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

PICCOLETO II Randomized Clinical Trial

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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;13:2840–9) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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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.

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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.

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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 database. 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

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

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.

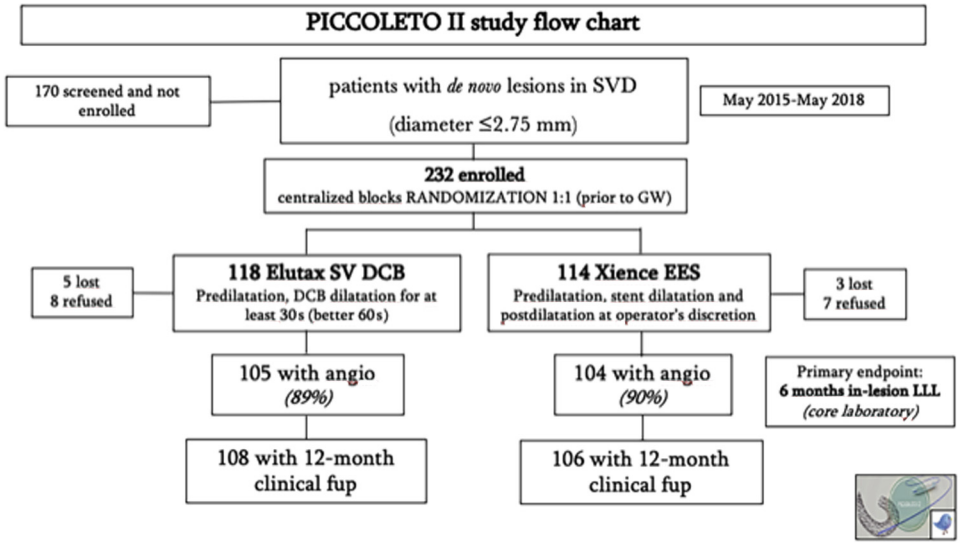
STUDY DEVICE. The technical characteristics of Elutax SV (also marketed as Emperor in some European countries) have been described previously (12). Briefly, this DCB elutes paclitaxel that is loaded on a folded balloon at dosage of ≅2.2 μg/mm^2 (tolerance of 1.4 to 3.00 μg/mm^2). The drug is added with 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 and Kaplan-Meier curves to analyze time-related

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.

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 pre-specified 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).

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 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.

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.

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 = 0.20). 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.

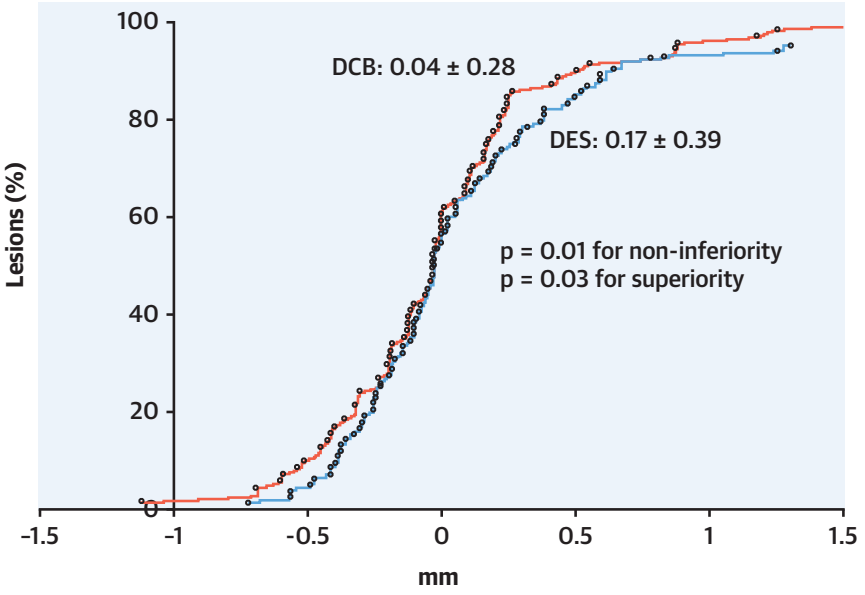
Twelve-month clinical follow-up (median 348, interquartile range: 292 to 390 days) was obtained in 108 DCB and 106 DES patients (92.2% of the enrolled population). MACE occurred in 7.5% of the DES group and in 5.6% of the DCB group (p = 0.55) (Table 4). There was a numerically, but not significantly, 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.

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 noninferiority 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;13(24):2840–9.

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).

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 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.

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 (%).

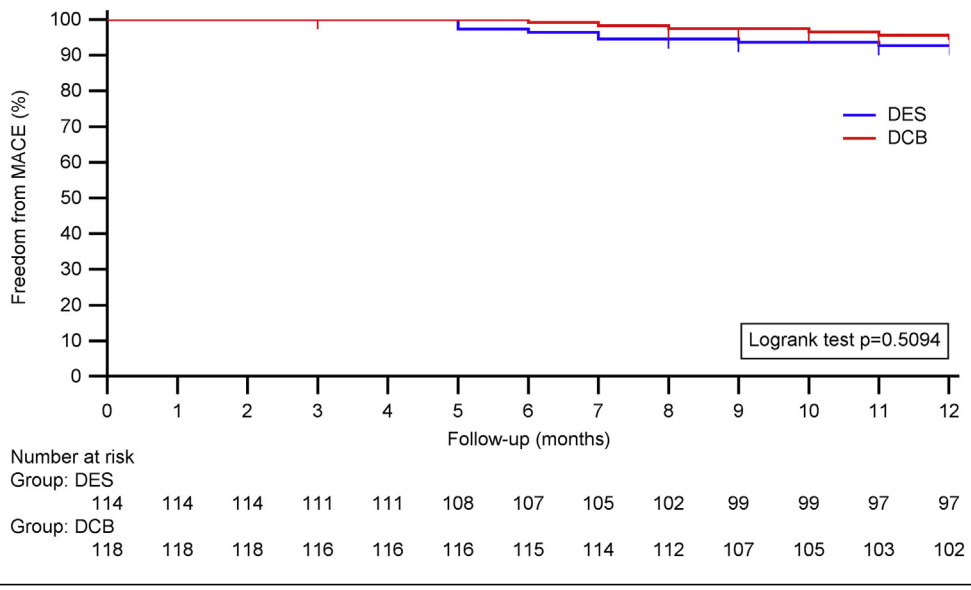
BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiac event(s); TLR = target lesion revascularization; other abbreviations as in Table 1.

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).

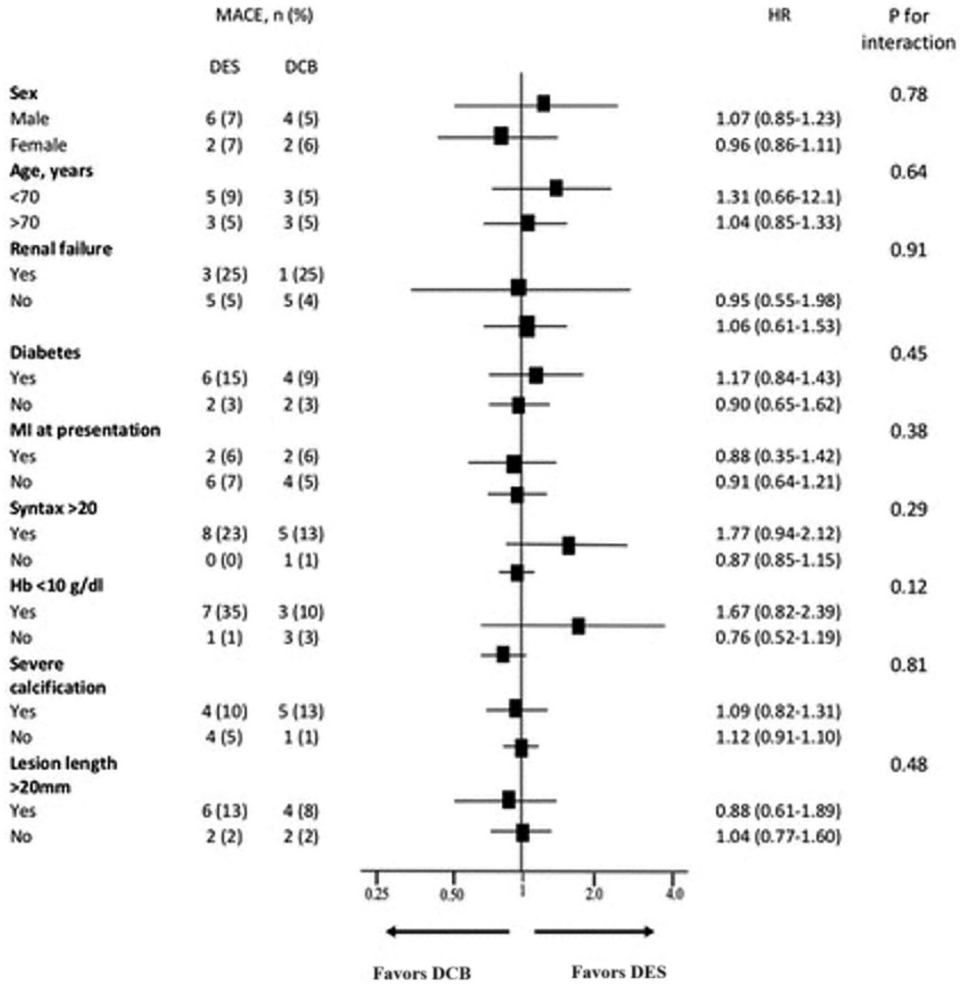
PREVIOUS STUDIES. To date, randomized studies on the use of DCB in small vessels brought variable results. The first-generation Dior DCB (Eurocor, Bonn, Germany) failed to show the angiographic noninferiority versus Taxus DES (Boston Scientific, Marlborough, Massachusetts) in the prematurely interrupted 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; 95% 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, 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 DISCLOSURES

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

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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.

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