Safety and efficacy of drug-coated balloons versus drug-eluting stents in acute coronary syndromes: A pre-specified analysis of BASKET-SMALL 2

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Clinical Perspective

What is Known?

- A drug-coated balloon (DCB) treatment strategy compared to drug-eluting stent implantation resulted in similar MACE rates at 1-year and 3-year follow-up in patients presenting with acute coronary syndromes (ACS).
- MACE rates in DCB treated patients with an ACS were low and similar to the rates of those receiving DCB treatment for chronic coronary syndrome.

What the Study Adds?

- The DCB treatment strategy has evolved for patients presenting with in-stent restenosis, de-novo small vessel coronary artery disease, and for patients at high bleeding risk.
- Our results expand the knowledge of this approach to patients presenting with an acute coronary syndrome supporting the concept of leaving nothing behind without compromising safety.

Abstract

Background: Drug-coated balloons (DCBs) are an established treatment strategy for coronary artery disease (CAD). Randomized data on the application of DCBs in patients with an acute coronary syndrome (ACS) are limited. We evaluated the impact of clinical presentation (ACS vs chronic coronary syndrome (CCS)) on clinical outcomes in patients undergoing DCB or drug-eluting stent (DES) treatment in a pre-specified analysis of the BASKET-SMALL 2 trial.

Methods: BASKET-SMALL 2 randomized 758 patients with small vessel CAD to DCB or DES treatment and followed them for 3 years regarding major adverse cardiac events (MACE: cardiac death, non-fatal myocardial infarction, and target-vessel revascularization).

Results: Among 758 patients, 214 patients (28.2%) presented with an ACS (15 patients (7%) ST elevation myocardial infarction; 109 patients (50.9%) non-ST elevation myocardial infarction; 90 patients (42.1%) unstable angina pectoris). At 1-year follow-up, there was no significant difference in the incidence of the primary endpoint by randomized treatment in patients with ACS (HR 0.50 [95%-CI 0.19; 1.26] for DCB vs. DES) or CCS (HR 1.29 [95%-CI 0.67; 2.47] for DCB vs. DES). There was no significant interaction between clinical presentation and treatment effect (p for interaction = 0.088). For cardiac death (p for interaction = 0.049) and non-fatal myocardial infarction (p for interaction = 0.010), a significant interaction between clinical presentation and treatment was seen at 1 year with lower rates of these secondary endpoints in ACS patients treated by DCB. At 3-years, there were similar MACE rates throughout groups without significant interaction between clinical presentation and treatment (p for interaction = 0.301). All-cause mortality was higher in ACS compared to CCS; however, there was no difference between DCB and DES irrespective of clinical presentation.

Conclusions: In this subgroup analysis of the BASKET-SMALL 2 trial, there was no interaction between indication for PCI (acute versus chronic coronary syndrome) and treatment effect of DCB versus DES in patients with small vessel CAD.

Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT01574534

Keywords: drug-coated balloon, drug-eluting stent, acute coronary syndrome, chronic coronary syndrome, MACE

Abbreviations:

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

Introduction

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy in patients presenting with acute coronary syndromes (ACS)[1-4] with latest-generation drug-eluting stents (DES) recommended irrespective of patient- and lesion related characteristics. [5, 6] However, drug-coated balloons (DCB) have emerged as a viable alternative for specific patient subgroups including in-stent restenosis (ISR), high bleeding risk, and small vessel coronary artery disease (CAD). [7] Data on the application of DCBs in ACS are scarce with non-randomized studies showing the feasibility and safety of this approach. [8-10] Recently, the randomized PEPCAD NSTEMI trial revealed that a DCB-only strategy was non-inferior to stent treatment in non–ST-segment elevation myocardial infarction concerning target lesion failure at 9 months. [11] Similar results were found in the REVELATION trial for ST-segment elevation myocardial infarction examining the fractional flow reserve of the infarct-related lesion at 9 months as a primary endpoint. [12] Adequately powered randomized trials including long-term follow-up to study clinical outcomes with DCB vs DES treatment in ACS are not available.

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 a DCB treatment against second-generation DES regarding a combined clinical endpoint after 1 year [13] with sustained efficacy and safety at 3 years in small vessel CAD. [14] Patients were eligible for BASKET-SMALL 2 if they had an indication for PCI including acute coronary syndrome, stable angina pectoris, or silent ischemia. Therefore, this study provides the opportunity to examine the clinical outcome of patients treated by DCB vs DES in the setting of an ACS compared to patients receiving this treatment for a chronic coronary syndrome (CCS), which was a pre-specified analysis of the BASKET-SMALL 2 trial. [15]

Methods

As secondary analyses of the trial 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 are finished, data might be made available from the last author (raban.jeger@usb.ch) upon reasonable request.

Study design

This manuscript reports the pre-specified sub-study on DCB and DES outcomes according to the clinical presentation of acute vs chronic coronary syndrome in the BASKET-SMALL 2 trial. [15] In general, target-lesion was also the culprit lesion in ACS since the indication (e.g. ACS, stable angina pectoris) was documented for target-lesion treatment. To verify the results derived from this stratification, patients were also divided into troponin positive vs negative. BASKET-SMALL 2 was an investigator-initiated, randomized, open-label non-inferiority trial. [13] The trial was performed in 14 centers in Germany, Switzerland, and Austria in from 2012 to 2020 in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The ethics committees approved the protocol at all participating centers.

Participants and randomization

Patients with an indication for PCI including an acute coronary syndrome, stable angina pectoris, or silent ischemia, and suitable angiographic anatomy in a small coronary vessel with a diameter between 2 and less than 3 mm were eligible for this study. Successful predilatation of the lesion with absence of higher grade dissections (National Heart, Lung, and Blood Institute grade C to F),[16] decreased blood flow (thrombolysis in myocardial infarction score ≤2), or residual stenosis >30% was obligatory for randomization. [15] Exclusion criteria included a concomitant PCI of lesions ≥3 mm in diameter in the same epicardial coronary artery, PCI of ISR, 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. In urgent cases, oral consent was given before the start of the intervention; oral consent was documented by a second medical person not involved in the trial, and written informed consent was given after the intervention. Randomization was performed using an

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

Procedures

Patients randomized to DCB were treated with the paclitaxel-coated SeQuent Please or SeQuent Please Neo balloon (B. Braun Melsungen AG, Melsungen, Germany), while patients randomized to DES were treated with either the everolimus-eluting Xience stent (72% of DES cases, Abbott Vascular, Santa Clara, CA, USA) or the paclitaxel-eluting Taxus Element stent (28% of DES cases, Boston Scientific, Natick, MA, USA) as described before. [13, 15] PCI with a DCB was performed according to current guidelines;[7] with the DCB 2 to 3 mm longer on each side than the predilatation balloon to avoid geographical mismatch, and inflation at nominal pressure for at least 30 sec. In the case of flow-limiting dissections after DCB treatment, PCI using DES was recommended. After PCI, a dual antiplatelet therapy (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 for 4 weeks after DCB or 6 months after DES in CCS, and in patients with ACS for 12 months irrespective of treatment randomization. In the case of a combination of DCB and bare-metal stents, DAPT was recommended for 3 months, and in the case of a combination of DCB and DES, DAPT was recommended for 6 months. In patients with oral anticoagulation, current guidelines were followed, [17] irrespective of DCB or DES treatment.

Outcomes

The primary endpoint of this analysis was 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. Myocardial infarction was defined according to the guidelines at the time of the study. [18] Secondary endpoints were the single components of the primary endpoint as well as all-cause death, probable or definite stent thrombosis according to the Academic Research Consortium definition,[19] and major bleeding defined as Bleeding

Academic Research Consortium type 3 to 5 bleeding.[20] Net clinical benefit was defined as the combination of major adverse cardiac event and major bleeding.

An independent and blinded clinical events committee adjudicated all endpoints. Follow-up was done after 1, 2, and 3 years with structured clinical questionnaires or phone calls to assess clinical events and medication. Here we report the outcomes at 1- and 3-year follow-up.

Statistical analysis

All statistical analyses were performed on the full analysis set (all patients matching inclusion criteria who provided informed consent and were assigned to a treatment group) according to the intention-to-treat principle. All analyses were conducted with the statistical software package R, using "two-sided" statistical tests and confidence intervals. 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 1 year 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 and adjusted for clinical presentation (ACS vs CCS or troponin positive vs negative). The Kaplan–Meier estimates of the event rates are reported along with the corresponding hazard ratios (HR) calculated as maximum likelihood estimators and 95% Wald confidence intervals (CI). In cases of complete separation, we calculated confidence intervals based on likelihood. 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. No correction for multiple testing was applied due to the exploratory nature of this analysis. Missing data were not an issue, since the endpoints of patients not experiencing an event were considered censored on the last observation date.

Results

Baseline and procedural characteristics

Among 758 patients randomized in the BASKET-SMALL 2 trial, 214 patients (28.2%) presented with an ACS including 15 patients (7%) with ST-elevation myocardial infarction, 109 patients (50.9%) with non-ST elevation myocardial infarction, and 90 patients (42.1%) with unstable angina pectoris.

Baseline characteristics are depicted in *Table* 1. In comparison to CCS patients, ACS patients were less often male (75.7% vs 67.8%, p=0.032), had higher rates of never-smoker (40.0% vs 51.4%, p<0.001), and had less often experienced a previous myocardial infarction (42.3% vs 29.4%, p=0.001), PCI (70.0% vs 44.4%, p<0.001) or coronary artery bypass graft surgery (10.8% vs 5.6%, p=0.037). All other baseline parameters were well balanced between groups.

Procedural characteristics are shown in *Table 2*. According to randomization, treatment with DCB and DES was equally distributed in CCS and ACS (CCS: 49.6% DCB and 50.4% DES; ACS: 52.3% DCB and 47.7% DES). The distribution of treated vessels was comparable between groups, however, ACS patients had less often multivessel disease (82.4% vs 70.1%, p<0.001). Within each treatment stratum, procedural success rates were comparable between groups and procedural factors were not clinically meaningful different between ACS and CCS. The overall duration of DAPT was longer in ACS than in CCS (362 [IQR 202; 472] days vs 316 [IQR 179; 368], p<0.001). The Kaplan-Meier estimates of the probability to remain on DAPT during 12 months, for patients who started on DAPT are shown in *Figure S1*. They were 50.0% in ACS-DCB, 36.7% in ACS-DES, 26.3% in DCB-CCS, and 27.8% in DES-CCS (p<0.001).

For detailed information on baseline and procedural characteristics according to clinical presentation and treatment group, please refer to *Tables S1-2*.

Clinical outcome at 1-year and 3-year follow-up

Outcomes according to clinical presentation and treatment stratum at 1-year and 3-year follow-up are summarized in *Table 3* and *Figure 1*. At 1-year follow-up, there was no significant difference in the incidence of the primary endpoint by randomized treatment in patients with ACS (HR 0.50 [95%-CI 0.19; 1.26] for DCB vs. DES) or CCS (HR 1.29 [95%-CI 0.67; 2.47] for DCB vs. DES). There was no

significant interaction between clinical presentation and treatment effect (p-value for interaction = 0.088). For cardiac death (p-value for interaction = 0.049) and non-fatal myocardial infarction (p-value for interaction = 0.010), a significant interaction between clinical presentation and treatment was seen at 1 year with lower rates of these secondary endpoints in ACS patients treated by DCB (cardiac death: HR 0.66 [95%-CI 0.15; 2.95]; non-fatal myocardial infarction: HR 0.00 [95%-CI 0.00; 0.32]). CCS patients treated by DCB had higher rates of cardiac death compared to CCS patients treated by DES at 1-year follow-up (HR 8.09 [95%-CI 1.02; 64.04], a finding that diminished over time (3-year follow-up: HR 1.60 [95%-CI 0.66; 3.87]). Regarding the remaining secondary endpoints, no significant interaction between clinical presentation and treatment effect was detected with comparable rates between DCB and DES in CCS and ACS patients.

At 3-year follow-up, there remained no significant difference in the incidence of the primary endpoint by randomized treatment in patients with ACS (HR 0.71 [95%-CI 0.35; 1.45] for DCB vs. DES) or CCS (HR 1.10 [95%-CI 0.70; 1.73] for DCB vs. DES), and no significant interaction between clinical presentation and treatment effect (p-value for interaction = 0.301). The secondary endpoints analysis revealed no significant interaction between clinical presentation and treatment effect with comparable rates between DCB and DES in CCS and ACS patients.

Probable or definite stent thrombosis occurred in both treatment groups since stents were also implanted in patients in the DCB group, typically in other parts of the coronary vasculature. Rates were low and not statistically different between the DCB and DES groups. There was no acute vessel closure in DCB lesions.

All-cause mortality was significantly higher in ACS compared to CCS at 1 year (HR 2.59 [95%-CI 1.13; 5.91]) and numerically higher at 3 years (HR 1.71 [95%-CI 0.96; 3.06]); however, there was no difference between DCB and DES-treated patients irrespective of clinical presentation at any time point indicating safety of the paclitaxel based treatment within the DCB group.

Analysis of troponin positive vs negative patients

Among 758 patients randomized in the BASKET-SMALL 2 trial, 124 patients (16.4%) presented with troponin positive coronary syndromes. The analysis of troponin positive vs negative resembled the findings of the main analysis supporting the robustness of the results (*Tables S3-7* and *Figure S2*)

Discussion

Three major findings arise from this pre-specified analysis of the BASKET-SMALL 2 trial. 1) There was no interaction between indication for PCI (acute versus chronic coronary syndrome) and treatment effect of DCB versus DES in patients with small vessel CAD. 2) At 3-year follow-up, sustained efficacy and safety of the DCB was evident in both ACS and CCS without significant interaction between treatment and clinical presentation. 3) All-cause mortality was higher in ACS patients throughout follow-up; however, it was not different between patients treated with DES or DCB proving the safety of paclitaxel coated balloons in coronary interventions for small vessel CAD.

The BASKET-SMALL 2 trial was the largest randomized clinical trial evaluating the safety and efficacy of DCB vs DES in small vessel CAD showing comparable MACE rates between both treatment forms after 1 year and during long term follow-up. [13, 14] According to the inclusion criteria of BASKET-SMALL 2, patients were eligible while presenting with both CCS and ACS. Therefore, 28.2% of all patients were treated for ACS, and 16.4% had a troponin positive ACS. Other clinical trials investigated the treatment effect of DCB vs DES in small vessel coronary artery disease using angiographic endpoints showing non-inferiority [21] or even superiority of DCBs to its DES comparator. [22, 23] In particular, the PICCOLETO II trial (n=232) included a substantial number of patients presenting with an ACS including 14.4% with unstable angina, 21.1% with NSTEMI, and 10.3% with STEMI (late presenter). [22] This study showed superiority of a paclitaxel-coated balloon (Elutax SV/Emperor) compared to an everolimus-eluting stent (Xience) with regard to in-lesion late lumen loss indicating the angiographic success of DCB treatment in a cohort of patients with a high proportion of ACS. Although not statistically powered, the clinical outcome was comparable between DCB and DES in this trial. [22] Our data in a larger series of patients support these positive results with comparable rates of MACE for DCB and DES in patients presenting with CCS and similar or even numerically lower event rates in patients with an ACS indicating the non-inferiority of DCB treatment of small vessel CAD in the setting of an ACS. Remarkably, at 1-year follow-up there was a significant interaction between the treatment and clinical presentation regarding the components cardiac death and non-fatal myocardial infarction with the lowest rates of those endpoints observed in ACS patients treated by DCB. Noteworthy, ACS patients

treated by DCB and being on DAPT at discharge also had the highest probability to be on DAPT at 1 year. Overall, this finding must be interpreted cautiously since these are only secondary endpoints in a pre-specified analysis of a non-inferiority trial that has not been powered for this sub-investigation. However, the consistently lower rates of MACE and its components in DCB treated ACS patients are encouraging. In general, MACE rates are higher in patients presenting with an ACS compared to CCS. [24] However, in our analysis, this was only true for ACS patients treated by DES, whereas DCB treated patients had comparable MACE rates to DCB treated CCS patients. Moreover, the sensitivity analysis of troponin positive vs negative coronary syndromes resembled the main analysis findings supporting the robustness and plausibility of our results. Overall, these data implicate that a DCB treatment strategy in ACS caused by small vessel CAD is a viable alternative to DES implantation. The numerically higher rates of cardiac and all-cause death in DCB treated CCS patients have already been extensively discussed elsewhere. [25] Briefly, most of the DCB patients experiencing unknown or sudden cardiac deaths were treated with both DCB and DES (before, concomitant or bail out) and, therefore, deaths cannot be ascribed to DCB alone.

Recently, two trials specifically investigated the effect of DCB vs DES in an ACS setting – the PEPCAD NSTEMI trial in patients with NSTEMI[11] and the REVELATION trial in patients presenting with STEMI. [12] In PEPCAD NSTEMI, 210 patients with NSTEMI were randomized to DCB vs stent implantation (DES (44%) or bare-metal stent (56%)). The primary endpoint was target lesion failure, a combined clinical endpoint consisting of cardiac or unknown death, reinfarction, and target lesion revascularization after nine months. During a follow-up of 9.2±0.7 months, DCB treatment was non-inferior to stent treatment with a target lesion failure rate of 3.8% versus 6.6% (intention-to-treat, p=0.53) with no significant interaction for DES vs bare-metal stent.[11] In the REVELATION trial, 120 patients presenting with STEMI were randomized to treatment with a DCB or DES. The primary endpoint of this analysis was fractional flow reserve at 9 months, thus allowing for a functional measurement of the infarct-related lesion. The mean fractional flow reserve was not different between groups at 9 months (0.92 ± 0.05 in the DCB group and 0.91 ± 0.06 in the DES group) indicating non-inferiority of a DCB vs DES strategy in patients with STEMI. A limitation of the study is the high dropout rate for the primary endpoint in both groups with only 57% in the DCB group and 65% in the

DES group having a FFR measurement at 9 months. Clinically, there was one abrupt vessel closure requiring treatment after treatment with DCB and two patients (1 in each group) required non-urgent target lesion revascularization during follow-up. [12] Our results in 214 ACS patients with small vessel CAD are in line with the findings of these two trials in specific ACS cohorts confirming the non-inferiority of a DCB compared to a DES strategy not only after 1-year but also after 3-year follow-up.

The most significant advantage of the DCB strategy is the avoidance of permanent implants and, therefore, preventing stent-related complications. Specifically, coronary vasodilator mechanisms are impaired in ACS with differing vessel geometry leading to an increased risk of stent malapposition and consequent complications like stent thrombosis. Indeed, in our study, the risk of stent thrombosis was 2.0% in ACS patients treated with a DES, whereas no acute vessel closure occurred in DCB treated ACS patients. These findings are supported by an angiographic subanalysis of the BASKET-SMALL 2 trial and the accompanying registry showing that complete thrombotic vessel occlusion only occurred in DES-treated patients.[26] In PEPCAD-NSTEMI, no patient in the DCB group experienced an acute vessel closure[11], and even in the setting of STEMI only 1 out of 60 patients experienced this complication. [12] Moreover, the Swedish SCAAR registry proved in almost 2400 propensity-matched patients that the overall rate of thrombotic vascular occlusion after DCB treatment compared to current-generation DES was significantly lower after five years with acute occlusion rate reduced after a successful DCB strategy. [27] Our data expand these positive findings to the cohort of patients presenting with an ACS caused by small vessel CAD indicating that a DCB treatment strategy is safe in this patient cohort.

Although suffering from major statistical limitations, a recent meta-analysis raised concerns regarding increased mortality in patients with peripheral arterial disease treated by paclitaxel stents and balloon. [28] However, no concerns for using paclitaxel-coated balloons in the coronary system have emerged since a patient-level meta-analysis in patients treated with DCBs for ISR [29] did not show increased mortality rates for paclitaxel-coated balloons. Another meta-analysis in 4.590 patients treated with DCBs for de novo CAD or ISR even proved lower all-cause and cardiac mortality rates at 3 years for paclitaxel-coated balloons vs alternative treatments, in the majority DES. [30] Indeed, all-cause mortality was higher in ACS patients throughout follow-up in our analysis; however, it was not different between patients treated with DCB or DES supporting the results of the aforementioned meta-analyses.

Limitations

The results of this study need to be interpreted in light of the following limitations. First, this is a predefined secondary analysis of a non-inferiority trial. Although reaching the primary endpoint in the main analysis, all further investigations should be considered hypothesis-generating. In particular, this analysis was neither designed nor powered to detect differences between patients presenting with ACS vs CCS. Patients were not randomized according to clinical presentation. Second, the results were obtained in a selected cohort of patients randomized after successful predilatation defined as the absence of >30% residual stenosis and/or flow-limiting dissection [15] supporting current recommendations for a DCB treatment strategy. [7] Thus, the observed results are restricted to the achievement of this angiographic situation prior to DCB treatment and can be defined as a DCB treatment strategy rather than pure DCB treatment. Third, the duration of DAPT was longer in ACS compared to CCS patients with ACS-DCB having the highest probability to be on DAPT at 1-year follow-up. This different medical therapy may limit the external validity of this analysis. Fourth, BASKET-SMALL 2 included only patients with small vessel coronary artery disease, therefore, the results are not transferrable to de-novo lesions in large vessels. Fifth, although being the largest outcome trial in DCB treatment for de-novo lesions, BASKET-SMALL 2 included only a limited number of patients with ACS, thereby reducing the statistical power for this analysis. Finally, the DES group was initially planned with a second-generation paclitaxel-eluting stent that became unavailable during the study leading to a switch of the comparator (everolimus-eluting stent) and an increase of the sample size. [13]

Conclusion

In this subgroup analysis of the BASKET-SMALL 2 trial, there was no interaction between indication for PCI (acute versus chronic coronary syndrome) and treatment effect of DCB versus DES in patients with small vessel CAD. The results for the combined endpoint and its components must be interpreted as hypothesis-generating and further studies in larger cohorts of ACS patients are required before definite conclusions can be drawn.

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Conflict of Interest

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RVJ reports lecture honoraria and travel support from B Braun and lecture honoraria from Cardionovum.

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GL is a medical user advisory board member for REVA Medical and has relationships with drug and device companies, including Terumo, Acrostak, Biosensors, Boston Scientific, Abbott Vascular, Impuls Medical, and Orbus Neich.

NG reports 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.

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All other authors declare no conflict of interest.

Supplemental Materials

Tables S1-7

Figures S1-2I

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Table 1. Baseline characteristics according to clinical presentation

	CCS (n=544)	**ACS (n=214)**	**p-value**
Mean age (SD) [years]	67.6 (10.2)	68.3 (10.7)	0.449
Male sex, n (%)	412 (75.7)	145 (67.8)	0.032
Mean body mass index (SD) [kg/m²]	28.3 (4.4)	28.2 (4.8)	0.772
Smoking, n (%)			<0.001
Current smoker	102 (19.1)	52 (25.0)	
Former smoker	218 (40.9)	49 (23.6)	
Never smoker	213 (40.0)	107 (51.4)	
Hypercholesterolemia, n (%)	379 (70.1)	142 (67.6)	0.574
Hypertension, n (%)	469 (86.2)	187 (88.2)	0.544
Family history of CAD, n (%)	207 (41.2)	71 (38.2)	0.535
Diabetes, n (%)			0.512
IDDM	67 (12.3)	28 (13.3)	
NIDDM	119 (21.9)	38 (18.1)	
None	358 (65.8)	144 (68.6)	
Previous MI, n (%)	230 (42.3)	63 (29.4)	0.001
Previous PCI, n (%)	381 (70.0)	95 (44.4)	<0.001
Previous CABG, n (%)	59 (10.8)	12 (5.6)	0.037
Heart failure, n (%)	64 (11.8)	19 (8.9)	0.306
Cerebrovascular insult, n (%)			0.740
Stroke	27 (5.0)	12 (5.6)	
TIA	21 (3.9)	6 (2.8)	
None	496 (91.2)	195 (91.5)	
PAOD, n (%)	42 (7.7)	11 (5.1)	0.271
COPD, n (%)	45 (8.3)	19 (8.9)	0.900
Renal dysfunction, n (%)	77 (14.2)	36 (16.8)	0.415
Liver disease, n (%)	10 (1.8)	6 (2.8)	0.581
Presentation, n (%)			n.a.
STEMI	-	15 (7.0)	
NSTEMI	-	109 (50.9)	
Unstable AP	-	90 (42.1)	
CCS	544 (100)	-	
Median LV-EF (IQR) [%]	60 (51; 62)	60 (55; 63)	0.551
Oral anticoagulation, n (%)	41 (7.7)	23 (11.2)	0.175

Values are numbers (%), mean (standard deviation), and median (interquartile range). CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; CAD, coronary artery disease; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; PAOD, peripheral artery occlusive disease; COPD, chronic obstructive lung disease; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; AP, angina pectoris; LV-EF, left ventricular ejection fraction.

Table 2. Procedural data according to clinical presentation

	CCS (n=544)	**ACS (n=214)**	**p-value**
Target vessel			0.390
Left anterior descending artery, n (%)	166 (30.5)	78 (36.5)	
Left circumflex artery, n (%)	261 (48.0)	98 (45.8)	
Right coronary artery, n (%)	115 (21.1)	37 (17.3)	
Left anterior descending and circumflex artery, n (%)	2 (0.4)	1 (0.5)	
Multi vessel disease	448 (82.4)	150 (70.1)	<0.001
Bifurcation lesion, n (%)	36 (6.8)	15 (7.1)	1.000
DAPT duration, days (IQR)			
Overall	316 (179; 368)	362 (202; 472)	<0.001
Clopidogrel	217 (174; 367)	350 (176; 577)	0.055
Ticagrelor/Prasugrel	357 (310; 555)	365 (337; 480)	0.142
DCB, n (%)	270 (49.6)	112 ((52.3)	0.555
Procedural success, % (SD)	97 (16)	94 (24)	0.129
Mean number DCB, n (SD)	1.21 (0.53)	1.14 (0.44)	0.207
Mean length DCB, mm (SD)	20.1 (5.3)	19.9 (4.4)	0.643
Mean effective size DCB, mm (SD)	2.5 (0.3)	2.6 (0.3)	0.052
Mean inflation pressure DCB, atm (SD)	10.8 (3.5)	11.1 (3.1)	0.448
Mean inflation duration DCB, sec (SD)	50 (30)	45 (24)	0.117
DES, n (%)	274 (50.4)	102 (47.7)	0.555
Procedural success, n (%)	98 (13)	98 (15)	0.791
Mean number DES, n (SD)	1.31 (0.64)	1.23 (0.52)	0.251
Mean length DES, mm (SD)	18.0 (5.5)	19 (6.0)	0.389
Mean effective size DES, mm (SD)	2.6 (0.3)	2.6 (0.3)	0.783
Mean inflation pressure DES, atm (SD)	13.3 (3.1)	13.1 (2.2)	0.638
Mean inflation duration DES, sec (SD)	26 (21)	17 (10)	<0.001

Values are numbers (%), mean (standard deviation), and median (interquartile range). CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; DCB, drug-coated balloon; DES, drug-eluting stent; DAPT, dual antiplatelet therapy.

Table 3. Outcomes at 1-year and 3-year follow-up according to clinical presentation

	1-year follow-up				p for interaction	3-year follow-up				p for interaction
	CCS		ACS			CCS		ACS		
MACE										
	DES	**DCB**	**DES**	**DCB**		**DES**	**DCB**	**DES**	**DCB**	
Events, n (%)	16 (6.0)	21 (8.0)	12 (12.0)	7 (6.3)	0.088	36 (14.3)	39 (15.5)	17 (17.3)	14 (13.6)	0.301
HR (95%-CI)	1.29 (0.67; 2.47)		0.50 (0.19; 1.26)			1.10 (0.70; 1.73)		0.71 (0.35; 1.45)		
Cardiac death										
Events, n (%)	1 (0.4)	9 (3.4)	4 (4.0)	3 (2.7)	0.049	8 (3.5)	13 (5.1)	5 (5.0)	4 (3.7)	0.320
HR (95%-CI)	8.09 (1.02; 64.04)		0.66 (0.15; 2.95)			1.60 (0.66; 3.87)		0.73 (0.20; 2.73)		
Non-fatal myocardial infarction										
Events, n (%)	7 (2.6)	6 (2.3)	6 (6.1)	0 (0)	0.010	15 (5.8)	16 (6.7)	8 (8.4)	3 (3.4)	0.108
HR (95%-CI)	0.88 (0.29; 2.63)		0.00 (0.00; 0.32)			1.09 (0.54; 2.21)		0.31 (0.08; 1.16)		
Target vessel revascularization										
Events, n (%)	12 (4.5)	9 (3.5)	5 (5.1)	4 (3.7)	0.866	24 (9.4)	20 (8.3)	8 (8.4)	10 (10.1)	0.687
HR (95%-CI)	0.77 (0.32; 1.82)		0.72 (0.19; 2.70)			0.87 (0.48; 1.58)		1.14 (0.45; 2.89)		
Stent thrombosis										
Events, n (%)	2 (0.7)	2 (0.8)	2 (2.0)	0 (0)	0.129	4 (1.5)	2 (0.8)	2 (2.0)	0 (0)	0.211
HR (95%-CI)	1.02 (0.14; 7.27)		0.00 (0.00; 1.53)			0.52 (0.09; 2.82)		0.00 (0.00; 1.53)		
All-cause death										
Events, n (%)	3 (1.1)	10 (3.8)	6 (5.9)	7 (6.3)	0.175	17 (6.9)	17 (6.6)	10 (10.0)	11 (9.9)	0.962
HR (95%-CI)	3.10 (0.85; 11.31)		1.01 (0.34; 3.02)			1.02 (0.52; 2.00)		0.97 (0.41; 2.29)		
Major bleeding										
Events, n (%)	7 (2.6)	1 (0.4)	2 (2.0)	3 (2.7)	0.120	9 (3.4)	3 (1.3)	5 (5.4)	3 (2.7)	0.685
HR (95%-CI)	0.15 (0.02; 1.20)		1.32 (0.22; 7.96)			0.34 (0.09; 1.26)		0.51 (0.12; 2.16)		
Net clinical benefit										
Events, n (%)	23 (8.6)	21 (8.0)	13 (13)	9 (8.2)	0.427	44 (17.3)	40 (15.9)	20 (20.4)	16 (15.4)	0.489
HR (95%-CI)	0.89 (0.49; 1.62)		0.61 (0.26; 1.44)			0.91 (0.59; 1.40)		0.71 (0.37; 1.37		

All values are numbers of events and Kaplan Meier estimates with the corresponding hazard ratios for DCB vs DES and 95%-Confidence Intervals. CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; DCB, drug-coated balloon; DES, drug-eluting stent.

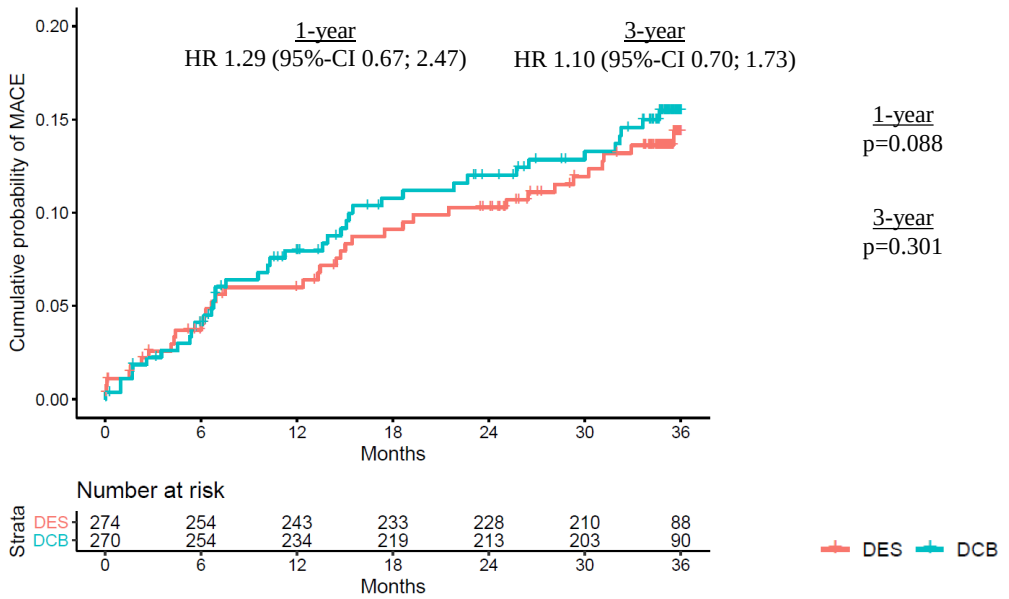
Figure legend

Figure 1: Kaplan-Meier analysis stratified by chronic coronary syndrome (left panels) vs acute coronary syndrome (right panels) comparing drug-coated balloon vs drug-eluting stent treatment for major adverse cardiac events (A) and the components cardiac death (B), non-fatal myocardial infarction (C) and target vessel revascularization (D). Hazard ratios and corresponding 95%-confidence interval are given for drug-coated balloon vs drug-eluting stent at 1-year and 3-year follow-up with p-values for interaction provided between the graphs. CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; DCB, drug-coated balloon; DES, drug-eluting stent; HR, hazard ratio; CI, confidence interval.

A)

CCS

p-value for interaction

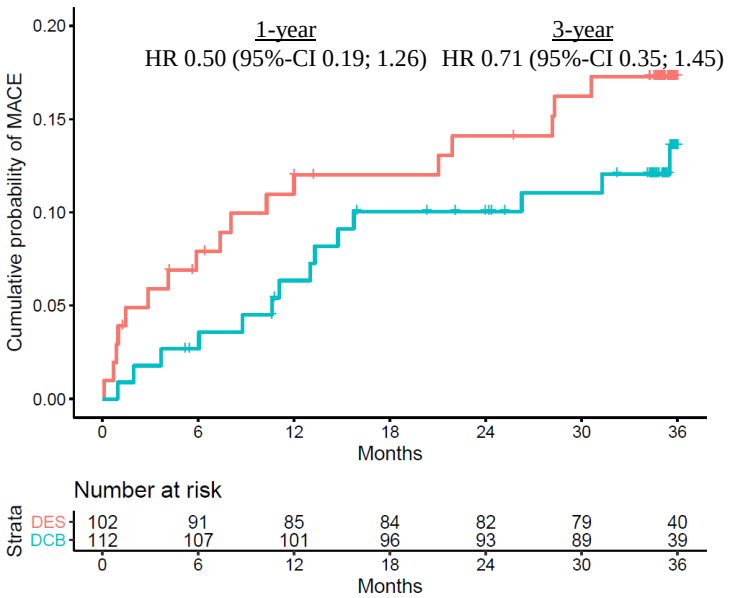


1-year
p=0.088

3-year
p=0.301

DES DCB

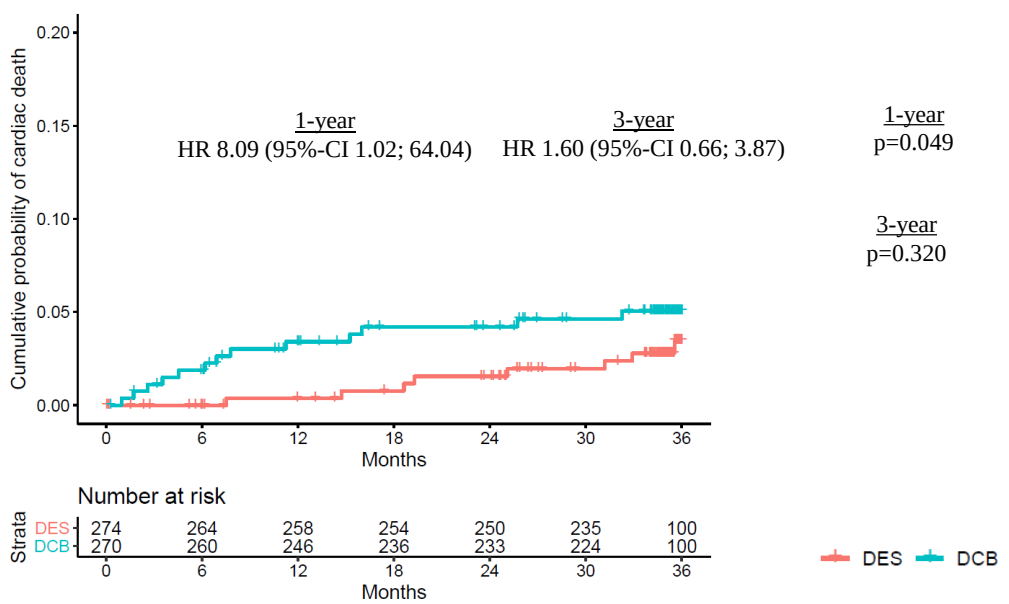
ACS



B)

CCS

p-value for interaction

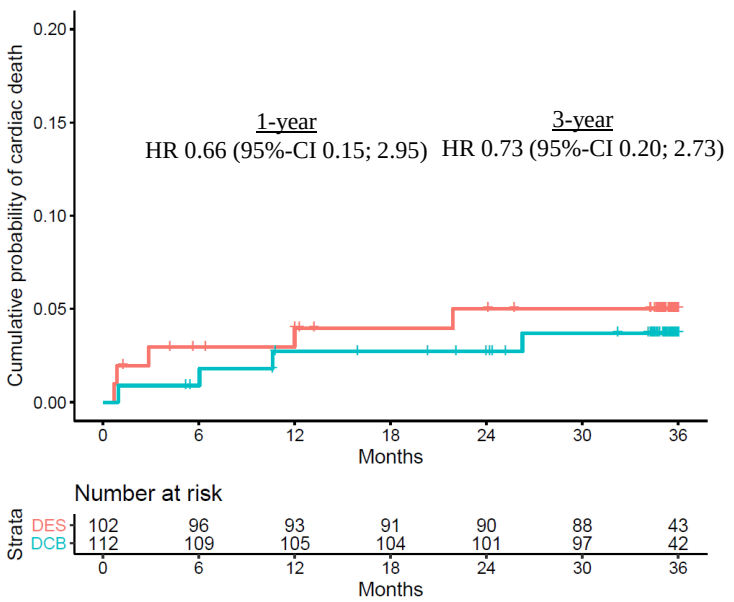


1-year
p=0.049

3-year
p=0.320

DES DCB

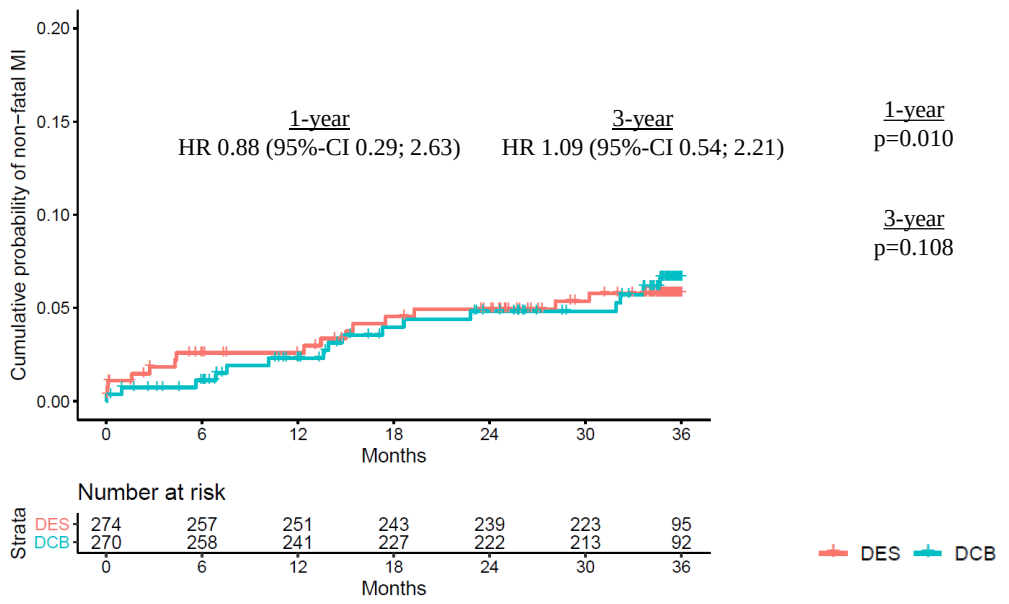
ACS



C)

CCS

p-value for interaction

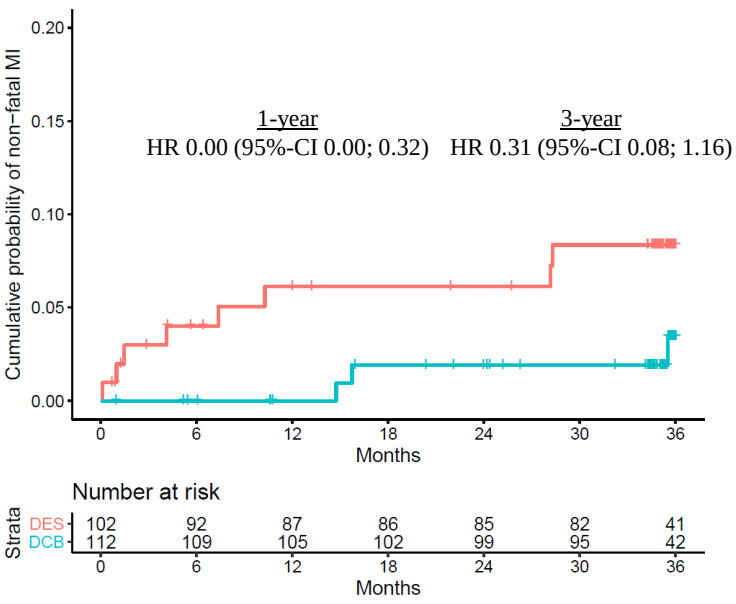


1-year
p=0.010

3-year
p=0.108

DES DCB

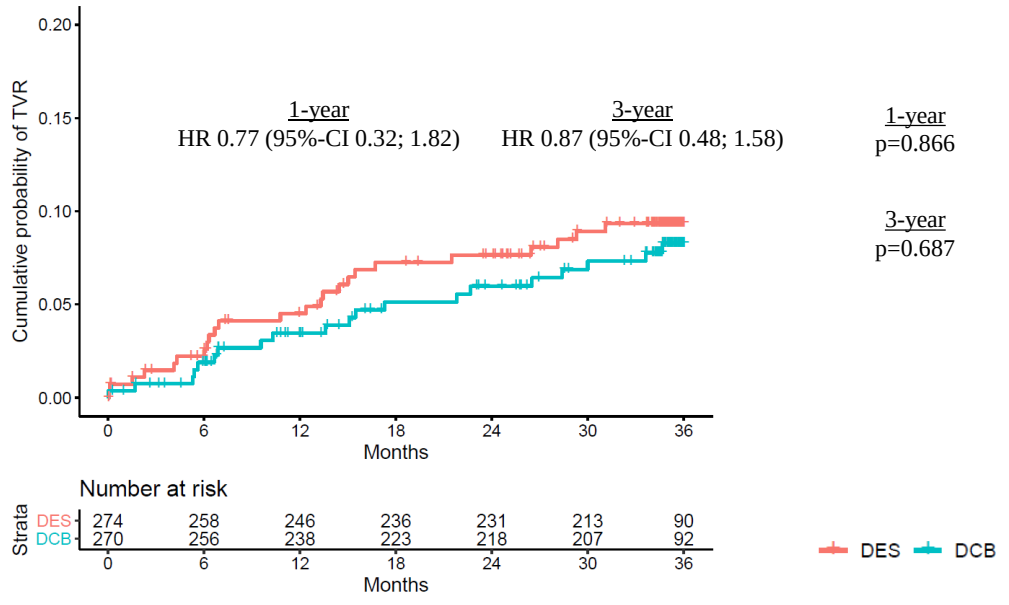
ACS



D)

CCS

p-value for interaction

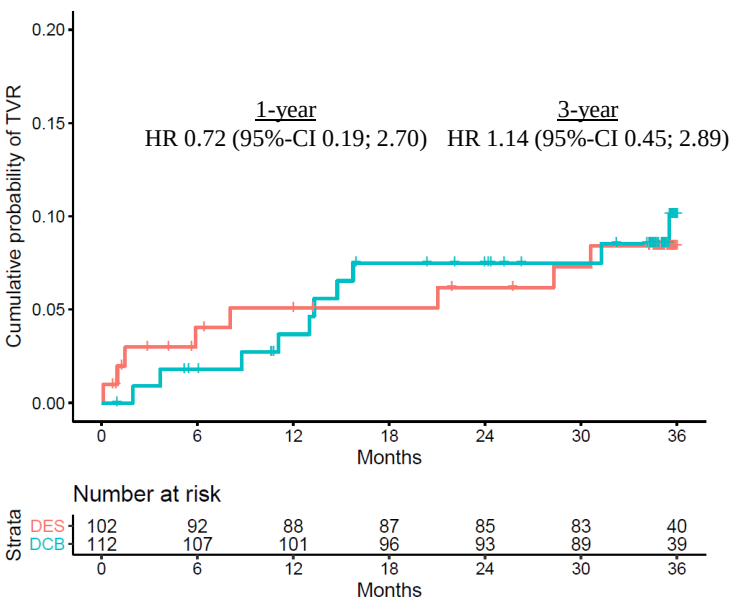


1-year
p=0.866

3-year
p=0.687

DES DCB

ACS



Supplemental Materials

Safety and efficacy of drug coated balloons versus drug eluting stents in acute coronary syndromes: A pre-specified analysis of BASKET-SMALL 2

Study organization

Figure S1: Kaplan-Meier estimates of the probability to remain on DAPT during 12 months, for patients who started on DAPT after the PCI.

Figure S2: Kaplan-Meier analysis stratified by troponin-negative coronary syndrome (Trop - , left panels) vs troponin-positive coronary syndrome (Trop + , right panels) comparing drug-coated balloon (DCB) vs drug-eluting stent (DES) treatment for major adverse cardiac events (A) and the components cardiac death (B), non-fatal myocardial infarction (C) and target vessel revascularization (D). Hazard ratios (HR) and corresponding 95%-confidence interval (CI) are given for DCB vs DES at 1-year and 3-year follow up with p-values for interaction provided between the graphs.

Table S1. Baseline characteristics according to clinical presentation (CCS vs ACS) and treatment group (DES vs DCB)

Table S2. Procedural data according to clinical presentation (CCS vs ACS) and treatment group (DES vs DCB)

Table S3. Baseline characteristics according to troponin-negative vs troponin-positive coronary syndrome

Table S4. Procedural data according to troponin-negative vs troponin-positive coronary syndrome

Table S5. Baseline characteristics according to clinical presentation (troponin-negative vs troponin-positive) and treatment group (DES vs DCB)

Table S6. Procedural data according to clinical presentation (troponin-negative vs troponin-positive) and treatment group (DES vs DCB)

Table S7. Outcomes at 1-year and 3-year of follow-up according to clinical presentation (troponin-negative vs troponin-positive)

Study Organization

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Figure S1. Kaplan-Meier estimates of the probability to remain on DAPT during 12 Months, for patients who started on DAPT after the PCI.

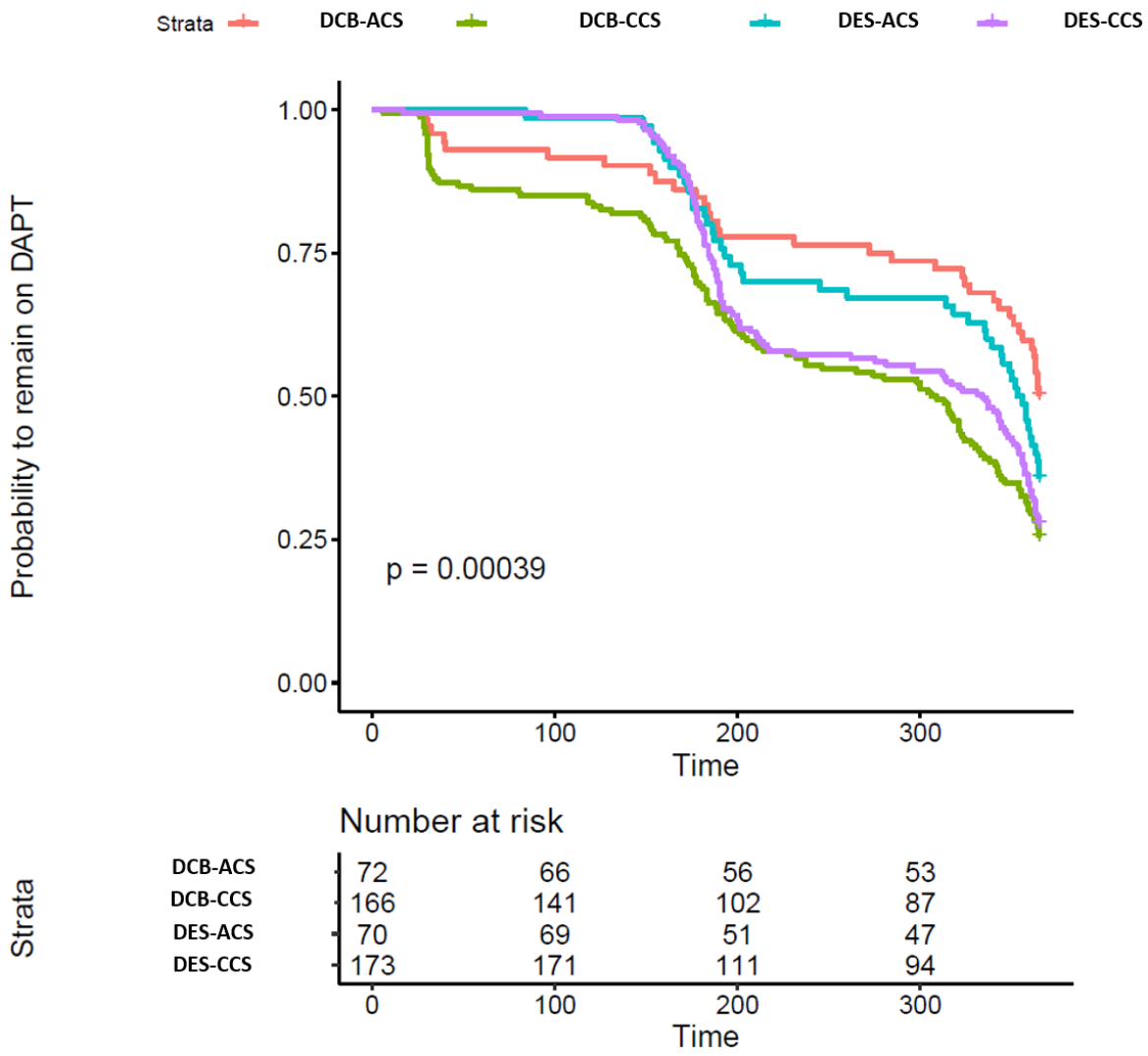
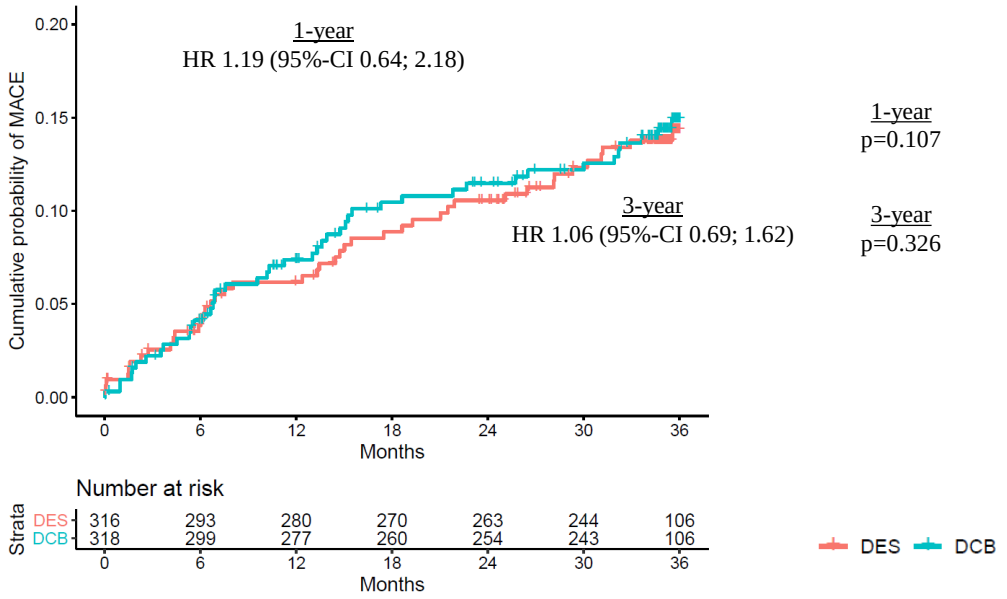


Figure S2. Kaplan-Meier analysis stratified by troponin-negative coronary syndrome (Trop - , left panels) vs troponin-positive coronary syndrome (Trop + , right panels) comparing drug-coated balloon (DCB) vs drug-eluting stent (DES) treatment for major adverse cardiac events (A) and the components cardiac death (B), non-fatal myocardial infarction (C) and target vessel revascularization (D). Hazard ratios (HR) and corresponding 95%-confidence interval (CI) are given for DCB vs DES at 1-year and 3-year follow up with p-values for interaction provided between the graphs.

A)

Trop -



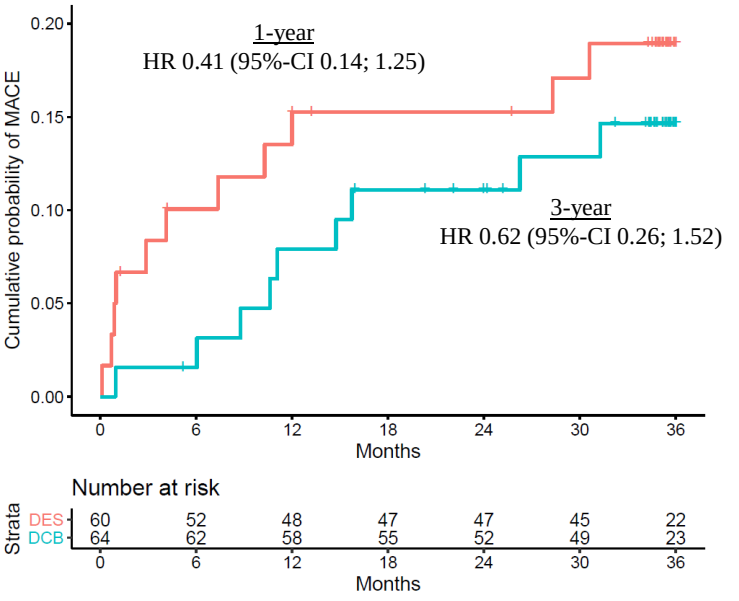
p-value for interaction

1-year
p=0.107

3-year
p=0.326

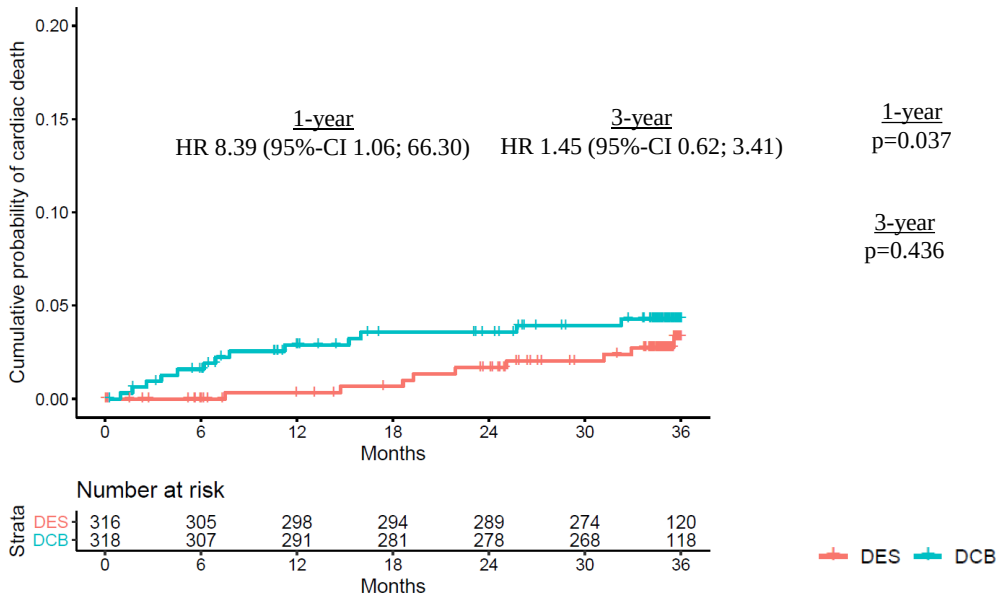
DES DCB

Trop +



B)

Trop -



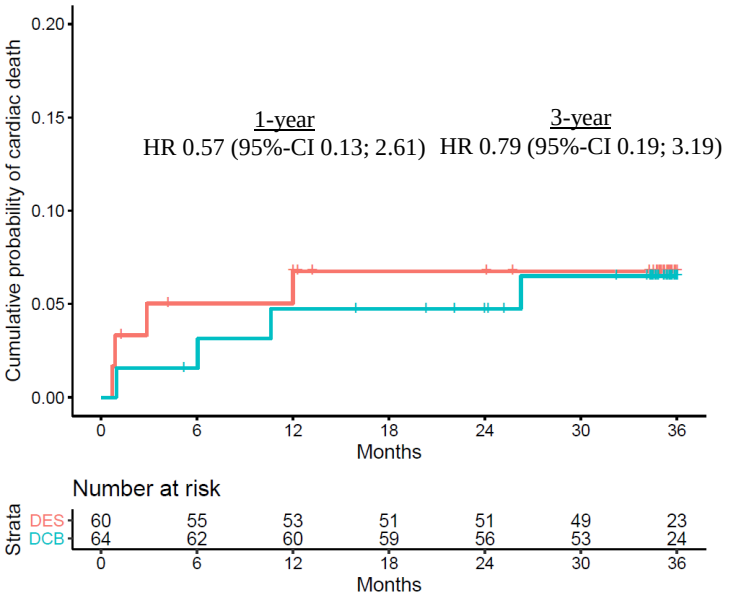
p-value for interaction

1-year
p=0.037

3-year
p=0.436

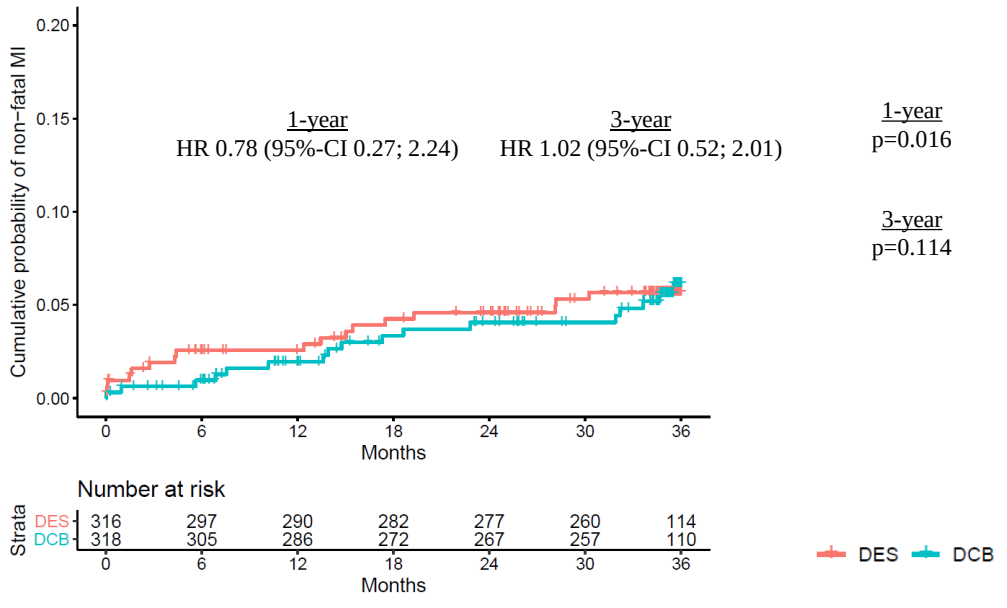
DES DCB

Trop +



C)

Trop -



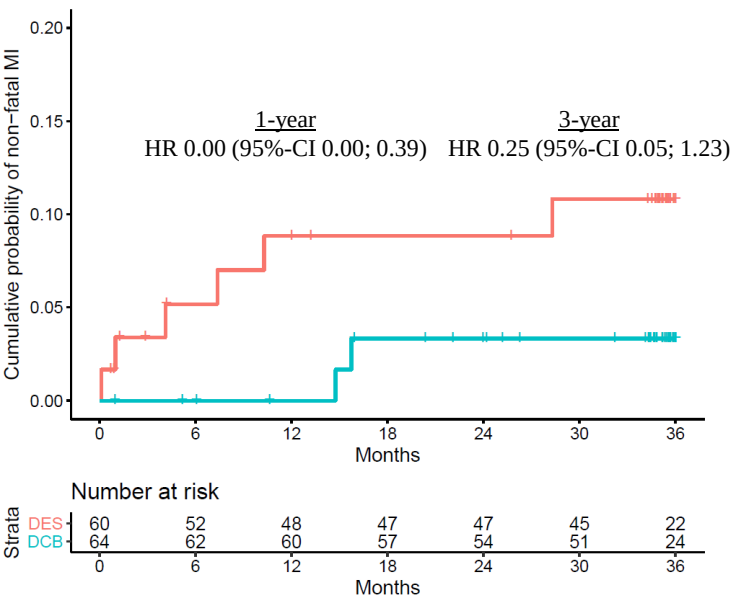
p-value for interaction

1-year
p=0.016

3-year
p=0.114

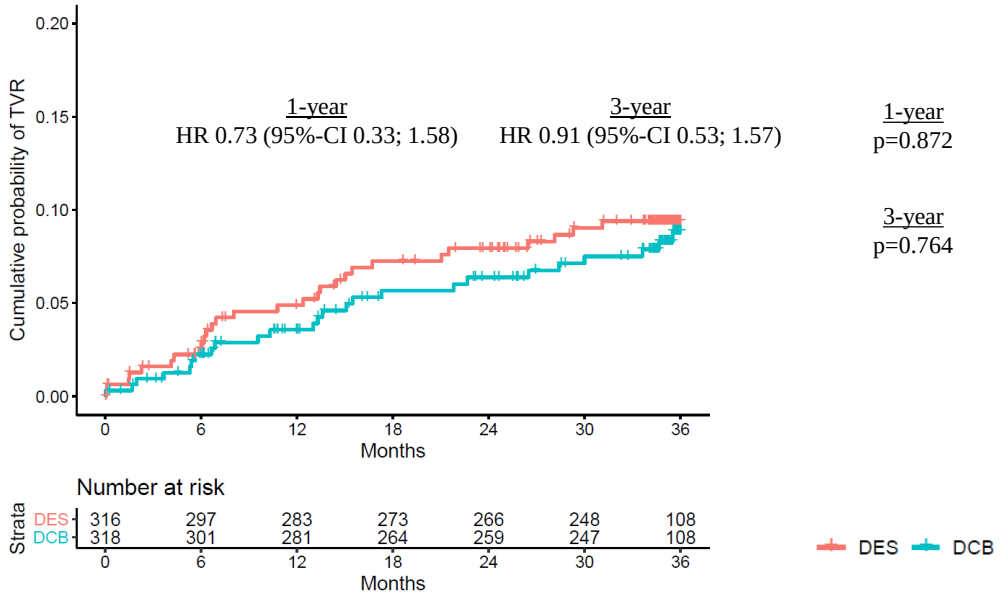
DES DCB

Trop +



D)

Trop -



p-value for interaction

1-year
p=0.872

3-year
p=0.764

DES DCB

Trop +

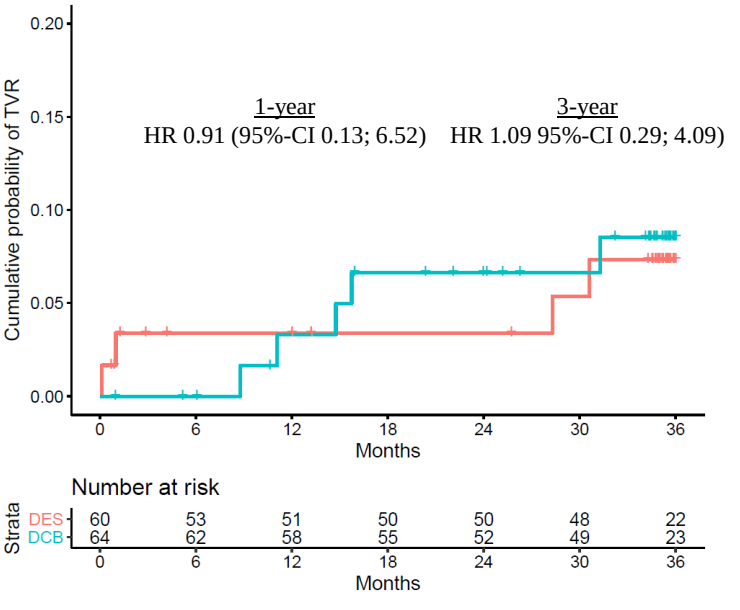


Table S1. Baseline characteristics according to clinical presentation (CCS vs ACS) and treatment group (DES vs DCB)

	CCS (n=544)			ACS (n=214)		
	DES (n=274)	**DCB (n=270)**	**p-value**	**DES (n=102)**	**DCB (n=112)**	**p-value**
Mean age (SD) [years]	68.1 (10.2)	67.1 (10.3)	0.264	69.3 (10.8)	67.3 (10.5)	0.179
Male sex, n (%)	198 (72.3)	214 (79.3)	0.071	64 (62.7)	81 (72.3)	0.177
Mean body mass index (SD) [kg/m²]	28.3 (4.4)	28.4 (4.5)	0.743	27.9 (4.9)	28.5 (4.8)	0.338
Smoking, n (%)			0.397			0.077
Current smoker	47 (17.6)	55 (20.7)		25 (25.0)	27 (25.0)	
Former smoker	106 (39.7)	112 (42.1)		17 (17.0)	32 (29.6)	
Never smoker	114 (42.7)	99 (37.2)		58 (58.0)	49 (45.4)	
Hypercholesterolemia, n (%)	193 (71.0)	186 (69.1)	0.714	66 (67.3)	76 (67.9)	1.000
Hypertension, n (%)	242 (88.3)	227 (84.1)	0.189	90 (90.0)	97 (86.6)	0.581
Family history of CAD, n (%)	99 (39.8)	108 (42.5)	0.590	29 (33.0)	42 (42.9)	0.216
Diabetes, n (%)			0.815			0.676
IDDM	33 (12.0)	34 (12.6)		14 (14.1)	14 (12.6)	
NIDDM	63 (23.0)	56 (20.7)		20 (20.2)	18 (16.2)	
None	178 (65.0)	180 (66.7)		65 (65.7)	79 (71.2)	
Previous MI, n (%)	106 (38.7)	124 (45.9)	0.105	27 (26.5)	36 (32.1)	0.448
Previous PCI, n (%)	193 (70.4)	188 (69.6)	0.911	48 (47.1)	47 (42.0)	0.541
Previous CABG, n (%)	30 (10.9)	29 (10.7)	1.000	4 (3.9)	8 (7.1)	0.468
Heart failure, n (%)	28 (10.2)	36 (13.4)	0.312	7 (6.9)	12 (10.7)	0.454
Cerebrovascular insult, n (%)			0.340			0.237
Stroke	16 (5.8)	11 (4.1)		7 (6.9)	5 (4.5)	
TIA	13 (4.7)	8 (3.0)		1 (1.0)	5 (4.5)	
None	245 (89.4)	251 (93.0)		94 (92.2)	101 (91.0)	
PAOD, n (%)	21 (7.7)	21 (7.8)	1.000	5 (4.9)	6 (5.4)	1.000
COPD, n (%)	26 (9.5)	19 (7.0)	0.378	10 (9.8)	9 (8.0)	0.831
Renal dysfunction, n (%)	43 (15.7)	34 (12.6)	0.361	16 (15.7)	20 (17.9)	0.810
Liver disease, n (%)	6 (2.2)	4 (1.5)	0.767	4 (3.9)	2 (1.8)	0.600
Presentation, n (%)			n.a.			n.a.
STEMI	-	-		4 (3.9)	11 (9.8)	
NSTEMI	-	-		56 (54.9)	53 (47.3)	
Unstable AP	-	-		42 (41.2)	48 (42.9)	
CCS	274 (100)	270 (100)		-	-	
Median LV-EF (IQR) [%]	60 (54; 64)	60 (50; 60)	0.261	60 (57; 65)	59 (50; 60)	0.002
Oral anticoagulation, n (%)	24 (9.0)	17 (6.5)	0.368	7 (7.1)	16 (15.1)	0.110

Values are numbers (%), mean (standard deviation), and median (interquartile range). CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; CAD, coronary artery disease; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; MI,

myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; PAOD, peripheral artery occlusive disease; COPD, chronic obstructive lung disease; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; AP, angina pectoris; LV-EF, left ventricular ejection fraction.

Table S2. Procedural data according to clinical presentation (CCS vs ACS) and treatment group (DES vs DCB)

	CCS (n=544)			ACS (n=214)		
	DES (n=274)	**DCB (n=270)**	**p-value**	**DES (n=102)**	**DCB (n=112)**	**p-value**
Target vessel			0.523			0.527
Left anterior descending artery, n (%)	82 (29.9)	84 (31.1)		34 (33.3)	44 (39.3)	
Left circumflex artery, n (%)	132 (48.2)	129 (47.8)		51 (50.0)	47 (42.0)	
Right coronary artery, n (%)	60 (21.9)	55 (20.4)		17 (16.7)	20 (17.9)	
Left anterior descending and circumflex artery, n (%)	0 (0)	2 (0.7)		0 (0)	1 (0.9)	
Multi vessel disease	216 (78.8)	232 (85.9)	0.040	69 (67.6)	81 (72.3)	0.551
Bifurcation lesion, n (%)	18 (6.8)	18 (6.8)	1.000	11 (11.1)	4 (3.6)	0.063
DAPT duration, days (IQR)						
Overall	334 (184; 369)	308 (169; 366)	0.089	355 (194; 404)	366 (281; 557)	0.309
Clopidogrel	320 (182; 366)	198 (140; 368)	0.012	353 (184; 477)	325 (152; 621)	0.296
Ticagrelor/Prasugrel	366 (315; 693)	343 (306; 390)	0.111	361 (331; 392)	368 (342; 655)	0.165
Procedural success, % (SD)	98 (13)	97 (16)	0.449	98 (15)	94 (24)	0.173
Mean number DES/DCB, n (SD)	1.31 (0.64)	1.21 (0.53)	0.068	1.23 (0.52)	1.14 (0.44)	0.213
Mean length DES/DCB, mm (SD)	18.0 (5.5)	20.1 (5.3)	<0.001	18.5 (6.0)	19.9 (4.4)	0.065
Mean effective size DES/DCB, mm (SD)	2.6 (0.3)	2.5 (0.3)	0.004	2.6 (0.3)	2.6 (0.3)	0.764
Mean inflation pressure DES/DCB, atm (SD)	13.3 (3.1)	10.8 (3.5)	<0.001	13.1 (2.2)	11.1 (3.1)	<0.001
Mean inflation duration DES/DCB, sec (SD)	25.7 (21.0)	49.9 (29.8)	<0.001	17.3 (9.6)	44.8 (23.8)	<0.001

Values are numbers (%), mean (standard deviation), and median (interquartile range). CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; DCB, drug-coated balloon; DES, drug-eluting stent; DAPT, dual antiplatelet therapy.

Table S3. Baseline characteristics according to troponin-negative vs troponin-positive coronary syndrome

	Troponin - (n=634)	**Troponin + (n=124)**	**p-value**
Mean age (SD) [years]	67.5 (10.3)	69.3 (10.5)	0.074
Male sex, n (%)	474 (74.8)	83 (66.9)	0.090
Mean body mass index (SD) [kg/m²]	28.3 (4.5)	28.0 (5.0)	0.479
Smoking, n (%)			<0.001
Current smoker	126 (20.3)	28 (23.5)	
Former smoker	243 (39.1)	24 (20.2)	
Never smoker	253 (40.7)	67 (56.3)	
Hypercholesterolemia, n (%)	450 (71.4)	71 (58.7)	0.007
Hypertension, n (%)	550 (86.8)	106 (86.9)	1.000
Family history of CAD, n (%)	238 (40.7)	40 (38.5)	0.751
Diabetes, n (%)			0.580
IDDM	77 (12.2)	18 (14.8)	
NIDDM	135 (21.4)	22 (18.0)	
None	420 (66.5)	82 (67.2)	
Previous MI, n (%)	265 (41.8)	28 (22.6)	<0.001
Previous PCI, n (%)	435 (68.6)	41 (33.1)	<0.001
Previous CABG, n (%)	65 (10.3)	6 (4.8)	0.085
Heart failure, n (%)	77 (12.2)	6 (4.8)	0.026
Cerebrovascular insult, n (%)			0.736
Stroke	32 (5.0)	7 (5.7)	
TIA	24 (3.8)	3 (2.4)	
None	578 (91.2)	113 (91.9)	
PAOD, n (%)	45 (7.1)	8 (6.5)	0.944
COPD, n (%)	52 (8.2)	12 (9.7)	0.716
Renal dysfunction, n (%)	94 (14.8)	19 (15.3)	0.997
Liver disease, n (%)	12 (1.9)	4 (3.2)	0.547
Presentation, n (%)			n.a.
STEMI	-	15 (7.0)	
NSTEMI	-	109 (50.9)	
Unstable AP	90 (14.2)	-	
CCS	544 (100)	-	
Median LV-EF (IQR) [%]	60 (53; 64)	60 (52; 60)	0.599
Oral anticoagulation, n (%)	49 (8.0)	15 (12.4)	0.162

Values are numbers (%), mean (standard deviation), and median (interquartile range). CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; CAD, coronary artery disease; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; PAOD, peripheral artery occlusive disease; COPD, chronic obstructive lung disease; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; AP, angina pectoris; LV-EF, left ventricular ejection fraction.

Table S4. Procedural data according to troponin-negative vs troponin-positive coronary syndrome

	Troponin - (n=634)	**Troponin + (n=124)**	**p-value**
Target vessel			0.684
Left anterior descending artery, n (%)	200 (31.5)	44 (35.5)	
Left circumflex artery, n (%)	301 (47.5)	58 (46.8)	
Right coronary artery, n (%)	130 (20.5)	22 (17.7)	
Left anterior descending and circumflex artery, n (%)	3 (0.5)	0 (0)	
Multi vessel disease	517 (81.5)	81 (65.3)	<0.001
Bifurcation lesion, n (%)	43 (7.0)	8 (6.6)	1.000
DAPT duration, days (IQR)			
Overall	321 (179; 373)	364 (321;479)	<0.001
Clopidogrel	241 (174; 373)	360 (185; 564)	0.070
Ticagrelor/Prasugrel	359 (315; 583)	364 (326; 465)	0.356
DCB, n (%)	318 (50.2)	64 (51.6)	0.843
Procedural success, % (SD)	97 (18)	94 (24)	0.290
Mean number DCB, n (SD)	1.20 (0.51)	1.17 (0.49)	0.706
Mean length DCB, mm (SD)	20.0 (5.2)	20.0 (3.9)	0.954
Mean effective size DCB, mm (SD)	2.5 (0.3)	2.6 (0.3)	0.046
Mean inflation pressure DCB, atm (SD)	10.8 (3.4)	11.5 (3.1)	0.116
Mean inflation duration DCB, sec (SD)	50 (30)	42 (23)	0.062
DES, n (%)	316 (49.8)	60 (48.4)	0.843
Procedural success, n (%)	98 (12)	97 (18)	0.457
Mean number DES, n (SD)	1.30 (0.63)	1.20 (0.48)	0.240
Mean length DES, mm (SD)	18.1 (5.6)	18.4 (6.1)	0.675
Mean effective size DES, mm (SD)	2.6 (0.2)	2.6 (0.3)	0.236
Mean inflation pressure DES, atm (SD)	13.3 (3.0)	13.1 (2.3)	0.678
Mean inflation duration DES, sec (SD)	24 (20)	18 (9)	0.018

Values are numbers (%), mean (standard deviation), and median (interquartile range). CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; DCB, drug-coated balloon; DES, drug-eluting stent; DAPT, dual antiplatelet therapy.

Table S5. Baseline characteristics according to clinical presentation (troponin-negative vs troponin-positive) and treatment group (DES vs DCB)

	Troponin - (n=634)			**Troponin + (n=124)**		
	DES (n=316)	**DCB (n=318)**	**p-value**	**DES (n=60)**	**DCB (n=64)**	**p-value**
Mean age (SD) [years]	68.1 (10.2)	66.9 (10.4)	0.152	70.2 (11.0)	68.5 (10.0)	0.371
Male sex, n (%)	222 (70.3)	252 (79.2)	0.012	40 (66.7)	43 (67.2)	1.000
Mean body mass index (SD) [kg/m²]	28.2 (4.4)	28.5 (4.5)	0.294	28.2 (5.2)	27.9 (4.8)	0.772
Smoking, n (%)			0.312			0.256
Current smoker	60 (19.4)	66 (21.1)		12 (20.7)	16 (26.2)	
Former smoker	114 (36.9)	129 (41.2)		9 (15.5)	15 (24.6)	
Never smoker	135 (43.7)	118 (37.7)		37 (63.8)	30 (49.2)	
Hypercholesterolemia, n (%)	229 (73.2)	221 (69.7)	0.385	30 (52.6)	41 (64.1)	0.276
Hypertension, n (%)	282 (89.2)	268 (84.3)	0.084	50 (86.2)	56 (87.5)	1.000
Family history of CAD, n (%)	116 (40.3)	122 (41.1)	0.910	12 (24.5)	28 (50.9)	0.010
Diabetes, n (%)			0.870			0.437
IDDM	38 (12.1)	39 (12.3)		9 (15.5)	9 (14.1)	
NIDDM	70 (22.2)	65 (20.5)		13 (22.4)	9 (14.1)	
None	207 (65.7)	213 (67.2)		36 (62.1)	46 (71.9)	
Previous MI, n (%)	122 (38.6)	143 (45.0)	0.123	11 (18.3)	17 (26.6)	0.379
Previous PCI, n (%)	221 (69.9)	214 (67.3)	0.528	20 (33.3)	21 (32.8)	1.000
Previous CABG, n (%)	32 (10.1)	33 (10.4)	1.000	2 (3.3)	4 (6.2)	0.736
Heart failure, n (%)	33 (10.4)	44 (13.9)	0.230	2 (3.3)	4 (6.2)	0.736
Cerebrovascular insult, n (%)			0.362			0.214
Stroke	19 (6.0)	13 (4.1)		4 (6.7)	3 (4.8)	
TIA	14 (4.4)	10 (3.1)		0 (0)	3 (4.8)	
None	283 (89.6)	295 (92.8)		56 (93.3)	57 (90.5)	
PAOD, n (%)	22 (7.0)	23 (7.2)	1.000	4 (6.7)	4 (6.2)	1.000
COPD, n (%)	29 (9.2)	23 (7.2)	0.455	7 (11.7)	5 (7.8)	0.673
Renal dysfunction, n (%)	50 (15.8)	44 (13.8)	0.554	9 (15.0)	10 (15.6)	1.000
Liver disease, n (%)	6 (1.9)	6 (1.9)	1.000	4 (6.7)	0 (0)	0.112
Presentation, n (%)			n.a.			n.a.
STEMI	-	-		4 (6.7)	11 (17.2)	
NSTEMI	-	-		56 (93.3)	53 (82.8)	
Unstable AP	42 (13.3)	48 (15.1)		-	-	
CCS	274 (86.7)	270 (84.9)		-	-	
Median LV-EF (IQR) [%]	60 (54; 65)	60 (50; 61)	0.038	60 (55; 63)	60 (50; 60)	0.064
Oral anticoagulation, n (%)	25 (8.1)	24 (7.8)	1.000	6 (10.0)	9 (14.8)	0.605

Values are numbers (%), mean (standard deviation), and median (interquartile range). CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; CAD, coronary artery disease; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; MI,

myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; PAOD, peripheral artery occlusive disease; COPD, chronic obstructive lung disease; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; AP, angina pectoris; LV-EF, left ventricular ejection fraction.

Table S6. Procedural data according to clinical presentation (troponin-negative vs troponin-positive) and treatment group (DES vs DCB)

	Troponin - (n=634)			Troponin + (n=124)		
	DES (n=316)	**DCB (n=318)**	**p-value**	**DES (n=60)**	**DCB (n=64)**	**p-value**
Target vessel			0.318			0.784
Left anterior descending artery, n (%)	96 (30.4)	104 (32.7)		20 (33.3)	24 (37.5)	
Left circumflex artery, n (%)	153 (48.4)	148 (46.5)		30 (50.0)	28 (43.8)	
Right coronary artery, n (%)	67 (21.2)	63 (19.8)		10 (16.7)	12 (18.8)	
Left anterior descending and circumflex artery, n (%)	0 (0)	3 (0.9)		0 (0)	0 (0)	
Multi vessel disease	250 (79.1)	267 (84.0)	0.141	35 (58.3)	46 (71.9)	0.163
Bifurcation lesion, n (%)	23 (7.6)	20 (6.4)	0.670	6 (10.3)	2 (3.1)	0.214
DAPT duration, days (IQR)						
Overall	334 (184; 370)	317 (172; 377)	0.293	361 (317; 465)	366 (324; 503)	0.658
Clopidogrel	330 (182; 373)	197 (127; 370)	0.003	362 (181; 439)	360 (222; 612)	0.990
Ticagrelor/Prasugrel	365 (300; 677)	356 (316; 464)	0.598	364 (349; 422)	365 (324; 510)	0.955
Procedural success, % (SD)	98 (12)	97 (18)	0.200	97 (18)	94 (24)	0.454
Mean number DES/DCB, n (SD)	1.30 (0.63)	1.20 (0.51)	0.024	1.20 (0.48)	1.17 (0.49)	0.748
Mean length DES/DCB, mm (SD)	18.1 (5.6)	20.1 (5.2)	<0.001	18.4 (6.1)	20.0 (3.9)	0.081
Mean effective size DES/DCB, mm (SD)	2.6 (0.2)	2.5 (0.3)	0.008	2.6 (0.3)	2.6 (0.3)	0.712
Mean inflation pressure DES/DCB, atm (SD)	13.3 (3.0)	10.8 (3.4)	<0.001	13.1 (2.3)	11.5 (3.1)	0.002
Mean inflation duration DES/DCB, sec (SD)	24.4 (20.1)	49.6 (29.0)	<0.001	17.9 (9.2)	42.2 (23.4)	<0.001

Values are numbers (%), mean (standard deviation), and median (interquartile range). CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; DCB, drug-coated balloon; DES, drug-eluting stent; DAPT, dual antiplatelet therapy.

Table S7. Outcomes at 1-year and 3-year of follow-up according to clinical presentation (troponin-negative vs troponin-positive)

	1-year follow up				p for interaction	3-year follow up				p for interaction
	Troponin -		Troponin +			Troponin -		Troponin +		
MACE										
	DES	**DCB**	**DES**	**DCB**		**DES**	**DCB**	**DES**	**DCB**	
Events, n (%)	19 (6.2)	23 (7.4)	9 (15.3)	5 (7.9)	0.107	42 (14.4)	44 (14.9)	11 (18.9)	9 (14.7)	0.326
HR (95%-CI)	1.19 (0.64; 2.18)		0.41 (0.14; 1.25)			1.06 (0.69; 1.62)		0.62 (0.26; 1.52)		
Cardiac death										
Events, n (%)	1 (0.3)	9 (2.9)	4 (6.8)	3 (4.7)	0.037	9 (3.3)	13 (4.3)	4 (6.8)	4 (6.5)	0.436
HR (95%-CI)	8.39 (1.06; 66.30)		0.57 (0.13; 2.61)			1.45 (0.62; 3.41)		0.79 (0.19; 3.19)		
Non-fatal myocardial infarction										
Events, n (%)	8 (2.6)	6 (2.0)	5 (8.8)	0 (0)	0.016	17 (5.7)	17 (6.1)	6 (10.8)	2 (3.3)	0.114
HR (95%-CI)	0.78 (0.27; 2.24)		0.00 (0.00; 0.39)			1.02 (0.52; 2.01)		0.25 (0.05; 1.23)		
Target vessel revascularization										
Events, n (%)	15 (4.9)	11 (3.6)	2 (3.4)	2 (3.3)	0.872	28 (9.4)	25 (8.8)	4 (7.3)	5 (8.6)	0.764
HR (95%-CI)	0.73 (0.33; 1.58)		0.91 (0.13; 6.52)			0.91 (0.53; 1.57)		1.09 (0.29; 4.09)		
Stent thrombosis										
Events, n (%)	2 (0.6)	2 (0.6)	2 (3.3)	0 (0)	0.146	4 (1.3)	2 (0.6)	2 (3.3)	0 (0)	0.227
HR (95%-CI)	0.96 (0.13; 6.85		0.00 (0.00; 1.50)			0.49 (0.09; 2.68)		0.00 (0.00; 1.50)		
All-cause death										
Events, n (%)	3 (1.0)	13 (4.2)	6 (10.0)	4 (6.3)	0.022	18 (6.3)	20 (6.6)	9 (15.1)	8 (12.7)	0.399
HR (95%-CI)	4.11 (1.17; 14.44)		0.52 (0.14; 1.85)			1.14 (0.60; 2.16)		0.62 (0.23; 1.69)		
Major bleeding										
Events, n (%)	7 (2.3)	1 (0.3)	2 (3.5)	3 (4.7)	0.129	10 (3.3)	3 (1.1)	4 (7.5)	3 (4.7)	0.466
HR (95%-CI)	0.15 (0.02; 1.20)		1.24 (0.21; 7.46)			0.30 (0.08; 1.11)		0.61 (0.14; 2.75)		
Net clinical benefit										
Events, n (%)	26 (8.4)	23 (7.4)	10 (16.9)	7 (11.1)	0.446	51 (17.2)	45 (15.3)	13 (22.4)	11 (17.8)	0.602
HR (95%-CI)	0.87 (0.49; 1.52)		0.57 (0.21; 1.50)			0.88 (0.30; 1.53)		0.68 (0.30; 1.53)		

All values are numbers of events and Kaplan Meier estimates with the corresponding hazard ratios for DCB vs DES and 95%-Confidence Intervals. CCS indicates chronic coronary syndrome; ACS, acute coronary syndrome; DCB, drug-coated balloon; DES, drug-eluting stent.

Drug-coated balloons versus drug-eluting stents in acute and chronic coronary syndromes

758 patients with small vessel coronary artery disease randomized to DCB vs DES treatment in the BASKET SMALL 2 trial

544 patients with CCS

DCB n=270

DES n=274

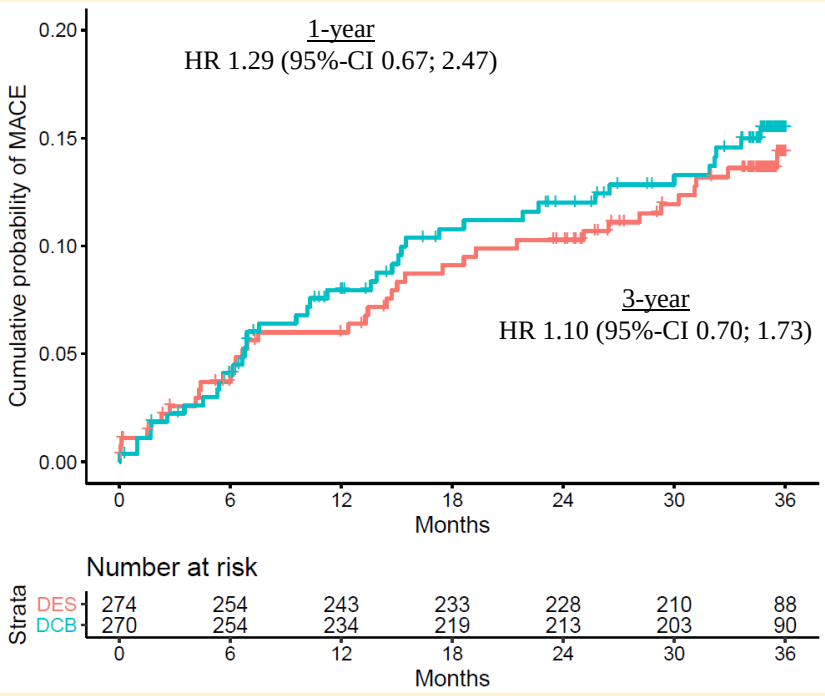
1° endpoint assessed after 1 and 3 years
MACE (cardiac death, non-fatal myocardial infarction, and target vessel revascularization

214 patients with ACS

DCB n=112

DES n=102

CCS



1-year
p for interaction=0.088

3-year
p for interaction=0.301

DES DCB

ACS