WILEY **CLINICAL CARDIOLOGY**

TRIAL DESIGNS

Drug-coated balloons for de novo lesions in small coronary arteries: rationale and design of BASKET-SMALL 2

Nicole Gilgen[1] | Ahmed Farah[2] | Bruno Scheller[3] | Marc-Alexander Ohlow[4] |
Norman Mangner[5] | Daniel Weilenmann[6] | Jochen Wöhrle[7] | Peiman Jamshidi[8] |
Gregor Leibundgut[9] | Sven Möbius-Winkler[10] | Robert Zweiker[11] | Florian Krackhardt[12] |
Christian Butter[13] | Leonhard Bruch[14] | Christoph Kaiser[1] | Andreas Hoffmann[1] |
Peter Rickenbacher[1] | Christian Mueller[1] | Frank-Peter Stephan[1] | Michael Coslovsky[1] |
Raban Jeger[1] ◉ | for the BASKET-SMALL 2 Investigators

[1]University Hospital Basel, University of Basel, Switzerland

[2]Knappschaftskrankenhaus, Klinikum Westfalen, Dortmund, Germany

[3]University Hospital Saarland, Homburg, Germany

[4]Central Clinic, Bad Berka, Germany

[5]University Hospital for Cardiology, Heart Center Leipzig, Germany

[6]Cantonal Hospital St, Gallen, Switzerland

[7]University Hospital Ulm, Germany

[8]Cantonal Hospital Luzern, Switzerland

[9]Cantonal Hospital Baselland, Liestal, Switzerland

[10]University Hospital Jena, Germany

[11]Medical University Graz, Austria

[12]Charité University Hospital, Berlin, Germany

[13]Heart Center Brandenburg, Bernau, Germany

[14]Unfallkrankenhaus Berlin, Germany

Correspondence
Raban Jeger, MD, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland
Email: raban.jeger@usb.ch

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The treatment of coronary small vessel disease (SVD) remains an unresolved issue. Drug-eluting stents (DES) have limited efficacy due to increased rates of instent-restenosis, mainly caused by late lumen loss. Drug-coated balloons (DCB) are a promising technique because native vessels remain structurally unchanged. Basel Stent Kosten-Effektivitäts Trial: Drug-Coated Balloons vs. Drug-Eluting Stents in Small Vessel Interventions (BASKET-SMALL 2) is a multicenter, randomized, controlled, noninferiority trial of DCB vs DES in native SVD for clinical endpoints. Seven hundred fifty-eight patients with de novo lesions in vessels <3 mm in diameter and an indication for percutaneous coronary intervention such as stable angina pectoris, silent ischemia, or acute coronary syndromes are randomized 1:1 to angioplasty with DCB vs implantation of a DES after successful initial balloon angioplasty. The primary endpoint is the combination of cardiac death, nonfatal myocardial infarction, and target-vessel revascularization up to 1 year. Secondary endpoints include stent thrombosis, Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding, and long-term outcome up to 3 years. Based on clinical endpoints after 1 year, we plan to assess the noninferiority of DCB compared to DES in patients undergoing primary percutaneous coronary intervention for SVD. Results will be available in the second half of 2018. This study will compare DCB and DES regarding long-term safety and efficacy for the treatment of SVD in a large all-comer population.

KEYWORDS

Angioplasty, Coronary Artery Disease, Drug-Coated Balloon, Randomized Controlled Trial, Small Coronary Vessel, Trial Design

1 | INTRODUCTION

Drug-eluting stents (DES) are an established treatment option for coronary artery disease.[1] However, the treatment of small native

coronary arteries remains an unresolved issue as DES have limited efficacy due to increased rates of instent-restenosis (ISR), mainly caused by late lumen loss in the context of local inflammation and intimal hyperplasia. These effects are more pronounced in smaller
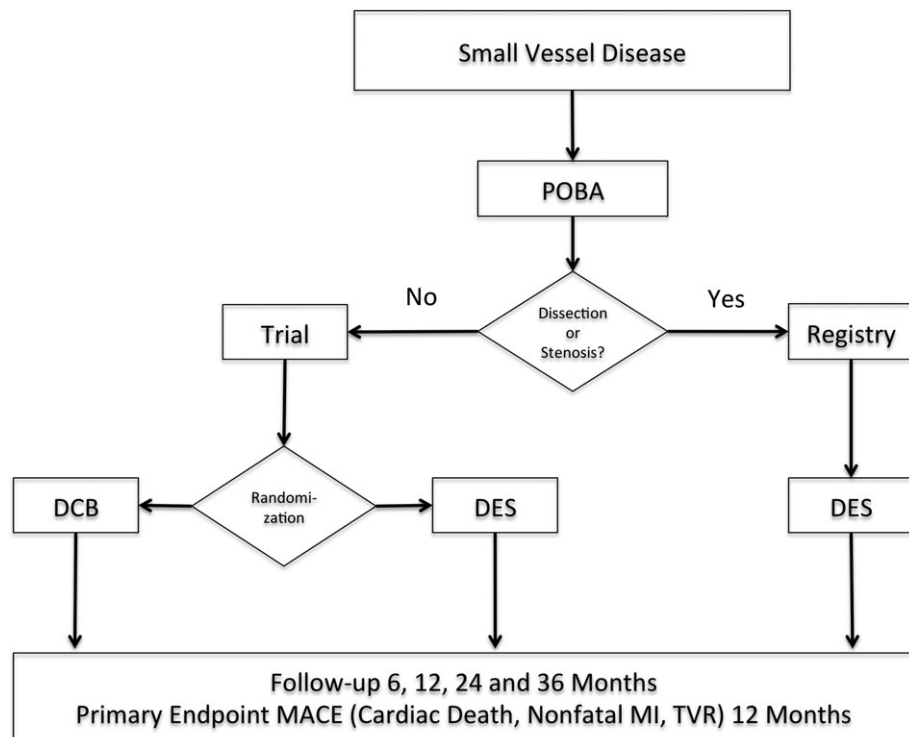
FIGURE 1 Patient flowchart. Abbreviations: DCB, drug coated balloon; DES, drug-eluting stent; MACE, major adverse cardiac events; MI, myocardial infarction; POBA, plain old balloon angioplasty; TVR, target vessel revascularization

compared to larger vessels.[2] Although in general, the use of newer generation DES has improved outcome compared with first-generation DES by reducing the rate of ISR, there are similarly high rates reported with first- and second-generation stents in small coronary vessels.[3,4]

Drug-coated balloons (DCB) are a modern concept for the treatment of coronary artery disease. Specifically, DCB compared to DES show a significant benefit in the treatment of ISR,[5–12] and current guidelines recommend the use of DCB for patients with coronary ISR (class I, level of evidence A).[13] However, there are other potential indications such as coronary small vessel disease and bifurcation lesions.[14,15] At the dawn of interventional cardiology, the treatment of coronary artery disease with balloon angioplasty alone was an established treatment option mainly limited by acute vessel closure due to acute recoil, flow-limiting dissections, and late restenosis.[16,17] Native vessels treated by stent- and polymer-free DCB keep their vasomotion properties, do not have a risk of ISR and late stent thrombosis, and remain possible targets for coronary artery bypass grafts. Therefore, potential advantages of DCB compared with DES include the absence of metallic struts and polymer causing less inflammation, and the unchanged integrity of the artery's original anatomy reducing abnormal flow patterns.[18] In addition, the duration of dual antiplatelet therapy can be shortened to 4 weeks with DCB.[19,20] However, given the variety of tested devices and inconsistencies in trial designs, published randomized controlled trial data show contradictory results for the use of DCB in native small vessel coronary artery disease.[21,22]

In view of all available data, DCB might be a promising new technique for the treatment of de novo stenosis in small-vessel disease. Thus, the aim of this study is to test the hypothesis of noninferiority of DCB vs DES regarding a composite clinical endpoint consisting of cardiac death, nonfatal myocardial infarction (MI), and target vessel revascularization (TVR) after 12 months in a large randomized controlled clinical trial.

2 | METHODS

2.1 | Study Design

The Basel Stent Kosten-Effektivitäts Trial: Drug-Coated Balloons vs. Drug-Eluting Stents in Small Vessel Interventions (BASKET-SMALL 2) (http://www.clinicaltrials.gov, ID: NCT01574534) is an investigator-initiated, prospective, randomized, active-controlled, open-label multicenter study. The primary objective of this study is to demonstrate the noninferiority of paclitaxel-coated balloons compared with DES in patients undergoing percutaneous coronary intervention (PCI) in small coronary vessels with a diameter <3 mm, irrespective of the indication with regard to the incidence of a major adverse cardiac event (MACE) after 12 months.

2.2 | Study population

The study patient flow is depicted in the Figure 1. Inclusion criterion is the indication for PCI in a small coronary vessel <3 mm, with either an acute coronary syndrome, typical symptoms of coronary ischemia, or silent ischemia as the reason for intervention (see Supporting Information, Appendix B, Table 1 in the online version of this article). Exclusion criteria are concomitant large-diameter PCI in the same epicardial coronary artery, PCI of ISR as the culprit lesion, life expectancy <12 months, pregnancy, enrollment in another coronary intervention study, or inability to give informed consent. By February 2017, enrollment of the planned sample size was complete.

TABLE 1 Key features of devices used

Comparator	Drug-Coated Balloon	Drug-Eluting Stent	
Device	Paclitaxel-coated balloon	Paclitaxel-eluting stent	Everolimus-eluting stent
Trade name	SeQuent Please (B. Braun Melsungen AG, Berlin, Germany)	TAXUS Element (Boston Scientific Corporation, Natick, MA)	Xience (Abbott Vascular, Santa Clara, CA), Promus (Xience distributed by Boston Scientific)
Platform	Polymer-free balloon	Platinum-chromium alloy	Cobalt-chromium alloy
Drug	Paclitaxel (3 $\mu g/mm^2$)	Paclitaxel (1 $\mu g/mm^2$)	Everolimus
Mode of action	Inhibition of M-phase	Inhibition of M-phase	Inhibition of G_1-phase
Matrix/polymer	Iopromide	Permanent polymer (poly[styrene-b-isobutylene-b-styrene])	Permanent polymer (poly[vinylidene fluoride-co-hexafluoropropylene])
Drug application	Single shot	Slow release	Slow release
Drug distribution	Homogenous	Strut-based inhomogenous	Strut-based inhomogenous

2.3 | Study devices

The different devices are specified in Table 1. As a balloon, the polymer-free paclitaxel-iopromide–coated balloon SeQuent Please (B. Braun Melsungen AG, Melsungen, Germany) is used. The DES group consists of 2 stent types: the everolimus-eluting Xience stent (Abbott Vascular, Santa Clara, CA; also distributed as the Promus stent by Boston Scientific Natick, MA), and the paclitaxel-eluting Taxus Element stent (Boston Scientific). Initially, the study was started with the paclitaxel-eluting Taxus Element stent as comparator to use devices with similar agents. However, after inclusion of 20% of patients, the paclitaxel-eluting stent was no longer available.[23,24] To continue the trial, the steering committee decided to replace the initial comparator stent with the best-in-class later-generation DES (ie, the everolimus-eluting stent). Accordingly, the sample size was increased to comply with the different efficacy of the 2 comparator stents.

2.4 | Concomitant medication

Before PCI, all patients are treated with dual antiplatelet therapy including acetylsalicylic acid and a thienopyridine or ticagrelor. After angioplasty, patients receive acetylsalicylic acid and a statin indefinitely. In stable patients, dual antiplatelet therapy with a thienopyridine is given for 4 weeks (DCB arm) or 12 months (DES arm).[20] In vessel dissections following DCB treatment and subsequent spot stenting or bifurcation PCI using a stent, dual antiplatelet therapy is given for 3 months (bare metal stents [BMS]) or 12 months (DES).[25] In acute coronary syndromes or use of a DES in an epicardial artery other than the culprit vessel, thienopyridines or ticagrelor are given for 12 months. In patients on oral anticoagulation, additional therapy with acetylsalicylic acid and clopidogrel is given based on their thromboembolic and bleeding risk according to current guidelines irrespective of DES or DCB treatment.[13]

2.5 | Primary endpoint

The primary endpoint is the incidence of a MACE after 12 months. A MACE is defined as the composite of cardiac death, nonfatal MI, and TVR. Cardiac death is defined as any death not clearly of extracardiac origin, whereas an MI is defined according to current guidelines.[26]

Non–MI-related TVR is defined as any revascularization of the target vessel not related to MI.

2.6 | Secondary endpoints

Secondary endpoints include the primary endpoint and its single components after 24 and 36 months: target lesion revascularization, stent thrombosis, Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding, net clinical benefit, and cost-effectiveness of DCB vs DES after 12, 24, and 36 months. The definition of stent thrombosis follows the recommendations of the Academic Research Consortium,[27] whereas bleeding is defined according to the BARC criteria.[28] Net clinical benefit is defined as the primary endpoint plus bleeding.

2.7 | Quantitative coronary angiographic measurements

Routine or control angiography during follow-up without a clinical indication is not allowed. However, event-driven coronary angiographies within the first year after initial PCI will be analyzed following a separate protocol.

2.8 | Randomization and baseline intervention

All patients undergoing PCI are screened for eligibility, and written informed consent will be obtained from all patients who meet all inclusion and no exclusion criteria. Because the vessel size is not known before catheterization, randomization is possible only after angiography and initial balloon dilatation. Randomization to 1 of the 2 treatment arms is performed 1:1 via an interactive Internet-based response system. In urgent or emergency cases where it is ethically not acceptable to postpone the intervention to obtain written informed consent prior to inclusion, patients are asked for oral consent before PCI, which is documented by a second medical person not being involved in the trial. Written consent is obtained after the intervention. Baseline PCI is performed according to local guidelines with predilatation of the stenosis with an angioplasty balloon. The DCB is used after successful predilatation only, in the absence of flow-limiting dissections (Thrombolysis in Myocardial Ischemia flow ≤2, dissection

grade C–F)[29] and a residual stenosis >30%. Subsequently, the DCB (on each side longer than the predilatation balloon by 2–3 mm to avoid geographical mismatch) is inflated at nominal pressure (8–10 bar) for a minimum of 30 seconds. If a flow-limiting dissection and/or a residual stenosis of >30% after DCB occurs, spot stenting may be recommended, again avoiding geographical mismatch (stent not specified). Baseline PCI can be performed in a single intervention or in multiple steps, if planned during the index procedure. Patients with a flow-limiting dissection or a residual stenosis >30% after initial balloon dilatation receive a DES and enter a prospective registry with the same follow-up procedures as in the randomized trial.

2.9 | Follow-up procedures

Follow-up is performed by structured clinical questionnaire letters or phone calls asking for endpoint-relevant clinical events and medication after 6, 12, 24, and 36 months. If the patient does not answer, his treating physician and/or the hospital are contacted to obtain the outcome information and medical documentation of endpoint events.

2.10 | Planned substudies

Planned substudies will include analyses of the different DES used, the different balloons used, the different antiplatelet drugs used, oral anticoagulation vs platelet inhibition only, acute vs stable coronary disease, diabetic vs non-diabetic patients, single vessel vs multi vessel disease, long vs short lesions, patients with DCB and additional spot stenting vs others, bifurcation lesions vs others, and the angiographic subgroup analysis according to a separate protocol as described above.

2.11 | Study management and data handling

The study organization is specified in the Supporting Information, Appendix A, in the online version of this article. The trial is led by the steering committee consisting of the principal investigator of the study and all local principal investigators from the different study sites. An independent critical event committee adjudicates all endpoints. Because there are no experimental devices tested, there is no specific data safety monitoring board deemed necessary for this trial. The Clinical Trial Coordination Center at the University Hospital Basel is responsible for study management and monitoring of all centers. Statisticians from the Clinical Trial Unit of the University Hospital Basel perform the analyses. Data are recorded and analyzed by the secuTrial electronic case report form located at the Clinical Trial Unit of the University Hospital Basel (SecuTrial®, interActive Systems Gmbh, Berlin, Germany). A specific angiographic core laboratory (Black Forest GmbH, Medical Quality Analysis Center, Bad Krozingen, Germany) will analyze the coronary angiographies according to a separate protocol. The local ethics committee in each center approved the study protocol.

2.12 | Statistical methods

Sample size was calculated to demonstrate noninferiority of DCB to DES regarding MACE within 12 months. It was based on an expected MACE rate of 7% for patients in the DCB arm compared with 10% for patients in the DES arm. Noninferiority would be declared if the upper limit of the 2-sided 95% confidence interval of the absolute risk difference is lower than 4% (noninferiority margin). The expected MACE rates for DCB were chosen slightly higher than the rate observed for DCB (6.1%),[25] because only 1 lesion per patient was treated in this study, whereas BASKET-SMALL 2 allows the inclusion of patients with >1 lesion. The expected MACE rate for DES was taken as the average of the rates observed in 2 previous studies for everolimus-eluting stents, that is 9.1% MACE[30] and 11% target vessel failure (TVF),[31] where TVF was the equivalent to MACE in the present study. Because event rates for paclitaxel-eluting stents are expected to be even higher (12.4%),[32,33] sample size calculation was based on the DES with expected lower rates of events.

Sample size was calculated using a resampling procedure. Samples were evaluated by sampling various sample sizes 9999 times from binomial distributions based on the expected rates. Confidence intervals for the difference between proportions were calculated using a continuity-corrected modification of Wilson's score method.[34] Sample size was set to ensure at least 90% power ($1 - \beta = 0.9$), at a significance level $\alpha = 5\%$. For this study, 758 patients are randomized to ensure 720 evaluable patients, considering an overall dropout rate of 5% after randomization.

For noninferiority testing, the analysis will be performed on the per-protocol set. The absolute difference of MACE risk difference at 12 months between the DES and the DCB groups and its 2-sided 95% confidence interval will be estimated in the per-protocol set by applying a continuity corrected modification of Wilson's score method.[34] Noninferiority will be declared if the upper limit of the 95% confidence interval for the absolute risk difference does not exceed the prespecified noninferiority margin. If noninferiority can be shown, a test for superiority of DCB vs DES using the Fisher exact test will follow. Time-dependent occurrence of events will be investigated with Cox proportional hazard models and Kaplan–Meier curves. Statistical tests will be performed at a 2-sided significance level of 0.05.

To increase the precision of the sample size estimation and to ensure sufficient power, a re-evaluation of the event rate for the primary endpoint was carried out that was blinded to the investigators. An internal-study design was used.[35] Blinded to study arm allocation, the overall rate of the primary endpoint was estimated, once 75% of the patients reached their 6-month follow-up visit. The original sample size calculation procedure was repeated using the updated rates. If the recalculated sample size were larger than the original, the study's sample size would be increased; no reduction of the original sample size would be performed in any case. However, the reevaluation analysis revealed that the sample size originally calculated can be maintained unchanged.

3 | RESULTS

The primary objective of the present study is to demonstrate the noninferiority of DCB to DES in patients undergoing PCI for de novo stenoses in small native vessels regarding the incidence of MACE after 12 months. The secondary objective is to compare the performance of DCB vs DES regarding a set of secondary endpoints as reported

TABLE 2 Preliminary baseline characteristics

Variable	Value
Age, yr, mean (SD)	67.8 (10.3)
Male, no. (%)	557 (74)
Body mass index, kg/m^2, mean (SD)	28.8 (12.5)
Smoking, no. (%)	
Current	154 (20)
Former	267 (35)
Hypercholesterolemia, no. (%)	521 (69)
Arterial hypertension, no. (%)	656 (87)
Family history of coronary artery disease, no. (%)	278 (37)
Diabetes mellitus, no. (%)	
Insulin and non-insulin debendent diabetes mellitus	
Insulin-dependent diabetes mellitus, no. (%))	95 (13)
Non–insulin-dependent diabetes mellitus, no. (%)	157 (21)
Prior myocardial infarction, no. (%)	293 (39)
Prior percutaneous coronary intervention, no. (%)	476 (63)
Prior coronary artery bypass graft surgery, no. (%)	71 (9)
Heart failure, no. (%)	83 (11)
Stroke/transient ischemic attack, no. (%)	
Stroke	39 (5)
Transient ischemic attack	27 (4)
Peripheral arterial occlusive disease, no. (%)	53 (7)
Chronic obstructive pulmonary disease, no. (%)	64 (8)
History of renal disease, no. (%)	113 (15)
Current renal dysfunction, no. (%)	173 (23)
Indication, no. (%)	
Stable coronary disease	543 (72)
Acute coronary disease	213 (28)

Abbreviations: SD = standard deviation.

above. The first results will be reported in the second half of the year 2018. A general overview of the enrolled trial population is given in Table 2.

4 | DISCUSSION

Given the limitations of DES, DCB might be a promising new technique for the treatment of de novo stenosis in small vessel disease. BASKET-SMALL 2 will test the noninferiority of DCB vs DES in patients undergoing PCI in small coronary vessels using clinical endpoints in a large all-comer population.

The DCB technique has successfully been tested in ISR, where it demonstrated good clinical efficacy.[7,9] However, clinical testing in small native vessels brought up discrepant results from observational studies and small randomized trials. In an observational study including 118 patients with de novo stenosis in small coronary vessels,[25] 82 of 118 patients (70%) received a DCB, whereas 32 patients (28%) required an additional BMS due to elastic recoil or dissections. In patients treated with a DCB without additional stent implantation, a MACE defined as target lesion revascularization, MI, stent thrombosis, or death was 6.1%, whereas late lumen loss was 0.18 ± 0.38 mm with an in-lesion binary restenosis rate of 5.5%. Of note, in patients treated

with a DCB and an additional BMS, MACE rate was increased at 37.5%, whereas late lumen loss was 0.73 ± 0.74 mm, with an in-lesion binary restenosis rate of 41.3%. These high restenosis rates in patients treated with a DCB and an additional BMS were explained by geographical mismatch that was present in 77% of patients with restenosis but only in 19% in patients without restenosis. In addition, there were 2 randomized trials in the field.[21,22] The PICCOLETO (Paclitaxel-Eluting Balloon Versus Paclitaxel-Eluting Stent in Small Coronary Artery Diseases) study compared a paclitaxel-eluting balloon (Dior; Eurocor, Bonn, Germany) to a first-generation paclitaxel-eluting stent (Taxus; Boston Scientific) in small coronary vessels. After enrollment of 57 patients, the study was interrupted because the primary endpoint was met at an interim analysis (percent diameter stenosis after 6 months DCB 44% vs DES 24%, P = 0.029). MACE rates were 36% in DCB vs 14% in DES (P = 0.054), mainly driven by higher target lesion revascularization rates in DCB vs DES (32% vs 10%, P = 0.15). However, this result was attributed to a lack of efficacy of the type of DCB used, which was later replaced by a newer-generation device, rather than a class effect of DCB per se.[36] In the first-generation Dior DCB technology (Eurocor), adherence of paclitaxel was mediated by the roughened surface of the balloon providing a significantly lower drug concentration in tissue and accordingly lower inhibition of neointimal proliferation, whereas in the water-soluble matrix of the SeQuent Please balloon technique, paclitaxel is released completely and homogenously after the first balloon expansion, resulting in high bioavailability on the target site.[37] In addition, a PCI technique not respecting the geographic mismatch issue might have increased MACE rates considerably in the DCB arm. The BELLO (Balloon Elution and Late Loss Optimization) study randomized 182 patients with lesions in small vessels <2.8 mm 1:1 to either paclitaxel-coated balloon (IN.PACT Falcon; Medtronic, Inc., Santa Rosa, CA) and provisional BMS or paclitaxel-eluting stent (Taxus Libertè; Boston Scientific) as per standard practice. Bailout stenting was required in 20.2% of patients in the DCB arm. Although the primary angiographic endpoint in favor of DCB vs DES was met, clinical outcomes after 6 months showed similar MACE rates defined as the composite of death, MI or TVR, and similar rates of restenosis and revascularization in both groups. The clinical efficacy of DCB was confirmed up to 3 years, showing a trend toward improved outcomes with regard to MACE.[38] BELLO supported the importance of routine predilatation, which was performed in 96.8% of interventions as compared to 25% in the PICCOLETO study. In BASKET-SMALL 2, predilatation and avoidance of geographical mismatch was therefore a prerequisite before randomization into a treatment arm. This new concept of DCB treatment (eg, optimal lesion preparation by conventional plain old balloon angioplasty and drug delivery with DCB in case of a good angiographic result) is novel and based on current guidelines.[22,23]

Our study started with paclitaxel-eluting stents as a comparator to the paclitaxel-coated balloon. When these stents were chosen at the time of study design, paclitaxel was accepted as a potentially beneficial drug in small-vessel disease and because a precursor pilot study showed some potential benefit.[4] However, this stent was temporarily not available, which forced the steering committee to change the comparator stent during the trial, and consequently, to increase the sample size to ensure the planned 90% power. The real-world mixture

of 2 newer generation DES with different drugs as used in the present study will give insight into some important clinical questions.

Given all the available data, DCB might represent a promising new technique for the treatment of de novo stenosis in small coronary vessels if accurate lesion preparation is performed and geographical mismatch is avoided. This hypothesis will be tested in the BASKET-SMALL 2 study in a real-world, prospective, randomized controlled trial setting.

5 | CONCLUSION

BASKET-SMALL 2 is the first prospective, randomized, controlled multicenter trial in a large all-comer population assessing the noninferiority of paclitaxel-iopromide–coated balloon angioplasty compared to DES in the treatment of de novo lesions in small native coronary vessels <3 mm in diameter with respect to clinical safety and efficacy up to 3 years.

Conflicts of interest

ORCID

Raban Jeger http://orcid.org/0000-0003-1290-5491

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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