Long-term efficacy and safety of drug-coated balloons vs. drug-eluting stents for small coronary artery disease (BASKET-SMALL 2): 3-year follow-up of a randomized non-inferiority trial

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Summary

Background: In the treatment of de-novo coronary small vessel disease, drug-coated balloons (DCB) are non-inferior to drug-eluting stents (DES) regarding clinical outcome up to 12 months, but data beyond 1 year is sparse.

Methods: In this prespecified long-term follow-up of a multicenter, randomized, open-label, non-inferiority trial, 758 patients with de-novo lesions in coronary vessels <3 mm and an indication for percutaneous coronary intervention were randomized 1:1 to DCB (n=382) or second-generation DES (n=376) and followed over 3 years for major adverse cardiac events (MACE, i.e., cardiac death, non-fatal myocardial infarction, and target-vessel revascularization [TVR]), all-cause death, probable or definite stent thrombosis, and major bleeding (Bleeding Academic Research Consortium bleeding type 3-5). Dual antiplatelet therapy (DAPT) was recommended for 1 month after DCB and 6 months after DES with stable symptoms but 12 months with acute coronary syndromes.

Findings: Rates of MACE (53/382 [15%] vs. 53/376 [15%], hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.68, 1.45, p=0.95) and their single components, i.e., cardiac death (17/382 [5%] vs. 13/376 [4%], HR 1.29, 95%CI 0.63, 2.66, p=0.49), non-fatal myocardial infarction (19/382 [6%] vs. 23/376 [6%], HR 0.82, 95%CI 0.45, 1.51, p=0.52), and TVR (30/382 [9%] vs. 32/376 [9%], HR 0.95, 95%CI 0.58, 1.56, p=0.83), were similar in DCB and DES. Rates of all-cause death were very similar in DCB vs. DES patients (28/382 [8%] vs. 27/376 [8%], HR 1.05, 95% CI 0.62, 1.77, p=0.87). Rates of probable or definite stent thrombosis (2/382 [1%] vs. 6/376 [2%], HR 0.33, 95%CI 0.07, 1.64, p=0.18) and major bleeding (6/382 [2%] vs. 14/376 [4%], HR 0.43, 95%CI 0.17, 1.13, p=0.088) were numerically lower in DCB vs. DES, however without reaching statistical significance.

Interpretation: There is maintained efficacy and safety of DCB vs. DES in the treatment of de-novo coronary small vessel disease up to 3 years.

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Abbreviations

CAD	Coronary artery disease
CI	Confidence interval
DAPT	Dual antiplatelet therapy
DCB	Drug-coated balloon
DES	Drug-eluting stent
HR	Hazard ratio
ISR	Instent-restenosis
MACE	Major adverse cardiac events
PCI	Percutaneous coronary intervention
TVR	Target vessel revascularization

Introduction

Second-generation drug-eluting stents (DES) are the mainstay of interventional therapy for coronary artery disease (CAD).[1] However, drug-coated balloons (DCB) represent a novel treatment alternative for specific patient subsets such as patients with instent-restenosis (ISR), high bleeding risk, or small vessel CAD.[2] DCB usually consist of semi-compliant balloons that are coated with an active drug embedded in a specific matrix; after inflation of the balloon, the drug is transferred rapidly into the vessel wall where it exerts its antiproliferative action. DCB may be used in the coronary vasculature if lesion preparation does not lead to flow-limiting dissections or leaves a residual stenosis >30%, and if drug transfer is not inhibited by the presence of a large intravascular thrombus. The main advantage of the DCB-only strategy is the absence of intravascular foreign material that may lead to delayed complications such as late or very late stent thrombosis after implantation of DES. Other advantages include the necessity of only short-term dual antiplatelet therapy (DAPT) of 4 weeks after DCB[2] and the possible long-term positive remodeling effect on the treated vessel associated with paclitaxel.[3,4]

While published data show a sustained effect of DCB treatment up to 5 years in patients with ISR,[5,6] only limited evidence exists in small vessel CAD.[7,8] The Basel Kosten Effektivitäts Trial – Drug-Coated Balloons versus Drug-eluting Stents in Small Vessel Interventions (BASKET-SMALL) 2 trial was a large multicenter randomized controlled trial that demonstrated the non-inferiority of DCB against second-generation DES regarding a combined clinical endpoint after 1 year.[9] As described in the study protocol,[10] a long-term follow-up was performed after 2 and 3 years, which gives the unique opportunity to test the long-term efficacy and safety of DCB regarding clinical endpoints in an all-comer population undergoing percutaneous coronary intervention (PCI).

Methods

Study design

The current analysis is the predefined long-term follow-up of BASKET-SMALL 2 as outlined before.[10] BASKET-SMALL 2 is an investigator-initiated, randomized, open-label non-inferiority trial whose primary analysis was published in 2018.[9] The trial was performed in 14 centers in Germany, Switzerland, and Austria (appendix) in the years 2012-2017 in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol (appendix) was approved by the ethics committees in all participating centers.

Participants

Patients were eligible for the study when they had an indication for PCI, i.e., an acute coronary syndrome, stable angina pectoris, or silent ischemia, and a suitable angiographic anatomy in a small coronary vessel with a diameter ≥2.0 to <3.0 mm. Successful predilatation of the lesion, i.e., absence of higher grade dissections (National Heart, Lung, and Blood Institute grade C to F),[11] decreased blood flow (thrombolysis in myocardial infarction score ≤2), or residual stenosis >30% was mandatory.[2] Exclusion criteria included a concomitant PCI of lesions ≥3 mm in diameter in the same epicardial coronary artery, PCI of in-stent restenosis, life expectancy of <12 months, pregnancy, enrollment in another randomized trial, or inability to give informed consent. All patients provided written informed consent before the intervention.

Randomization and masking

Randomization was performed using an interactive internet-based system. Patients were selected 1:1 to be treated by either DCB or DES. The selection of therapy was open-label without investigators being masked to the treatment.

Procedures

Patients randomized to DCB were treated with the paclitaxel-coated SeQuent Please balloon (B. Braun Melsungen AG, Melsungen, Germany), while patients randomized to DES were treated with either the everolimus-eluting Xience stent (72% of cases, Abbott Vascular, Santa Clara, CA, USA) or the paclitaxel-eluting Taxus Element stent (28% of cases, Boston Scientific, Natick, MA, USA). The study was started with Taxus Element as the comparator, but later (between June 19, 2013, and Jan 24, 2014) had to be continued with Xience because the initial stent became unavailable. The sample size was increased to conform to the different efficacy of the two DES as described before.[9,10] PCI, specifically in the DCB group, was performed according to current guidelines.[2] After successful predilatation, the DCB needed to be 2 to 3 mm longer on each side than the predilatation balloon to avoid geographical mismatch, and was inflated at nominal pressure for at least 30 sec. When there were flow-limiting dissections after DCB treatment despite an acceptable result after lesion preparation, PCI using DES was recommended. After PCI, DAPT was prescribed using acetylsalicylic acid (100 mg per day) and either clopidogrel (75 mg per day), prasugrel (10 mg per day), or ticagrelor (90 mg twice per day); DAPT was continued in stable patients for 4 weeks for DCB or 6 months for DES and in patients with acute coronary syndrome for 12 months. In the case of a combination of DCB and bare metal stents, DAPT was recommendend for 3 months, and in the case of a combination of DCB and DES, DAPT was recommendend for 6 months. In patients with oral anticoagulation, current guidelines were followed,[1] irrespective of DCB or DES treatment.

A blinded critical events committee had access to all medical data required and adjudicated all endpoints. Follow-up was done after 24 and 36 months with structured clinical questionnaires or phone calls to patients to assess clinical events and medication.

Outcomes

The primary endpoint of this analysis is major adverse cardiac events (MACE) defined as the composite of cardiac death, non-fatal myocardial infarction, and target vessel revascularization (TVR). Cardiac death was defined as any death that was not clearly of extracardiac origin, and

myocardial infarction was defined according to current guidelines.[12] Secondary endpoints were the single components of the primary endpoint, all-cause death, probable or definite vessel or stent thrombosis according to the Academic Research Consortium definition,[13] and major bleeding defined as Bleeding Academic Research Consortium type 3 to 5 bleeding.[14] Net clinical benefit was defined as the combination of MACE and major bleeding.

Statistical analysis

All statistical analyses were performed on the full analysis set according to the intention-to-treat principle. For the database, the secuTrial software (interActive Systems GmbH, Berlin, Germany) was used, and all analyses were conducted with the statistical software package R (version 4.0.2),[15] using “two-sided” statistical tests and confidence intervals. P-values and confidence intervals must be interpreted with care in view of the multiple testing problem. Categorical data are presented as frequencies and percentages (with the difference between study arms analyzed by Pearson’s chi-squared test). For numerical variables, the mean and standard deviation, or the median and interquartile range are presented, as appropriate, with the difference between study arms analyzed by Student’s t-test or Wilcoxon–Mann–Whitney test, respectively. Treatment effects on the times to event within 2 and 3 years were tested by Cox regressions with study center as a stratifying factor to account for differences in baseline hazards between study centers for the different endpoints. The Kaplan–Meier estimates of the event rates in both study arms are reported along with the corresponding hazard ratios (HR) and 95% confidence intervals (CI). The proportional hazards assumption of the Cox models and the homogeneity of the treatment effects among study centers were checked by testing the correlation of the scaled Schoenfeld residuals with time and the interaction of the stratifying factor study center with treatment in the Cox models, respectively. Missing data were not an issue, since the endpoints of patients not experiencing an event were considered as censored on the last observation date.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, and data interpretation, or writing of the report, and did not participate in the decision to submit the manuscript for publication. The principle investigator (RVJ) and NG had full access to all data. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between 2012 and 2017, 883 patients were enrolled in the study. After successful lesion preparation, 758 (86%) patients entered the randomized trial and were randomly assigned to the DCB (n=382) or the DES group (n=376).[9]

Baseline characteristics are depicted in Table 1. Patients were on average 68 years old, mostly men, and had high rates of cardiovascular risk factors including diabetes mellitus in one third of cases. Parameters were well balanced between the groups, except for male sex that was more frequent in DCB than DES patients (77 vs. 70%, p=0.023). Duration of DAPT with clopidogrel was shorter in DCB than DES (209 [146, 384] vs. 336 [182, 374] days, p=0.009), while duration of DAPT with either prasugrel or ticagrelor being used in acute coronary syndrome patients was similar in both groups (360 [318, 483] vs. 364 [318, 599] days, p=0.62).

Follow-up after 3 years was complete in 349 (91%) patients in the DCB and 345 (92%) patients in the DES group (Fig. 1, Table 2). Rates of the primary endpoint MACE (53/382 [15%] vs. 53/376 [15%], HR 0.99, 95% CI 0.68, 1.45, p=0.95; Fig. 2, Fig. appendix) were similar in DCB vs. DES patients. Rates of the secondary endpoints, i.e., cardiac death (17/382 [5%] vs. 13/376 [4%], HR 1.29, 95% CI 0.63, 2.66, p=0.49), non-fatal myocardial infarction (19/382 [6%] vs. 23/376 [6%], HR 0.82, 95% CI 0.45, 1.51, p=0.52), and TVR (30/382 [9%] vs. 32/376 [9%], HR 0.95, 95% CI 0.58, 1.56, p=0.83) were similar in both groups as well. Rates of all-cause death were very similar in the two groups (DCB vs. DES, 28/382 [8%] vs. 27/376 [8%], HR

1.05, 95% CI 0.62, 1.77, p=0.87). Rates of probable or definite vessel or stent thrombosis (2/382 [1%] vs. 6/376 [2%], HR 0.33, 95% CI 0.07, 1.64, p=0.18) and major bleeding (6/382 [2%] vs. 14/376 [4%], HR 0.43, 95% CI 0.17, 1.13, p=0.088) were numerically lower in DCB vs. DES patients, however without reaching statistical significance. Net clinical benefit was similar in DCB vs. DES patients (56/382 [16%] vs. 64/376 [18%], HR 0.86, 95% CI 0.60, 1.24, p=0.43). Bailout stent implantation was necessary in 19/382 (5.2%) patients in the DCB group.

Regarding the different device subgroups, rates of MACE were numerically but not statistically different (DCB only 49/367 [14%]; Xience 29/256 [13%], HR 0.83, 95% CI 0.52, 1.31, p=0.42; Taxus Element 19/93 [21%], HR 1.59, 95% CI 0.93, 2.74, p=0.093; DCB combined with DES 5/20 [26%], HR 1.92, 95% CI 0.76, 4.87, p=0.17, all vs. DCB only; overall comparison p=0.11; Fig. 3).

Discussion

In this predefined long-term analysis of a major clinical trial, DCB treatment of de-novo coronary small vessel disease demonstrates maintained efficacy and safety. Based on current results, DCB represents a genuine alternative to DES for selected de-novo lesions in coronary arteries with an excellent long-term safety and efficacy profile.

There were four major findings in the current analysis: First, patients treated with DCB had similarly low clinical event rates as patients treated with DES over the follow-up period of 3 years. Second, event rates in patients treated with either a DCB-only strategy or an everolimus-eluting stent were similar and low, while event rates in patients treated with either a paclitaxel-eluting stent or the combination of a DCB with any stent were numerically higher. Third, rates of both major bleeding and of probable and definite stent thrombosis tended to be lower in the DCB group than in the DES group, however without reaching statistical significance. Fourth, all-cause mortality was very similar in the two treatment groups.

DCB are an increasingly used treatment option for various clinical situations in CAD. Based on the fast transfer of antiproliferative drugs into the vessel wall by one single inflation of the underlying balloon, DCB have the advantage of an implant-free treatment of CAD without the risk of late or very late implant-associated complications such as stent thrombosis or neo-atherosclerosis. Just recently, several publications have corroborated the efficacy and safety of DCB in different settings as described in the newest version of the International DCB Consensus Group recommendations.[2] While the use of DCB is an established treatment option for ISR of both DES and bare metal stents,[1,16] there are other emerging indications such as de-novo stenosis in small coronary vessels,[9,17-20] acute coronary syndromes,[21-23] and elevated bleeding risk.[24] Although data from PEPCAD I[7] and BELLO[8] demonstrated sustained efficacy and safety of paclitaxel-coated balloons in de-novo stenosis of small coronary vessel disease, long-term evidence is still limited.[25] Of note, the 3-year follow-up of BELLO showed a beneficial effect of DCB compared with DES regarding a composite of clinical endpoints.[8] The current analysis corroborates the findings of these smaller trials in a large patient population regarding clinical endpoints. Moreover, it expands the favorable 1-year findings of the BASKET-SMALL 2 trial up to 3 years, with comparable rates of the primary endpoint and its single components between the two randomized groups.

In a subgroup analysis of the present long-term follow-up, patients treated with a DCB-only approach or the everolimus-eluting stent had similar and low event rates, while patients treated with paclitaxel-eluting stents or a combination of DCB and DES exhibited higher event rates. Based on this finding, three conclusions can be drawn. First, a DCB-only approach using paclitaxel-eluting balloons is as efficacious and safe as a strategy using everolimus-eluting stents. Second, paclitaxel used in the setting of a stent does not have the same efficacy and safety as the same drug used on a balloon. Third, the population with a failed DCB-only approach and treated with bail-out DES represents a high-risk group with an unfavorable outcome, probably due to a negative selection bias based on an unfavorable vessel anatomy. Therefore, the paclitaxel-eluting DCB utilized in this trial can safely be used in de-novo stenosis of small coronary arteries if no additional treatment with a stent is necessary. To achieve this

goal, a strict adherence to current guideline recommendations[2] should be followed, specifically regarding lesion preparation to achieve an optimal result.

Previous data from BASKET-SMALL 2 demonstrated that there were no DCB patients with acute vessel closures but a relevant percentage of DES patients that experienced an acute stent thrombosis.[26] The current analysis corroborates this finding and expands it up to 3 years, since patients in the DCB group exhibit lower rates of vessel or stent thrombosis than DES patients – despite the fact that DAPT duration in DCB patients with stable symptoms was shortened to 1 month only. The short DAPT duration of only 4 weeks in stable patients with DCB treatment is a major advantage of the DCB-only approach since it lowers rates of major bleeding without increasing the risk of stent thrombosis.

Previous reports of elevated mortality rates in patients treated with paclitaxel-coated balloons in peripheral artery disease have fueled discussions about the safety of these devices in the coronary field.[27] However, the mentioned analyses were subject to major inherent methodological limitations that prevent reliable interpretation of the primary findings, as stated by an official PCR statement.[28] In addition, the situation in CAD seems to be different than in the peripheral territory as demonstrated by large meta-analyses in populations undergoing PCI using paclitaxel-coated balloons in ISR[16] and de-novo stenosis[29] where no increased mortality rates for DCB were shown. Specifically, patients treated with DCB for de-novo stenosis in coronary arteries had lower all-cause and cardiac mortality rates when compared with control treatments after 3 years.[29] Accordingly, the long-term follow-up of BASKET-SMALL 2 shows very similar rates of all-cause death after 3 years in the two treatment groups, which corroborates the safety of DCB treatment in a clinical setting. Of note, most cases of unknown or sudden cardiac death in the DCB group occurred in patients that were previously treated with stents as demonstrated in a previous analysis of the causes of death in BASKET-SMALL 2 until 1 year.[30] Given the fact that no acute vessel closure in DCB but several acute stent thrombosis in DES patients were found, alternative reasons for unknown or sudden cardiac deaths in this patient group are more likely, e.g., late stent thrombosis.[26]

As a predefined secondary analysis of a randomized controlled trial, our study has some inherent limitations, as already addressed before.[9] For the present analysis, follow-up was complete in more than 90% of patients with only 39 (5%) patients lost to follow-up, which is an excellent number given the long observational time. Some post-hoc comparisons did not reach statistical significance because of the low number of patients in the different subgroups. In our study, 28% of patients received paclitaxel-eluting stents, while implantation of bail-out stents was necessary in 5% of cases. Since patients in the study received treatment with paclitaxel-iopromide-coated DCB, these long-term results can only be extrapolated to those who received these devices.

In summary, this is the long-term follow-up of the largest randomized controlled trial testing paclitaxel-coated balloons against second-generation DES regarding clinical endpoints in an all-comer population with de-novo small CAD. The study demonstrates the maintained efficacy and safety of DCB in de-novo lesions of small coronary vessels up to 3 years, without any evidence of increased all-cause or cardiac mortality in DCB patients.

Contributors

RVJ, NG, CK, and BS designed the study, collected and interpreted the data, and drafted the manuscript. AF, M-AO, NM, SM-W, DW, JW, GS, SM, GL, PR, and SO collected the data and critically revised the work for important intellectual content. MC designed the study and analyzed the data. All authors approved the final version.

Declaration of interests

RVJ has received lecture honoraria and travel support from B Braun and lecture honoraria from Cardionovum and Nipro. M-AO has received proctoring honoraria and travel support from Biosensors and research support from Terumo. NM reports personal fees from Edwards LifeScience, Medtronic, Biotronik, Novartis, Sanofi Genzyme, and AstraZeneca, outside the

submitted work. GL is a medical user advisory board member for REVA Medical and has relationships with drug and device companies, including Terumo, Acrostak, Bionsensors, Boston Scientific, Abbott Vascular, Impuls Medical, and Orbus Neich. NG has received travel support from B Braun. BS is a shareholder of InnoRa GmbH and was named as co-inventor on patent applications submitted by Charité University Hospital, Berlin, Germany. All other authors declare no competing interests.

Data sharing

As secondary analyses are in progress, data collected for the study, including individual participant data and a data dictionary defining each field in the set, will not be made available to others. When all analyses will be finished, data may made available.

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Figure legends

Fig. 1: Trial profile. TIMI, thrombolysis in myocardial infarction; DCB, drug-coated balloons; DES, drug-eluting stents

Fig. 2: Kaplan-Meier estimates of the cumulative probabilities of major adverse cardiac events (MACE) in the two study arms during 3 years for the full analysis set. DCB, drug-coated balloons; DES, drug-eluting stents.

Fig. 3: Kaplan-Meier estimates of the cumulative probabilities of major adverse cardiac events (MACE) in the different device subgroups during 3 years. DCB, drug-coated balloons; DES, drug-eluting stents.

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Table 1: Baseline Characteristics for the full analysis set

	Overall	**DCB**	**DES**
n	758	382	376
Age (mean, SD)	67.79 (10.34)	67.18 (10.33)	68.42 (10.32)
Male Sex (%)	557 (73.5)	295 (77.2)	262 (69.7)*
BMI (mean, SD)	28.29 (4.54)	28.42 (4.54)	28.15 (4.55)
Smoking (%)			
- Current smoker	154 (20.8)	82 (21.9)	72 (19.6)
- Former smoker	267 (36.0)	144 (38.5)	123 (33.5)
- No	320 (43.2)	148 (39.6)	172 (46.9)
Hypercholesterolemia (%)	521 (69.4)	262 (68.8)	259 (70.0)
Hypertension (%)	656 (86.8)	324 (84.8)	332 (88.8)
Family history (%)	278 (40.3)	150 (42.6)	128 (38.0)
Diabetes (%)			
- IDDM	95 (12.6)	48 (12.6)	47 (12.6)
- NIDDM	157 (20.8)	74 (19.4)	83 (22.3)
- No	502 (66.6)	259 (68.0)	243 (65.1)
Prior myocardial infarction (%)	293 (38.7)	160 (41.9)	133 (35.4)
Prior PCI (%)	476 (62.8)	235 (61.5)	241 (64.1)
Prior CABG (%)	71 (9.4)	37 (9.7)	34 (9.0)
Heart failure (%)	83 (11.0)	48 (12.6)	35 (9.3)

	Overall	DCB	DES
Stroke/TIA (%)			
- No	691 (91.3)	352 (92.4)	339 (90.2)
- Stroke	39 (5.2)	16 (4.2)	23 (6.1)
- TIA	27 (3.6)	13 (3.4)	14 (3.7)
PAOD (%)	53 (7.0)	27 (7.1)	26 (6.9)
COPD (%)	64 (8.4)	28 (7.3)	36 (9.6)
Coronary disease (%)			
- STEMI	15 (2.0)	11 (2.9)	4 (1.1)
- NSTEMI	109 (14.4)	53 (13.9)	56 (14.9)
- Unstable angina	90 (11.9)	48 (12.6)	42 (11.2)
- Stable angina	544 (71.8)	270 (70.7)	274 (72.9)
Renal disease (%)	113 (14.9)	54 (14.1)	59 (15.7)
Liver disease (%)	16 (2.1)	6 (1.6)	10 (2.7)
LVEF (median, IQR)	60 [53, 62]	60 [50, 60]	60 [55, 65]
DAPT duration (median, IQR)			
- Overall	337 [183, 378]	328 [177, 390]	343 [186, 374]
- Clopidogrel	296 [175, 376]	209 [146, 384]	336 [182, 374]
- Ticagrelor or prasugrel	361 [318, 527]	360 [318, 483]	364 [318, 599]

BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; DCB, drug-coated balloon; DES, drug-eluting stent; IDDM, insulin-dependent diabetes mellitus; IQR, interquartile range; LVEF, left ventricular ejection fraction; NIDDM, non insulin-dependent diabetes mellitus; NSTEMI, non ST-elevation myocardial infarction; PAOD, peripheral arterial obstructive disease; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction; TIA, transitory ischemic attack.

Table 2: Primary and secondary endpoints

Type of event	Study arm	1-y events (rate)	1-y HR [95% CI]	2-y events (rate)	2-y HR [95% CI]	3-y events (rate)	3-y HR [95% CI]
MACE	DES	28 (8%)	0.97 [0.58, 1.64]	41 (11%)	1.01 [0.66, 1.56]	53 (15%)	0.99 [0.68, 1.45]
	DCB	28 (7%)		42 (11%)		53 (15%)	
Cardiac death	DES	5 (1%)	2.33 [0.82, 6.62]	9 (3%)	1.53 [0.66, 3.55]	13 (4%)	1.29 [0.63, 2.66]
	DCB	12 (3%)		14 (4%)		17 (5%)	
Non-fatal MI	DES	13 (4%)	0.46 [0.17, 1.20]	19 (5%)	0.74 [0.37, 1.47]	23 (6%)	0.82 [0.45, 1.51]
	DCB	6 (2%)		14 (4%)		19 (6%)	
TVR	DES	17 (5%)	0.75 [0.36, 1.55]	26 (7%)	0.89 [0.51, 1.56]	32 (9%)	0.95 [0.58, 1.56]
	DCB	13 (4%)		23 (6%)		30 (9%)	
Major bleeding	DES	9 (3%)	0.45 [0.14, 1.46]	13 (4%)	0.32 [0.10, 0.97]	14 (4%)	0.43 [0.17, 1.13]
	DCB	4 (1%)		4 (1%)		6 (2%)	
Net clinical benefit	DES	36 (10%)	0.81 [0.50, 1.32]	52 (14%)	0.84 [0.56, 1.25]	64 (18%)	0.86 [0.60, 1.24]

Type of event	Study arm	1-y events (rate)	1-y HR [95% CI]	2-y events (rate)	2-y HR [95% CI]	3-y events (rate)	3-y HR [95% CI]
	DCB	30 (8%)		44 (12%)		56 (16%)	
Stent thrombosis	DES	4 (1%)	0.50 [0.09, 2.73]	6 (2%)	0.33 [0.07, 1.64]	6 (2%)	0.33 [0.07, 1.64]
	DCB	2 (1%)		2 (1%)		2 (1%)	
All-cause death	DES	9 (2.43%)	1.86 [0.83, 4.17]	17 (4.66%)	1.29 [0.68, 2.43]	27 (7.71%)	1.05 [0.62, 1.77]
	DCB	17 (4.51%)		22 (5.90%)		28 (7.63%)	

CI, confidence interval; DCB, drug-coated balloon;, DES, drug-eluting stent; HR, hazard ratio; MACE,major adverse cardiac events; MI; myocardial infarction; TVR, target vessel revascularization.

Figure 1

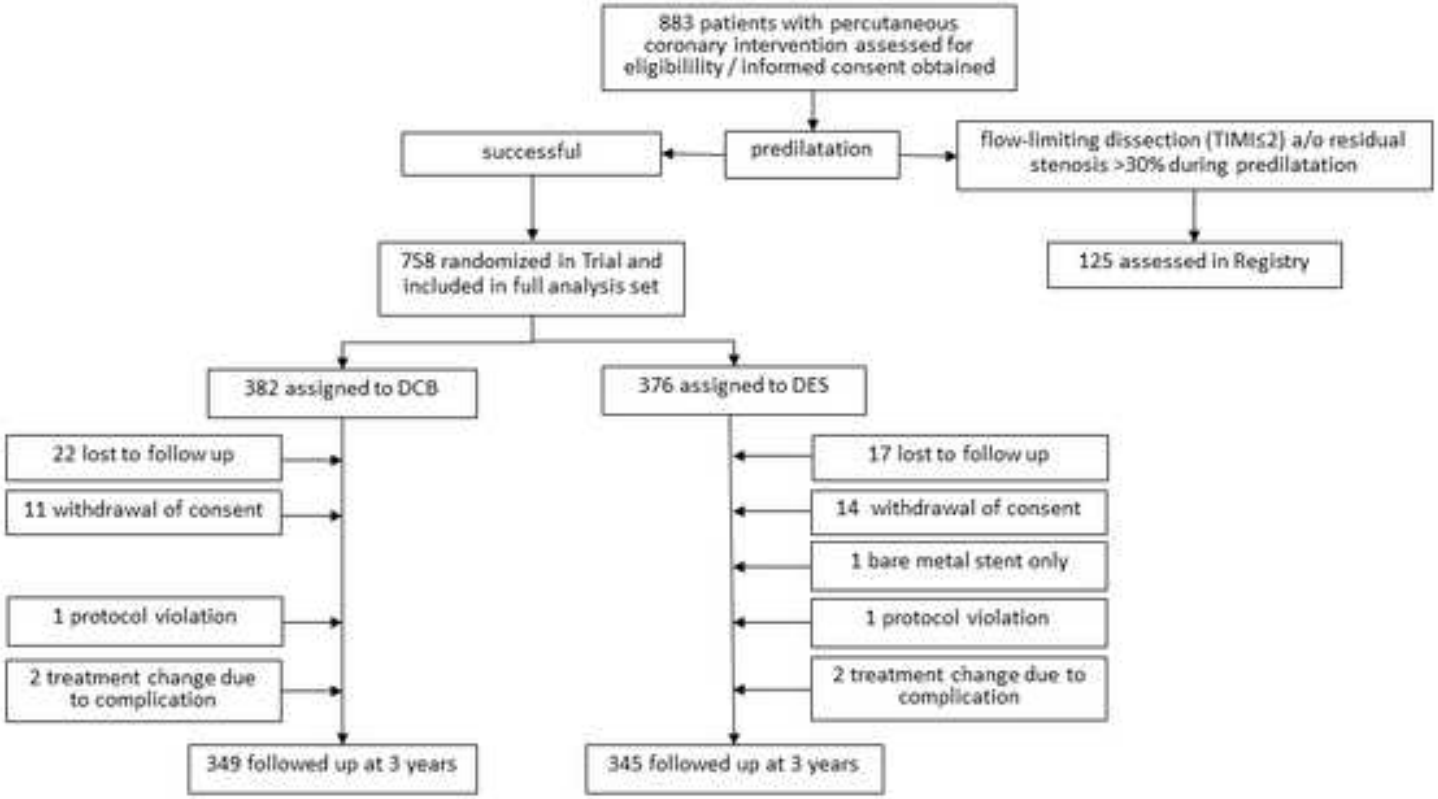

883 patients with percutaneous coronary intervention assessed for eligibility / informed consent obtained
predilatation
successful
flow-limiting dissection (TIMI≤2) a/o residual stenosis >30% during predilatation
125 assessed in Registry
758 randomized in Trial and included in full analysis set
382 assigned to DCB
376 assigned to DES
22 lost to follow up
11 withdrawal of consent
1 protocol violation
2 treatment change due to complication
17 lost to follow up
14 withdrawal of consent
1 bare metal stent only
1 protocol violation
2 treatment change due to complication
349 followed up at 3 years
345 followed up at 3 years

Figure 2

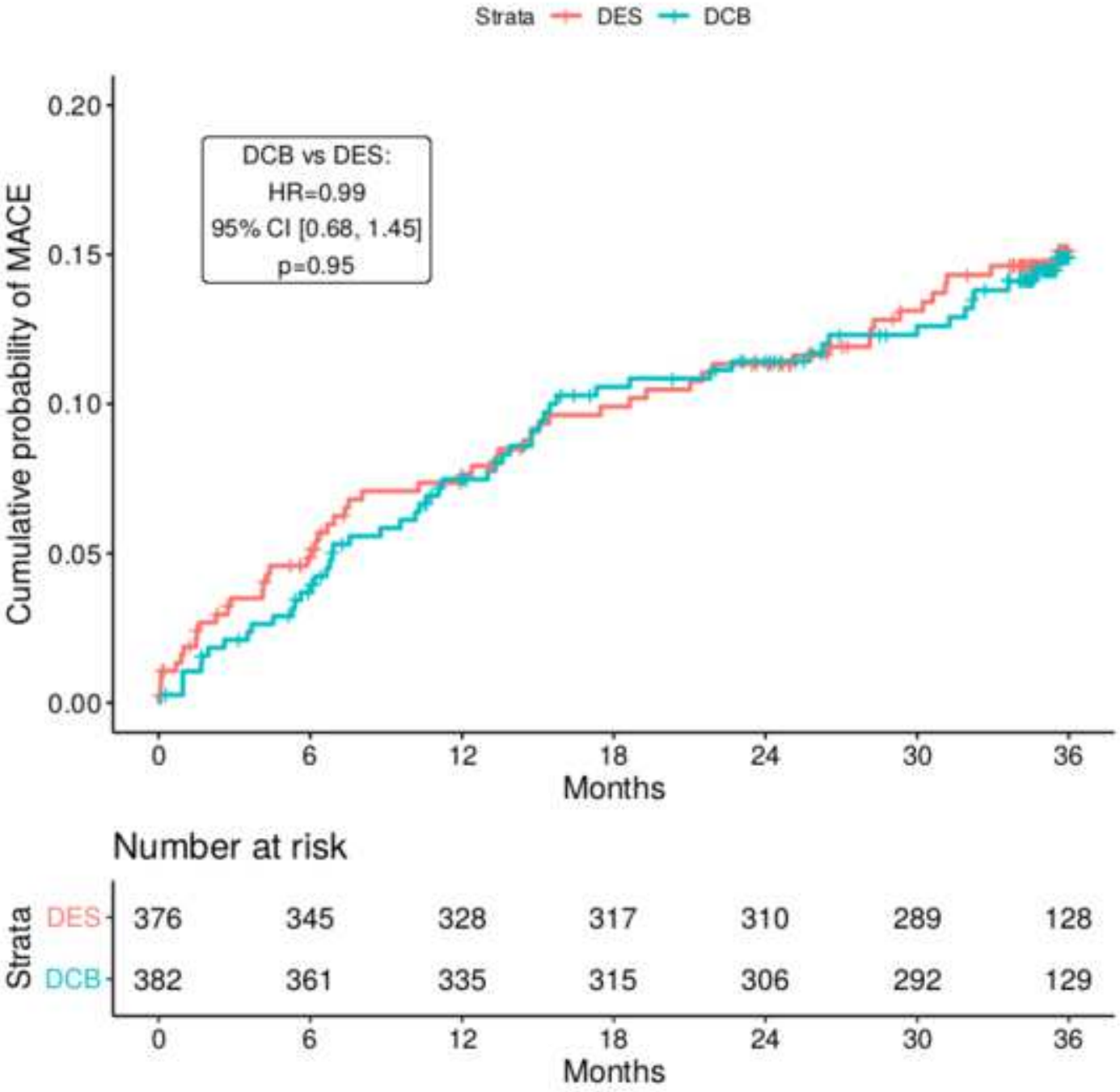
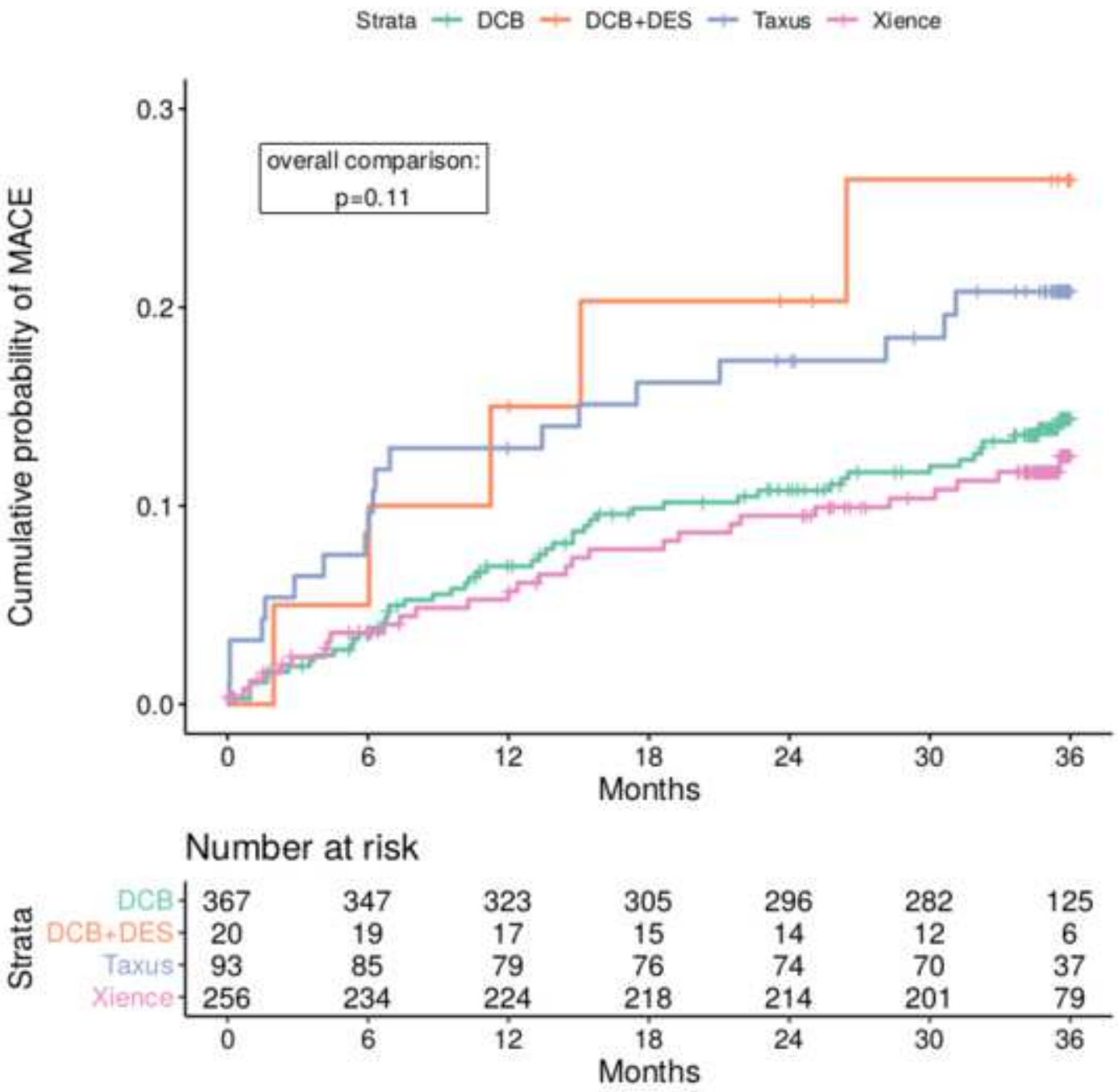

Strata DES DCB
0.20
0.15
0.10
0.05
0.00
Cumulative probability of MACE
DCB vs DES:
HR=0.99
95% CI [0.68, 1.45]
p=0.95
0
6
12
18
24
30
36
Months
Number at risk
Strata
DES 376 345 328 317 310 289 128
DCB 382 361 335 315 306 292 129
0
6
12
18
24
30
36
Months

Figure 3


Strata DCB DCB+DES Taxus Xience
overall comparison:
p=0.11
Cumulative probability of MACE
0.0
0.1
0.2
0.3
0
6
12
18
24
30
36
Months
Number at risk
Strata
DCB 367 347 323 305 296 282 125
DCB+DES 20 19 17 15 14 12 6
Taxus 93 85 79 76 74 70 37
Xience 256 234 224 218 214 201 79
0
6
12
18
24
30
36
Months

Appendix

Contents

Study Organization

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Clinical Protocol

Basel Stent Kosten Effektivitäts Trial
Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions
(BASKET-SMALL 2)

A prospective, randomized, controlled, open label, multicenter trial to test the non-inferiority of drug eluting balloon vs. drug eluting stent treatment in de novo stenosis of small native vessels regarding efficacy and safety

(Protocol Version 5.02_July 18, 2011)

Amendment 5

May 31th, 2016

Sponsor: Department Cardiology, University Hospital Basel, Switzerland

Primary Investigator/Clinical Trial Leader: Prof Dr. med. Raban V. Jeger

Medical Expert: Prof Dr. med. Raban V. Jeger, Cardiology University Hospital Petersgraben 4, CH-4031 Basel, Switzerland, raban.jeger@usb.ch

Signature: _____ Date: 31.May 2016

Principle Investigator Site:

Name: _____ Site: _____

Signature: _____ Date: _____

Protocol synopsis: BASKET-SMALL 2

Title	Basel Stent Kosten Effektivitäts Trial – Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions.
Hypothesis	In a real-world population undergoing percutaneous coronary intervention (PCI) for de-novo stenoses in small native vessels with a diameter <3 mm, drug eluting balloons (DEB) are non-inferior to drug eluting stents (DES).
Design	Prospective, randomized, controlled, open-label, multicenter, non-inferiority trial. Concomitant registry of patients with suitable inclusion criteria but flow-limiting dissections (Thrombolysis In Myocardial Infarction [TIMI] flow ≤2) or residual stenoses >30% after initial balloon inflation (see below).
Inclusion criteria	PCI of de-novo stenoses in vessels ≥2.0 to <3.0 mm without a flow-limiting dissection or a residual stenosis with the need for stent implantation after initial balloon inflation.
Main exclusion criteria	Instent-restenosis, concomitant large-diameter PCI in the culprit coronary artery.
Intervention	Randomization 1:1 for DES (paclitaxel-eluting Taxus Element®, stent, Boston Scientific Corp, Natick MA, or everolimus-eluting Xience® stent Abbott Vascular, Santa Clara, California, USA) vs. DEB (paclitaxel-eluting SeQuent® Please balloon, B. Braun Melsungen AG, Berlin, Germany).
Registry	Patients without exclusion criteria but flow-limiting dissections and residual stenoses >30% after initial balloon inflation will receive the same DES as in the randomized trial but enter a prospective registry.
Primary endpoint	Major adverse cardiac events (MACE), defined as cardiac death, non-fatal myocardial infarction, and target vessel revascularization after 12 months.
Secondary endpoints	MACE after 24 and 36 months; single components of the primary endpoint, target lesion revascularization, stent thrombosis (possible, probable, definite), overall mortality, TIMI major bleeding, net clinical benefit endpoint (primary endpoint and TIMI major bleeding), and cost-effectiveness after 12, 24, and 36 months.
Sample size	This non-inferiority trial aims to enroll 758 patients to ensure 720 evaluable patients. Assuming a dissection/residual stenosis rate of 33% and a drop-out rate of 5%, a total of 1131 patients will need to be consented.

1. Background

1.1. Treatment of de novo stenoses in small native vessels

In small native vessels, target lesion restenosis after percutaneous coronary intervention (PCI) remains an unresolved issue. Instent-restenosis in small vessels is a clinical problem because lumen loss after stent implantation comprises a larger percentage of the total lumen diameter in small than large vessels. Lumen loss 8 months after balloon angioplasty of small native vessels ≤3.0 mm is 0.56 ± 0.53 mm with a reference diameter of 2.53 ± 0.41 mm, with restenosis rates as high as 50% (1). Although bare metal stent (BMS) implantation after angioplasty reduces restenosis rates considerably compared with angioplasty alone, they still remain high at 25% (2, 3).

Drug-eluting stents (DES) are able to reduce restenosis rates compared with BMS with an even greater benefit in small than large native vessels (4). However, for first-generation DES restenosis rates after DES implantation in small native vessels ≤2.75 mm still lay between 5% and 25% with somewhat better results for sirolimus-eluting than paclitaxel-eluting stents (5-10). Results for newer generations of DES were similar (11, 12).

1.2. Drug eluting balloons

The drug-eluting balloons (DEB) technique has mainly been tested in the clinical scenario of instent-restenosis where DEB demonstrated a similar clinical efficacy as DES (13). The proposed coronary angioplasty balloon catheters (SeQuent Please, B. Braun Melsungen AG, Berlin, Germany) are coated with 3 µg of paclitaxel/mm^2 of balloon surface using iopromide as hydrophilic spacer, with >90% drug release per single balloon inflation.

Recently, a clinical trial testing the use of DEB in native small vessels showed encouraging results (14). In an observational manner, 118 patients with de-novo stenoses in small native vessels with a diameter of 2.25-2.8 mm were treated with a paclitaxel-coated DEB. In this study, 82 of 118 patients (70%) received a DEB, while 32 patients (28%) required an additional BMS due to elastic recoil or dissections. Clinical follow-up was done in all patients after 12 months, while angiographic follow-up was performed in 86% of all patients after 9 months. In patients treated with DEB without BMS implantation, rate of major adverse clinical events (MACE) defined as target lesion revascularization (TLR), myocardial infarction (MI), stent thrombosis, or death, was 6.1% (TLR 4.9%, MI 1.3%), while late lumen loss was 0.18 ± 0.38 mm (minimal in-lesion lumen diameter 1.68 ± 0.34 mm) with an in-lesion binary restenosis rate of 5.5%. Of note, in patients treated with DEB and an additional BMS, MACE rate was 37.5% (TLR 28.1%, MI 3.1%, stent thrombosis 6.3%), while late lumen loss was 0.73 ± 0.74 mm (minimal in-lesion lumen diameter 1.35 ± 0.72 mm) with an in-lesion binary restenosis rate of 41.3%. These high restenosis rates in patients treated with DEB and an additional BMS were explained by the so-called “geographical mismatch” effect. This effect describes the situation of an excessive length of the implanted BMS in comparison to the length of the previously inflated DEB. Geographical mismatch was present in 77% of patients with restenosis but only in 19% in patients without restenosis.

Another recently published randomized trial compared a paclitaxel-eluting balloon (first generation Dior®, Eurocor, Bonn, Germany) to a first-generation paclitaxel-eluting stent (Taxus, Boston Scientific, Natick MA) in small native vessels ≤2.75 mm in diameter (15). Primary endpoint of this study was percent angiographic stenosis after 6 months, while secondary endpoints included MACE, i.e., overall death, new ST elevation MI, and TLR, after 9 months. After enrollment of 57 patients (DEB n=28, DES n=29), the study was interrupted because the primary endpoint was met at interim analysis (percent diameter stenosis after 6 months DEB 44% vs. DES 24%, p=0.029). MACE rates were 36% vs. 14% (p=0.054), mainly driven by higher TLR rates in DEB vs. DES (32% vs. 10%, p=0.15). However, this result was

attributed to a lack of efficacy of the DEB used which has been replaced by a newer-generation device already, rather than a class effect of DEB in native coronary vessels (16).

Given all the available data, DEBs are a promising new technique for the treatment of de-novo stenosis in small vessels if pre-dilatation is performed and geographical mismatch is avoided. This hypothesis needs to be tested in a prospective randomized controlled trial.

1.3. Current state of own research

The BAsel Stent Kosten Effektivitäts Trial (BASKET) was an investigator-driven prospective study performed at the University Hospital Basel to test the cost-effectiveness of DES compared with BMS in PCI irrespective of the indication (17). It showed that DES, i.e., the Cypher® (Cordis Johnson & Johnson, Miami Lakes, FL) and TAXUS® (Boston Scientific Corporation, Natick, MA) stents, were not superior to BMS, i.e., the Vision® stent (Guidant, Indianapolis, IN), in terms of cost-effectiveness with an incremental cost-effectiveness ratio of €18,000 at 6 months or €53,000 at 18 months to prevent one clinical event (18). However, in high-risk patient subgroups, such as patients with PCI in long or small vessels, patients with multivessel disease or multivessel interventions, and elderly patients, DES were more cost-effective or even cost saving. BASKET-LAte Thrombotic Events (BASKET-LATE) was a prospective observational follow-up study of BASKET in survivors of the initial 6 months which were followed for another 12 months and identified an excess in late cardiac deaths or myocardial infarctions in patients treated with DES compared with BMS, most likely due to late or very late stent thrombosis (19). Moreover, analysis of specific subgroups revealed that patients with saphenous vein grafts and small vessel, i.e., <3.0 mm, benefited most from DES, not only by reducing target vessel revascularization, but also rates of cardiac death and nonfatal myocardial infarctions (4). Therefore, several new randomized controlled trials were initiated, such as BASKET-PROVE comparing the effect of DES vs. BMS in large native vessels (20), BASKET-SAVAGE comparing the effect of DES vs. BMS in saphenous venous grafts, and BASKET-SMALL.

BASKET-SMALL (Late Clinical Events After Drug-eluting Stents With Versus Without Bioresorbable Polymer in Patients With Small Vessel Stenting) was a prospective randomized open-label single-center trial that tested two different DES, i.e., the first-generation Taxus® stent (Boston Scientific Corporation, Natick MA), a paclitaxel-eluting stainless steel stent with durable polymer, against the second-generation Endeavor® DES (Medtronic Inc., Minneapolis MN, USA), a zotarolimus-eluting cobalt-chromium stent with a biocompatible phosphorylcholine polymer mimicking a natural cell membrane, in terms of major adverse clinical events (cardiac death, non-fatal myocardial infarction) after 18 months. Enrollment in BASKET-SMALL ended in January 2010, and final results will be available in 2013. The present study is planned as a follow-up study to BASKET-SMALL with a new comparator arm (DEB) which will be tested against either a paclitaxel-eluting or an everolimus-eluting stent. The Taxus Element® stent (Boston Scientific Corporation, Natick MA) is a platinum chromium alloy paclitaxel-eluting stent designed to improve radial strength, radiopacity, and deliverability, while safely providing comparable restenosis benefit compared with a previous-generation paclitaxel-eluting stent (12, 21). The Xience® (Abbott Vascular, Santa Clara, California, USA) stent is a cobalt-chromium alloy everolimus-eluting stent which is currently the most often sold drug-eluting stent worldwide (22, 23).

2. Study hypothesis

In a real-world population undergoing PCI for de-novo stenosis in small native vessels with a diameter of ≥2.0 to <3.0 mm and without flow-limiting dissections and residual stenosis of >30% after initial balloon inflation, i.e., without the need for stent implantation, DEB are non-inferior to DES in reducing MACE rates at 12 months.

3. Study objectives

The primary objective of this study is to demonstrate the non-inferiority of drug-eluting balloons (DEB) to drug-eluting stents (DES) in patients undergoing percutaneous coronary intervention (PCI) for de-novo stenosis in small native vessels with a diameter <3 mm, with regard to the incidence of major adverse cardiac events after 12 months.

The primary endpoint is the incidence of a MACE after 12 months. MACE is defined as the composite of

- Cardiac death
- Non-fatal myocardial infarction defined according to current guidelines (24)
- Target vessel revascularization

Secondary endpoints are

- MACE after 24 and 36 months.
- The single components of the primary endpoint including target lesion revascularization after 12, 24, and 36 months.
- Possible, probable, and definite stent thrombosis defined according to the ARC criteria (25) after 12, 24, and 36 months; all stent thrombosis defined according to the ARC criteria (25) after 12, 24, and 36 months.
- Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding after 12, 24, and 36 months (24).
- Net clinical benefit consisting of the primary endpoint and the BARC Type 3 to 5 bleeding after 12, 24, and 36 months.
- Cost-effectiveness of DEB vs. DES after 12, 24, and 36 months.

All events will be adjudicated by an independent Critical Events Committee.

4. Investigational plan

4.1. Study design

This is a prospective, randomized, controlled, open-label, multicenter non-inferiority trial. Patients with de-novo stenosis of small native vessels ≥2.0 to <3.0 mm in diameter undergoing PCI will be randomized in a 1:1 fashion to either angioplasty with a DEB (paclitaxel-eluting SeQuent® Please balloon, B. Braun Melsungen AG, Berlin, Germany) or implantation of a DES (Xience®, Abbott Vascular, Santa Clara, California, USA, or Taxus Element® stent, Boston Scientific Corporation, Natick MA). All generations of Xience stents (Xience V®, Xience Prime®, Xience Xpedition®, Xience Alpine®) and Sequent balloons are allowed (Sequent Please®, Sequent Please Neo®).

4.2. Screening and enrollment

All patients undergoing PCI in small native vessels ≥2.0 to <3.0 mm will be screened for eligibility irrespective of the indication for PCI. Since the vessel size is not known before catheterization, randomization is possible in the cathlab only. After informed consent, patients with matching inclusion and missing exclusion criteria will be enrolled into the study (either randomized trial or registry). Randomization of patients without emergency intervention will be included in the study after giving written informed consent. Since BASKET-SMALL 2 is an all-comer, real-world trial, the quality of the trial strongly depends on

inclusion of not only elective, but also emergency patients with acute coronary syndrome and myocardial infarction. Since these patients commonly suffer from acute chest pain and dyspnea and since every minute of time delay would adversely affect prognosis, it is ethically not acceptable to postpone the intervention to obtain written informed consent prior to study inclusion (in accordance with the Swiss federal law on drugs and medical devices [Heilmittelgesetz], Art. 56). Thus, as soon as coronary intervention is planned and the patient fulfills study entry criteria, the patient will be informed about the trial and asked for oral consent by the operator in charge. This will be done in parallel to preparation of material for coronary intervention, guaranteeing no time delay by inclusion of the patient in the study. Oral consent will be documented on the informed consent form by a second medical person not being involved in the trial. After the PCI-procedure the patient will have to give the definitive written informed consent.

Before PCI, all patients must be treated with an adequate dose of acetylsalicylic acid and a thienopyridine (clopidogrel or prasugrel) or ticagrelor (either continuous therapy or loading dose).

PCI will be performed with pre-dilatation of the stenosis with an angioplasty balloon (plain old balloon angioplasty, POBA) using standard compliant balloons, non-compliant balloons and cutting or scoring balloons). If the lesion shows a flow-limiting dissection (TIMI ≤2), i.e., a dissection type C to F according to the National Heart, Lung, and Blood Institute classification (26), or a residual stenosis >30% after initial balloon inflation as estimated by the physician in charge, patients will not be enrolled into the randomized trial, but enter a prospective registry with the same follow-up as in the randomized trial. In these patients, the same type of DES as in the randomized arm of the study will be used.

In the DEB arm, treatment should follow the recommendations of the German Consensus Group on DEB interventions (27):

- According to the “DEB-only” strategy for small vessel disease the stenosis should be pre-dilated with a POBA catheter with a balloon/vessel ratio 0.8 to 1.0. In case of non-complete balloon inflation the use of a cutting or scoring balloon should be considered. The DEB should be used after successful pre-dilatation only. Subsequently, the DEB (on each side longer than the POBA balloon by 2-3 mm to avoid geographical mismatch) is inflated at nominal pressure (8-10 bar) for a minimum of 30 seconds (14). If a significant dissection and/or a residual stenosis of >30% after DEB occurs, spot stenting using a DES (stent not specified) may be recommended, again avoiding geographical mismatch (stent not specified).
- In bifurcation lesions, both main and side branch pre-dilatation should be performed. If the main branch exhibits a good result without dissection, both side and main branch should be treated by DEB (no kissing-balloon technique required). If the main branch exhibits a dissection, the side branch should be treated by DEB first followed by the main branch that should be treated by DES (stent not specified); in case of a >75% stenosis of the side branch or a TIMI flow <3, a final treatment by kissing-balloon inflation should be performed.

For specific recommendations regarding the use of the DEB, see Appendix 1.

Any additional lesion in the culprit artery must be treated by DEB. If patients have a concomitant lesion in an epicardial artery other than the culprit vessel requiring a stent ≥3.0 mm, this lesion should be treated by DES (stent not specified).

After angioplasty, patients will receive acetylsalicylic acid and a statin indefinitely. In stable patients, dual antiplatelet therapy with a thienopyridine or ticagrelor should be given for 4 weeks (DEB arm) or 12 months (DES arm) (27). In vessel dissections and subsequent spot stenting or bifurcation PCI in the index vessel using a DES or use of a DES in an epicardial artery other than the culprit vessel, dual antiplatelet therapy should be given for at least 6

months (14). In acute coronary syndromes, thienopyridines or ticagrelor should be given for 12 months.

In patients on oral anticoagulation, additional therapy with acetylsalicylic acid and clopidogrel should be given based on their thromboembolic and bleeding risk according to the current guidelines below irrespective of DES or DEB treatment.(28) (see Appendix 3).

4.3. Inclusion/exclusion criteria

To be eligible for the study, patients must meet all of the following criteria:

- Angina pectoris Canadian Cardiovascular Society (CCS) 2 to 4 or silent ischemia as assessed by ergometry, stress echocardiography, stress cardiac magnetic resonance, myocardial perfusion scintigraphy, or fractional flow reserve.
- PCI of de-novo stenosis in vessels ≥2.0 to <3.0 mm in diameter irrespective of the indication (concomitant PCI of a vessel ≥3.0 mm in diameter is permitted if the stenosis is located in a coronary artery other than the culprit vessel).
- No flow-limiting dissection (TIMI ≤2) or residual stenosis >30% after initial dilatation with a standard or non-compliant balloon, as assessed by the physician in charge.
- Written informed consent.

Patients meeting any of the following criteria will be ineligible for the study

1. Concomitant large-diameter PCI in the same coronary artery (LAD, RCX, RCA)
2. PCI of instent-restenoses (culprit lesions)
3. Life expectancy <12 months
4. Pregnancy
5. Enrolled in another coronary intervention study
6. Unable to give informed consent

Patients with a flow-limiting dissection (TIMI ≤2) or a residual stenosis >30% after initial dilatation with a standard or noncompliant balloon will enter a prospective registry with the same follow-up procedures as in the randomized trial. Study procedures will be similar in the registry and the randomized trial.

4.4. Study procedures

Study procedures will be performed as follows:

	Baseline	6 Months	12 Months	24 Months	36 Months
Informed consent	X				
Medical history	X				
Relevant concomitant medication	X	X	X	X	X
Quality of life (EQ-5D)[1]	X	X	X	X	X
Physical exam	X				
Blood sample[2]	X				
Angiography[3]	X				
Clinical event checklist (structured clinical questionnaire)		X	X	X	X

[1] Quality of life is assessed by the validated EQ-5D questionnaire, which consists of a self classifier and a visual analogue scale (29, 30).

[2]Troponin, CPK, Creatinine, Hb, Tc, INR, Quick if available - no extra blood samples

[3]LVEF% if available

PCI Procedure

Baseline PCI can be performed in a single intervention or in multiple steps ('multiple step procedure') if planned during the index procedure.

Routine-/control-angiography without an indication due to symptoms are not allowed.

Follow-up

Follow-up contacts are scheduled after 6 (±1 month), 12 (±2 months), 24 (±2 months), and 36 months (±2 months). Medical history, concomitant medication, and adverse events (heart events, bleeding events, death) will be recorded. Data will be collected by a structured clinical questionnaire and the EQ-5D.

If patients do not answer to follow-up letters and cannot be contacted by phone for follow-up, private physician and/or hospital will be contacted to obtain information regarding clinical events and medication.

5. Statistical methods and power calculation

Detailed methodology for summaries and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. The statistical analysis plan will be finalized before database closure and will be under version control at the Clinical Trial Unit, University Hospital Basel.

5.1 Analysis Data Sets

The intention to treat (ITT) set consists of all patients who were randomized to one of the trial arms. Patients who do not receive the device congruent with the trial arm to which they were randomized will be summarized according to the randomized treatment. The per protocol (PP) set consists of patients in the ITT set without any major protocol violation (defined in the statistical analysis plan) and who have a complete follow-up. Detailed rationale and data listings will be given for patients who sign the consent form but will not undergo an intervention or do not receive an investigational product, as it will be the case for patients with a flow-limiting dissection or a residual stenosis after initial pre-dilatation of the target vessel (see below).

5.2 Patient demographics and baseline characteristics

Demographics and relevant baseline variables will be listed by patient and/or summarized for the PP set. Categorical data will be presented as frequencies and percentages. For continuous variables, means and standard deviations will be presented.

5.3 Primary Objective

The primary objective is to demonstrate the non-inferiority of drug-eluting balloons (DEB, paclitaxel-eluting SeQuent® Please balloon, Braun Melsungen AG, Berlin, Germany) to drug-eluting stents (DES, Xience®, Abbott Vascular, Santa Clara, California, USA, or paclitaxel-eluting TAXUS® Element stent, Boston Scientific, Natick, MA, USA) in patients undergoing percutaneous coronary intervention (PCI) for de-novo stenoses in small native vessels with a diameter of ≥2.0 to <3 mm, with regard to the incidence of MACE after 12 months.

5.4 Primary Endpoint

The primary endpoint is the incidence of a major adverse cardiac event (MACE) after 12 months. MACE is defined as the composite of cardiac death, non-fatal myocardial infarction (MI), and target vessel revascularization (TVR).

5.5 Statistical hypothesis, model, and method of analysis

We will test the following null-hypothesis:

$H_0 : \pi_{DEB} \geq \pi_{DES} + \delta$

where δ is the non-inferiority margin. The alternative hypothesis is:

$H_1 : \pi_{DEB} < \pi_{DES} + \delta$

We set the non-inferiority margin to $\delta = 0.04$ (4% absolute risk difference) (31). In a meta-analysis comparing bare-metal stenting (BMS) with balloon angioplasty in small vessels (< 3 mm), the average observed MACE rates were 17.6% and 22.7%, respectively (2, 3) Thus, if non-inferiority can be shown, also superiority of DEB to BMS, considered as putative placebo, is established ($\pi_{DES} + \delta = 17.5\%$) (32).

The difference in MACE rate $\pi_{DEB} - \pi_{DES}$ will be compared with the non-inferiority margin, using a two-sided 95% confidence interval, using a continuity-corrected modification of the Wilson's score method (33).

The analysis will be performed on the PP set, since in non-inferiority trials, ITT analysis will often increase the risk of falsely claiming non-inferiority (type I error).

Subsequent superiority analysis: If non-inferiority can be shown, a test for superiority of DEB vs. DES using Fisher's exact test will follow. This analysis will be performed on the ITT set, the recommended, more conservative strategy for superiority trials.

Sensitivity analysis: A sensitivity analysis will be done on the ITT set and the results will be compared to the analysis on the PP set to inspect the influence of the missing measurements.

Subgroup investigation: To assess the homogeneity of the difference between DEB and DES the following patient subgroups will be investigated:

- Taxus vs. Xience stents
- Compliant balloons vs. non-compliant balloons vs. cutting or scoring balloons
- Acute, i.e., ST-elevation, non-ST-elevation myocardial infarction, unstable angina, vs. stable coronary disease; ST-elevation myocardial infarction vs. others
- Diabetics vs. non-diabetics
- Coronary 1-vessel disease vs. ≥ 2-vessel disease
- Long lesions ≥ 25 mm vs. short lesions <25 mm
- Prasugrel vs. clopidogrel vs. ticagrelor
- Oral anticoagulation vs. others
- Patients with DEB and additional BMS spot stenting vs. others
- Bifurcation lesions vs. others; in patients with bifurcation lesions: DEB vs. BMS/DEB main branch

Handling of missing values/censoring/discontinuations Careful trial planning and conducting will minimize the occurrence of missing data as far as possible.

5.6 Secondary objective

The secondary objective is to compare the performance of DEB and DES, in patients undergoing PCI for de-novo stenoses in small native vessels with a diameter of ≥2.0 to <3 mm, with regard to a set of secondary endpoints.

Secondary endpoints

- MACE after 24 and 36 months
- The single components of the primary endpoint after 12, 24, and 36 months
- Target lesion revascularization after 12, 24, and 36 months
- Possible, probable, and definite stent thrombosis defined according to the ARC criteria after 12, 24, and 36 months
- Thrombolysis In Myocardial Infarction (TIMI) major bleeding after 12, 24, and 36 months
- Net clinical benefit consisting of the primary endpoint and the TIMI major bleeding after 12, 24, and 36 months
- Cost-effectiveness of DEB vs. DES after 12, 24, and 36 months

Subgroup investigation: The same subgroups as for the primary endpoint may be investigated.

5.7 Estimation of the sample size

Sample size was calculated to be able to show the non-inferiority of DEB to DES regarding the MACE rate within 12 months.

Sample size calculation was based on an expected MACE rate of 7% for patients in the DEB-arm compared with 10% for patients in the DES-arm. Non-inferiority would be declared if the upper limit of the two-sided 95% confidence interval of the absolute risk difference were lower than 4% (non-inferiority margin). The expected MACE rates for DEB is chosen slightly higher than the rate observed for DEB in the PEPCAD 1 study (6.1%) (14) because only one lesion per patient was treated in these studies. In contrast, BASKET SMALL 2 will allow the inclusion of patients with > 1 lesion. The expected MACE rate for DES in small native vessels is the average of the rates observed in two previous studies for everolimus-eluting stents, i.e., 9.1% MACE in (23) and 11% target vessel failure (TVF) in (22) where TVF is the equivalent to MACE in BASKET SMALL 2. Since event rates for paclitaxel-eluting stents are expected to be even higher (12.4%) (12, 21), sample size calculation is based on the DES with expected lower rates of events.

Sample size was calculated using a re-sampling procedure. Each sample size, n_i=1,...,41 = 400, ..., 1200, was evaluated by sampling 9999 times n_i individual samples based on the assumptions described above. Confidence intervals for the difference between proportions were calculated using a continuity-corrected modification of Wilson's score method (33). Sample size was set to ensure at least 90% power ($1 - \beta = 0.9$), at a significance level α = 5%.

For this study, 758 patients should be randomized to ensure 720 evaluable patients considering an overall drop-out rate of 5% after randomization (death due to non cardiac causes, missing follow-up). However, since we expect that only 67% of the patients undergoing initial pre-dilatation with a POBA will be enrolled in the randomized trial, the required number of patients giving consent to trial participation (100%) amounts to 1131. We assume that 33% of the patients will be lost due to flow-limiting dissection (TIMI ≤ 2) or a residual stenosis ≥ 30%. Because patients with > 1 lesion will be included in BASKET

SMALL 2, we expect a higher proportion of patients to be lost than observed in the PEPCAD 1 study (28%) (14).

5.8 Interim analysis: sample size review

The estimation of MACE rates for the two study arms is critical for determining the sample size of the study, yet can be difficult. The MACE rates observed in the trial may considerably deviate from initial guesses, as previously experienced (20). We will therefore re-estimate the sample size after recruitment of a certain proportion of the initially estimated number of patients. If necessary, the sample size will be increased. A sample size reduction or early stopping of the trial will not be considered.

Since at most an increase in the sample size is planned, the sample size review will occur relatively late, after 75% of the patients have been randomized to one of the trial arms (i.e., 569 out of 758 patients).

We will re-estimate the MACE rates π_{DEB} nd π_{DES} in a blinded manner based on the overall MACE rate, as described in Friede et al.(32). Since no hypothesis test is performed, no p-value adjustment to control type I error is needed.

The primary endpoint of the study is MACE after 12 months and the first two follow-up checks are scheduled at 6 and 12 months. Data from all patients having had at least one follow-up can be used for the sample size review. For patients who only had the 6-months follow-up (n_{6mt}), the proportion with MACE events after 12 months ($\pi_{6mt \rightarrow 12m}$) will be estimated from the proportion with MACE events after 6 months (π_{6mt}), assuming a constant hazard rate.

Using the re-estimated MACE rates, the sample size ~*N'* will be re-estimated as before (see above). The sample size will be increased in order to include *N'* evaluable patients whenever *N'* > N preserving a power of 90%.

6. Study management

6.1. Investigators

Principal investigator: R. Jeger

6.2. Participating centers

1. Department of Cardiology University Hospital Basel, Switzerland: C. Kaiser, R. Jeger (Local Principal Investigators)
2. Department of Cardiology Cantonal Hospital St. Gallen, Switzerland: D. Weilenmann (Local Principal Investigator)
3. Department of Cardiology Heart Center Leipzig, Germany: N. Mangner (Local Principal Investigator)
4. Department of Medicine/Cardiology, University Hospital Saarland Homburg/Saar, Germany: B. Scheller (Local Principal Investigator)
5. Department of Cardiology, Zentralklinik Bad Berka, Germany: M.-A. Ohlow (Local Principal Investigator)
6. Department of Internal Medicine/Cardiology University Hospital Ulm, Germany: J. Wöhrle (Local Principal Investigator)
7. Department of Cardiology Cantonal Hospital Luzern, Switzerland: P. Jamshidi, F. Cuculi (Local Principal Investigators)
8. Department of Cardiology Immanuel Clinics Bernau Brandenburg, Germany: C. Butter

9. Department of Internal Medicine Unfallkrankenhaus Berlin, Germany: L. Bruch
10. Department of Internal Medicine Cardiology Charité Berlin, Germany: F. Krackhardt
11. Department of Internal Medicine Klinikum Westphalen Knappschaftskrankenhaus Dortmund, Germany: A. Farah
12. Department of Cardiology, University Hospital Graz, Austria: R. Zweiker
13. Department of Cardiology, University Hospital Ulsan, Jeonha-dong, Korea: S.-E. Shin (Local Principle Investigator)
14. Department of Cardiology Cantonal Hospital Liestal, Switzerland: G. Leibundgut (Local Principle Investigator)
15. Department of Cardiology, University Hospital Jena, Germany: S. Möbius-Winkler (Local Principle investigator)

6.3. Executive Steering Committee

The Steering Committee consists of the study Principle Investigator from each site.

6.4. Critical Events Committee

P. Rickenbacher (Chair), University Hospital Bruderholz, Switzerland; C. Müller and D. Conen, Department of Internal Medicine, University Hospital Basel, Switzerland.

6.5. Monitoring, audit and inspection

The study protocol will undergo Ethics Committee approval at each center. The study will be conducted according to the Good Clinical Practice (GCP) guidelines. Each patient will give written informed consent.

An initiation visit will be performed with all involved study staff on site for training on the protocol before study start. A field monitor will perform monitoring visits on a regular basis to ensure the quality of data and the adherence to the protocol and GCP on site. The aim of monitoring is to evaluate the progress of the study, to verify the accuracy and completeness of case report forms (CRF), to ensure that all protocol requirements, applicable local and national authority regulations and investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records. The extent of monitoring is in the responsibility of the sponsor. The investigator will allow the sponsor to periodically monitor at mutually convenient times during and after the study. Audits by the sponsor or inspections by regulatory authorities during study or after study closure can be performed to ensure proper study conduct and data handling procedures according to GCP guidelines and regulatory requirements. The investigator will permit study related monitoring visits, audits, and regulatory inspections, and provide direct access to all source data. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Definitions of adverse events, serious adverse events, and suspected unexpected serious adverse reactions and the way how they should be reported are listed in Appendix 2.

6.6. Data handling, study documentation, archiving and data retention

Documentation of all study relevant source data of every study participant will be done by completing the study specific CRF. Entries in the CRF must be consistent with information recorded in the source documents. CRF data should be accurate, consistent, complete and reliable and in accordance with GCP principles. For confidentiality reasons CRF must not contain any personal data of study participants that can identify the participant. After data verification (all source documentation, paper CRF, study data base), the data set will be locked by the field monitor. The data can no longer be altered without password, which is

known to the monitor and the clinical trial leader. For data entry, a specific website will be used. The database is located on a password protected drive on the internal computer system of the University Hospital Basel. The data saving process is done every 24 hours by the internal IT service. An investigator site file (IF) is designed to gather all the information related to the study in the center. The IF permits evaluation of study conduct and compliance of the investigator with GCP. The IF must be maintained and updated throughout the study and kept in a secure place.

The investigator will maintain all study-related records, such as CRFs, medical records, laboratory reports, informed consent documents, safety reports, information regarding participants who discontinued, and other pertinent data. All records are to be retained by the investigator as long as required by the applicable regulatory requirement(s) or by an agreement with the sponsor.

7. Funding and Insurance

The study will be planned, conducted, analyzed and interpreted entirely by the investigators and independently from industry. It will be founded by research grants of industry, of the Basel Cardiovascular Research Foundation, and other foundations. DES and DEB will be used as clinically indicated and therefore be paid by health insurers.

For this study with marketed medicinal products in registered indications with no interventions during the follow-up no additional insurance is mandatory for the German sites. However for the Swiss and Austrian sites a supplemental insurance is contracted.

8. Estimated study duration and time table

August 2011	Approval by Ethics Committee
April 2012	Inclusion of first patient
October 2017	Inclusion of last patient
October 2018	Follow-up for primary endpoint completed
October 2020	Long-term follow-up completed

9. Clinical relevance

If DEB proved non-inferiority over DES, a paradigm shift in clinical cardiology might take place regarding the management of symptomatic small-vessel disease. In this case, the implantation of stents in small vessels would only be needed if dissections or residual stenoses after balloon inflation occurred, but not if the initial result was good. Therefore, in app. 75% of all PCI in small vessels, a strategy of balloon inflation would be sufficient to treat patients with stenoses in small vessels. Potential benefits of an approach with balloon inflation only include the absence of instent-restenoses, instent-thromboses, and long-term dual antiplatelet therapy which would affect many patients worldwide.

10. References

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Appendix 1:

SeQuent® Please Interventional Recommendations

1. Handling is the same as with an uncoated balloon catheter.
2. Flushing of guide-wire lumen can be done as usual.
3. Do not unnecessary touch the coated balloon.
4. Avoid mechanical stress on the folded balloon.
5. Avoid unfolding and/or inflation of the balloon before the lesion is reached.
6. The coated balloon should completely cover the lesion.
7. Assure sufficient overlap of balloons if long lesions are treated.
8. Inflation time of 30-60 sec is preferred.
9. Complete release of the drug upon first inflation.
10. SeQuent® Please can be used for post dilatation without drug release.
11. In case of optional stent implantation the DEB should exceed the length of the stent on both sides for 2-3 mm.

Appendix 2:

Pharmacovigilance

1. Defining Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient during or following administration of an investigational product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the trial drugs, whether or not considered related to the trial drugs.

2. Defining Serious Adverse Events (SAEs)

A Serious Adverse Event is defined in general as an untoward (unfavourable) event, associated with trial drug or trial procedure, which:

- is fatal. Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 30 days of the last administration of the study agent must be treated as an SAE and reported as such. All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAE and reported as such,
- is life-threatening
- requires or prolongs hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or a birth defect, or
- may require medical or surgical intervention to prevent one of the outcomes listed above.
- Any other significant clinical event, not falling into any of the criteria above, but which in the opinion of the investigator requires reporting.

3. Defining Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SAEs assigned by the local investigator as both suspected to be related to the trial drugs and unexpected are subject to expedited reporting. An event is unexpected when information is not consistent with the available product information or investigator brochure, or if they add significant information on the specificity or severity of an expected reaction.

4. Reporting AEs

For this study AEs will be reported only if

- event is an ambulant unplanned coronary intervention: PCI with DEB or stent implantation,
- event is associated with any ambulant bleeding, hemorrhage, hematoma, drop of hemoglobin, anemia, blood transfusion,
- event meets SAE criteria as described in section 5.

AEs will be collected for all patients from first intervention of protocol treatment until last follow-up.

Information about AEs, whether volunteered by the patient, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded in the study files.

If requested, details of collected AEs will be made available after completion of the study.

5. Reporting SAEs

For this study SAEs will be reported only if

- event is associated with any cardiac sign or symptom, cardiac diagnostics, cardiac intervention and/or treatment,
- event is associated with any bleeding, hemorrhage, hematoma, drop of hemoglobin, anemia, blood transfusion,
- death will be reported in any case irrespective of cause.

Information about SAEs, whether volunteered by the patient, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded in the study files.

SAEs will be collected for all patients beginning with informed consent. SAEs have to be reported to local Ethics Committee / regulatory authorities according to local regulations.

6. Reporting SUSARs

All SAEs assigned by the local investigator as both suspected to be related to study protocol (treatment/procedures) and unexpected (see definition in section 3) will be reviewed by the Principal Investigators (PIs).

Such SAEs will be classified as SUSARs and will be subject to expedited reporting to concerned ethic committees (EC) and regulatory authorities (RA) according to definitions and timelines specified in the local laws and regulations and according to any specific requests made by regulatory authorities.

As a general guideline the following requirements should be used:

- SUSARs must be reported to the EC / RA within 7 calendar days of the PI (or his research team) being informed of the event, if they result in death or are deemed to be life-threatening.
- Any SUSARs not resulting in death or deemed to be life-threatening must be reported to the EC / RA within 15 calendar days of the PI (or his research team) being informed of the event.

In addition, the sponsor shall inform all participating investigators of findings that could adversely affect the safety of study subjects. The information can be aggregated in a line listing of SUSARs in periods as warranted by the nature of the clinical project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the investigational medicinal product.

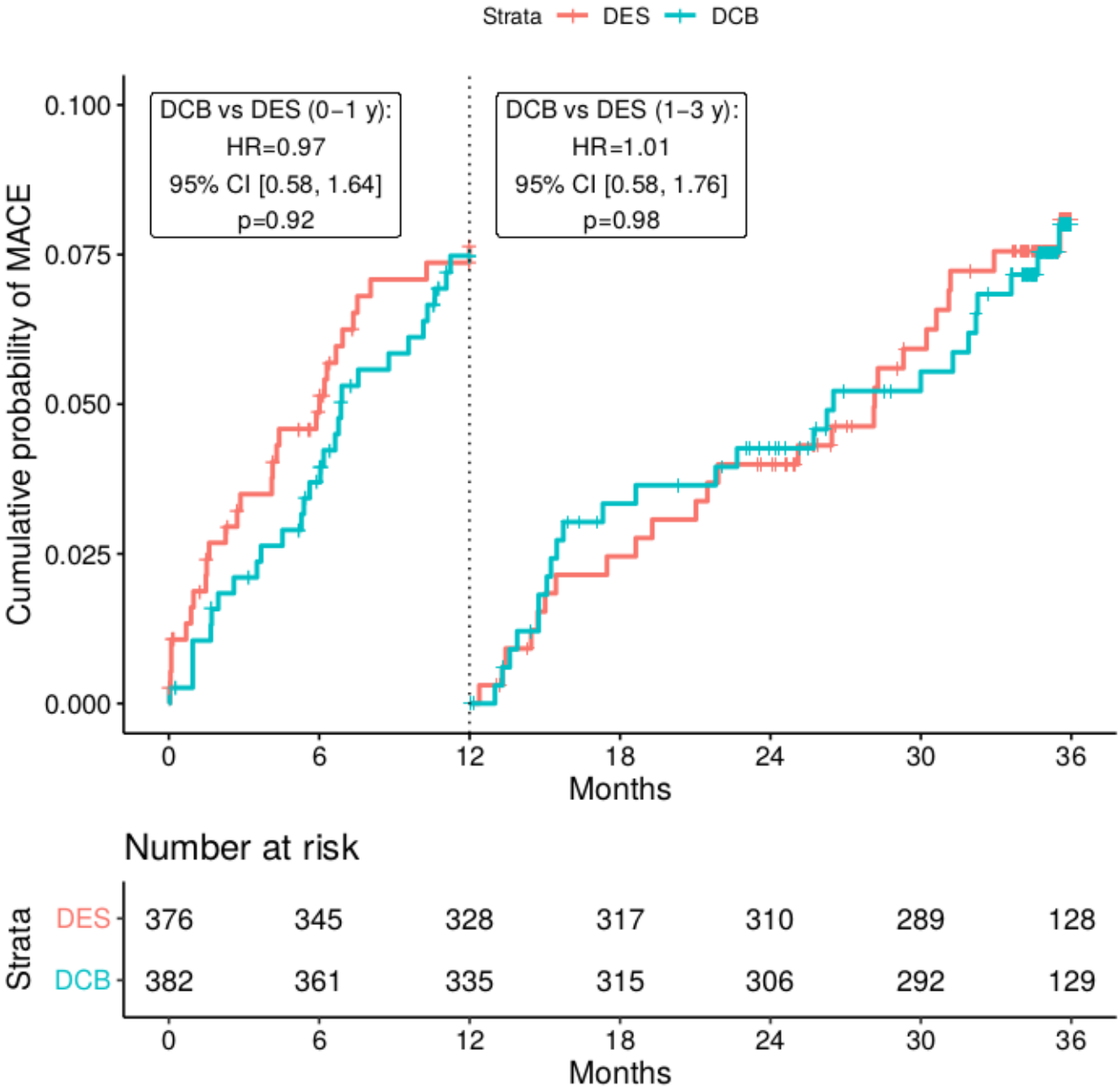
All SUSARs occurring whilst on trial (until 30 days after the last day of the last treatment) must be reported.

Appendix 3:

2014 ESC/EACTS Guidelines on myocardial revascularization

Recommendations	Class[a]	Level[b]	Ref[c]
In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy.	I	C	
New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2).	IIa	C	
In patients with SCAD and atrial fibrillation with CHA_2DS_2-VASc score ≥2 at low bleeding risk (HAS-BLED ≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of at least 1 month after BMS or new-generation DES followed by dual therapy with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
DAPT should be considered as alternative to initial triple therapy for patients with SCAD and atrial fibrillation with a CHA_2DS_2-VASc score ≤1.	IIa	C	
In patients with ACS and atrial fibrillation at low bleeding risk (HAS-BLED≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 6 months irrespective of stent type followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
In patients requiring oral anticoagulation at high bleeding risk (HAS BLED ≥3), triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 1 month followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) irrespective of clinical setting (SCAD or ACS) and stent type (BMS or new-generation DES).	IIa	C	
Dual therapy of (N)OAC and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.	IIb	B	865,870
The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended.	III	C	
Anticoagulation therapy after PCI in ACS patient			
In selected patients who receive ASA and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered in the setting of PCI for ACS if the patient is at low bleeding risk.	IIb	B	855
Anticoagulation during PCI in patients on oral anticoagulation			
It is recommended to use additional parenteral anticoagulation, regardless of the timing of the last dose of (N)OAC.	I	C	
Periprocedural parenteral anticoagulants (bivalirudin, enoxaparin or UFH) should be discontinued immediately after primary PCI.	IIa	C	

Reference: Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, 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(37):2541-619.


Strata DES DCB
DCB vs DES (0–1 y):
HR=0.97
95% CI [0.58, 1.64]
p=0.92
DCB vs DES (1–3 y):
HR=1.01
95% CI [0.58, 1.76]
p=0.98
Cumulative probability of MACE
0.100
0.075
0.050
0.025
0.000
0
6
12
18
24
30
36
Months
Number at risk
Strata
DES 376 345 328 317 310 289 128
DCB 382 361 335 315 306 292 129
0
6
12
18
24
30
36
Months