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

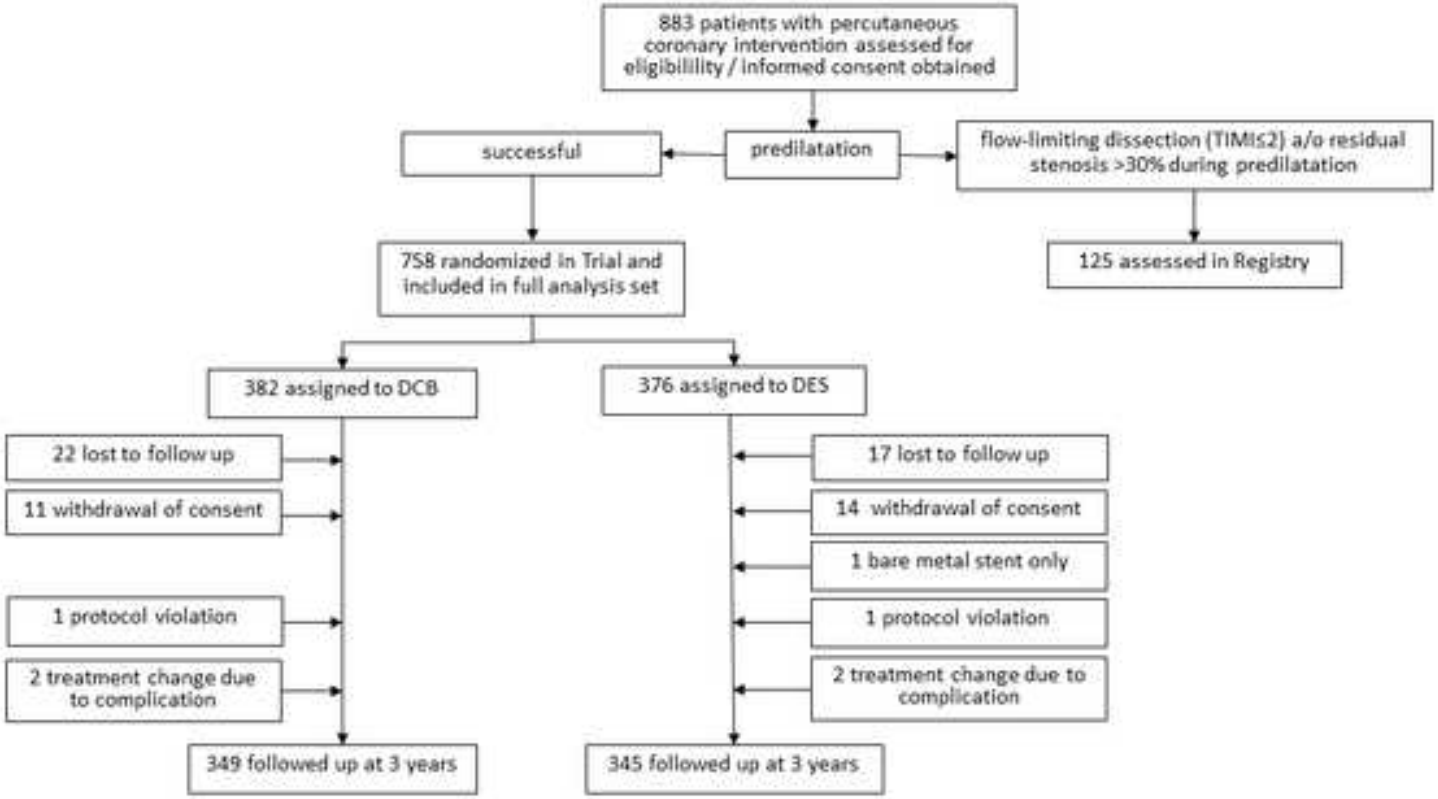

883 patients with percutaneous coronary intervention assessed for eligibility / informed consent obtained
predilatation
successful
flow-limiting dissection (TIMI≤2) a/o residual stenosis >30% during predilatation
125 assessed in Registry
758 randomized in Trial and included in full analysis set
382 assigned 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

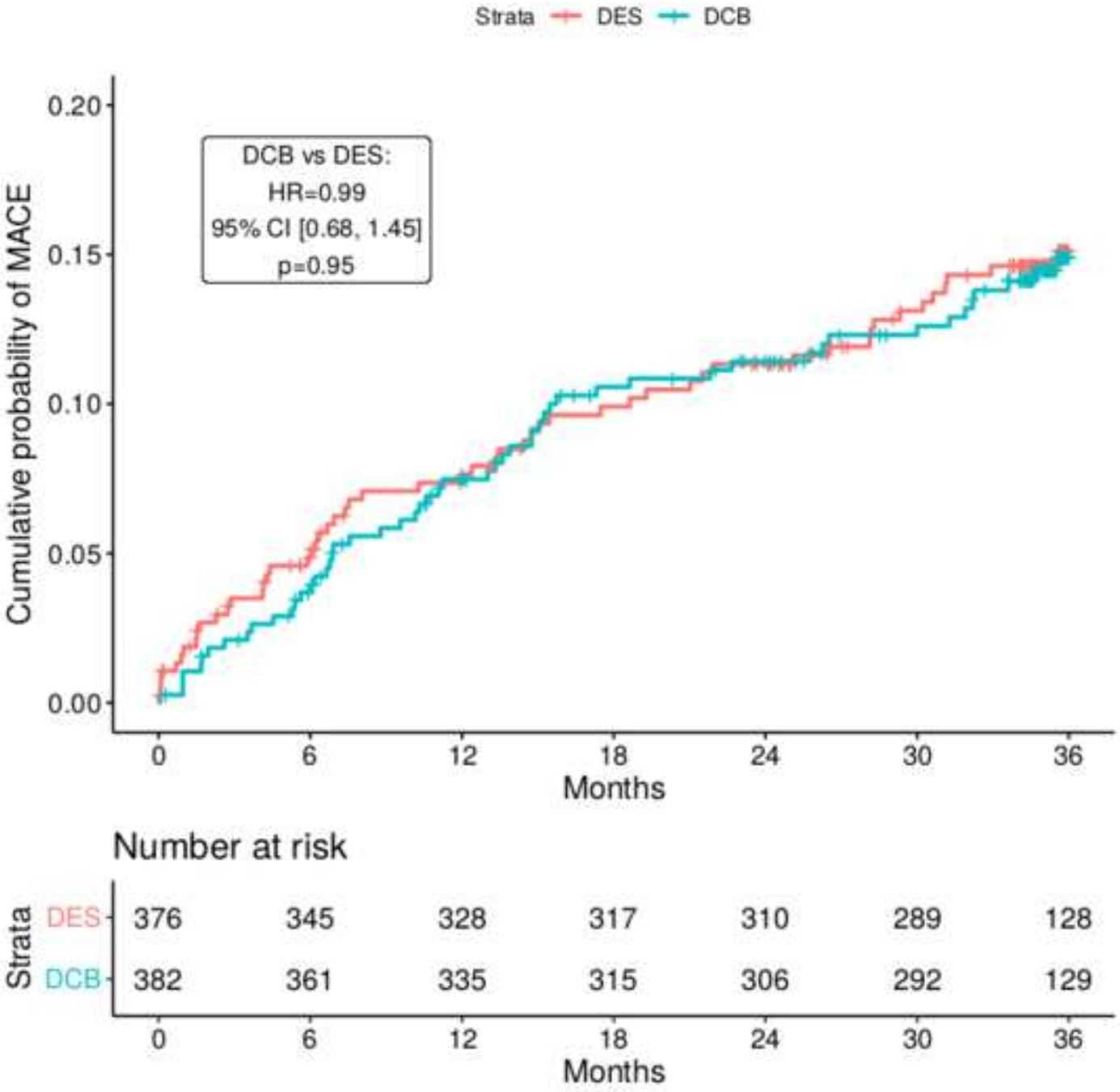
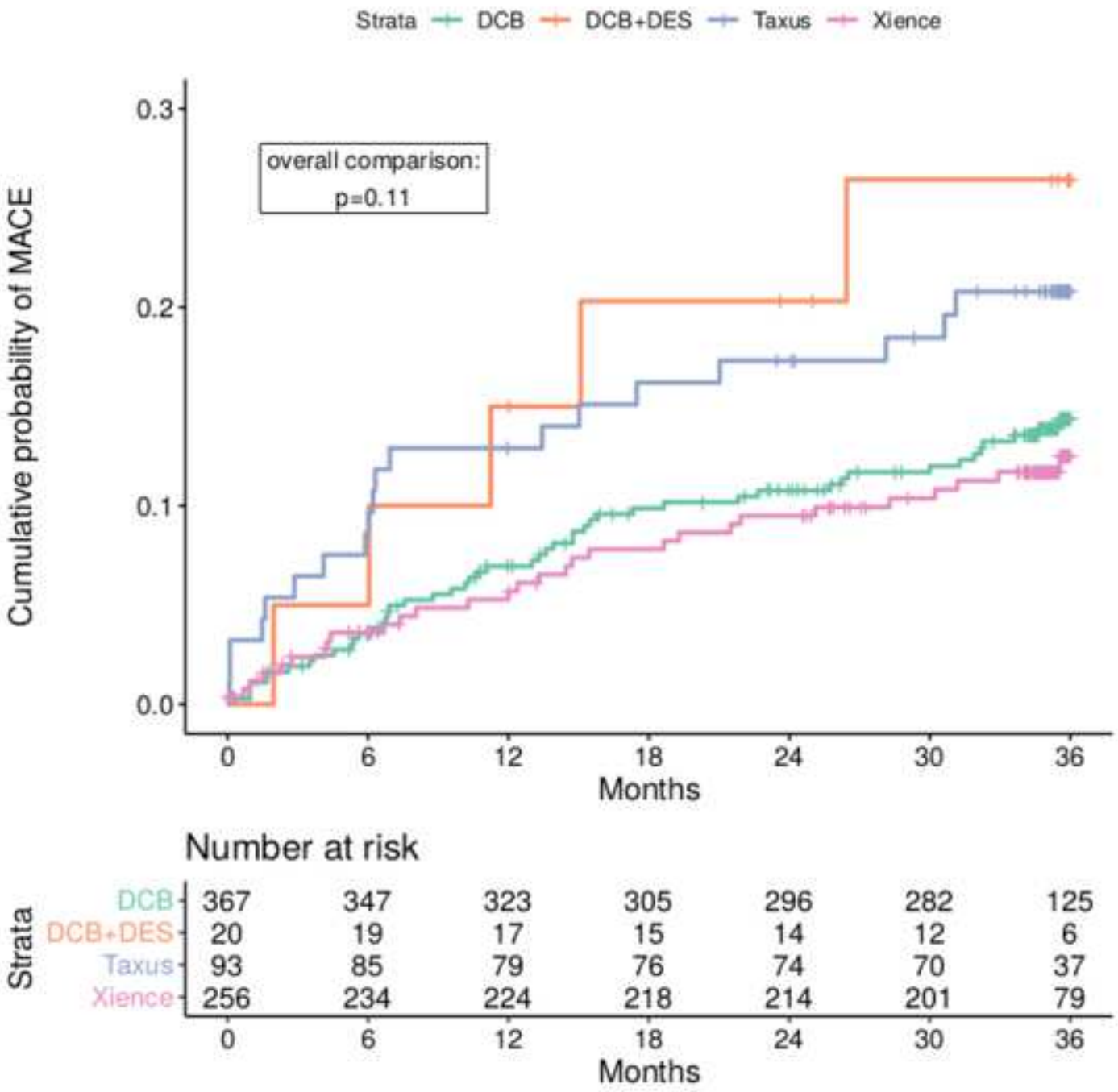

Strata DES DCB
0.20
0.15
0.10
0.05
0.00
Cumulative probability of MACE
DCB vs DES:
HR=0.99
95% CI [0.68, 1.45]
p=0.95
0
6
12
18
24
30
36
Months
Number at risk
Strata
DES 376 345 328 317 310 289 128
DCB 382 361 335 315 306 292 129
0
6
12
18
24
30
36
Months

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