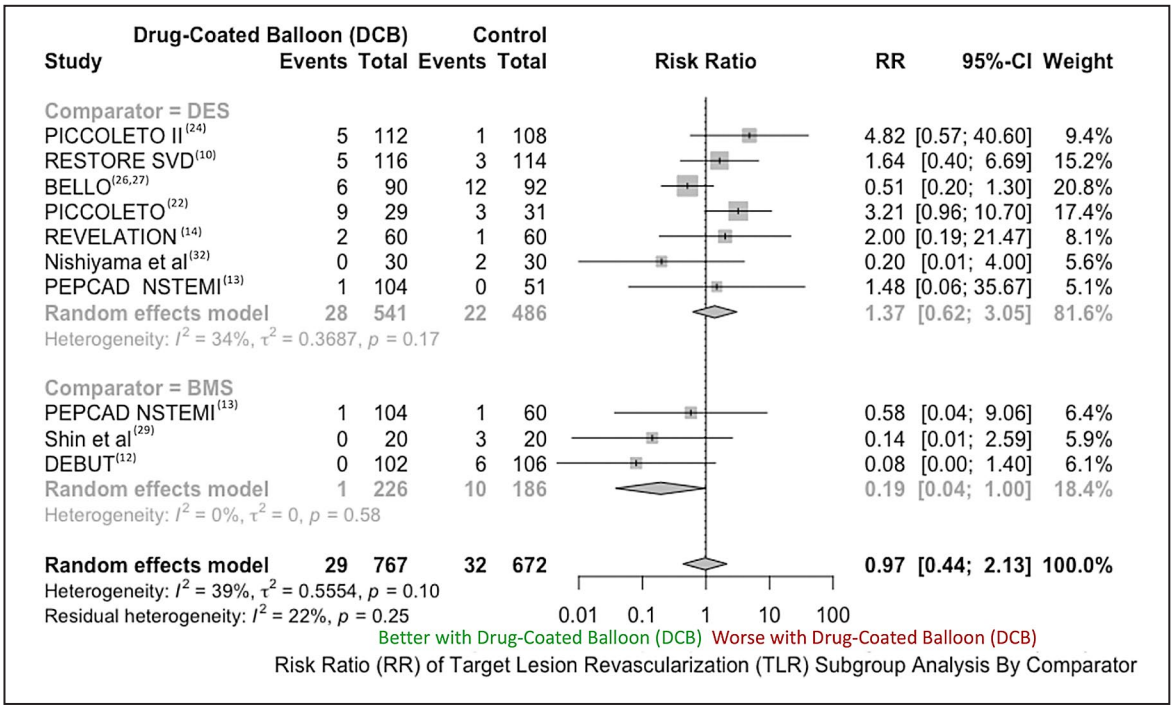


Figure 5. Subgroup analysis for target lesion revascularization comparing bare metal and drug-eluting stents.
The relative size of the data markers indicates the weight of the sample size from each study. Drug-coated balloon use was associated with lower target lesion revascularization compared with bare metal stents and similar target lesion revascularization compared with drug-eluting stents ($P_{interaction}$=0.03). DCB indicates drug-coated balloon; and TLR, target lesion revascularization.

was lower with DCBs. However, these findings were based on a small number of trials and the number of events was low, and therefore should be only considered as hypothesis-generating. Altogether, our findings strongly suggest the value of DCBs as an attractive "leave–nothing-behind strategy" for selected patients with de novo coronary lesions provided a satisfactory result is obtained after lesion predilation.

DCBs offer the advantage of locally delivering the antiproliferative drug without the need for

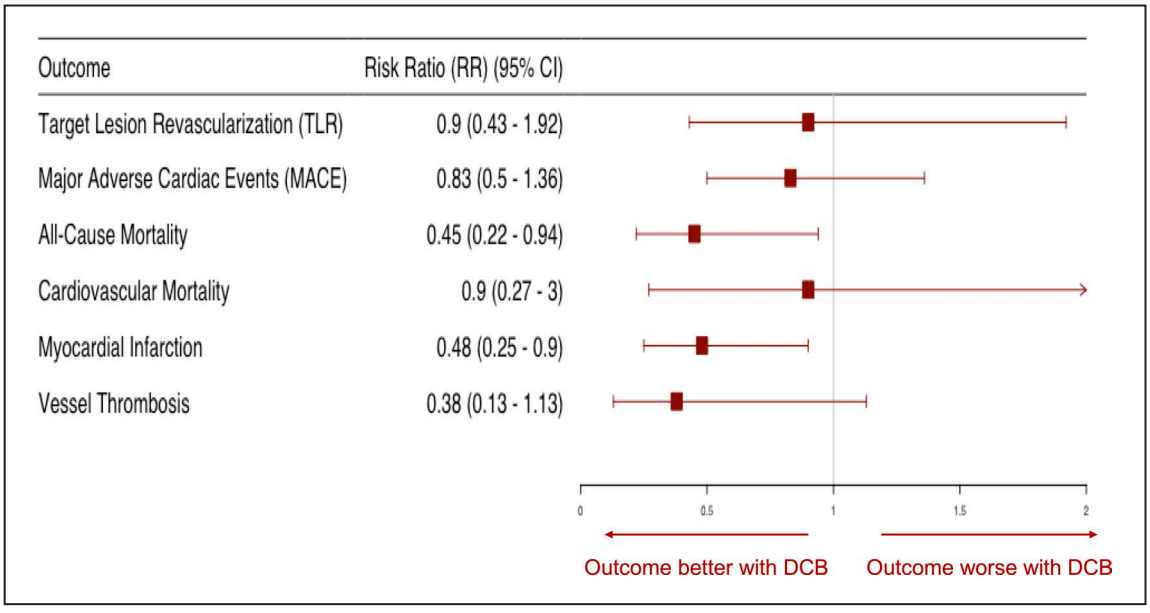


Figure 6. Forest plots for the clinical outcomes evaluated in this meta-analysis.
For each comparison, boxes and horizontal lines correspond to the respective point estimate and accompanying 95% CI. DCB indicates drug-coated balloon; MACE, major adverse cardiac events; and TLR, target lesion revascularization.

Downloaded from http://ahajournals.org by on November 17, 2020

metal struts, thus directly inhibiting the process of neointimal hyperplasia and negative remodeling.[4] Although use of DCBs in patients with in-stent restenosis has been extensively investigated,[9] trials evaluating DCBs for de novo lesions have been small and evaluated specific indications. Our meta-analysis, including the most recent trials, has demonstrated that DCBs were associated with favorable clinical outcomes irrespective of the indication, even when compared with second-generation DESs. Although most patients undergoing percutaneous coronary intervention are treated with a second-generation DES,[1] BMSs are still used in a minority of patients, such as those with a high risk of bleeding to minimize the duration of antiplatelet therapy. Our meta-analysis showed that DCBs represent a reasonable therapeutic strategy for this subset of patients.

Second-generation DESs may not offer an effective therapeutic strategy in small vessels due to the late lumen loss resulting in late in-stent restenosis.[34] In this challenging setting, several randomized trials have shown that DCBs are noninferior to DESs for major adverse cardiac events.[10,11] By significantly increasing the sample size, the current meta-analysis has extended our knowledge by showing that DCBs are associated with similar TLR compared with any control, including second-generation DESs. Moreover, our meta-regression analysis has shown that there was no difference in treatment effect based on the reference vessel diameter.

One meta-analysis of randomized trials has raised some concerns about late mortality with DCBs for patients with peripheral artery disease.[35] That meta-analysis was subject to several limitations,[36] and the late mortality finding was not replicated in several large observational studies and patient-level meta-analysis.[37,38] Our meta-analysis provides some support for the use of DCBs for coronary lesions. However, the lower mortality seen with DCBs in our meta-analysis should be interpreted with caution given the limited number of studies that evaluated all-cause mortality and the low number of events.

Previous meta-analyses addressed use of DCBs for a specific indication, such as small-vessel disease or bifurcational lesions.[39–41] In addition, those meta-analyses included observational studies, which are prone to ascertainment and selection biases.[39–41] Furthermore, those works did not include the results of several recently published and presented trials.[10,13,14,24] The present meta-analysis only included randomized trials and has provided a comprehensive overview of the angiographic and clinical outcomes of DCBs irrespective of indication. In addition, we performed several subgroup and sensitivity analyses to explore the statistical heterogeneity.

Our meta-analysis has several limitations. First, although all the included studies used a paclitaxel-coated balloon, there are several pharmacokinetic differences between the devices. For example, one trial used the first-generation Drior paclitaxel-coated balloon, which was shown to be inferior in terms of deliverability and is no longer available. Thus, we performed a sensitivity analysis excluding this trial for the primary clinical outcome. Second, there were differences in the core laboratory assessment of the angiographic outcomes across the trials, which could be a source of the significant heterogeneity noted with these outcomes. However, we observed no heterogeneity for most of the angiographic outcomes on the sensitivity analysis comparing DCBs with second-generation DESs. Third, we noted a moderate degree of statistical heterogeneity for the primary clinical outcome (ie, TLR). We attempted to mitigate this by using a random-effects model. In addition, we performed multiple subgroup, sensitivity, and meta-regression analyses to explore the heterogeneity; however, the number of studies included in some of these subgroup and sensitivity analyses was small, so the findings can only be considered as hypothesis-generating. Fourth, one of the included trials was at high risk for bias,[32] so we performed a sensitivity analysis excluding that trial for TLR. Fifth, despite the extensive subgroup, sensitivity, and meta-regression analyses conducted, there may be some considerations about clinical and methodologic heterogeneity, because the meta-analysis included different comparators and the indication for DCBs were variable. Finally, the lack of patient-level data precluded a careful evaluation for the patient and lesion characteristics that would benefit most from DCBs.

CONCLUSIONS

In this meta-analysis of 14 randomized trials comprising 2483 patients with de novo coronary lesions, DCBs were associated with similar MLD, diameter stenosis, acute lumen gain, binary restenosis, and lower late lumen loss compared with control on routine angiographic follow up. There was no difference in the incidence of TLR between DCBs compared with control. This effect was observed regardless of indication (ie, small-vessel disease, high bleeding risk, MI, or bifurcational lesions), and was maintained when compared with second-generation DES alone. Finally, DCBs were associated with lower risk of MI and all-cause mortality, albeit with a low number of events, so our work should be only considered hypothesis-generating. Our findings support the need for a randomized trial powered for clinical outcomes evaluating the role of the DCBs in all-comers.

Downloaded from http://ahajournals.org by on November 17, 2020

ARTICLE INFORMATION

Received February 12, 2020; accepted April 8, 2020.

Affiliations

From the Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA (I.Y.E.); Department of Medicine, Cleveland Clinic Foundation, Cleveland, OH (M.M.G.); Division of Cardiovascular Medicine, University of Florida, Gainesville, FL (A.Y.E., A.M.); Division of Cardiology, University of Washington, Seattle, WA (A.N.M.); Cardiology Department, Hospital Universitario de La Princesa, IIS-IP, CIBER-CV, Universidad Autónoma de Madrid, Spain (J.C., F.R., F.A.).

Sources of Funding

None.

Disclosures

None.

Supplementary Materials

Tables S1–S4
Figures S1–12
References 10–14, 22, 24–27, 29, and 31

REFERENCES

1. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, Vlachojannis GJ, Jensen LO, Christiansen EH, Berencsi K, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2015;65:2496–2507.
2. Otsuka F, Vorpahl M, Nakano M, Foerst J, Newell JB, Sakakura K, Kutys R, Ladich E, Finn AV, Kolodgie FD, et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation*. 2014;129:211–223.
3. Mahmoud AN, Barakat AF, Elgendy AY, Schneibel E, Mentias A, Abuzaid A, Elgendy IY. Long-term efficacy and safety of everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents: a meta-analysis of randomized trials. *Circ Cardiovasc Interv*. 2017;10:e005286.
4. Kleber FX, Rittger H, Bonaventura K, Zeymer U, Wöhrle J, Jeger R, Levenson B, Möbius-Winkler S, Bruch L, Fischer D, et al. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. *Clin Res Cardiol*. 2013;102:785–797.
5. Giacoppo D, Alfonso F, Xu B, Claessen BEPM, Adriaenssens T, Jensen C, Pérez-Vizcayno MJ, Kang DY, Degenhardt R, Pleva L, et al. Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study). *Eur Heart J*. 2019;ehz594. DOI: 10.1093/eurheartj/ehz594. [Epub ahead of print].
6. Elgendy IY, Mahmoud AN, Elgendy AY, Cuesta J, Rivero F, Alfonso F. Meta-analysis comparing the frequency of target lesion revascularization with drug-coated balloons or second-generation drug-eluting stents for coronary in-stent restenosis. *Am J Cardiol*. 2019;123:1186–1187.
7. Elgendy IY, Mahmoud AN, Elgendy AY, Mojadidi MK, Elbadawi A, Eshtehardi P, Pérez-Vizcayno MJ, Wayangankar SA, Jneid H, David Anderson R, et al. Drug-eluting balloons versus everolimus-eluting stents for in-stent restenosis: a meta-analysis of randomized trials. *Cardiovasc Revasc Med*. 2019;20:612–618.
8. Siontis GC, Stefanini GG, Mavridis D, Siontis KC, Alfonso F, Pérez-Vizcayno MJ, Byrne RA, Kastrati A, Meier B, Salanti G, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. *Lancet*. 2015;386:655–664.
9. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165.
10. Tang Y, Qiao S, Su X, Chen Y, Jin Z, Chen H, Xu B, Kong X, Pang W, Liu Y, et al. Drug-coated balloon versus drug-eluting stent for small-vessel disease: the RESTORE SVD China randomized trial. *JACC Cardiovasc Interv*. 2018;11:2381–2392.
11. Jeger RV, Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Leibundgut G, Weilenmann D, Wöhrle J, Richter S, Schreiber M, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet*. 2018;392:849–856.
12. Rissanen TT, Uskela S, Eränen J, Mäntylä P, Olli A, Romppanen H, Siljander A, Pietilä M, Minkkinen MJ, Tervo J, et al. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. *Lancet*. 2019;394:230–239.
13. Scheller B, Ohlow MA, Ewen S, Kische S, Rudolph TK, Clever YP, Wagner A, Richter S, El-Garhy M, Böhm M, et al. Randomized comparison of bare metal or drug-eluting stent versus drug coated balloon in non-ST-elevation myocardial infarction—PEPCAD NSTEMI. *EuroIntervention*. 2020;15:1527–1533.
14. Vos NS, Fagel ND, Amoroso G, Herrman JR, Patterson MS, Piers LH, van der Schaaf RJ, Slagboom T, Vink MA. Paclitaxel-coated balloon angioplasty versus drug-eluting stent in acute myocardial infarction: the REVELATION randomized trial. *JACC Cardiovasc Interv*. 2019;12:1691–1699.
15. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162:777–784.
16. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Syst Rev*. 2012;1:2.
17. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
19. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis*. 1985;27:335–371.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in metaanalyses. *BMJ*. 2003;327:557–560.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
22. Cortese B, Micheli A, Picchi A, Coppolaro A, Bandinelli L, Severi S, Limbruno U. Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. *Heart*. 2010;96:1291–1296.
23. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med*. 2002;21:1559–1573.
24. Cortese B. Drug-coated balloon vs. drug-eluting stent for small coronary vessel disease: 6 months primary outcome of the PICCOLETO II randomized clinical trial. Presented at the Transcatheter Cardiovascular Therapeutic meeting, San Francisco, CA, September 2019.
25. Funatsu A, Nakamura S, Inoue N, Nanto S, Nakamura M, Iwabuchi M, Ando K, Asano R, Habara S, Saito S, et al. A multicenter randomized comparison of paclitaxel-coated balloon with plain balloon angioplasty in patients with small vessel disease. *Clin Res Cardiol*. 2017;106:824–832.
26. Latib A, Colombo A, Castriota F, Micari A, Cremonesi A, De Felice F, Marchese A, Tespili M, Presbitero P, Sgueglia GA, et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. *J Am Coll Cardiol*. 2012;60:2473–2480.
27. Latib A, Ruparelia N, Menozzi A, Castriota F, Micari A, Cremonesi A, De Felice F, Marchese A, Tespili M, Presbitero P, et al. 3-year follow-up of the Balloon Elution and Late Loss Optimization Study (BELLO). *JACC Cardiovasc Interv*. 2015;8:1132–1134.
28. Gobić D, Tomulić V, Lulić D, Židan D, Brusich S, Jakljević T, Zaputović L. Drug-coated balloon versus drug-eluting stent in primary percutaneous coronary intervention: a feasibility study. *Am J Med Sci*. 2017;354:553–560.
29. Shin ES, Lee JM, Her AY, Chung JH, Eun Lee K, Garg S, Nam CW, Doh JH, Koo BK. Prospective randomized trial of paclitaxel-coated balloon versus bare-metal stent in high bleeding risk patients with de novo coronary artery lesions. *Coron Artery Dis*. 2019;30:425–431.

Downloaded from http://ahajournals.org by on November 17, 2020

30. Kleber FX, Rittger H, Ludwig J, Schulz A, Mathey DG, Boxberger M, Degenhardt R, Scheller B, Strasser RH. Drug eluting balloons as stand alone procedure for coronary bifurcational lesions: results of the randomized multicenter PEPCAD-BIF trial. *Clin Res Cardiol*. 2016;105:613–621.
31. López Mínguez JR, Nogales Asensio JM, Doncel Vecino LJ, Sandoval J, Romany S, Martínez Romero P, Fernández Díaz JA, Fernández Portales J, González Fernández R, Martínez Cáceres G, et al. A prospective randomised study of the paclitaxel-coated balloon catheter in bifurcated coronary lesions (BABILON trial): 24-month clinical and angiographic results. *EuroIntervention*. 2014;10:50–57.
32. Nishiyama N, Komatsu T, Kuroyanagi T, Fujikake A, Komatsu S, Nakamura H, Yamada K, Nakahara S, Kobayashi S, Taguchi I. Clinical value of drug-coated balloon angioplasty for de novo lesions in patients with coronary artery disease. *Int J Cardiol*. 2016;222:113–118.
33. Alfonso F, Elgendy IY, Cuesta J. Drug-coated balloons versus drug-eluting stents for in-stent restenosis: the saga continues. *EuroIntervention*. 2018;14:1069–1072.
34. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.
35. Beckman JA, White CJ. Paclitaxel-coated balloons and eluting stents: is there a mortality risk in patients with peripheral artery disease? *Circulation*. 2019;140:1342–1351.
36. Freisinger E, Koeppe J, Gerss J, Goerlich D, Malyar NM, Marschall U, Faldum A, Reinecke H. Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis. *Eur Heart J*. 2019;ehz698. DOI: 10.1093/eurheartj/ehz698. [Epub ahead of print].
37. Schneider PA, Laird JR, Doros G, Gao Q, Ansel G, Brodmann M, Micari A, Shishehbor MH, Tepe G, Zeller T. Mortality not correlated with paclitaxel exposure: an independent patient-level meta-analysis of a drug-coated balloon. *J Am Coll Cardiol*. 2019;73:2550–2563.
38. Megaly M, Rofael M, Saad M, Rezq A, Kohl LP, Kalra A, Shishehbor M, Soukas P, Abbott JD, Brilakis ES. Outcomes with drug-coated balloons in small-vessel coronary artery disease. *Catheter Cardiovasc Interv*. 2019;93:E277–E286.
39. Li M, Guo C, Lv YH, Zhang MB, Wang ZL. Drug-coated balloon versus drug-eluting stent in de novo small coronary vessel disease: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2019;98:e15622.
40. Megaly M, Rofael M, Saad M, Shishehbor M, Brilakis ES. Outcomes with drug-coated balloons for treating the side branch of coronary bifurcation lesions. *J Invasive Cardiol*. 2018;30:393–399.

Downloaded from http://ahajournals.org by on November 17, 2020

Supplemental Material

Downloaded from http://ahajournals.org by on November 17, 2020

Table S1. Search strategy.

Database	Search Strategy	Filters	Number
Pubmed	((Eluting balloon AND coronary) OR (coated balloon AND coronary)	Human Species	326
CENTRAL	((Eluting balloon) OR (coated balloon) AND (coronary))	Clinical trials	131
Embase	((Eluting balloon) OR (coated balloon) AND (coronary))	Controlled clinical trial/ Randomized controlled trial	102

Downloaded from http://ahajournals.org by on November 17, 2020

Table S2. Definition of major adverse cardiac events per the individual trials.

Trial (ref#)	Definition of major adverse cardiac events
PICCOLETO II[24]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization
RESTORE SVD[10]	Cardiac death, target vessel myocardial infarction, target lesion revascularization
BASKET-SMALL 2[11]	Cardiac death, non-fatal myocardial infarction, target vessel revascularization
Funatsu et al[25]	Cardiac death, non-fatal myocardial infarction, target vessel revascularization
BELLO[26,27]	All-cause death, non-fatal myocardial infarction, target vessel revascularization
PICCOLETO[22]	Death, ST elevation myocardial infarction, target lesion revascularization
PEPCAD NSTEMI[13]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization
REVELATION[14]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization
Gobic et al[28]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization, stent thrombosis
Shin et al[29]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization, stent thrombosis
DEBUT[12]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization
BABILON[31]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization

Downloaded from http://ahajournals.org by on November 17, 2020

Table S3. Baseline patient and trial characteristics.

Trial (ref#)	Single/multicenter	Country	Trial registration number	Age, years	Men, %	Diabetes mellitus, %	Hypertension, %	Acute coronary syndrome, %
PICCOLETO II[24]	Multicenter	Italy	NCT03899818	64/66	70/77	38/35	65/67	45/44
RESTORE SVD[10]	Multicenter	China	NCT02946307	60/61	66/77	40/42	67/75	69/71
BASKET-SMALL 2[11]	Multicenter	Switzerland, Germany, Austria	NCT01574534	67/68	77/70	32/35	85/89	30/27
Funatsu et al[25]	Multicenter	Japan	UMIN000026760	68/69	78/68	48/32	84/73	NR
BELLO[26,27]	Multicenter	Italy	NCT01086579	65/66	80/77	43/38	80/82	24/22
PICCOLETO[22]	Single center	Italy	EudraCT: 2009-012268-15	68/67	79/76	38/46	75/71	54/55
PEPCAD NSTEMI[13]	Multicenter	Germany	NCT01489449	66/67	66/68	27/36	79/88	100/100
REVELATION[14]	Single center	Netherlands	NCT02219802	57/57	87/87	13/7	30/32	100/100
Gobic et al[28]	Single center	Croatia	NR	57/54	71/73	5/11	32/35	100/100
Shin et al[29]	Single center	Korea	NCT02456402	58/62	70/75	35/25	40/45	30/40
DEBUT[12]	Multicenter	Finland	NCT01781546	78/76	62/64	26/49	MACE	46/46
PEPCAD-BIF[30]	Multicenter	Germany	NR	66/69	75/72	34/38	87/91	28/19
BABILON[31]	Multicenter	Spain	NCT01278186	64/66	64/66	27/38	NR	68
Nishiyama et al[32]	Single center	Japan	NR	67/70	67/80	40/43	77/90	100/100

Data are reported as drug-coated balloon/control

NR= not reported

Downloaded from http://ahajournals.org by on November 17, 2020

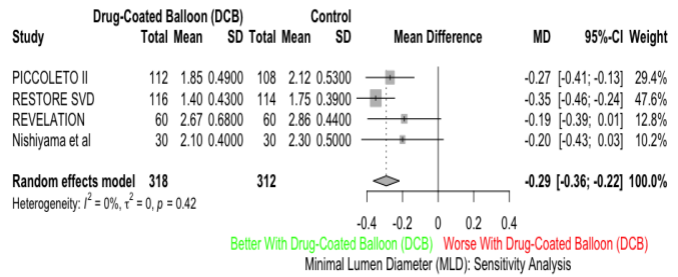
Table S4. Risk of bias of the individual studies by Cochrane risk assessment tool.

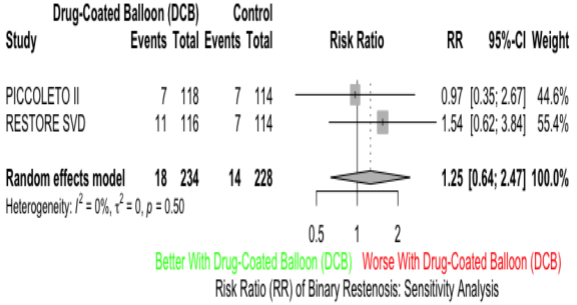
	PICCOLETO II[24]	RESTORE SVD[10]	BASKET-SMALL 2[11]	Funatsu et al[25]	BELLO[26,27]	PICCOLETO[22]	PEPCAD NSTEMI[13]	REVELATION[14]	Gobic et al[28]	Shin et al[29]	DEBUT[12]	PEPCAD-BIF[30]	BABILON[31]	Nishiyama et al[32]
Random sequence generation *(Selection bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Allocation concealment *(Selection bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	?
Blinding of participants and personnel *(Performance bias)*	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blinding of outcome assessment *(Detection bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Incomplete outcome data *(Attrition bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Selective reporting *(Reporting bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other sources of bias	+	+	+	+	+	+	+	+	+	+	+	+	+	+

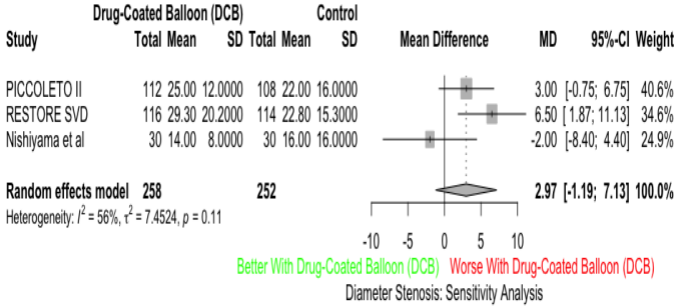
+ = Low risk of bias - = Risk of bias ? = Unclear

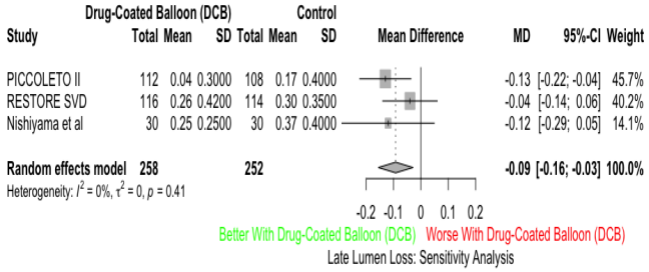
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S1. Sensitivity analysis for the angiographic outcomes limited to trials with second-generation drug eluting stents as control.



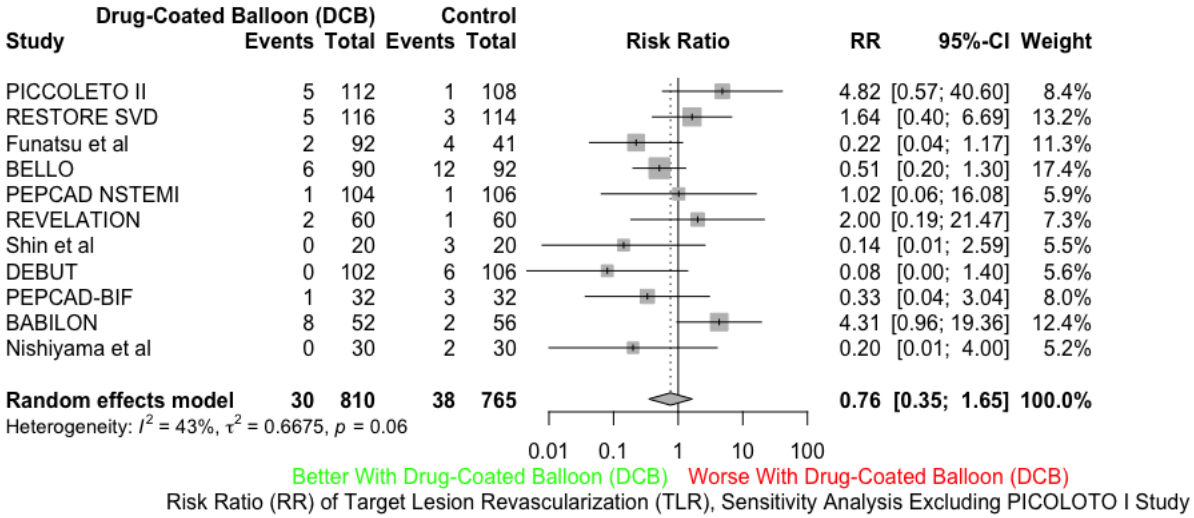






Downloaded from http://ahajournals.org by on November 17, 2020

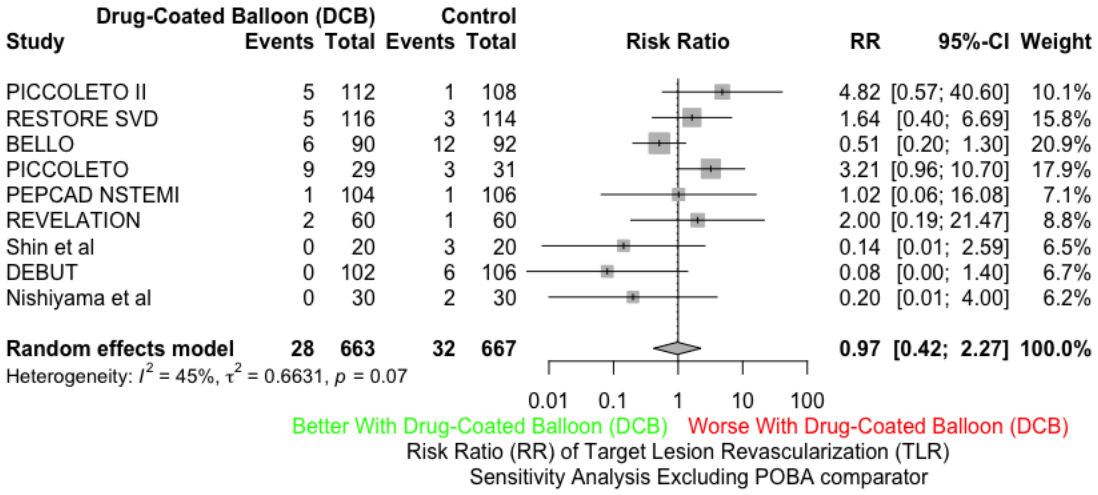
Figure S2. Sensitivity analysis for target lesion revascularization excluding trial using older generation drug coated balloon.



Risk Ratio (RR) of Target Lesion Revascularization (TLR), Sensitivity Analysis Excluding PICOLOTO I Study

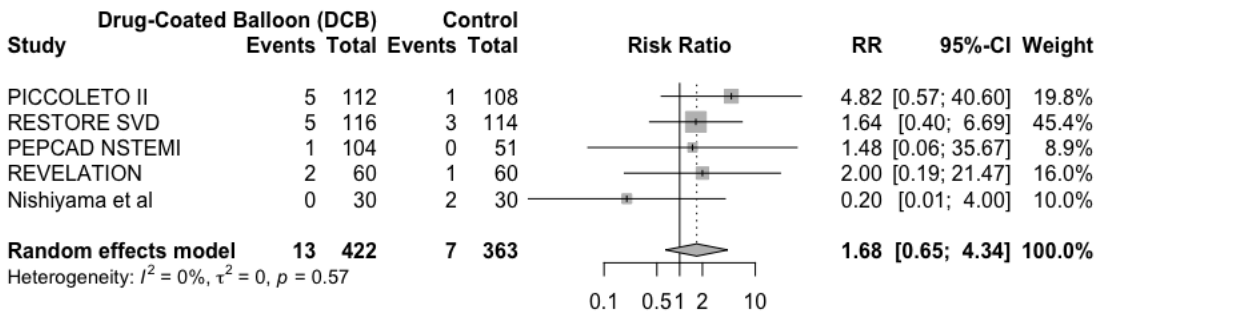
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S3. Sensitivity analysis for target lesion revascularization excluding trials using angioplasty alone in the control arm.



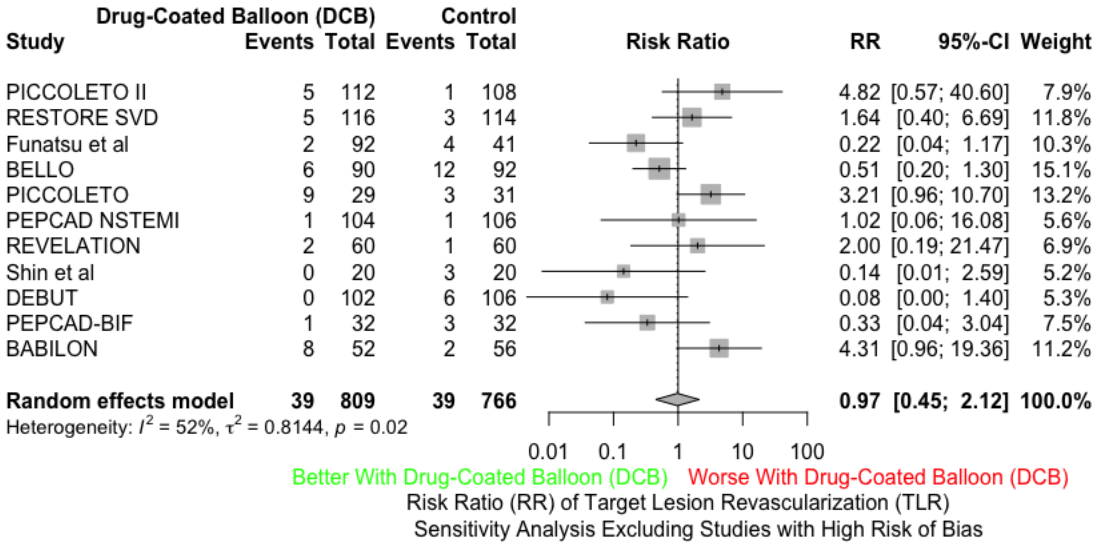
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S4. Sensitivity analysis for target lesion revascularization limited to trials utilizing second-generation drug-eluting stent as control.



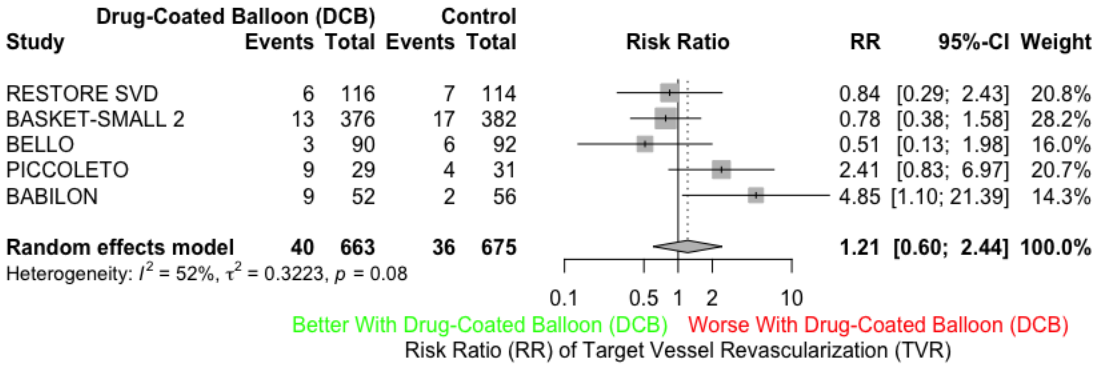
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S5. Sensitivity analysis for target lesion revascularization excluding the trial at high risk of bias.



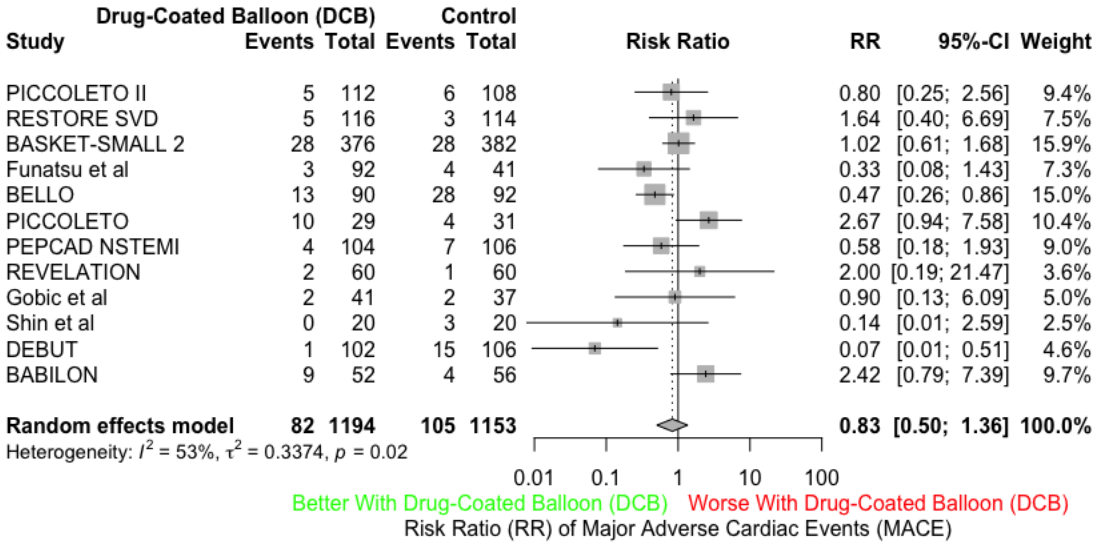
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S6. Forest plot for target vessel revascularization.



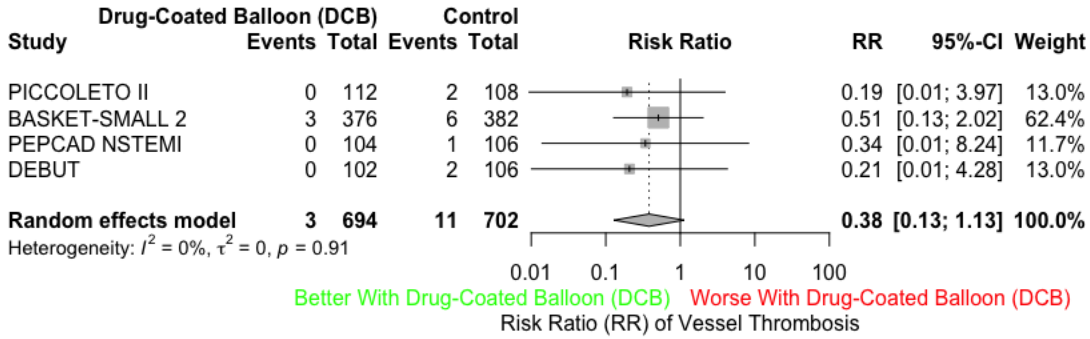
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S7. Forest plot for major adverse cardiac events.



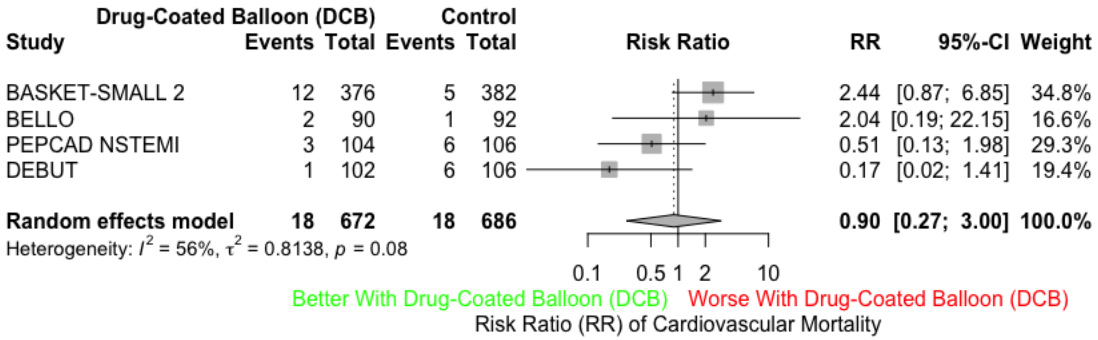
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S8. Forest plot for vessel thrombosis.



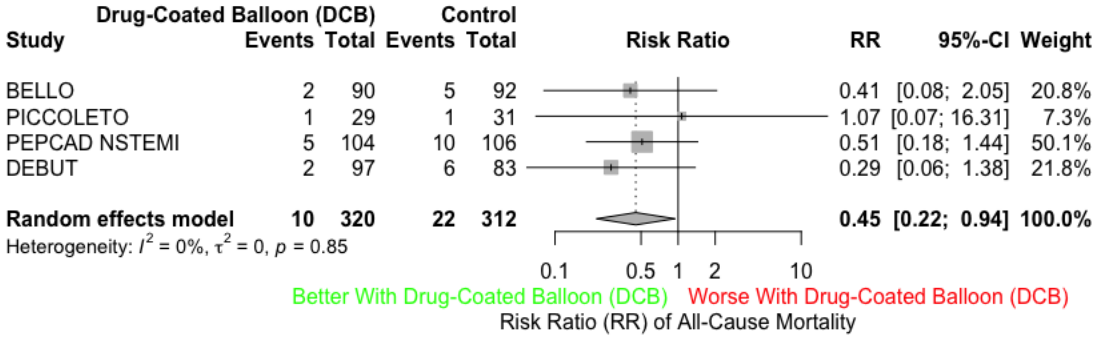
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S9. Forest plot for cardiovascular mortality.



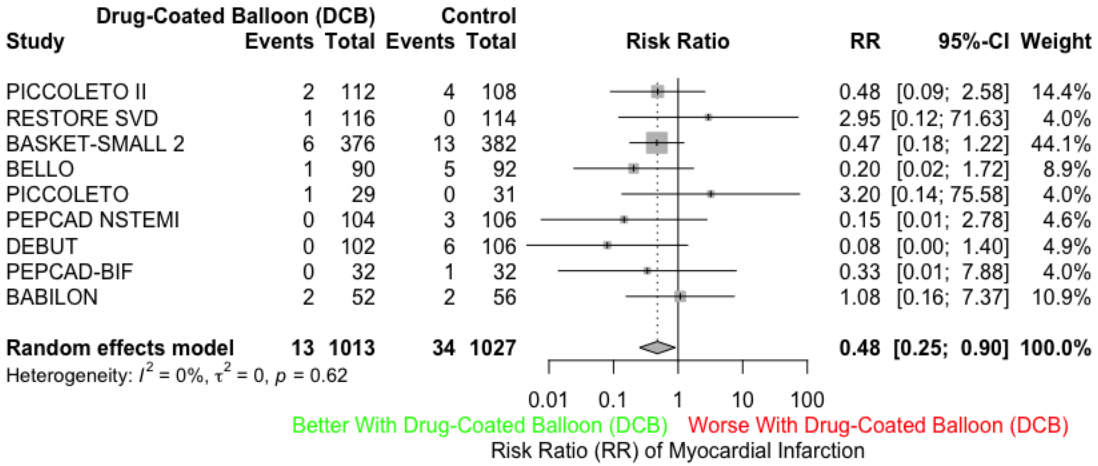
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S10. Forest plot for all-cause mortality.



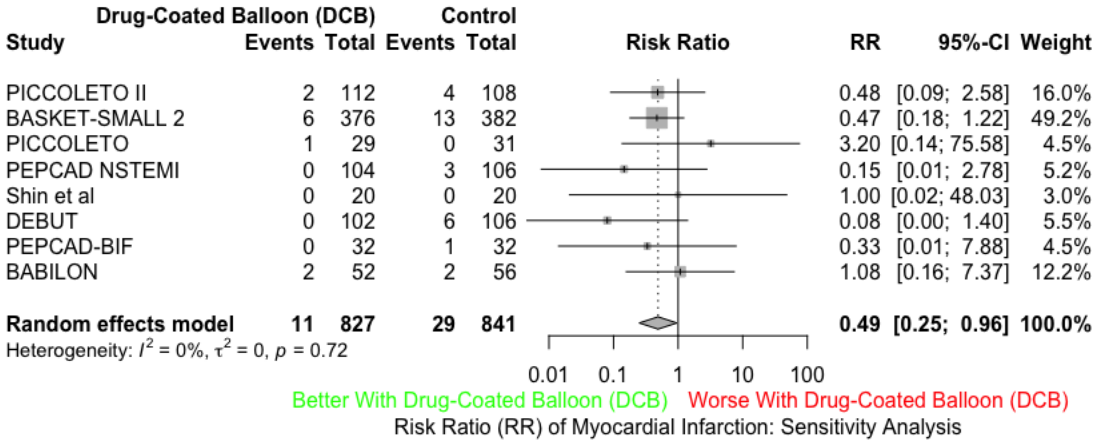
Downloaded from http://ahajournals.org by on November 17, 2020

Figure S11. Forest plot for myocardial infarction.



Downloaded from http://ahajournals.org by on November 17, 2020

Figure S12. Sensitivity analysis limited to spontaneous myocardial infarction.



Downloaded from http://ahajournals.org by on November 17, 2020

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 15, 2015
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2015.08.029

Effect of Drug-Coated Balloons in Native Coronary Artery Disease Left With a Dissection

Bernardo Cortese, MD,* Pedro Silva Orrego, MD,* Pierfrancesco Agostoni, MD, PhD,† Dario Buccheri, MD,*‡ Davide Piraino, MD,*‡ Giuseppe Andolina, MD,‡ Romano Giuseppe Seregni, MD*

ABSTRACT

OBJECTIVES The authors sought to understand the clinical and angiographic outcomes of dissections left after drug-coated balloon (DCB) angioplasty.

BACKGROUND Second-generation DCB may be an alternative to stents in selected populations for the treatment of native coronary lesions. However, the use of these devices may be hampered by a certain risk of acute vessel recoil or residual coronary dissection. Moreover, stenting after DCB has shown limited efficacy. Little is known about when a non–flow-limiting dissection is left after DCB angioplasty.

METHODS This was a prospective observational study whose aim was to investigate the outcome of a consecutive series of patients with native coronary artery disease treated with second-generation DCB and residual coronary dissection at 2 Italian centers. We evaluated patient clinical conditions at 1 and 9 months, and angiographic follow up was undertaken at 6 months.

RESULTS Between July 2012 and July 2014, 156 patients were treated with DCB for native coronary artery disease. Fifty-two patients had a final dissection, 4 of which underwent prosthesis implantation and 48 were left untreated and underwent angiographic follow-up after 201 days (interquartile range: 161 to 250 days). The dissections were all type A to C, and none determined an impaired distal flow. Complete vessel healing at angiography was observed in 45 patients (93.8%), whereas 3 patients had persistent but uncomplicated dissections, and 3 had binary restenosis (6.2%). Late lumen loss was 0.14 mm (−0.14 to 0.42). Major adverse cardiovascular events occurred in 11 patients in the entire cohort and in 4 of the dissection cohort (7.2% vs. 8.1%; p = 0.48). We observed 8 and 3 target lesion revascularizations, respectively (5.3% vs. 6.2%; p = 0.37).

CONCLUSIONS In this cohort of consecutive patients treated with new-generation DCB and left with a final dissection, this strategy of revascularization seemed associated with the sealing of most of dissections and without significant neointimal hyperplasia. (J Am Coll Cardiol Intv 2015;8:2003–9) © 2015 by the American College of Cardiology Foundation.

Drug-coated balloons (DCB) were developed to overcome neointimal hyperplasia and have been widely tested for the treatment of in-stent restenosis, in which setting they have shown an efficacy comparable to drug-eluting stents (DES) in terms of target lesion revascularization (TLR) (1–4). For this indication, DCB gained a Class I, Level of Evidence: A in the latest European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines for myocardial revascularization (5).

However, from the mechanical point of view, DCB behave just like simple balloons, thus they share some of the main limitations of these devices after angioplasty, namely coronary dissection and acute recoil.

Very preliminary observations seem to show how new-generation DCB could be associated with a faster spontaneous healing of an arterial dissection left after balloon angioplasty, especially in case of angioplasties of the femoropopliteal region and for the treatment of in-stent restenosis (6,7). The aim of this study was to test this hypothesis in a consecutive series of patients with native coronary vessel disease.

From the *Cardiac Department, A.O. Fatebenefratelli, Milano, Italy; †Cardiac Department, University Medical Center Utrecht, Utrecht, the Netherlands; and the ‡Cardiac Department, A.O.U.P. Paolo Giaccone, Palermo, Italy. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 14, 2015; revised manuscript received June 30, 2015, accepted August 17, 2015.

ABBREVIATIONS AND ACRONYMS

DCB = drug-coated balloon(s)

DES = drug-eluting stent(s)

LLL = late lumen loss

MACE = major adverse cardiac event(s)

MLD = minimal lumen diameter

PCI = percutaneous coronary intervention

RVD = reference vessel diameter

TLR = target lesion revascularization

METHODS

This is an observational study conducted at 2 centers expert in DCB angioplasty. The aim of the study was to investigate the outcome of consecutive coronary dissections left after DCB angioplasty in native vessels.

SEE PAGE 2010

Inclusion criterion was any percutaneous coronary intervention (PCI) performed with DCB in native coronary vessels. Exclusion criteria were any use of DCB for reasons different from the aforementioned (e.g., for in-stent restenosis); ST-segment elevation myocardial infarction that occurred in the previous 48 h; or life expectancy <1 year. Other clinical indications for PCI, unstable hemodynamics at presentation, and the presence of renal insufficiency were not exclusion criteria. We had a restrictive use of DCB in case of big vessel size (e.g., >3 mm in diameter) or in case of very calcific vessels, especially when we feared possible vessel recoil.

In the current study, the following devices were used: Restore (Cardionovum, Milano, Italy) and Elutax SV (Aachen Resonance, Lainate, Italy) DCB. These 2 devices, both eluting paclitaxel, may be considered a second-generation DCB because of a more efficient delivery of paclitaxel to the vessel wall, which results in a longer persistence of the drug. Restore DCB has a concentration of paclitaxel of 3.0 μg/mm^2 of balloon surface, and shellac is used as a carrier. Elutax SV DCB has a concentration of paclitaxel of 2.2 μg/mm^2 of balloon surface, and is embedded in a 3-layer matrix. Available measures for both devices used in this study included diameters of 2.0, 2.5, and 3.0 mm, and lengths of 15, 20, 25, and 30 mm.

The intervention was performed according to international guidelines and the recent Italian position paper on DCB PCI (8). Specifically, pre-dilation with an undersized semicompliant balloon was mandatory (the recommended size was 0.9:1 of DCB). In case of flow-limiting dissection after pre-dilation, we recommended considering conversion to a stent PCI without using a DCB. The DCB was inflated for 30 to 45 s at nominal pressure, according to the morphological characteristics of the lesion (e.g., degree of calcification, length, tortuosity). After DCB use, final assessment was undertaken after at least 5 min, in order to catch early vessel recoil. In this event, bailout stent implantation was considered. The type of stent or scaffold was left to the operator's discretion.

Patients with any residual coronary dissection after DCB use entered the current analysis. It is our habit not to stent coronary dissections of type A to C (National Heart, Lung, and Blood Institute [NHBLI] classification system for intimal tears, developed by the Coronary Angioplasty Registry) with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. In case of coronary dissections of type D or higher and/or impaired distal flow, it is our habit to implant a stent.

After sheath insertion, all patients were administered unfractionated heparin (single bolus of 5,000 IU, then adjunctive boluses following activated clotting time) or bivalirudin (bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure). A bailout glycoprotein IIb/IIIa receptor inhibitor strategy was allowed in case of high thrombus burden. All patients received aspirin (either 100 mg/day for at least 3 days before PCI or with a pre-PCI 300-mg intravenous bolus), and clopidogrel (300 or 600 mg as a loading dose, followed by 75 mg daily) or prasugrel (60 mg as a loading dose, followed by 10 mg daily) or ticagrelor (180 mg as a loading dose, followed by 90 mg twice a day) following clinical indication. The duration of prescribed dual antiplatelet treatment was 1 month, or 6 months in case of stent implantation; after this time, patients were prescribed only aspirin.

Angiographic success was defined as a final residual stenosis <50% by visual estimate, with TIMI flow

TABLE 1 Patients' Clinical Characteristics

	All DCB Population, Native Vessels (N = 156)	No Dissection Cohort (n = 104)	Dissection Cohort (n = 52)	p Value
Age, yrs	61 (54–67)	59 (51–64)	60 (54–66)	0.18
Female	50 (32.0)	31 (29.8)	19 (36.5)	0.31
Hypertension	91 (58.3)	59 (56.7)	32 (63.5)	0.21
Hypercholesterolemia	95 (60.9)	65 (62.5)	30 (57.7)	0.32
Diabetes	55 (35.2)	37 (35.6)	18 (34.6)	0.86
Prior MI	14 (9.3)	10 (9.6)	4 (8.4)	0.48
Prior revascularization	17 (10.9)	9 (8.7)	8 (13.5)	0.16
Multivessel coronary disease	78 (50)	52 (50)	26 (50)	0.91
Stable angina	82 (52.6)	55 (52.9)	27 (51.9)	0.84
Unstable angina	31 (19.9)	19 (18.3)	12 (23.0)	0.33
Non-ST-segment elevation MI	43 (27.6)	30 (28.8)	13 (25)	0.75
Culprit vessel				
Left anterior descending artery	88 (56.4)	52 (50)	35 (67.0)	**0.02**
Left circumflex artery	13 (8.3)	10 (9.6)	3 (5.8)	0.06
Right coronary artery	55 (35.2)	42 (40.4)	14 (26.9)	0.842

Values are median (interquartile range) or n (%). p Value in **bold** have reached statistical significance.

DCB = drug-coated balloon; MI = myocardial infarction.

grade 3. Procedural success was defined as angiographic success without the occurrence of in-hospital major adverse cardiac events (MACE) (defined as any occurrence of ST-segment elevation acute myocardial infarction, target vessel revascularization, TLR, or death). Periprocedural myocardial infarction was defined as a post-procedural increase in cardiac troponin T >5 × 99th percentile of the upper reference limit.

All patients underwent clinical follow-up after 1 and 9 months; all patients in the dissection cohort underwent angiographic follow-up with quantitative coronary assessment after 6 months, in order to assess the degree of coronary dissection healing. All measurements were performed on cineangiograms recorded after 200 mg of intracoronary nitroglycerin administration. Identical projections were used for each comparison. Quantitative analysis of angiographic data were initially assessed by a single experienced investigator, and afterwards validated by an internal committee of experts, using the CAAS II research system (Pie Medical Imaging, Maastricht, the Netherlands). The following parameters were analyzed: reference vessel diameter (RVD), minimal lumen diameter (MLD), percent diameter stenosis (the difference between RVD and MLD divided by RVD), late lumen loss (LLL) (defined as the difference between MLD after index PCI and MLD at angiographic follow up), lesion length, binary restenosis, and persistence of dissection (NHBLI classification). Measurements included the whole segment treated plus 5 mm proximally and distally. Binary restenosis was defined as stenosis of at least 50% of the luminal diameter at angiographic follow-up.

Primary endpoint of this study was the percentage of dissection healing detected at angiographic follow-up. Secondary endpoints included TLR, binary restenosis, LLL, and the occurrence of MACE.

Data are presented as mean ± SD or median (interquartile range) as appropriate for continuous variables, and as proportions (%) for dichotomous variables. The differences between groups were assessed by chi-square test or Fisher exact test for categorical data, and paired Student *t* test for continuous data. The relative risk and its 95% confidence interval were calculated for each study endpoint. A 2-sided p value <0.05 was considered statistically significant.

RESULTS

The study population consisted of 156 consecutive patients treated between July 2012 and July 2014 at 2 centers with second-generation DCB for native coronary artery disease (87 with Restore and 69 with Elutax SV), that were prospectively entered in the database. Thirty-five percent of patients had diabetes, and clinical indication was stable angina in 82, unstable angina in 31, and non-ST-segment elevation myocardial infarction in 43 patients. Procedural success was achieved in all patients.

TABLE 2 Procedural Characteristics

	All DCB Population, Native Vessels (N = 156)	No Dissection Cohort (n = 104)	Dissection Cohort (n = 52)	p Value
Radial approach	144 (92.3)	96 (92.3)	48 (92.3)	0.95
Total occlusion	18 (11.5)	9 (8.7)	9 (17.3)	0.47
Reference vessel diameter, mm	2.83 (2.12–3.01)	2.87 (2.15–3.0)	2.80 (2.07–2.97)	0.21
Minimal lumen diameter, mm	0.4 (0.0–0.73)	0.37 (0.03–0.65)	0.41 (0.00–0.79)	0.11
Stenosis severity, %	83 (72–100)	82 (71–100)	84 (70–100)	0.18
Lesion length, mm	21 (10–33)	19 (10–28)	22 (12–33)	0.10
Severe-moderate calcification (visual estimation)	100 (64.1)	60 (57.7)	40 (76.9)	**0.01**
Pre-dilation balloon diameter, mm	2.45 (2.0–3.0)	2.35 (2.0–3.0)	2.5 (2.0–3.0)	**0.04**
DCB diameter, mm	2.55 (2.0–3.0)	2.50 (2.0–3.0)	2.60 (2.0–3.0)	**0.035**
DCB length, mm	25 (15–30)	24 (15–30)	25 (15–30)	0.37
Max pressure during DCB angioplasty, atm	12 (8–14)	11 (9–14)	12 (8–15)	0.49
DCB inflation duration, s	35 (30–45)	37 (32–45)	34 (30–42)	0.33
OCT/IVUS guidance	15 (9.6)	11 (10.6)	4 (7.7)	0.13
Minimal lumen diameter after PCI, mm	2.21 (1.75–2.67)	2.17 (1.75–2.58)	2.24 (1.84–2.67)	0.22
Procedural success	156 (100)	104 (100)	52 (100)	0.87
Periprocedural myocardial infarction	21 (13.5)	13 (12.5)	8 (15.4)	0.42
Bivalirudin	15 (9.6)	9 (8.7)	6 (11.5)	0.23
Dual antiplatelet therapy				
ASA + clopidogrel	130 (83.3)	85 (81.7)	45 (86.5)	0.24
ASA + ticagrelor/prasugrel	26 (16.7)	19 (18.3)	7 (13.5)	0.36

Values are n (%) or median (interquartile range). Values in **bold** have reached statistical significance.

ASA = acetylsalicylic acid; DCB = drug-coated balloon; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PCI = percutaneous coronary intervention.

TABLE 3 Angiographic Follow-Up of Patients With Dissection After DCB PCI

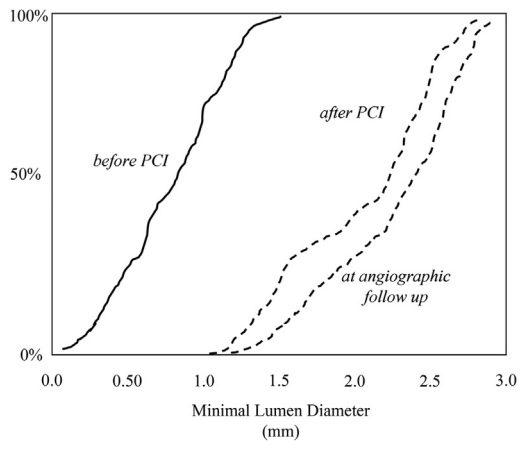
	Dissection Cohort (n = 48)
Reference vessel diameter, mm	2.87 (2.11 to 2.98)
Minimal lumen diameter, mm	2.42 (2.22 to 2.66)
Diameter stenosis, %	12 (8 to 20)
LLL, mm	0.14 (−0.14 to 0.42)
Complete vessel healing	45 (93.8)
Binary restenosis	3 (6.2)

Values are median (interquartile range) or n (%). Follow-up was at 201 days (interquartile range 161 to 250 days).

LLL = late lumen loss; other abbreviations as in Table 2.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 8, NO. 15, 2015
DECEMBER 28, 2015:2003–9

FIGURE 1 MLD Before DCB PCI, After DCB PCI, and at Angiographic Follow-Up in Patients Left With a Dissection



Notably, there was a diffuse lumen enlargement at angiographic control. DCB = drug-coated balloon; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention.

For the purpose of this analysis, we studied the 52 patients that had an angiographically detectable dissection after DCB angioplasty. All patients of this cohort underwent programmed coronary angiography after 6 to 9 months. Baseline clinical characteristics and clinical indication to PCI of the entire population and of the 2 cohorts are shown in Table 1. The dissection study group did not differ significantly from the entire DCB group, if we exclude a higher incidence of left anterior descending artery as the culprit vessel, the degree of calcification of the culprit lesion, the size of balloon used for predilation, and the size of the DCB (Table 2). Baseline angiographic characteristics are shown in Table 2. Of note, the vessel diameter was 2.83 mm in the entire population, and 2.80 mm in the dissection population.

Of the 52 patients with residual dissection after DCB PCI, 4 had a prosthesis implanted (2 a bare-metal stent, 1 a DES, and 1 a biovascular scaffold). The reason for implanting a stent/scaffold was impairment of distal flow in 3 patients, and the presence of a spiral, type D dissection in 1.

All patients with a final dissection underwent scheduled angiographic follow-up with quantitative coronary assessment, that was undertaken after 201 days (interquartile range 161 to 250 days). Angiographic outcome is presented in Table 3. Of note, LLL was as low as 0.14 ± 0.28 mm in this group. We also observed a late lumen enlargement in the treated segments (Figure 1).

Complete vessel healing at angiography was observed in 45 of 48 patients (93.8%) (Figure 2). The 3 patients that had an unhealed dissection had, respectively, a type A, type B, and type C coronary dissection after the index PCI. TLR occurred in 3 patients (6.2%) in the dissection cohort and in 8 patients (5.3%) in the entire DCB population ($p = 0.49$) (Figure 3). Of the 3 patients that underwent TLR in the dissection cohort, the first 2 had recurrence of angina after 4 and 6 months, respectively; angiography showed subocclusive coronary stenoses (of 85% and 90%, respectively) at the site of the previous PCI that were successfully treated with DES implantation. The third patient was asymptomatic but had a persisting, chronic coronary dissection discovered at angiographic follow-up that was sealed with DES implantation.

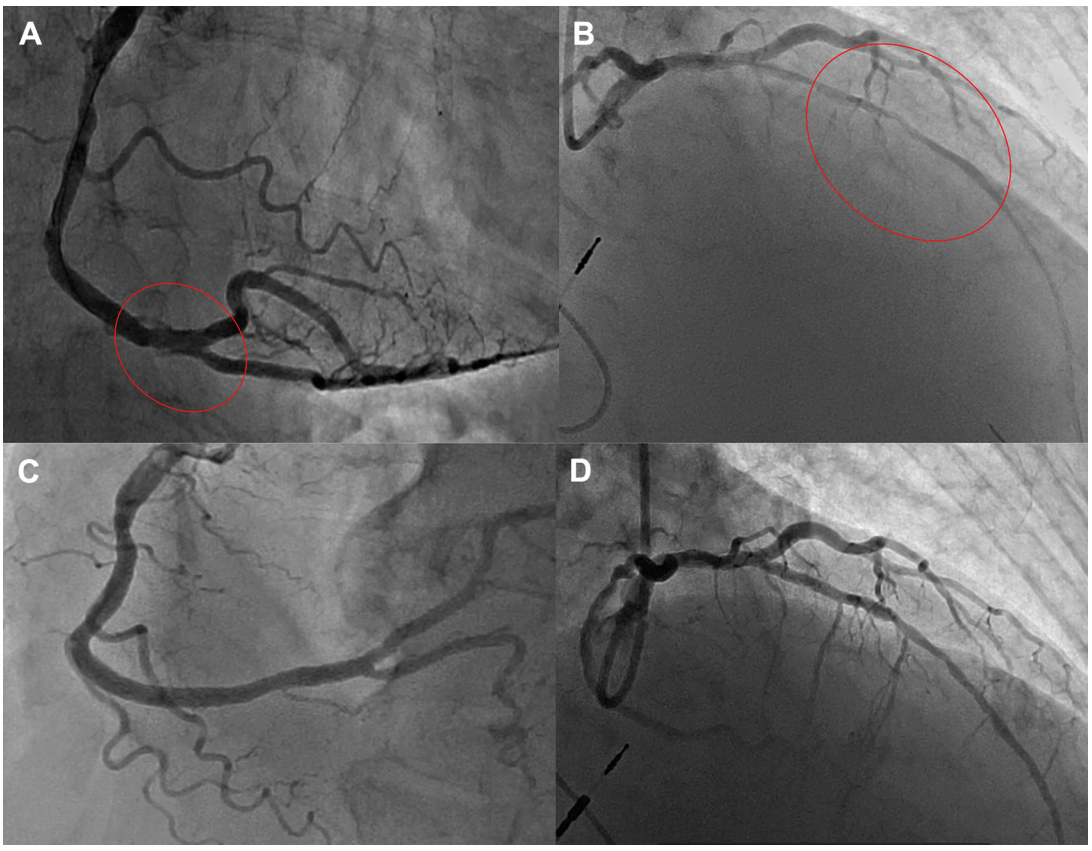
The other clinical endpoints showed no significant differences between the whole group and the groups with and without dissection (Figure 3). Interestingly, we did not observe cases of target vessel myocardial infarction during the entire clinical follow-up (average length 9 ± 3 months). Finally, there were no significant differences between the 2 devices tested in terms of clinical and angiographic endpoints.

DISCUSSION

This prospective observational study describes the first consecutive series of patients treated with DCB for native coronary artery disease and with final dissection left “unsealed” with prosthesis. Our results confirm that leaving a non-flow-limiting dissection untreated after DCB PCI is safe and not associated with an increase in myocardial infarction and TLR, despite the short-term (1 month) dual antiplatelet treatment. Notably, we did not observe a correlation between the type of dissection at baseline (type A, B, or C) and the propensity to healing (Figure 4).

DCB were developed to overcome neointimal hyperplasia and have been first tested in the in-stent restenosis setting with good results maintained for years (3,9). However, the use of DCB for the treatment of native vessels seems particularly encouraging, especially in the case of small vessels and distal lesions, where the encumbrance of a stent may limit its potential and is associated with increased rates of restenosis and stent thrombosis. However, the application of this technology as standalone procedure in de novo lesions has resulted in conflicting results. After some early mistakes, such as the ones depicted in the PICCOLETO (Paclitaxel-Eluting Balloon Versus Paclitaxel-Eluting Stent in Small

FIGURE 2 **Angiographic Outcome of Dissections Left After DCB Angioplasty**



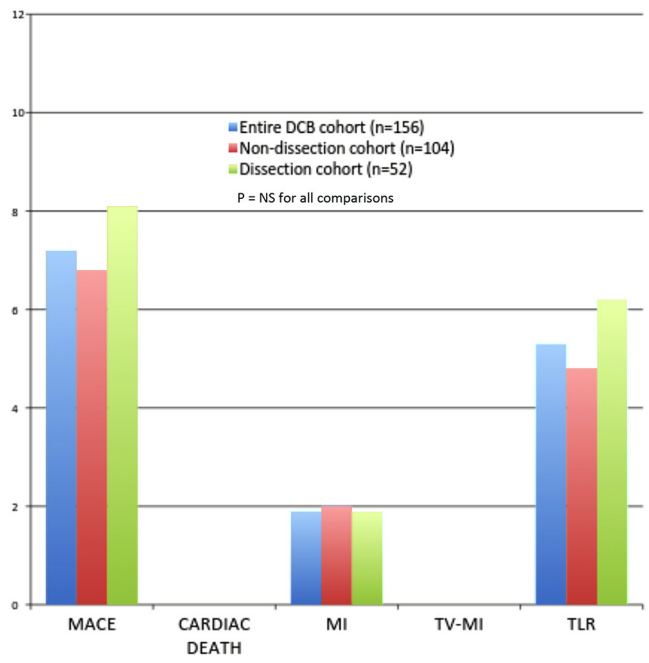
A and B show the final dissections (respectively, a type C and a long type A dissection, **red circles**); after 6 months, both dissections were healed **(C and D)**. DCB = drug-coated balloon.

Coronary Artery Diseases) study (10,11), a newer generation of DCB has been tested in the BELLO (Balloon Elution and Late Loss Optimization) study for the treatment of native coronary vessels. Here, DCB overcame Taxus DES for the treatment of small vessel disease in terms of the primary endpoint of LLL (0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm; 95% confidence interval: −0.34 to −0.09; p = 0.001) (12). Recently, the 2-year follow up of the BELLO study, that showed persisting good results of DCB in terms of clinical endpoints, has been published. (13) Similar encouraging results for this technology in native coronary vessels were shown in large registries with different, new-generation DCB (14,15).

This study was performed with 2 devices of the latest available technology, that provides optimal paclitaxel delivery to the vessel wall and contemporarily allows its longer persistence.

The central point of our findings is the safety of leaving a dissection after DCB angioplasty. Early experiences have shown how leaving a dissection after plain old balloon angioplasty was associated with increased rates of thrombotic events, early reocclusion, and recurrence of restenosis, and this was one of the main indications for the use of stents in an earlier era (16). The widespread use of more potent antiplatelet regimens (e.g., the association of aspirin with a $P2Y_{12}$ receptor inhibitor) has undoubtedly improved the early outcome of this type of patient. In the early stent era, a previous series of patients treated consecutively with plain angioplasty and with a final dissection, despite a very low occurrence of thrombotic events and an acceptable rate of restenosis (12%), 36.7% of dissections left were still visible at 6-month angiographic follow-up (17). With this current study, we have opened the hypothesis that the effect of paclitaxel, when correctly delivered to the vessel wall, may have a role in facilitating the healing of coronary vessels.

FIGURE 3 Clinical Follow-Up After 9 Months in the Entire Population and in the Dissection and No-Dissection Cohorts



p Values are not significant for all comparisons. DCB = drug-coated balloon; MACE = major cardiovascular event(s); MI = myocardial infarction; TLR = target lesion revascularization; TV = target vessel.

FIGURE 4 The Fate of Dissections After DCB Angioplasty

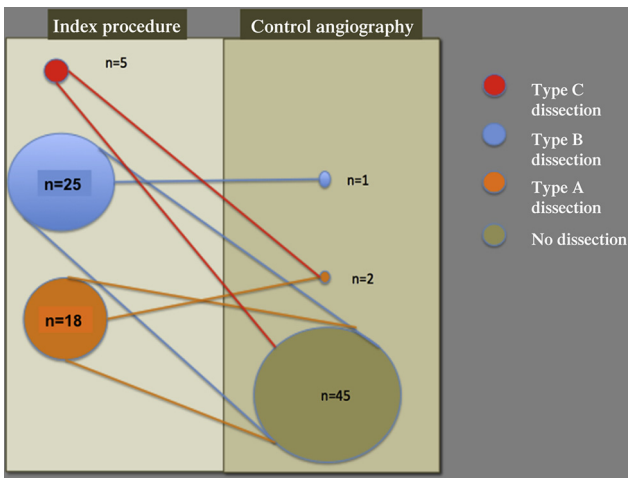


Figure shows what happened to dissections at 6-month angiography: 45 were healed and 3 were chronic. There was not an apparent correlation between the type of initial dissection left after DCB angioplasty and its fate. We followed the NHLBI classification for coronary dissections. DCB = drug-coated balloon; NHLBI = National Heart, Lung, and Blood Institute.

This effect was already described in a post-hoc analysis of the THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries) study (6), where patients with femoropopliteal disease were randomized to simple angioplasty or DCB. In this analysis, patients treated with DCB resulting in final dissection of any grade had significantly lower LLL than patients with dissection after simple angioplasty (0.4 vs. 1.9 mm; $p = 0.001$), especially if the dissection grade was severe (type C to E) (0.4 vs 2.4 mm; $p = 0.05$). This result was maintained for all the duration of the 2-year follow-up, with a TLR of 10% versus 56% respectively ($p = 0.002$) (6). In another study, Agostoni et al. (18) have found how leaving small dissections after DCB angioplasty for in-stent restenosis resulted in complete dissection healing at optical coherence tomography after 6 months. In addition to this information, we also found that our patients, who did not have a "caged" coronary artery because they did not have in-stent restenosis, also had an improved late lumen gain, as already described in another series of patients treated with DCB for native coronary vessel disease (19). This late lumen enlargement (**Figure 1**) is another interesting effect of DCB that needs further, dedicated analysis.

In this study, we decided to limit the degree of dissections left to a low-medium grade (type A to C) because of ethical reasons (the eventual vessel occlusion would result in myocardial infarction). Now with our results, if the dissection is of low-medium grade, it seems safe to leave it untreated. In fact, data from the literature show how any stent strategy associated with DCB use is unsafe or yields unsatisfactory results (20,21). There are some initial data on the use of DES after DCB, but such data are limited in number and are without angiographic follow-up (22), thus the contemporary use of 2 different antirestenotic drugs with stent metal layers needs to be better understood before recommending this strategy. Moreover, in this case, the advantages of using a DCB are immediately lost (23).

STUDY LIMITATIONS. First, the population is limited and derives from 2 centers expert in this type of PCI, thus it may not be reproducible everywhere without an adequate learning curve. Moreover, we have to disclose an initial bias at the time of decision of leaving the dissection untreated. So far, these results are not easily reproducible in all settings. Our findings, although a confirmation of other previous studies, are the first assessment of this property of new-generation DCB in native coronary lesions, and need to be validated in other ad hoc clinical studies.

CONCLUSIONS

In a consecutive series of patients treated with new-generation DCB for native coronary artery disease and with a final non-flow-limiting dissection, these lesions tended to heal despite their initial severity. After DCB angioplasty, a strategy of bailout stenting should be reserved to more severe, flow-limiting dissections.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Bernardo Cortese, Interventional Cardiology, A.O. Fatebenefratelli Milano, Bastioni di Porta Nuova 21, 20100 Milano, Italy. E-mail: bcortese@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? DCB are a useful tool for the treatment of small coronary arteries. However, little is known regarding the fate of dissections left unsealed after DCB PCI.

WHAT IS NEW? With this study, for the first time in the coronary tree, we showed a pro-healing effect of DCB when a final dissection was left at the end of PCI.

WHAT IS NEXT? We now need an adequately powered study (e.g., a randomized controlled study) to test this preliminary report in a broader population of coronary artery disease patients.

REFERENCES

1. Xu B, Gao R, Wang J, et al. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. J Am Coll Cardiol Intv 2014;7:204–11.

2. Unverdorben M, Vallbracht C, Cremers B, 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 2014 Aug 30 [E-pub ahead of print].

3. Scheller B, Clever YP, Kelsch B, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. J Am Coll Cardiol Intv 2012;5:323–30.

4. Lee JM, Park J, Kang J, et al. Comparison among drug-eluting balloon, drug-eluting stent, and plain balloon angioplasty for the treatment of in-stent restenosis: a network meta-analysis of 11 randomized, controlled trials. J Am Coll Cardiol Intv 2015;8:382–94.

5. Authors/Task Force Members, Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.

6. Tepe G, Zeller T, Schnorr B, et al. High-grade, non-flow-limiting dissections do not negatively impact long-term outcome after paclitaxel-coated balloon angioplasty: an additional analysis from the THUNDER study. J Endovasc Ther 2013;20:792–800.

7. Chan YH, Agostoni P. SEDUCEd by optical coherence tomography in drug-eluting balloon assessment. EuroIntervention 2014;10:415–7.

8. Cortese B, Berti S, Biondi-Zoccai G, et al. Drug-coated balloon treatment of coronary artery disease: a position paper of the Italian Society of Interventional Cardiology. Catheter Cardiovasc Interv 2014;83:427–35.

9. Cortese B, Sgueglia GA. The future is now: comment on a recent editorial suggesting the need for a new technology in the treatment of DES restenosis. J Am Coll Cardiol Intv 2012;5:1093, author reply 1093–4.

10. Cortese B, Micheli A, Picchi A, et al. Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. Heart 2010;96:1291–6.

11. Cortese B. The PICCOLETO study and beyond. EuroIntervention 2011;7 Suppl K:K53–6.

12. Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. J Am Coll Cardiol 2012;60:2473–80.

13. Naganuma T, Latib A, Sgueglia GA, et al. A 2-year follow-up of a randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels the BELLO study. Int J Cardiol 2015;184C:17–21.

14. Basavarajaiah S, Latib A, Shannon J, et al. Drug-eluting balloon in the treatment of in-stent restenosis and diffuse coronary artery disease: real-world experience from our registry. J Interv Cardiol 2014;27:348–55.

15. Pastormerlo LE, Ciardetti M, Trianni G, et al. Drug eluting balloon: a multipurpose tool for coronary revascularization with optimal long-term follow-up results. J Interv Cardiol 2014;27:574–9.

16. Cowley MJ, Dorros G, Kelsey SF, Van Raden M, Detre KM. Acute coronary events associated with percutaneous transluminal coronary angioplasty. Am J Cardiol 1984;53:12C–6C.

17. Cappelletti A, Margonato A, Rosano G, et al. Short- and long-term evolution of unstented nonocclusive coronary dissection after coronary angioplasty. J Am Coll Cardiol 1999;34:1484–8.

18. Agostoni P, Belkacemi A, Voskuil M, Nathoe HM, Doevendans PA, Stella PR. Serial morphological and functional assessment of drug-eluting balloon for in-stent restenotic lesions: mechanisms of action evaluated with angiography, optical coherence tomography, and fractional flow reserve. J Am Coll Cardiol Intv 2013;6:569–76.

19. Kleber FX, Schulz A, Waliszewski M, et al. Local paclitaxel induces late lumen enlargement in coronary arteries after balloon angioplasty. Clin Res Cardiol 2015;104:217–25.

20. Fischer D, Scheller B, Schäfer A, et al. Paclitaxel-coated balloon plus bare metal stent vs. sirolimus-eluting stent in de novo lesions: an IVUS study. EuroIntervention 2012;8:450–5.

21. Liistro F, Porto I, Angioli P, et al. Elutax paclitaxel-eluting balloon followed by bare-metal stent compared with Xience V drug-eluting stent in the treatment of de novo coronary stenosis: a randomized trial. Am Heart J 2013;166:920–6.

22. Costopoulos C, Latib A, Naganuma T, et al. The role of drug-eluting balloons alone or in combination with drug-eluting stents in the treatment of de novo diffuse coronary disease. J Am Coll Cardiol Intv 2013;6:1153–9.

23. Cortese B, Bertoletti A. Paclitaxel coated balloons for coronary artery interventions: A comprehensive review of preclinical and clinical data. Int J Cardiol 2012;161:4–12.

KEY WORDS angiographic follow-up, coronary dissection, dissection healing, drug-coated balloon

Effect of drug-coated balloons in native coronary artery disease left with a dissection.

Subanalysis and comparison between Restore and Elutax SV drug-coated balloons

This prospective observational study invesigated the outcome of native coronary artery disease treated with second-generation DCB and residual coronary dissections with angiographic follow up after 6 months.

The current sub-analysis of the study investigated the performance of Restore DCB vs. Elutax SV DCB in the study population (see main publication: B. Cortese et al., JACC Interventions, Dec. 2015).

The intervention was performed according to international guidelines and the recent Italian Position Paper on DCB-PCI.(8) Specifically, predilatation with an undersized semicompliant balloon was mandatory (the recommended size was 0.9:1 of DCB). In case of flow-limiting dissection after predilatation, we recommended to consider conversion to a stent-PCI without using a DCB. DCB was inflated for 30-45 seconds at nominal pressure, according to the morphological characteristics of the lesion (e.g., degree of calcification, length, tortuosity). After DCB use, final assessment was undertaken after at least 5 minutes, in order to catch early vessel recoil. In this evenience, bailout stent implantation was considered. The type of stent or scaffold was left at operator's discretion. It is our habit not to stent coronary dissections of type A to C (National Heart, Lung, and Blood Institute (NHBLI) classification system for intimal tears, developed by the Coronary Angioplasty Registry) with TIMI 3 flow grade. In case of coronary dissections of type D or higher and/or impaired distal flow it is our habit to implant a stent.
Angiographic success was defined as a final residual stenosis <50% by visual estimate, with TIMI 3 flow. Procedural success was defined as angiographic success without the occurrence of in-hospital major adverse cardiac events (MACE: any occurrence of ST-elevation acute myocardial infarction, target vessel revascularisation, TLR, or death).

All patients underwent clinical follow up after 1 and 9 months; all patients in the dissection cohort underwent angiographic follow up with quantitative coronary assessment (QCA) after 6 months, in order to assess the degree of coronary dissection healing. All measurements were

performed on cineangiograms recorded after 200mg of intracoronary nitroglycerin administration. Identical projections were used for each comparison. Quantitative analysis of angiographic data were initially assessed by a single experienced investigator, and afterwards validated by an internal committee of experts, using the CAAS II research system (Pie Medical Imaging). The following parameters were analyzied: reference vessel diameter (RVD), minimal lumen diameter (MLD), percent diameter stenosis (the difference between RVD and MLD divided by RVD), late lumen loss (LLL, the difference between MLD after index-PCI and MLD at angiographic follow up) lesion length, binary restenosis, persistence of dissection (NHBLI classification). Measurements included the whole segment treated plus 5 mm proximally and distally. Binary restenosis was defined as stenosis of at least 50% of the luminal diameter at angiographic follow up.

Primary endpoint of the study was the percentage of dissection healing detected at angiographic follow up. Secondary endpoints included TLR, binary restenosis, LLL and the occurrence of MACE.

The study population consisted of 156 consecutive patients treated between July 2012 and July 2014 at 2 centers with II generation DCB for native coronary artery disease (87 with Restore and 69 with Elutax SV), that were prospectively entered in the database.

For the purpose of this analysis, we studied the 52 patients that had an angiographically-detectable dissection after DCB-angioplasty. All patients of this cohort underwent programmed coronary angiography after 6-9 months. Of the 52 patients with residual dissection after DCB-PCI, 4 had a prosthesis implanted (2 a bare-metal stent, one a DES and one a bio-vascular scaffold). The reason for implanting a stent/scaffold was impairment of distal flow in 3 patients, and the presence of a spiral, type D dissection in one.

All patients with a final dissection underwent scheduled angiographic follow up with QCA, that was undertaken after 201 days (I.Q. range: 161-250 days). The main results of this sub-analysis are shown in the Table below.

	Restore	***Elutax SV***	***p***
Late lumen loss, mm	0.20 (0.07 to 0.42)	0.08 (-0.14 to 0.28)	0.073
Vessel healing, %	89	98	NS
Binary restenosis, %	9.4	3	0.05
Target lesion revascularization, %	9.5	3	0.049
Cardiac death, %	0	0	NS

In conclusion, in a consecutive series of patients treated with new generation DCB for native coronary artery disease and with a final not flow-limiting dissection, these lesions tended to heal despite their initial severity. In this limited patient population, Elutax SV seems to achieve an improved angiographic outcome.

International Journal of Cardiology 187 (2015) 238–239

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Drug-coated balloon angioplasty: An intriguing alternative for the treatment of coronary chronic total occlusions

Bernardo Cortese [a,*], Dario Buccheri [a,b], Davide Piraino [a,b], Pedro Silva-Orrego [a], Romano Seregni [a]

[a] Interventional Cardiology, A.O. Fatebenefratelli, Milano, Italy
[b] Interventional Cardiology, A.O.U.P. Paolo Giaccone, Palermo, Italy

ARTICLE INFO

Article history:
Received 17 February 2015
Accepted 17 March 2015
Available online 18 March 2015

Keywords:
Drug-coated balloon (DCB)
Chronic coronary total occlusion (CTO)
Percutaneous coronary intervention (PCI)
Dual antiPlatelet therapy (DAPT)
Drug-eluting stent (DES)

Dear Editor,

The treatment of coronary chronic total occlusions (CTOs) is one of the most exciting and, at the same time, delicate challenges for the interventional cardiologist. In the last few years specific devices have been implemented in order to increase the rate for a successful CTO recanalization. Current treatment options are drug-eluting stents, surgery or medical treatment. We here present an emblematic case of a new approach to this disorder.

An 80-year-old male was admitted at our department for worsening effort angina. In his medical history he had an anterior myocardial infarction managed with PCI and DES implantation of the left anterior descending artery (2008), and thereafter he underwent successful simple angioplasty of the ostium of 2nd obtuse marginal (OM2) due to subocclusive stenosis (Fig. 1A–B, Movie 1). Subsequently he developed a HCV-related hepatitis with episodes of gut and upper airway bleeding.

Coronary angiography showed a chronic total occlusion (CTO) of the ostial OM2 (Fig. 1C, Movie 2) for which we attempted antegrade recanalization. The lesion was not easily wired by a 12-g CTO guidewire supported by a 1.5 mm balloon. We thus performed further predilatations with 2.0 and 2.5 mm balloons obtaining adequate angiographic result. Given the high bleeding risk of the patient, we delivered a 2.5/30 mm drug-coated balloon (DCB), obtaining a good angiographic result with TIMI 3 grade flow and without visible dissection (Fig. 1D, Movie 3). The patient was discharged on dual antiplatelet treatment (DAPT) and after 30 days withdrew clopidogrel. Six-month scheduled coronarography showed persisting good angiographic result with improved lumen gain (Fig. 2A–B, Movie 4). One year later, the patient was still angina-free and had no ischemic or bleeding adverse events.

The use of DCB for the management of coronary artery disease is increasing for several clinical indications/anatomical settings. Specifically, we believe that this device could represent a new intriguing alternative to stents for the treatment of CTO as well [1]. To the best of our knowledge, this is a unique case in which a coronary CTO was managed with a DCB-only strategy. DCB delivers paclitaxel with a single shot and determines a homogeneous distribution of the drug on the vessel wall, resulting in a high concentration during the first days, when the restenotic process is developing [2]. Another advantage is that no permanent prosthesis is delivered, thus reducing the risk of late thrombotic events and the need for prolonged DAPT [3]. More so, the increased risk of late thrombotic events of newer generation DES may be explained by a delayed struts coverage if delivered for a CTO instead of other coronary lesions, thus requiring longer DAPT [4]. Conversely, a DCB-only strategy allows DAPT withdrawal after 2–4 weeks only, especially in patients at higher bleeding risk [5].

We believe that DCB may be a reasonable alternative to stents for the management of CTO. A dedicated study of DCB-only angioplasty seems a provocative idea and is eagerly awaited, especially for those patients that cannot undergo prolonged DAPT.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.03.223.

* Corresponding author at: Interventional Cardiology, A.O. Fatebenefratelli Milano, Bastioni di Porta Nuova 21, 20100 Milano, Italy.
E-mail address: bcortese@gmail.com (B. Cortese).

http://dx.doi.org/10.1016/j.ijcard.2015.03.223
0167-5273/© 2015 Elsevier Ireland Ltd. All rights reserved.

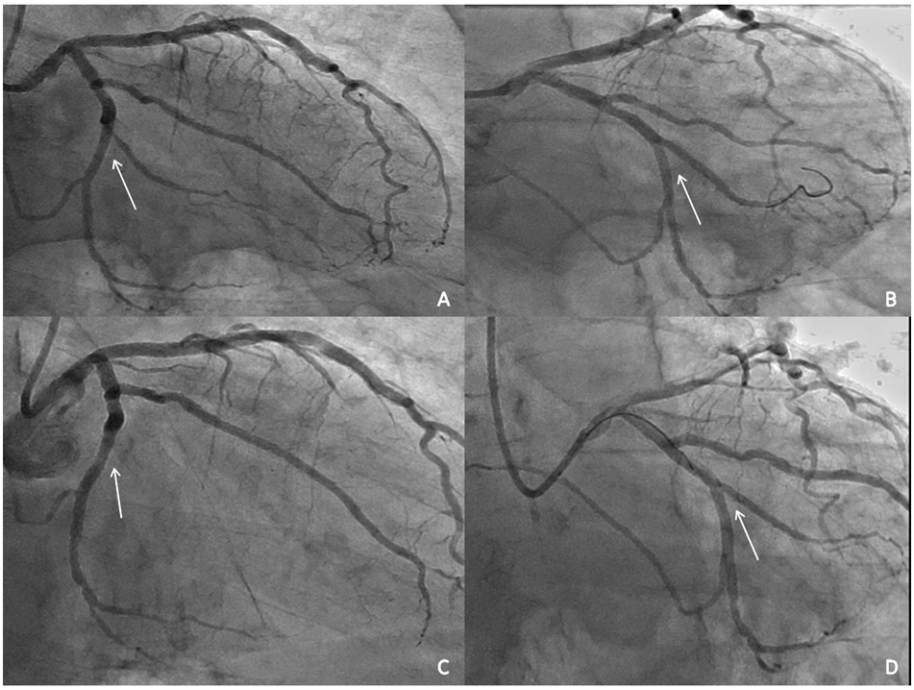


Fig. 1. A: subocclusive stenosis of the ostium of 2nd obtuse marginal branch (OM2). 1B and Movie 1: final angiographic result after simple balloon angioplasty. 1C and Movie 2: chronic total occlusion of the ostium of OM2. 1D and Movie 3: final angiographic result after drug-coated balloon angioplasty.

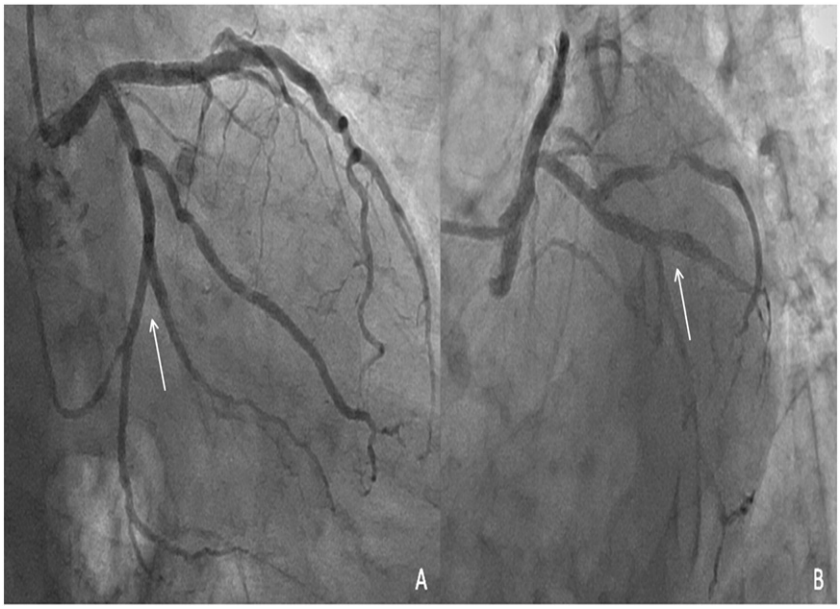


Fig. 2. A–B and Movie 4: six-month angiographic follow-up showing good patency of index lesion and increased vessel diameter.

References

[1] B. Cortese, G.A. Sgueglia, J.F. Granada, Paclitaxel coated balloons, the time for awareness has come, Int. J. Cardiol. 164 (2013) 1–2.
[2] B. Cortese, A. Bertoletti, Paclitaxel coated balloons for coronary artery interventions: a comprehensive review of preclinical and clinical data, Int. J. Cardiol. 161 (2012) 4–12.
[3] L. Mauri, D.J. Kereiakes, R.W. Yeh, P. Driscoll-Shempp, D.E. Cutlip, P.G. Steg, S.L.T. Normand, E. Braunwald, S.D. Wiviott, D.J. Cohen, D.R. Holmes, M.W. Krucoff, J. Hermiller, H.L. Dauerman, D.I. Simon, D.E. Kandzari, K.N. Garratt, D.P. Lee, T.K. Pow, P. Ver Lee, M.J. Rinaldi, J.M. Massaro, DAPT Study Investigators, Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents, N. Engl. J. Med. 371 (2014) 2155–2166.
[4] C.H. Heeger, A. Busjahn, L. Hildebrand, M. Fenski, F. Lesche, F. Meincke, K.H. Kuck, M.W. Bergmann, Delayed coverage of drug-eluting stents after interventional revascularisation of chronic total occlusions assessed by optical coherence tomography: the ALSTER-OCT-CTO registry, EuroIntervention (2014)http://dx.doi.org/10.4244/EIJY14M10_01 (Oct 7. pii: 20140422-07).
[5] B. Cortese, S. Berti, G. Biondi-Zoccai, A. Colombo, U. Limbruno, F. Bedogni, A. Cremonesi, P. Leon Silva, G.A. Sgueglia, Drug-coated balloon treatment of coronary artery disease: a position paper of the Italian Society of Interventional Cardiology, Catheter. Cardiovasc. Interv. 83 (2014) 427–435.

Cardiovascular Revascularization Medicine 18 (2017) 482–486

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

First experience of drug-coated balloons for treatment of bioresorbable vascular scaffold restenosis☆

Mostafa Elwany [a,b], Roberto Adriano Latini [a], Gaetano Di Palma [a], Pedro Silva Orrego [a], Bernardo Cortese [a,c,*]

[a] Interventional Cardiology, ASST Fatebenefratelli-Sacco, Milano, Italy
[b] Faculty of Medicine, University of Alexandria, Egypt
[c] Fondazione G. Monasterio CNR-Regione Toscana, Pisa, Massa, Italy

ARTICLE INFO

Article history:
Received 18 March 2017
Accepted 22 March 2017

Keywords:
Bioresorbable vascular scaffold (BVS)
In-scaffold restenosis
Drug coated balloons (DCB)

ABSTRACT

Objectives: The aim of this study is to evaluate the role of drug-coated balloons (DCB) for the management of bioresorbable vascular scaffold (BVS) restenosis.
Methods and results: In a series of 25 BVS restenosis discovered during systematic angiographic follow up of 246 consecutive BVS implantations at our institution, DCB was used as a primary therapeutic tool in 9 patients and 3 different types of DCB were used. Follow-up coronary angiography at 12 months after DCB treatment was performed to all the patients. Among the 9 patients treated with DCB, angiographic follow up revealed failure in two patients that experienced type III restenosis (both of them treated with the same type of DCB). Both patients were treated with drug eluting stent implantation.
Conclusions: In this case series of consecutive patients with BVS restenosis, the use of certain types of DCB is safe and effective in order to maintain vessel patency at mid-term follow up. Despite the small sample size and the study limitations, DCB can provide therefore an alternative treatment option in this setting, avoiding the implantation of further metallic stents in a patient where a different strategy was initially planned.
© 2017 Elsevier Inc. All rights reserved.

1. Introduction

The use of drug-coated balloons (DCB) is one of the treatments of choice for both bare metal stent and drug-eluting stent (DES) restenosis [1]. Bioresorbable vascular scaffolds (BVS) are one of the most recent revolutionary steps in interventional cardiology. Studies are ongoing to evaluate the long-term efficacy of these biodegradable devices in a real world setting. There are limited data regarding the clinical outcome following target lesion revascularization (TLR) for BVS failure, with the optimal management currently unclear [2]. Several treatments are commonly used in this setting, including DES, re-BVS and DCB use. Currently, only few data are addressing the safety and the efficacy of DCB in the management of BVS restenosis.

The aim of this study, in the form of case series of consecutive patients, is indeed to evaluate the role of DCB in the management of BVS restenosis.

2. Methods

Out of 246 consecutive BVS implantations (Abbott Vascular, Santa Clara, CA, USA) between January 2013 and December 2015 performed at our institution, 210 underwent scheduled angiographic follow up after institutional review board approval and patient's informed consent. At a mean of 12 months, coronary angiography revealed 26 in-scaffold restenosis, defined as >50% restenosis at treatment site: 4 of them were left untreated due to the absence of evident signs of myocardial ischemia, 9 underwent DES implantation, 3 underwent further BVS implantation due to edge-restenosis, 1 underwent coronary artery bypass grafting and 9 patients received revascularization with DCB. At 12 months, a second coronary angiography was scheduled for the patients treated with DCB. Quantitative coronary angiography (QCA) performed by one single expert operator was used for the assessment of all procedures. Optical coherence tomography (OCT) (Ilumien, St. Jude Medical, MN, USA) was used for the assessment of the scaffold failure. Angiographic pattern of scaffold restenosis was classified according to Mehran's classification [3]. Data are presented as mean ± SD. Categorical variables are expressed as count and percentages.

3. Results

From the analysis of our data emerges a complex population. Table 1 describes the clinical characteristics of the patient and baseline procedural data, whereas Table 2 describes the procedural characteristics of

☆ Fundings, grants, financial support, conflicts of interest: none.
* Corresponding author at: Interventional Cardiology, ASST Fatebenefratelli Sacco, Fatebenefratelli Hospital, Corso di Porta Nuova, 23, 20121 Milano, Italy. Tel.: +39 02 63632271; fax: +39 02 63632760.
E-mail address: bcortese@gmail.com (B. Cortese).

http://dx.doi.org/10.1016/j.carrev.2017.03.020
1553-8389/© 2017 Elsevier Inc. All rights reserved.

Table 1
Clinical characteristics and procedural details at the initial procedure (time of BVS implantation).

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Clinical characteristics	Age	56	42	57	70	55	76	81	58	79
	Sex	Female	Male	Male	Male	Male	Male	Male	Male	Male
	DM	No	No	Yes	No	Yes	No	No	Yes	No
Initial Procedure	Vessel	LCX-OM1	D2	Distal LAD	Prox. RCA	Proximal LCX	RI	Distal. RCA	LCX-OM1	Prox. LAD
(BVS implantation)	Lesion length (mm)	25	18	25	25	15	25	25	24	15
	RVD (mm)	2.75	2.5	2.5	3.5	2.5	2.5	3	2.5	3
	MLD (mm)	0.75	0.1	0.75	0.4	0.5	0.3	0.1	0	0.3
	% Stenosis	70	99	70	90	80	90	99	100	90
	Lesion type	B1	B1	B1	B1	B1	Type II ISR	Type II ISR	C	B1
	Degree of calcification	No	No	Mild	No	Mild	No	No	Mild	No
	Pre-dilatation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Scaffold length (mm)	28	18	28	28	18	28	28	28	18
	Scaffold diameter (mm) Mean= 2.66 ± 0.35 mm	2.5	2.5	2.5	3.5	2.5	2.5	2.5	2.5	3
	Post-dilatation	yes	yes	yes	yes	yes	yes	yes	yes	yes
	MLD	2.5	2.5	2.5	3.5	2	2.5	3	2.5	3
	Residual stenosis post-procedure(%)	0	0	0	0	20	0	0	0	0
	Acute again (mm)	2	2.4	1.75	3.1	16	2.2	2.9	2.5	2.7

the DCB procedure. At baseline, 6 patients had type B1 lesions, 1 type C lesion and 2 had type II ISR. Mean BVS diameter was 2.7 ± 0.35 mm and mean scaffold length was 24.7 ± 5 mm. The average time from the index procedure to scaffold failure was 12 ± 3 months. At index procedure, all the lesions were predilated by semi-compliant balloons in order to reach a <30% lesion stenosis. The mean diameter of the DCB was 2.6 ± 0.33 mm while the mean DCB length was 24.3 ± 7.8 mm (Table 2) and 3 different types of DCB were used.

Angiographic follow-up after the use of DCB was available for all the patients at a mean of 12 ± 2.6 months (Table 3). We observed two cases of DCB failure, both of them treated with Restore DCB (Cardionovum, Germany). For demonstrative purposes, 3 lesions were represented in Figs. 1–3. In particular, the first lesion was treated by 2.5 × 28 mm BVS at the LCX–OM1 bifurcation. The patient had unstable angina and coronary angiography revealed BVS failure with an 80% stenosis. This lesion was managed as mentioned by the use of 2.5 × 25 mm Restore DCB. At the scheduled angiographic follow-up we observed a recurrent 80% type III ISR, which was treated by the implantation of DES.

The other case of DCB failure the patient had received a 2.5 × 18 BVS in the proximal LCX. After 14 months angiographic follow-up performed for myocardial ischemia at stress test showed BVS failure with a 99% stenosis, and was managed by the use of one 2.5 × 20 Restore DCB. At the 6 months scheduled angiographic follow-up, the patient had type III restenosis that was managed by the implantation of 1 DES (Fig. 1).

During angiographic follow up, late lumen loss observed with DCB was 0.68 ± 0.7 mm. Clinical follow up revealed no hard clinical events.

4. Discussion

The BVS, heralded as the "fourth revolution in interventional cardiology [4], offers the possibility of transient scaffolding of the vessel to prevent acute vessel closure and recoil while eluting an antiproliferative drug to counteract the constrictive remodeling and the neointimal hyperplasia.

Absorb-BVS is the first drug-eluting BVS available for human use and is composed of PLLA and PDLLA. The bioresorbable polymer poly (L-lactide) (PLLA) scaffold is coated with a blend of the antiproliferative drug everolimus and bioresorbable polymer poly (D, L-lactide) (PDLLA) and pre-mounted on a rapid exchange (RX) scaffold delivery system. The scaffold is comprised of a series of circumferentially oriented sinusoidal rings that open during expansion. Two platinum markers are embedded at each end to enable fluoroscopic visualization, as the scaffold material is not radiopaque [5]. The first-generation of BVS was tested in the ABSORB Cohort A study, which showed late lumen enlargement, feasibility of non-invasive imaging with computed tomography (CT) scanning, and restoration of vasomotor and endothelial function at 2 years [6]. The second-generation of the device, tested in the ABSORB Cohort B, demonstrated a MACE rate of 9.0% (3 non-Q-wave MI, 6 ischemia-driven TLR, and no cardiac death) during the 2-year follow-up, with no alarming safety issues [7].

Later, Absorb II trial aimed at assessing the efficacy and safety of BVS in a broader patient population, and BVS was directly compared to Xience DES (Abbott Vascular, USA) [8]. The 3-year follow up of the trial, recently published, revealed a higher rate of target lesion failure

Table 2
Procedural details of the index procedure (Time of DCB use).

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Procedural Characteristics of the index procedure	Time from BVS implantation Mean= 12 ± 3 months	17	7	11	11	14	11	12	13	11
(DCB use)	MLD	0.5	0	0.75	1	0.3	0.75	1.09	0	0.9
	% stenosis	80	100	70	70	99	70	60	100	70
	DCB type	Restore	Elutax SV	Elutax SV	In.Pact Falcon	Restore	In.Pact Falcon	In.Pact Falcon	Elutax SV	Elutax SV
	DCB length Mean= 24.3 ± 7.8 mm	25	30	20	20	20	14	20	40	30
	DCB diameter Mean= 2.61 ± 0.33 mm	2.5	2	2.5	3	2.5	2.5	3	2.5	3
	Final MLD	2.5	2	2.5	3	2	2.5	3	2.5	3
	Final % stenosis	0	0	0	0	20	0	0	0	0

Table 3
Angiographic and clinical follow up after DCB use.

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Follow up after DCB	Time from DCB PCI (months)	7	8	8	12	6	6	15	6	11
	MLD (mm)	0.5	2	2.5	3.5	0.5	1.75	1.8	1.5	2.7
	% Stenosis	80	0	0	0	80	30	28	40	10
	Late lumen loss Mean= 0.68 ± 0.7 mm	2.25	0	0	0	2	0.75	1.2	1	0.3
	Death	No	No	No	No	No	No	No	No	No
	MI	No	No	No	No	No	No	No	No	No
	TLR	Yes	No	No	No	Yes	No	No	No	No

in the BVS group (7 vs. 3%, p = 0.07). In this trial, BVS failure was either caused by scaffold thrombosis (including 6 very late definite cases) and restenosis (11 cases at 3 years).

In terms of restenosis, many mechanisms were suggested to explain BVS failure, such as: neointimal hyperplasia, neoatherosclerosis, BVS collapse, fracture, edge phenomenon and late dismantling. In our experience, BVS failure is most likely caused by neointimal proliferation if it occurs during the first months. After the device has lost its integrity (usually after 6–12 months), contrary to metallic stents BVS failure can be also caused by scaffold recoil, although limited data are available in the literature on this topic [9]. Based on the assumption that BVS and metallic stents both share the same pathogenesis for restenosis, accordingly DCB appears to be an appealing option in this subset of patients. In our study, immediate and late angiographic success was achieved in 7 patients, all treated with latest-generation DCB. We can only speculate on the pathogenesis of BVS failure in this case series; however, the use of intravascular imaging seems to us an important tool in order to understand its etiology.

Historically, failure of re-PCI after ISR occurs in 30–70% of the cases regardless of the technique used [10,11]. In our study, DCB failure occurred in 2 patients who were both treated with Restore DCB. Nowadays, it is quite clear how all DCB were not created equal, probably because of the complex mechanisms under this technology that firstly aim at protecting paclitaxel while reaching the target lesion, and later should allow its diffusion and persistence in the vessel wall [11,12].

This case series has several limitations that need to be accounted. First, despite the complete angiographic follow up, sample size is small. Second, although clinical and angiographic outcomes are promising, the nature of this case series does not allow a comparison of different types of DCB. Larger studies, prospectively designed, with a larger population and a comparison with DES seem the best way to deeply understand if DCB may have a role for the treatment of BVS restenosis.

5. Conclusions

Management of BVS restenosis requires a deep understanding of its pathogenesis. In this case series of consecutive patients treated with DCB we suggest that this strategy is a safe and effective option to maintain the vessel patency at mid-term. Larger studies to address the etiology of BVS failure and to assess the role of DCB in such lesions are needed.

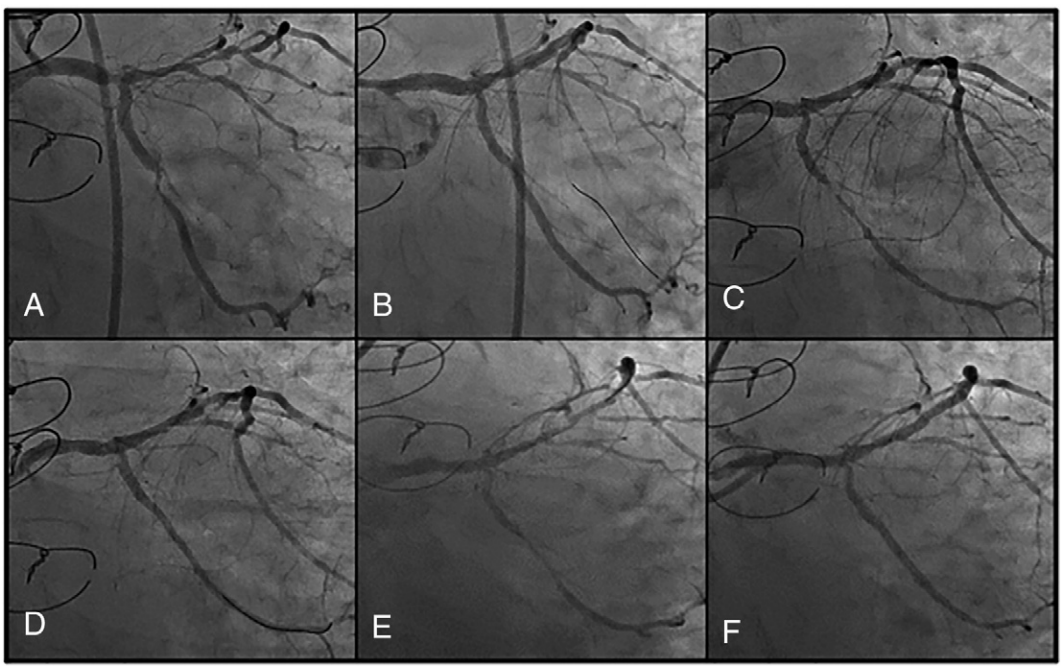


Fig. 1. A: significant stenosis at mid LCX at the initial procedure, B: result after BVS implantation. C: BVS restenosis, D: immediate angiographic result after DCB use, E: OCT revealing well apposition of the BVS, F: angiographic follow up showing DCB failure, F: OCT showing scaffold failure secondary to neointimal hyperplasia, G: angiographic result after DES implantation (Patient 1).

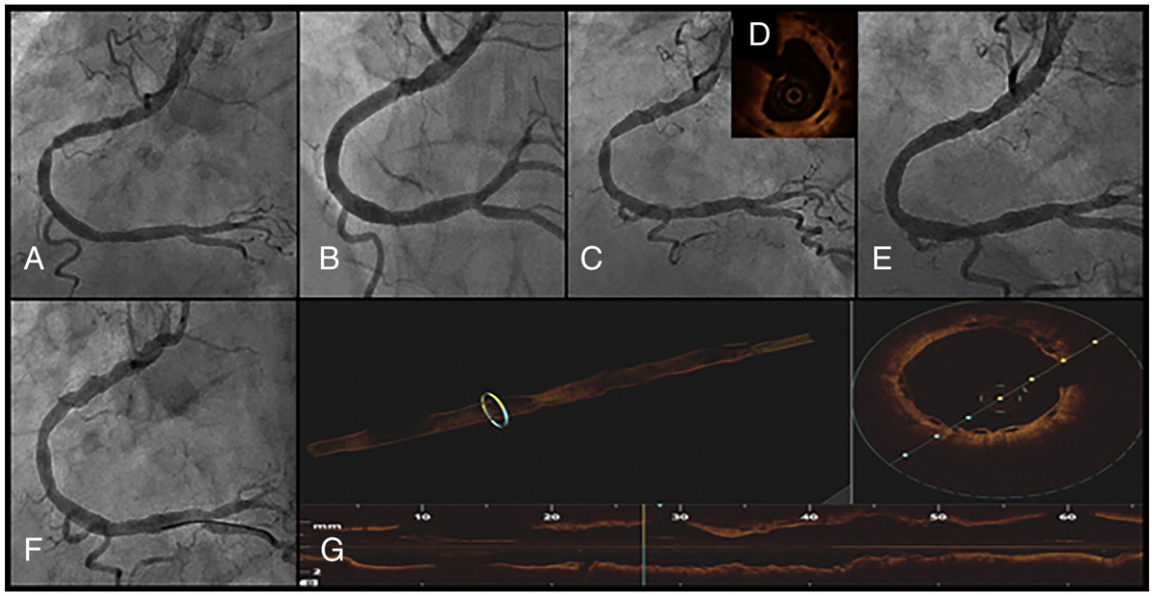


Fig. 2. A: significant stenosis at mid RCA during the initial procedure, B: angiographic result after BVS implantation, C: BVS restenosis occurred at 11 months, D: OCT analysis, showing neointimal hyperplasia within the BVS with preserved integrity of the scaffold, E: angiographic result immediately after DCB, F: angiographic follow up after 12 months, G: OCT run showing sustained good result at 12-months angiographic follow-up after DCB use (Patient 4).

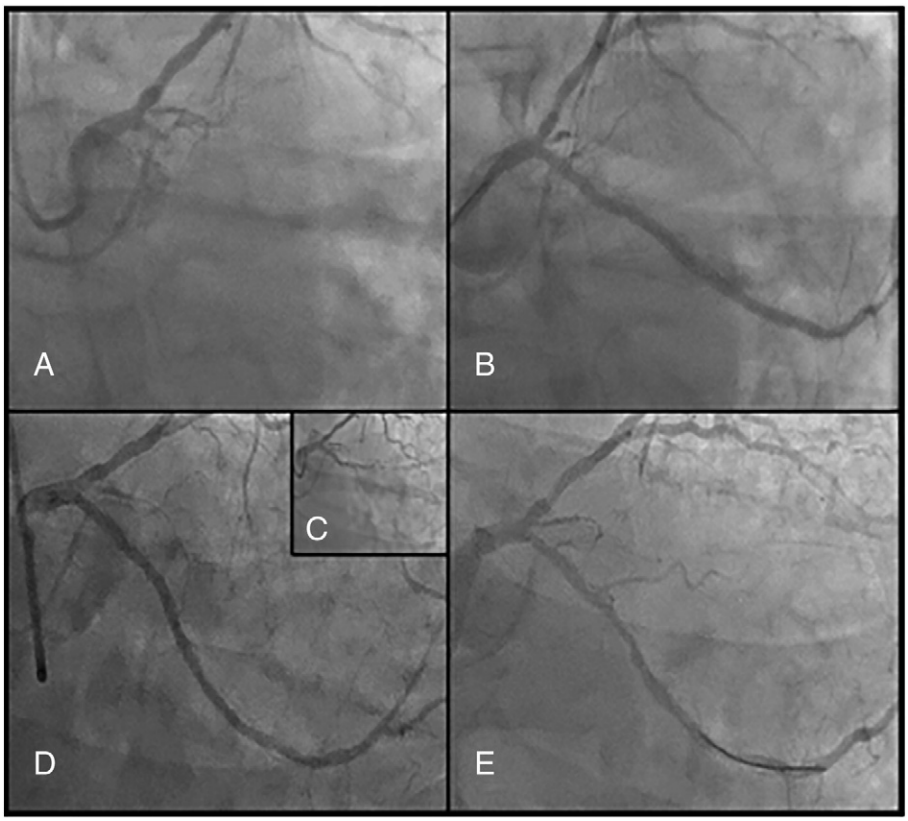


Fig. 3. A: total occlusion at the proximal LCX, B: angiographic result after BVS implantation, C: BVS restenosis occurred at 13 months, D: angiographic result after DCB use, E: angiographic follow up showing mild restenosis (Patient 8).

References

[1] Authors/Task Force membersWindecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACT guidelines on myocardial revascularization of the European society of cardiology (ESC) and the European association of cardiothoracic surgeons (EACTS). Developed with the special contribution of the European association of percutaneous cardiovascular interventions (EAPCI). Eur Heart J 2014;35:2541–619.

[2] Tanaka Akihito, Latib Azeem, Kawamoto Hiroyoshi, Jabbour Richard J, Mangieri Antonio, Pagnesi Matteo, et al. Clinical outcomes following target lesion revascularization for bioresorbable vascular scaffold failure. Catheter Cardiovasc Interv 2016; 87:8832–6.

[3] Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872–8.

[4] Onuma Y, Serruy PW. Bioresorbable scaffold: the advent of a new era in percutaneous and peripheral revascularization? Circulation 2011;123:770–99.

[5] Iqbal J, Onuma Y, Ormiston J, Abizaid A, Waksman R, Serruys P. Bioresorbable scaffolds: rationale, status, challenges, and future. Eur Heart J 2014;35:765–76.

[6] Dudek D, Onuma Y, Ormiston JA, Thuesen L, Miquel-Hebert K, Serruys PW. Four-year clinical follow-up of the ABSORB everolimus-eluting bioresorbable vascular scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention 2012;7:1060–1.

[7] Serruys PW, Onuma Y, Garcia-Garcia HM, Muramatsu T, van Geuns RJ, de Bruyne B, et al. Dynamics of vessel wall changes following the implantation of the Absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study at 6, 12, 24 and 36 months. EuroIntervention 2014;9:1271–84.

[8] Diletti R, Serruys PW, Farooq V, Sudhir K, Dorange C, Miquel-Hebert K, et al. Absorb II randomized controlled trial: a clinical a clinical evaluation to compare the safety, efficacy and performance of the Absorb Everolimus eluting bioresorbable vascular scaffold system against the Xience Everolimus eluting coronary stent system in the treatment of the subjects with ischemic heart diseasecaused by the native coronary artery lesions. Am Heart J 2012;164:654–63.

[9] Bastante T, Rivero F, Benedicto A, Cuesta J, Alfonso F. Recurrent Neoatherosclerosis after Bioresorbable vascular scaffold treatment of in-stent restenosis. JACC Cardiovasc Interv 2015;8:1264–5.

[10] Waksman R, Bhargava B, White L, Chan RC, Mehran R, Lansky AJ, et al. Intracoronary beta-radiation therapy inhibits recurrence of in-stent restenosis. Circulation 2000; 101:1895–8.

[11] Cortese B, Sgueglia GA. The future is now: comment on a recent editorial suggesting the need for a new technology in the treatment of des restenosis. JACC Cardiovasc Interv 2012;5:1093.

[12] Tarantini G, Saia F, Capranzano P, Cortese B, Mojoli M, Boccuzzi G, et al. SICI-GISE position paper: use of Absorb BVS in clinical practice. G Ital Cardiol (Rome) 2016;17: 28–44.

tctMD/the heart beat

NEWS • INTERVENTIONAL | TCT 2019

PICCOLETO II: More Support for DCB Safety and Efficacy in Small Coronaries

In-lesion late lumen loss was similar for a gel-based balloon versus an EES, but a trend was seen for more thrombosis with the stents.

By L.A. McKeown October 04, 2019

SAN FRANCISCO, CA—A new gel-based paclitaxel drug-coated balloon (DCB) outperformed an everolimus-eluting stent (EES) in terms of late lumen loss and resulted in comparable diameter stenosis, binary restenosis, and short-term clinical outcome in patients with small-vessel CAD, results from PICCOLETO II suggest.

Presenting here at TCT 2019, Bernardo Cortese, MD (Clinica San Carlo, Milan, Italy), said that although the study is small and not powered for hard endpoints, it adds to existing data hinting that drug delivery via a balloon may optimize outcomes better in small vessels than a stent.

"The best-in-class drug-eluting stents show a rate of target lesion failure

This website uses cookies to ensure you get the best experience on our website. Read More

GOT IT

the superiority of DCB in terms of angiographic outcome," he told TCTMD.

PICCOLETO II is the latest trial to show DCB as a potential alternative to DES in patients with small-diameter lesions. At EuroPCR 2019, investigators from the BASKET-SMALL 2 trial presented new angiographic data showing similar late lumen loss with both treatments out to 1 year. Surprisingly, the angiographic data also showed eight cases of stent thrombosis in the DES group versus no complete thrombotic vessel occlusions in the DCB group. The PICCOLETO II data line up with those results.

"Similarly, we found a 1.8% rate of stent thrombosis in the EES arm, and no thrombosis in the DCB arm," Cortese told TCTMD. "We thus confirm the findings of BASKET-SMALL 2. The opportunity not to leave a stent in small vessels may protect from thrombotic events."

Gel May Improve Drug Delivery

PICCOLETO II is a follow up to the PICCOLETO study, in which patients with stable or unstable angina undergoing PCI of small coronary vessels (≤ 2.75 mm) were randomized to the Dior DCB (Eurocor) or Taxus DES (Boston Scientific).

As Cortese explained to TCTMD, the first study used a balloon that had paclitaxel sprayed onto the surface. The drug was lost during transit and manipulation, which the researchers believed prevented it from having the desired effect. For PICCOLETO II, they instead used the Elutax SV (Aachen Resonance), "a new-generation DCB with a gel which protects and mostly helps [paclitaxel] to be delivered to the vessel wall, and persist there for 4 to 6 weeks in order to obtain its effect," Cortese noted. The gel is hydrophilic, which is intended to help the drug stay on the balloon longer and prolong the absorption time. The paclitaxel dose on the balloon is 2.2 µg/мм^2 .

For the multicenter, open-label trial, 118 patients similar to those in the earlier PICCOLETO trial were randomized to the DCB and 114 to the Xience EES (Abbott Vascular). Predilatation was strongly recommended for both strategies, with at least a 30- to 60-second dilatation of the balloon but no specific advice for the EES.

Aside from a higher percentage of renal failure patients in the EES group, there were no significant baseline differences between the two arms. More than half of patients in each group had stable angina and about 20%

This website uses cookies to ensure you get the best experience on our website. Read More
GOT IT

Predilatation was performed in 69% of the EES group and 84% of the DCB group, while postdilatation was performed in nearly 60% of the EES group and only 3% of the DCB group ($P = 0.001$). The number of devices used in the DCB group was lower than in the EES arm, but length of devices was a bit longer (8.2 mm vs 6.9 mm; $P = 0.04$).

At 6 months, in-lesion late lumen loss, the primary endpoint, was 0.17 ± 0.39 mm in the EES group and 0.04 ± 0.28 mm in the DCB group, meeting noninferiority criteria for the balloon ($P = 0.03$). There were no significant differences in clinical outcomes, although a trend was seen toward higher TLR in the DCB group ($P = 0.23$).

Minimum lumen diameter, a secondary endpoint, increased more in the DES group (from 0.83 mm before the procedure to 2.29 mm after the procedure) than in the DCB group (0.82 mm to 1.89 mm). Percent diameter stenosis changes, however, were similar in both arms. Other secondary endpoints of percent diameter stenosis and binary restenosis were similar between the treatment arms at 6 months (both in-stent and in-segment).

Smaller Lesions, Bigger Payoff With DCBs?

According to Cortese, the PICCOLETO II outcomes with regard to late lumen loss are among the best so far in small-vessel disease, a setting that includes studies such as PEPCAD SVD, BELLO, RESTORE SVD, and FASICO NATIVES.

Discussant Fernando Alfonso, MD, PhD (Hospital Universitario La Princesa. Madrid, Spain), said he was “nicely surprised” by the results of PICCOLETO II.

In theory, as you go smaller and smaller, the benefits of non-scaffold-based therapy might be even greater," added discussant Robert M. Bersin, MD (Swedish Heart & Vascular, Kirkland, WA). “Have you broken this down to the very small [lesion] subsets, like 2.22 mm and smaller to see whether or not you get a signal of superiority with DCB? Overall you have equivalence here, but you may even be superior the smaller you go.”

Cortese responded that the study is a proof-of-concept, and while that possibility does exist, it remains to be shown in future trials.

Given that the drug on the balloon is paclitaxel and that a meta-analysis recently turned the endovascular community on its head with suggestion that this drug may increase mortality when used to treat PAD, Cortese told TCTMD that long-term follow up of patients will be conducted “even if all the studies performed in the coronary arena till now never gave

This website uses cookies to ensure you get the best experience on our website. Read More

GOT IT

Sources

Cortese B. Drug-coated balloon vs drug eluting stent for small coronary vessel disease: 6-mo primary outcome of the PICCOLETO II randomized clinical trial. Presented at: TCT 2019. September 27, 2019. San Francisco, CA.

Disclosures

Cortese reports consulting for Abbott Vascular, Astra Zeneca, Kardia, Innova, Stentys, Daiichi Sankyo, Philips-Spectranetics, Reva, Bayer, and Cardinal; honorarium from Amgen, Stentys, Sanofi, B. Braun, Servier, and Alvimedica; and institutional research/grant support from AB Medica, St Jude, and Abbott.

TCTMD is produced by the Cardiovascular Research Foundation (CRF). CRF is committed to igniting the next wave of innovation in research and education that will help doctors save and improve the quality of their patients' lives. For more information, visit http://www.crf.org.

This website uses cookies to ensure you get the best experience on our website. Read More

GOT IT

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 9, 2023
© 2023 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

NEW RESEARCH PAPER

CORONARY

Long-Term Outcome of Drug-Coated Balloon vs Drug-Eluting Stent for Small Coronary Vessels

PICCOLETO-II 3-Year Follow-Up

Bernardo Cortese, MD,[a,b] Gabriella Testa, MD,[c] Fernando Rivero, MD,[d] Andrea Erriquez, MD,[e] Fernando Alfonso, MD[d]

ABSTRACT

BACKGROUND Native vessel coronary artery disease represents 1 of the most attractive fields of application for drug-coated balloons (DCBs). To date, several devices have been compared with drug-eluting stents (DESs) in this setting with different outcomes.

OBJECTIVES The authors sought to compare the short- and long-term performance of the paclitaxel DCB with the everolimus-eluting stent in patients with de novo lesions in small coronary vessel disease.

METHODS PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) was an academic, international, investigator-driven, multicenter, open-label randomized clinical trial in which patients were allocated to a DCB (n = 118) or DES (n = 114). We previously reported the superiority of DCBs regarding in-lesion late lumen loss at 6 months. Herein we report the final 3-year clinical follow-up with the occurrence of major adverse cardiac events (MACEs), a composite of cardiac death, nonfatal myocardial infarction, target lesion revascularization, and its individual components.

RESULTS The 3-year clinical follow-up (median 1,101 days; IQR: 1,055-1,146 days) was available for 102 patients allocated to DCB and 101 to DES treatment. The cumulative rate of all-cause death (4% vs 3.9%; $P = 0.98$), cardiac death (1% vs 1.9%; $P = 0.56$), myocardial infarction (6.9% vs 2%; $P = 0.14$), and target lesion revascularization (14.8% vs 8.8%; $P = 0.18$) did not significantly differ between DCBs and DESs. MACEs and acute vessel occlusion occurred more frequently in the DES group (20.8% vs 10.8% [$P = 0.046$] and 4% vs 0% [$P = 0.042$], respectively).

CONCLUSIONS The long-term clinical follow-up of the PICCOLETO II randomized clinical trial shows a higher risk of MACEs in patients with de novo lesions in small vessel disease when they are treated with the current-generation DES compared with the new-generation paclitaxel DCB. (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment [PICCOLETO II]; NCT03899818) (J Am Coll Cardiol Intv 2023;16:1054–1061) © 2023 by the American College of Cardiology Foundation.

From the [a]Fondazione Ricerca e Innovazione Cardiovascolare, Milan, Italy; [b]DCB Academy, Milano, Italy; [c]Policlinico Universitario P. Giaccone, Palermo, Italy; [d]Cardiology Department, Hospital Universitario de la Princesa, Universidad Autonoma de Madrid, Madrid, Spain; and the [e]Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Cona, Italy.

Arnold Seto, MD, served as Guest Editor for this paper. H. Vernon "Skip" Anderson, MD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 20, 2022; revised manuscript received January 30, 2023, accepted February 12, 2023.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2023.02.011

In the last decade, the necessity of developing newer therapies to mitigate the potential risk of long-term adverse events after percutaneous coronary interventions (PCIs) has emerged. Although drug-eluting stents (DESs) represented a terrific improvement from the technological point of view, leading to the treatment of theoretically any complex coronary anatomy,[1] their performance in some lesion settings, including small vessel disease (SVD), is lower and associated with an almost 2-fold risk of target lesion failure (TLF) at 1 year.[2-4] Moreover, with the currently available DESs, the long-term fate remains associated with a low but constant increase in adverse events.[5] In this regard, some devices have been developed aimed at reducing late-occurring adverse events. Among them, drug-coated balloons (DCBs) have been increasingly adopted for de novo coronary lesions, particularly in SVD.

Several DCBs have been tested in the native coronary artery disease setting with good angiographic and clinical results compared with first- or second-generation DESs,[6-8] but only a few of them have long-term clinical data available.

The aim of PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) was to test the long-term efficacy and safety of 1 of the latest-generation paclitaxel DCBs in comparison with 1 of the most widely used DESs (Xience everolimus-eluting stent, Abbott Vascular) in patients with de novo SVD.

METHODS

STUDY DESIGN AND POPULATION. PICCOLETO II (NCT03899818) is an academic, investigator-driven, randomized, multicenter, open-label, clinical trial performed at 5 European centers. The study protocol was presented and approved at the coordinating center (ASST Fatebenefratelli-Sacco), and all participating centers' ethics committees in 2015. Patients included in this study were enrolled between May 2015 and May 2018. The protocol was designed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All participants provided written informed consent before being enrolled in the study.

We included patients hospitalized either for stable or unstable coronary artery disease scheduled for PCI. The angiographic inclusion criterion was native coronary vessel disease with a reference diameter between 2 and 2.75 mm and stenosis >70% (by investigator's judgment and visual estimation). The exclusion criteria have been reported elsewhere.[6] In brief, they are recent ST-segment elevation myocardial infarction (<48 hours), highly calcific coronary artery, highly tortuous target vessel, index lesion located in the left main trunk, aorto-ostial lesion, previous stent implantation at target vessel, target lesion with chronic total occlusion or longer than 25 mm, high thrombus burden, and target lesion involving a major bifurcation. Figure 1 shows the study flowchart.

INTERVENTION. The open-label randomization was performed just after coronary angiography, and patients were randomized 1:1 between the DCB (Elutax SV) and the DES (Xience everolimus-eluting stent), allowing 1 single lesion per patient. In case of the necessity of additional lesion treatment, this should have been performed before the study lesion with any device deemed necessary by the operator. The study protocol strongly encouraged predilatation with any device in both arms in order to ensure optimal angiographic results. The DCB inflation time had to be at least 30 seconds. If the lesion preparation or the DCB in the DCB arm led to major, flow-limiting dissection or vessel recoil, the investigator was allowed to implant a DES as a bailout. Conversely, investigators were encouraged not to stent the type A-B coronary dissections according to previous experiences. In case of bailout stenting, the protocol suggested using stents shorter than the DCB previously used.

The PCI procedure and antithrombotic agent used were performed according to current European Society of Cardiology guidelines.[9] The subsequent antithrombotic regimen in the DCB arm followed the GISE (Italian Society of Interventional Cardiology) Consensus Document with a minimum of 30 days of dual antiplatelet treatment in case of stable coronary artery disease and 6 to 12 months in case of acute patients. In DES-treated patients, we followed the European guidelines with a minimum of 6 months of dual antiplatelet therapy (12 months in acute coronary syndrome patients).

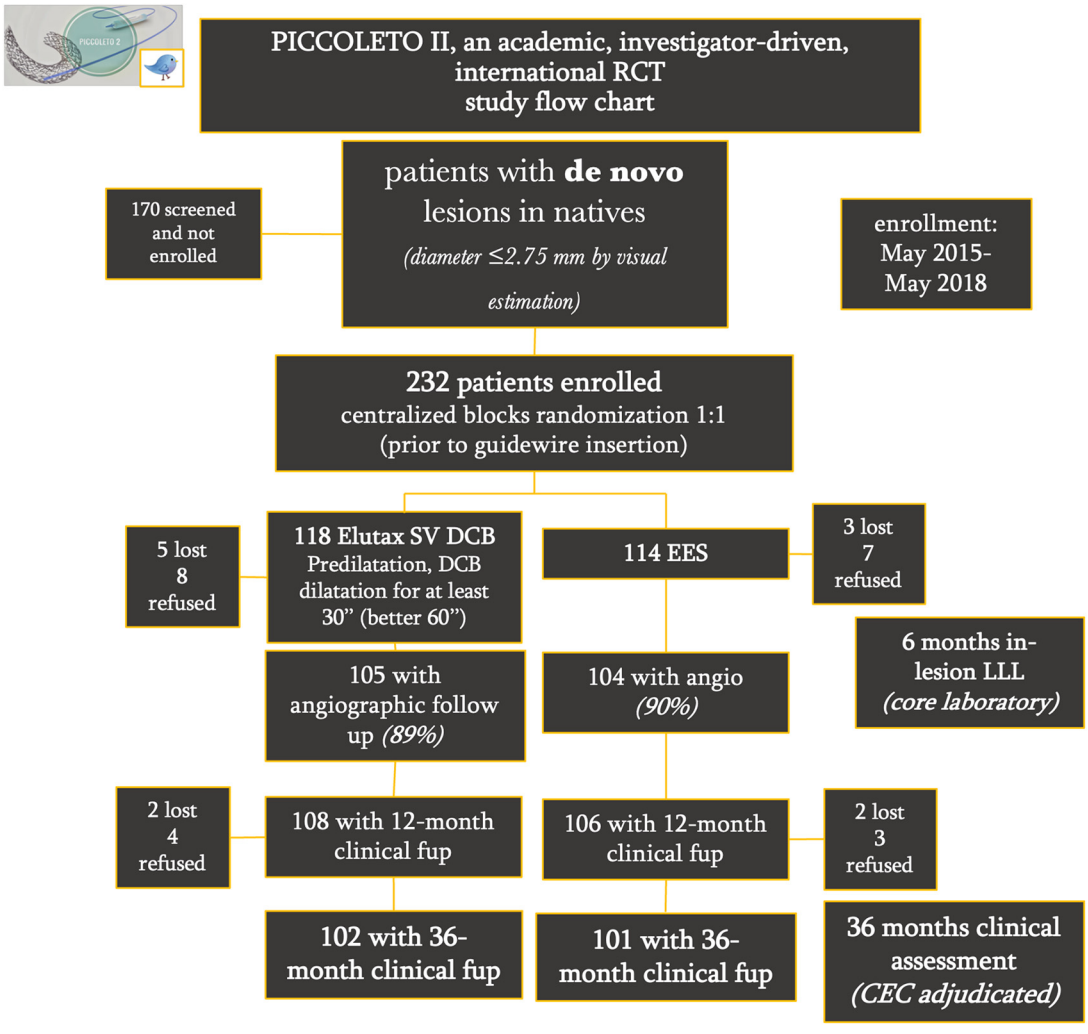
STUDY DEVICE. The technical characteristics of the study devices have been described previously.[10] This DCB elutes paclitaxel loaded on a folded balloon at a dosage of ≅2.2 μg/mm^2 (tolerance of 1.4-3.00 μg/mm^2). The drug is added with the matrix dextran aiming at preserving paclitaxel delivery to the vessel wall, ensuring tissue persistence for the following days.[10]

STUDY ENDPOINTS. The primary endpoint of this study was the angiographic in-lesion late lumen loss (LLL) assessed by an independent core laboratory

ABBREVIATIONS AND ACRONYMS

DCB = drug-coated balloon
DES = drug-eluting stent
LLL = late lumen loss
MACE = major adverse cardiovascular event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
SVD = small vessel disease
TLF = target lesion failure
TLR = target lesion revascularization

FIGURE 1 Study Flowchart and Follow-Up of PICCOLETO II Study



CEC = clinical events committee; DCB = drug-coated balloon; EES = everolimus eluting stent(s); fup = follow-up; LLL = late lumen loss; SV = small vessel.

(University of Ferrara), and noninferiority was hypothesized. The other study endpoints were procedural success, which was defined as angiographic success and the absence of in-hospital cardiovascular complications, and major adverse cardiovascular events (MACEs), a composite of cardiac death, all myocardial infarctions (MIs), target lesion revascularization (TLR), and the individual components of MACEs at 1 and 3 years. All clinical events have been censored and assessed by an independent clinical events committee after blindly reviewing all documents. The 3-year clinical follow-up was prespecified in the study protocol.

STATISTICAL ANALYSIS. The study hypothesis was that the DCB was noninferior to the DES in terms of in-lesion LLL. Accordingly, we assumed an LLL of 0.20 mm in the DES arm with a delta of 0.35, alpha of 5%, power of 90%, and a noninferiority margin of 0.25 mm. Thus, a total of 230 patients to be enrolled in the PICCOLETO II trial, including a possible attrition rate of 10%, was calculated. Cox proportional hazards models and Kaplan-Meier curves were used to analyze time-related events. HRs were presented with 95% CIs. For baseline characteristics, continuous variables were reported as mean ± SD (Mann-Whitney *U* test) and categoric variables as frequency with

TABLE 1 Clinical Characteristics of the Study Population at Baseline

	DES (n = 114)	DCB (n = 118)	*P* Value
Male	87 (76.9)	83 (70.3)	0.25
Age, y	66 (50-82)	64 (48-80)	0.32
Hypertension	76 (67.2)	77 (65.2)	0.74
Diabetes	40 (35.4)	45 (38)	0.65
Insulin-dependent diabetes	15 (13.3)	21 (17.8)	0.66
Smoke	19 (16.7)	23 (19.5)	0.84
Dyslipidemia	63 (55)	72 (61)	0.66
Renal failure (eGFR <60 mL/min)	12 (10.6)	4 (3.3)	0.03
Previous MI	34 (30)	45 (38)	0.19
Previous CABG	4 (3.5)	4 (3.3)	0.95
Previous PCI	60 (53)	59 (50)	0.33
LVEF	58 [7]	58 [10]	0.89
Clinical presentation			
Stable angina	63 (55.7)	64 (54.2)	0.81
Unstable angina	18 (16)	17 (14.4)	0.74
NSTEMI	23 (20.3)	25 (21.1)	0.87
STEMI, late comers	9 (8)	12 (10.3)	0.34

Values are n (%) or median (IQR) unless otherwise indicated.

CABG = coronary artery bypass grafting; DCB = drug-coated balloon; DES = drug-eluting stent; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Lesion Characteristics and Procedural Aspects

	DES (n = 114)	DCB (n = 118)	*P* Value
SYNTAX score	17 [12]	16 [11]	0.36
Bifurcation lesion	14 (12.3)	15 (12.7)	0.94
Multivessel disease	86 (76)	86 (72.8)	0.5
Target vessel LAD	44 (39)	47 (40)	0.31
Target vessel LCX	35(31)	44 (37.2)	0.12
Target vessel RCA	34 (30.2)	27 (22.8)	0.19
Total contrast use, mL	155 [67-289]	152 [75-301]	0.37
Total fluoroscopy time, min	11 [4-67]	13 [5-59]	0.22
Predilatation	78 (69)	99 (84)	0.007
Postdilatation	66 (59.4)	4 (3.3)	0.001
Scoring balloon use for lesion preparation	18 (15.8)	26 (22)	0.13
Number of devices used	1.12 [1-1.41]	1.03 [1-1.12]	0.004
Length of device used, mm	18.3 ± 6.9	21.8 ± 8.2	0.006
Mean inflation pressure, atm	13.7 ± 2.5	11.4 ± 3.3	0.03
Mean duration of inflation, s	21.4 ± 11.8	49.2 ± 14.5	0.002
Bailout stenting	–	8 (6.7)	–
Angiographic success	113 (99.1)	116 (98.3)	0.88
Procedural success	112 (98.2)	116 (98.3)	0.92
Intracoronary imaging use	11 (9.6)	12 (10.2)	0.62
Peak troponin I after the intervention, ng/mL	6.14 ± 5.80	3.6 ± 3.21	0.09

Values are mean ± SD or n (%) unless otherwise indicated.

LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; other abbreviations as in Table 1.

percentage, with 95% CIs determined by the Wilson score method. Adjusted odds ratios were calculated with the logistic regression model and the HR with the Cox model. All analyses were performed by intention-to-treat. All *P* values <0.05 were considered statistically significant. All statistical analyses were performed with SPSS software (version 26, SPSS, Inc).

RESULTS

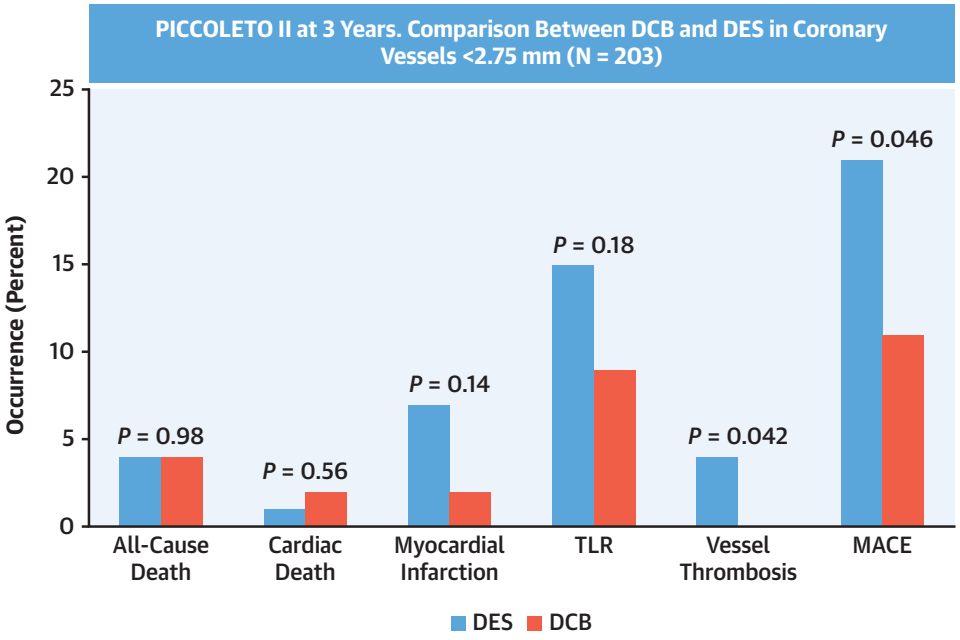
Of the 232 patients enrolled in the study, 114 patients were allocated to the DES and 118 to the DCB group. Importantly, group allocation was performed before lesion preparation. Significant differences between groups regarding the main clinical characteristic of the population enrolled were not observed (Table 1). Table 2 describes the procedural characteristics, with more patients undergoing lesion predilatation in the DCB arm and longer devices used in the DCB arm. The bailout stenting rate, which was always performed with the DES, was only 6.7%.

We previously reported the primary endpoint of the PICCOLETO II study, which showed the superiority of the DCB vs the DES in terms of in-lesion LLL (0.04 ± 0.28 mm vs 0.17 ± 0.39 mm; $P = 0.03$).[6] Other angiographic and procedural parameters were not significantly different between the 2 study groups as well as the 12-month clinical outcome.[6]

After a median of 1,101 days (IQR: 1,055-1,146 days), 102 patients (86%) in the DCB arm and 101 (88.5%) in the DES arm underwent the scheduled clinical follow-up or had available clinical information. All-cause mortality occurred in 4 patients per group ($P = 0.98$); 2 patients died of cardiac causes in the DCB group (1 fatal MI not related to the target vessel and 1 end-stage heart failure) and 1 in the DES group (unexplained and unwitnessed sudden death) ($P = 0.56$). Four cases of target vessel thrombosis in the DES arm and none in the DCB arm ($P = 0.042$) were observed. TLR was not significantly lower in the DCB arm (9 patients [8.8%] vs 15 [14.8%] in the DES arm; $P = 0.18$). The MACE rate (ie, the primary endpoint of the present study) was significantly lower in the DCB arm compared with the DES arm (n = 11 [10.8%] vs n = 11 [20.8%]; $P = 0.046$) (Central Illustration, Table 3).

Figure 2 depicts the Kaplan-Meier curves of MACEs according to treatment allocation for the entire length of follow-up.

CENTRAL ILLUSTRATION **Long-Term Study Findings**



Cortese B, et al. J Am Coll Cardiol Intv. 2023;16(9):1054–1061.

Comparison between drug-coated balloons (DCBs) and drug-eluting stents (DES) in coronary vessels <2.75 mm. MACE = major adverse cardiac event(s); PICCOLETO II = Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment; TLR = target lesion revascularization.

DISCUSSION

SUMMARY OF THE STUDY RESULTS. PICCOLETO II was a multicenter, multinational, open-label investigator-driven, randomized clinical trial aiming at assessing the short angiographic performance of a novel paclitaxel DCB and its long-term outcome compared with a new-generation DES. The similar angiographic performance of the 2 strategies (but superiority in the case of the primary endpoint LLL for the DCB) was previously reported. The results of the latest clinical follow-up of PICCOLETO II, herewith presented, confirm the safety and the efficacy of this device with DCB, showing for the first time a significant reduction in MACEs and target vessel thrombosis at 3 years compared with the modern DES.

LONG-TERM EVENTS WITH DESs. The currently available DESs are highly performing devices in terms of safety and efficacy. However, in the very long-term, they still remain associated with a very low but constant risk of adverse events such as TLF every year. In a recently reported very long-term outcome study, this event rate with current DESs eventually reached 43.8% after 10 years, with a yearly rate of 3.3% after year 1.[5] On top of this, in the case of more complex lesion subsets, such as SVD or in case of long stenting, this late failure can lead to a 2-fold rate in TLF.[2-4] The current patient population routinely treated in all catheterization laboratories shares a high bleeding risk, a phenomenon also associated with higher rates of adverse clinical events after DESs.[11]

COULD DCB PREVENT LONG-TERM EVENTS?. Theoretically, DCB angioplasty could be associated with a flattening of the adverse event curve in the long-term because this technology does not require any prosthesis implantation, and DESs are associated with adverse events, probably related to the permanent metallic prosthesis itself. Moreover, some paclitaxel DCBs have shown a late positive vessel remodeling effect when used in native vessel disease, eventually leading to an LLL proximal to 0 mm.[12,13]

TABLE 3 Clinical Outcome After 3 Years (Kaplan-Meier Estimates)

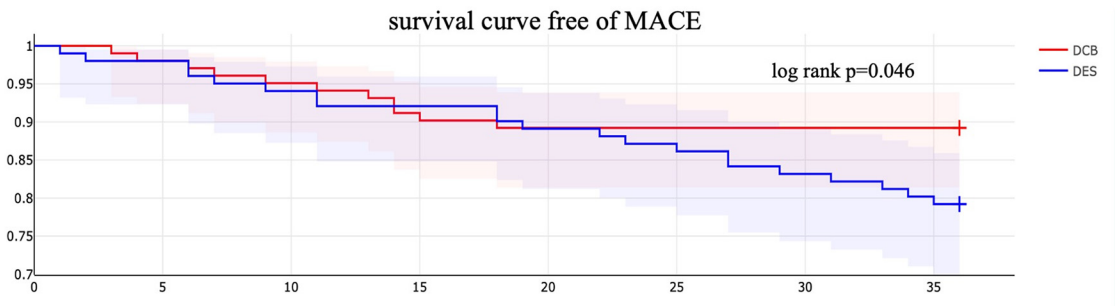
	DES (n = 101)	DCB (n = 102)	*P* Value
All-cause death	4 (3.96)	4 (3.92)	0.98
Cardiac death	1 (1)	2 (1.96)	0.56
Myocardial infarction	7 (6.9)	2 (1.96)	0.14
TLR	15 (14.8)	9 (8.8)	0.18
Vessel thrombosis	4 (3.96)	0	0.042
MACE	21 (20.8)	11 (10.8)	0.046

Values are n (%) unless otherwise indicated.
MACE = major adverse cardiac event(s); TLR = target lesion revascularization; other abbreviations as in Table 1.

Of note, this effect can be particularly appealing in small- or midsize vessels like the ones treated in the current study. Other studies have previously shown a drastic reduction in TLF after the first 9 to 12 months after DCB application. In the BELLO (Balloon Elution and Late Loss Optimization) randomized trial, the In-Pact Falcon paclitaxel DCB (Invatec-Medtronic) showed a significant reduction in the rate of MACEs compared with first-generation DESs (14% vs 30%; $P = 0.015$) with very few events after 7 months from the index procedure.[14] Similarly, a meta-analysis of 4,590 patients treated with the paclitaxel DCB vs other treatment options showed reduced rates of cardiac (risk ratio [RR]: 0.53; 95% CI: 0.33-0.85; $P = 0.009$) and total (RR: 0.73; 95% CI: 0.53- 1.00; $P = 0.047$) mortality with few adverse events after 12 months.[15] The long-term follow-up of PICCOLETO II shows a divergence between the curve of events after 20 months, with an almost straight line in the DCB arm. It is difficult to speculate on the behavior of the DCB after the first months from intervention, with 1 possibility being the quiescence of any effect related to a DCB PCI, compared with some detrimental effects of the permanent prostheses implanted on the vessel wall at the long-term clinical follow-up. However, the findings of this report should be put into the context of a study not powered for clinical endpoints, with 14% of patients lost at follow-up and with more patients with renal failure (glomerular filtration rate <60 mL/min) in the DES arm. Moreover, the low use of intravascular imaging (10% in each group) might be responsible for a higher risk of stent underexpansion, leading to a higher risk of stent thrombosis.

MORTALITY AFTER DCB USE. A few years ago a meta-analysis shed light on a hypothetical increase in mortality after paclitaxel application for peripheral interventions.[16-19] Conversely, a meta-analysis on "coronary" applications for DCBs and other large reports and data sets showed no association between paclitaxel DCB use and mortality.[15,20] The 3-year outcome of the BASKET SMALL II (Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs Drug Eluting Stents in Small Vessel Interventions) study shows similar cardiac (HR: 1.29; 95% CI: 0.63-2.66; $P = 0.49$) and all-cause mortality (HR: 1.05; 95% CI: 0.62-1.77; $P = 0.87$) between DCBs and DESs.[21] Our current 3-year findings reported here further confirm the lack of any association between all-cause mortality and paclitaxel application in the coronary field, with 4 cases both in the DCB and the DES arm but none of them related to a potentially toxic effect of

FIGURE 2 Kaplan-Meier Curves of the Study Endpoint MACEs According to Treatment Allocation for the 3-Year Follow-Up



number at risk								
group DES	114	108	99	98	95	90	85	80
group DCB	118	116	105	102	101	96	95	91

MACE = major adverse cardiac event(s); other abbreviations as in Figure 1.

this drug in other organs. All these findings corroborate the thesis that a correlation between the currently available paclitaxel DCB and mortality does not exist in the coronary field.

STUDY LIMITATIONS. As previously stated,[6] this study has several limitations. First, treatment assignment was performed in an open-label fashion; thus, biases in the initial reports and the clinical follow-up cannot be completely eliminated despite the blinded clinical event committee and the independent core laboratory used. Second, the selection of centers to participate in PICCOLETO II was done according to a 5-year experience using DCBs for native vessel disease, which was also reflected by the low bailout stenting rate; thus, such results might not be reproducible in other settings. Another limitation is that we decided to include the MACE rate as the cumulative secondary endpoint instead of target vessel failure, with the inherent limitation of including MI and not target vessel MI as an endpoint. At the time of protocol drafting, we did not expect a major role determined by this endpoint at the long-term follow-up. Finally, and most importantly, we report a 3-year clinical outcome that was prespecified in the study protocol, but the study design and the final population were not powered enough for drawing definitive conclusions on the long-term clinical outcome. A study including a larger population and an ad hoc clinical primary endpoint is necessary to confirm our preliminary findings.

CONCLUSIONS

PICCOLETO II long-term data show for the first time a reduction in late adverse clinical events with DCBs compared with current era DESs in de novo lesions, mainly driven by a reduction of vessel thrombosis and MACEs after 1 year with DCBs. An adequately powered study should be conducted to confirm these preliminary findings.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

PICCOLETO II is an investigator-driven study endorsed by the Italian Society of Interventional Cardiology GISE. The role of GISE was to coordinate the centers and submit the protocol to the ethics committees. GISE had no other role, including protocol drafting, data analysis, and manuscript writing. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Bernardo Cortese, Fondazione Ricerca e Innovazione Cardiovascolare Milano, Via Vico, 2 Milano, Italy. E-mail: bcortese@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? Small vessel coronary artery disease still represents a challenging subset for DESs with an increase in long-term adverse events.

WHAT IS NEW? This is the first randomized study between the new-generation DCB vs the DES in small vessels to show 1) an improved angiographic outcome at 6 months and 2) reduced clinical events (MACEs and acute vessel closure) after 3 years.

WHAT IS NEXT? A larger study adequately powered for hard clinical endpoints is needed in order to confirm these findings in a larger data set of patients.

REFERENCES

1. Chichareon P, Katagiri Y, Asano T, et al. Mechanical properties and performances of contemporary drug-eluting stent: focus on the metallic backbone. *Expert Rev Med Devices*. 2019;16(3):211-228. https://doi.org/10.1080/17434440.2019.1573142

2. Claessen BE, Smits PC, Kereiakes DJ, et al. Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) randomized trials. *J Am Coll Cardiol Intv*. 2011;4(11):1209-1215. https://doi.org/10.1016/j.jcin.2011.07.016

3. van der Heijden LC, Kok MM, Danse PW, et al. Small-vessel treatment with contemporary newer-generation drug-eluting coronary stents in all-comers: insights from 2-year DUTCH PEERS (TWENTE II) randomized trial. *Am Heart J*. 2016;176:28-35. https://doi.org/10.1016/j.ahj.2016.02.020

4. van der Heijden LC, Kok MM, Löwik MM, et al. Three-year clinical outcome of patients with coronary disease and increased event risk treated with newer-generation drug-eluting stents: from the randomized DUTCH PEERS trial. *Cardiology*. 2017;137(4):207-217. https://doi.org/10.1159/000464320

5. Kufner S, Ernst M, Cassese S, et al. 10-year outcomes from a randomized trial of polymer-free versus durable polymer drug-eluting coronary stents. *J Am Coll Cardiol*. 2020;76(2):146-158. https://doi.org/10.1016/j.jacc.2020.05.026

6. Cortese B, Di Palma G, Guimaraes MG, et al. Drug-coated balloon versus drug-eluting stent for small coronary vessel disease: PICCOLETO II randomized clinical trial. *J Am Coll Cardiol Intv*. 2020;13(24):2840-2849. https://doi.org/10.1016/j.jcin.2020.08.035

7. Tang Y, Qiao S, Su X, et al. Drug-coated balloon versus drug-eluting stent for small-vessel disease: the RESTORE SVD China randomized trial. *J Am Coll Cardiol Intv*. 2018;11(23):2381-2392. https://doi.org/10.1016/j.jcin.2018.09.009

8. Jeger RV, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease

(BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet*. 2018;392(10150):849–856. https://doi.org/10.1016/S0140-6736(18)31719-7

9. Kolh P, Windecker S. ESC/EACTS myocardial revascularization guidelines 2014. *Eur Heart J*. 2014;35(46):3235–3236. https://doi.org/10.1093/eurheartj/ehu422

10. Cortese B, D'Ascenzo F, Fetiveau R, et al. Treatment of coronary artery disease with a new-generation drug-coated balloon: final results of the Italian Elutax SV rEgistry-DCB-RISE. *J Cardiovasc Med (Hagerstown)*. 2018;19(5):247–252. https://doi.org/10.2459/JCM.0000000000000632

11. Cortese B, Sanchez-Jimenez E. Back to the future: DCB use instead of DES for the treatment of complex, native coronary artery disease. *Eur Heart J Suppl*. 2021;23(Suppl E):E63–E67. https://doi.org/10.1093/eurheartj/suab091

12. Cortese B, Silva Orrego P, Agostoni P, et al. Effect of drug-coated balloons in native coronary artery disease left with a dissection. *J Am Coll Cardiol Intv*. 2015;8(15):2003–2009. https://doi.org/10.1016/j.jcin.2015.08.029

13. Kleber FX, Schulz A, Waliszewski M, et al. Local paclitaxel induces late lumen enlargement in coronary arteries after balloon angioplasty. *Clin Res Cardiol*. 2015;104(3):217–225. https://doi.org/10.1007/s00392-014-0775-2

14. Latib A, Ruparelia N, Menozzi A, et al. 3-year follow-up of the Balloon Elution and Late Loss Optimization Study (BELLO). *J Am Coll Cardiol Intv*. 2015;8(8):1132–1134. https://doi.org/10.1016/j.jcin.2015.04.008

15. Scheller B, Vukadinovic D, Jeger R, et al. Survival after coronary revascularization with paclitaxel-coated balloons. *J Am Coll Cardiol*. 2020;75(9):1017–1028. https://doi.org/10.1016/j.jacc.2019.11.065

16. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7(24):e011245. https://doi.org/10.1161/JAHA.118.011245

17. Cortese B, Granada JF. Mortality increase and paclitaxel-coated device use: a plausible but inconclusive hypothesis. *J Am Coll Cardiol Intv*. 2019;12(24):2538–2540. https://doi.org/10.1016/j.jcin.2019.10.044

18. Cortese B, Alfonso F, Pellegrini D, Sing KR, Granada JF. The hypothesis of an increased mortality following paclitaxel coated device use in peripheral vascular interventions (and the emerging era of meta-analysis based evidence). *Catheter Cardiovasc Interv*. 2020;95(2):329–331. https://doi.org/10.1002/ccd.28600

19. Fanelli F, Cortese B, Zeller T. Use of paclitaxel-eluting technologies in the femoropopliteal segment under scrutiny over possible link to late all-cause mortality: time to panic or an opportunity to resurge? *J Endovasc Ther*. 2019;26(1):41–43. https://doi.org/10.1177/1526602818824682

20. Sanz Sánchez J, Chiarito M, Cortese B, et al. Drug-coated balloons vs drug-eluting stents for the treatment of small coronary artery disease: a meta-analysis of randomized trials. *Catheter Cardiovasc Interv*. 2021;98(1):66–75. https://doi.org/10.1002/ccd.29111

21. Jeger RV, Farah A, Ohlow MA, 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*. 2020;396(10261):1504–1510. https://doi.org/10.1016/S0140-6736(20)32173-5

KEY WORDS drug-coated balloon, everolimus-eluting stent(s), long-term comparison with drug-eluting stent(s), native vessel disease, small coronary vessel disease

Department of Pediatric Cardiology, University of Erlangen-Nürnberg
Head of Department: Prof. Dr. med. Sven Dittrich

Universitätsklinikum Erlangen

Balloon dilatation of pulmonary vein stenosis using PACLITAXEL eluting balloon: midterm result in an infant

A. Koch, M. Glöckler, C. Breuer, O. Toka, S. Dittrich

Introduction:

Pulmonary vein stenosis has an unfavorable outcome because neither surgical nor interventional therapy prevents restenosis.

According to promising results in pre-clinical studies, single infants with pulmonary vein stenosis have been treated by balloon dilatation using balloons coated with PACLITAXEL, an antimitotic agent from cancer therapy [1]. First results were encouraging, however, follow-up was cut off early in the two patients published so far, because both died within a few weeks [1,2].

Case Report:

A girl with univentricular heart, increased pulmonary perfusion, and mesocardia was treated by pulmonary banding at 3 weeks. Within the next weeks an increasing stenosis of the left sided pulmonary veins was suspected by echocardiography and confirmed by cardiac catheterization. Subsequently a Damus-Kaye-Stansel anastomosis, an aortopulmonary shunt, and a sutureless repair of the left sided pulmonary venous obstruction were performed at the age of 4 months.

At the age of 6 months, stenosis of the aortopulmonary shunt caused implantation of a 4mm coronary stent. Concurrently severe restenosis of the left pulmonary veins was diagnosed (fig.1) and treated by balloon dilatation.

6 weeks later, re-evaluation in the cath lab revealed severe restenosis, and again dilatation of the left pulmonary veins was performed now using PACLITAXEL coated balloons (5 and 6mm diameter).

This procedure was repeated at the age of 10, 13, and 16 months. 2 weeks after the last intervention (fig.2), surgical treatment with right sided Glenn anastomosis and left sided aortopulmonary shunt (5mm) was performed. 8 days after surgery the girl went home.

Out-patient follow-up after 6 weeks revealed the girl in a proper clinical condition with accelerated left-sided pulmonary venous return (Doppler Vmax 2.3m/s).

At the age of 22 months the girl was transferred to the cath lab for re-evaluation because of mildly increasing cyanosis. The left sided pulmonary vein showed moderate obstruction, and again re-dilatation was performed using a 6mm PACLITAXEL coated balloon (fig.3).

The right sided Glenn anastomosis was without obstruction, but there was a big anomalous venovenous connection between the superior vena cava and a paravertebral venous plexus draining to the inferior vena cava. The collateral was closed using an Amplatzer duct occluder (fig.4).

Conclusion:

Repeated balloon dilatation of pulmonary venous obstruction using paclitaxel eluting balloons may be useful in the interventional treatment of this frequently fatal condition. Although restenosis occurred also in our patient after the use of paclitaxel eluting balloons, the diameter of the treated vessel showed a reasonable increase, and the patient was able to undergo the next surgical step.

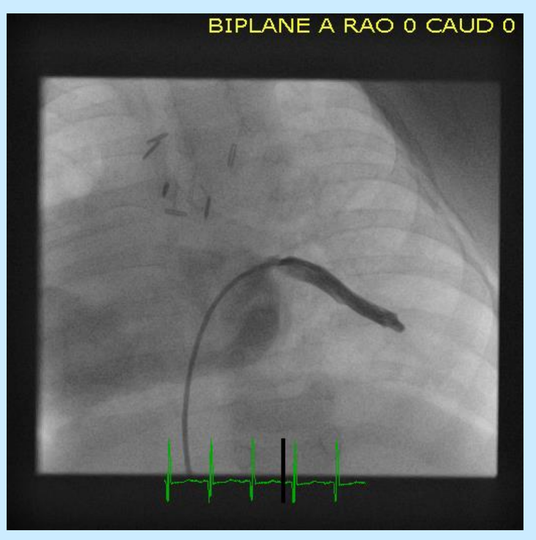


Fig.1: Pulmonary vein stenosis at the age of 6 months

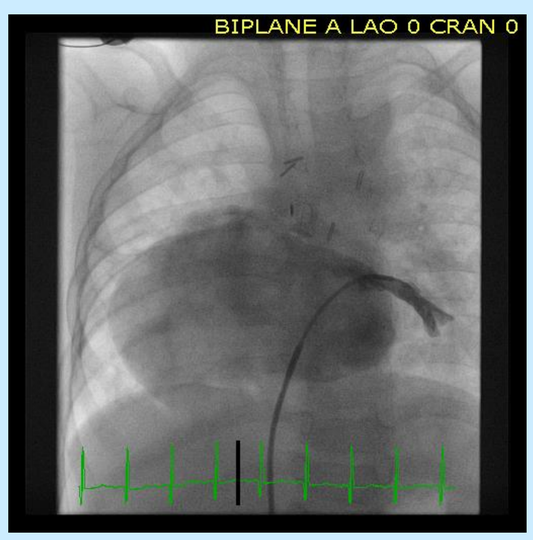


Fig.2: Pulmonary vein at the age of 16 months before surgery

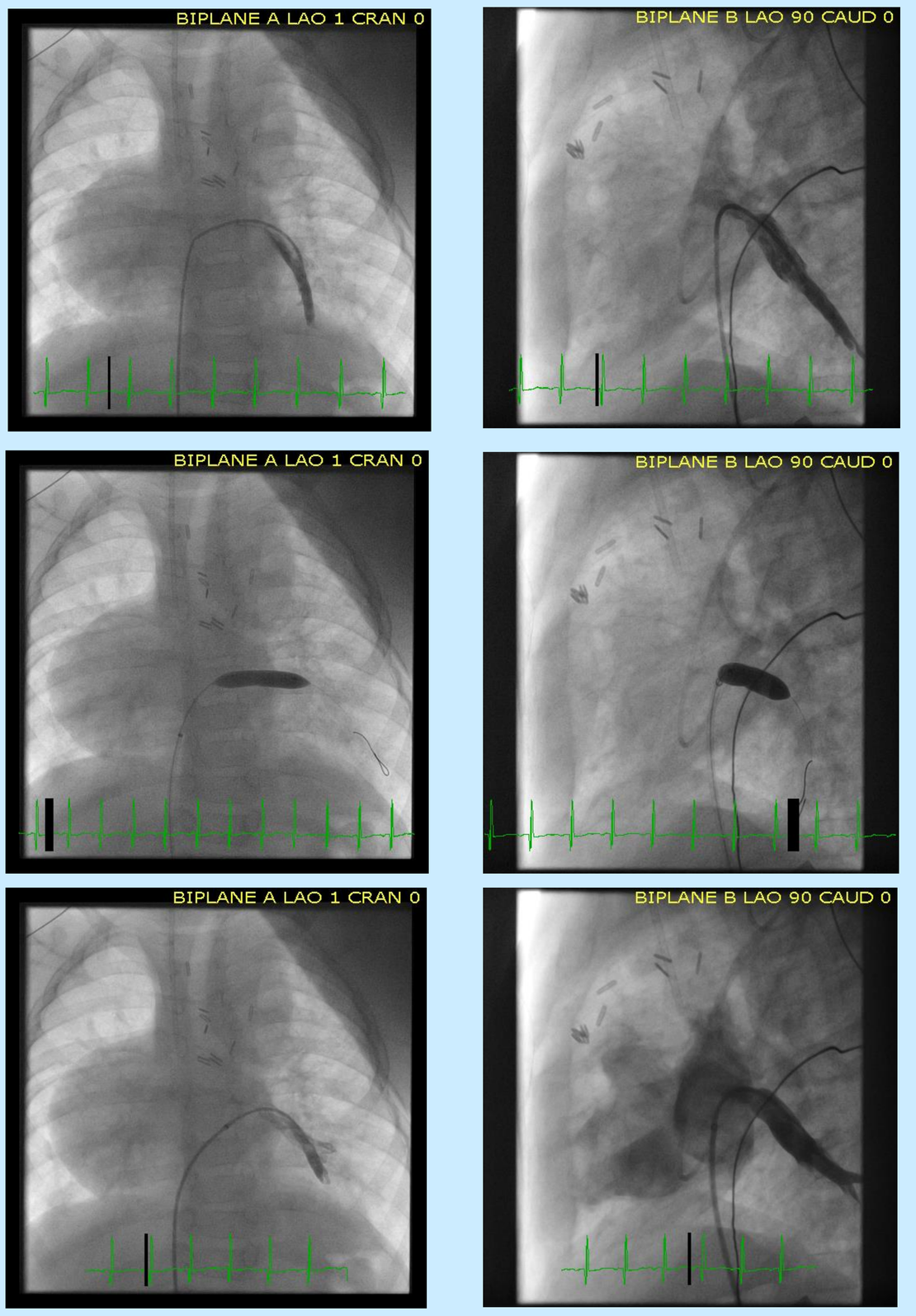


Fig. 3: Left pulmonary vein at the age of 22 months before (a,b), and after (e,f) redilatation using a 6mm PACLITAXEL coated balloon (c,d).

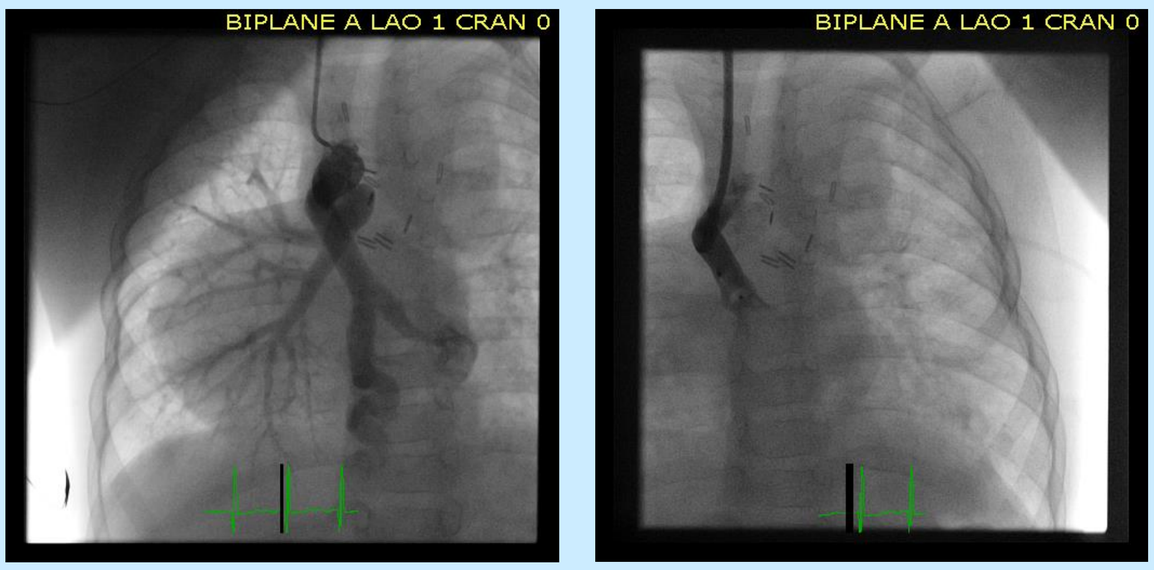


Fig. 4: Venovenous collateral (a), occlusion by Amplatzer duct occluder (b).

References:

[1] Müller GC, Dodge-Khatami A, Weil J. "First experience with a new drug-eluting balloon for the treatment of congenital pulmonary vein stenosis in a neonate", *Cardiol Young 2010;20:455-8.*

[2] Müller MJ, Krause U, Paul T, Schneider HE. "Serum levels after everolimus-stent implantation and paclitaxel-balloon angioplasty in an infant with recurrent pulmonary vein obstruction after repaired total anomalous pulmonary venous connection", *Pediatr Cardiol 2011;32:1036-9*

Friedrich-Alexander-Universität Erlangen-Nürnberg

Contact:
andreas.koch@uk-erlangen.de
Universitätsklinikum Erlangen, Kinderkardiologische Abteilung, Loschgestr. 15, 91054 Erlangen, Germany