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# Biolimus-A9 polymer-free coated stent in high bleeding risk patients with acute coronary syndrome: a *Leaders Free ACS* sub-study

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## Aims

Although a true clinical challenge, high bleeding risk patients with an acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) have never been specifically studied. *Leaders Free ACS*, a pre-specified *Leaders Free* sub-study, determined efficacy, and safety of a combination of 1-month dual anti-platelet therapy (DAPT) with implantation of either a polymer-free Biolimus-A9-coated stent (BA9-DCS) or a bare-metal stent (BMS) in these patients.

## Methods and results

*Leaders Free* included 2466 patients undergoing PCI who had at least 1 of 13 pre-defined factors for an increased bleeding risk. Of these, 659 ACS patients were included in this analysis (BA9-DCS 330, BMS 329). At 12-month follow-up, treatment with the BA9-DCS was more effective (clinically driven target-lesion revascularization 3.9 vs. 9.0%,  $P = 0.009$ ) and safer (cumulative incidence of cardiac death, myocardial infarction, or definite or probable stent thrombosis 9.3 vs. 18.5%,  $P = 0.001$ ), driven by significantly lower rates of cardiac mortality (3.4 vs. 6.9%,  $P = 0.049$ ) and myocardial infarction (6.9 vs. 13.8%,  $P = 0.005$ ).

## Conclusion

We believe that the results of this sub-analysis from the *Leaders Free* trial are likely to significantly impact clinical practice for high bleeding risk patients presenting with an ACS: the use of a BMS can, in our view, no longer be recommended, and, given the paucity of available data for second-generation DES with shortened DAPT in these patients, the BA9-DCS should currently be considered as the device with the strongest evidence to support its use for this indication.

## Keywords

Acute coronary syndrome • High bleeding risk • Bare-metal stent • Drug-coated stent • Percutaneous coronary intervention

## Introduction

Appropriate and timely antithrombotic therapy is essential for the outcome of patients presenting with acute coronary syndromes (ACS). The individual bleeding risk has to be balanced with the ischaemic threat. High bleeding risk patients presenting with an ACS, undergoing percutaneous coronary intervention (PCI), have never been specifically studied.

For these patients, current guidelines suggest the implantation of drug-eluting stents (DES) with 3–6 months dual anti-platelet therapy (DAPT) or bare-metal stents (BMS) with 1-month DAPT.<sup>1–3</sup> *Leaders Free ACS* is a pre-specified sub-study of *Leaders Free*<sup>4,5</sup> which is a randomized double-blind trial, designed to assess the combination of 1 month of DAPT with either a polymer-free Biolimus-A9-coated stent (drug-coated stent; DCS) or a BMS in patients with at least one criterion for an increased bleeding risk such as advanced

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age, oral anticoagulant treatment, recent bleeding, anaemia, chronic renal failure, or cancer. In this patient group, DCS treatment displayed superiority not only with respect to clinically driven target-lesion revascularization at 390 days but also regarding the composite safety endpoint which was the incidence of cardiac death, myocardial infarction, or definite or probable stent thrombosis.

The aim of this analysis was to focus on the efficacy and safety of a polymer-free BA9-coated stent with 1-month DAPT in high bleeding risk patients presenting with non-ST-segment-elevation myocardial infarction (NSTEMI) or ST-segment-elevation myocardial infarction (STEMI).

## Methods

### Patients and methods

All patients from *Leaders Free* presenting with STEMI or NSTEMI, undergoing PCI were included. Methods and proceedings for *Leaders Free* have been described previously<sup>4,5</sup> and are summarized here. *Leaders Free* is a randomized, double-blind, clinical trial, which enrolled 2466 patients at 68 sites in 20 countries. Patients were required to meet one or more of the criteria for an increased bleeding risk listed in *Table 1*. They were 1:1 randomly assigned to undergo PCI with a polymer-free BA9-DCS (Biofreedom™ DCS Biosensors Europe, Morges, Switzerland) or a similar bare-metal stent (Gazelle™, Biosensors Interventional Technologies, Singapore). Randomization was performed with the use of either a Web-based system or a telephone interactive voice-response system (Merge Healthcare, [www.merge.com](http://www.merge.com)) in blocks of 16 with no further stratification. All patients received 1 month of DAPT followed by single anti-platelet therapy lifelong.

### Study proceedings

Percutaneous coronary intervention was performed according to standard techniques. Vascular access, peri-procedural antithrombotic regimen, and lesion preparation were left to the operator. All target lesions were treated with at least one study stent. Staged procedures were permitted within 1 week after the index procedure. The protocol mandated that all patients receive both aspirin and a P2Y12 inhibitor for 30 days, followed by a single anti-platelet agent.

Per protocol patients who were included in the trial because of planned oral anti-coagulation post-PCI should receive either the WOEST regimen or triple therapy.

A patient follow-up visit on site was performed at 30 days and 360 days. Further contacts were made at 60 and 120 days. Ischaemia testing and angiographic evaluation during follow-up were left to the discretion of the investigator.

### Study endpoints

The primary safety endpoint was the cumulative incidence of a composite of cardiac death, myocardial infarction, or definite or probable stent thrombosis; the primary efficacy endpoint was the incidence of clinically driven target-lesion revascularization. Primary endpoint events and bleeding events were recorded for up to 390 days in order to capture events occurring soon after the 1-year visit. Myocardial infarction was defined according to the third universal definition of myocardial infarction,<sup>6</sup> stent thrombosis according to the ARC definitions,<sup>7</sup> and bleeding according to the BARC definitions.<sup>8</sup>

Clinically driven target-lesion revascularization was defined as PCI or surgery either for operator-defined restenosis in the treated lesion together with angina symptoms or documented ischaemia or, for a

core-laboratory-defined restenosis of >70% of the artery diameter without symptoms or ischaemia.

### Statistical analyses

Continuous variables are presented as mean  $\pm$  SD, categorical data as counts and percentages. Categorical variables were compared using a  $\chi^2$  test, continuous variables were compared using a two sample t-test. Whenever appropriate a Fisher exact test was used instead.

For time-to-event variables, hazard ratio or its 95% confidence interval was derived from an unadjusted Cox proportional hazard model. Cumulative incidence rates come from the Kaplan–Meier estimator with log-rank *P*-value to test if the plots differ over time. Proportional hazard assumptions were checked using Schoenfeld residuals. There was no adjustment for covariates or imputation for missing data. All available data were used in the analysis of all endpoints. We performed additional Cox proportional hazard models to analyze if the DAPT, P2Y12 inhibitor, or anticoagulant therapy prescription had an impact on the primary endpoints. The same method was used to analyze the potential impact of imbalances at baseline. All data were analyzed using SAS V.9.3 (SAS Institute, Cary, NC, USA).

## Results

### Patients and procedures

Six hundred and fifty-nine patients in *Leaders Free* presenting with an ACS, underwent PCI (*Figure 1*). Of these, 554 patients had an NSTEMI, 105 had an STEMI. 330 were assigned to the BA9-coated DCS and 329 were assigned to the BMS. Baseline biomarkers and other patient features are displayed in *Table 1*.

The patient population was of advanced age and displayed conditions indicative of an increased bleeding risk. Three or more of the criteria for high bleeding risk were met in 132 patients (20%), 2 criteria in 256 (39%), and only 1 criterion in 271 (41%). The criteria were well balanced between treatment groups.

Regarding baseline characteristics, there were no significant differences except previous stroke, being more frequent in the DCS group (14.1 vs. 7.9%; *P* = 0.01), while history of atrial fibrillation was more frequent in the BMS group (25.5 vs. 33.1%; *P* = 0.03). Given multiple testing across available baseline variables, these findings are compatible with the play of chance and had no significant impact on the primary endpoints.

Procedural data are displayed in *Table 2*. A total of 63.6% of the procedures in the DCS group and 64.0% in the BMS group were performed through radial access (*P* = 0.91). 3.8 and 8.9% of the procedures in the respective groups were staged (*P* = 0.01). The latter had no significant influence on the primary endpoints. 18.7% of the procedures in the DCS group and 23.0% in the BMS group involved multi-vessel revascularization (*P* = 0.16).

Among the 166 patients who were on oral anti-coagulation at Day 23 post-PCI, data were available for 164 patients. Most patients (*n* = 158; 96.3%) received triple therapy and only 6 (3.7%) followed the WOEST regimen. There was no difference between the treatment groups and no impact on outcomes.

At 23 days, DAPT was used in the DCS and BMS groups in 95.6 and 97.8%, respectively (*P* = 0.18). In detail, ASA was given in 97.3 and 99.1%, Clopidogrel in 85.0 and 85.2%, Ticagrelor in 11.7 and 11.1%, and Prasugrel in 1.8 and 2.5%. At 37 days, DAPT was

**Table 1** Baseline patient characteristics and inclusion criteria<sup>a</sup>

	Drug-coated stent (N = 330)	Bare-metal stent (N = 329)	P-value
Baseline characteristics			
Age (years)	76.9 ± 10.0	76.5 ± 9.9	0.17
Female sex	122 (37.0)	110 (33.4)	0.34
Body mass index	26.7 ± 4.8	26.7 ± 4.5	0.98
Diabetes, n/total	111/328 (33.8)	108/329 (32.8)	0.78
Hypertension, n/total	248/330 (75.2)	249/327 (76.1)	0.77
Hypercholesterolaemia	180/322 (55.9)	156/321 (57.9)	0.60
STEMI	57 (17.2)	48 (14.5)	0.40
NSTEMI	273 (82.8)	281 (85.5)	0.40
Creatinine kinase (U/L)	4.14 ± 7.16	3.12 ± 6.40	0.17
Creatinine kinase MB (U/L)	28.19 ± 73.06	16.38 ± 30.10	0.13
High-sensitive troponin (ng/L)	12.77 ± 18.94	13.80 ± 70.18	0.92
Multi-vessel disease	207/327 (64.1)	220/323 (68.1)	0.28
Previous myocardial infarction	63/329 (19.1)	82/329 (24.9)	0.07
Previous PCI	55/330 (16.7)	67/328 (20.4)	0.22
Previous CABG	24/330 (7.3)	23/328 (7.0)	0.90
Congestive heart failure	29/328 (8.8)	43/329 (13.1)	0.08
Atrial fibrillation	84/330 (25.5)	109/329 (33.1)	0.03
Previous stroke	46/326 (14.1)	26/329 (7.9)	0.01
Peripheral vascular disease	47/325 (14.5)	49/328 (14.9)	0.86
Chronic obstructive lung disease	39/330 (11.8)	45/328 (13.7)	0.47
Crusade score	36.4 ± 13.8	36.6 ± 14.1	0.87
Criteria for high risk of bleeding			
Oral anti-coagulation planned to continue after PCI	79 (23.9)	101 (30.7)	0.05
Age ≥ 75 years	232 (70.3)	229 (69.6)	0.85
Haemoglobin < 11 g/L or transfusion within 4 weeks before randomization	73 (22.1)	79 (24.0)	0.57
Platelet count < 100 000/mm <sup>3</sup>	4 (1.2)	6 (1.8)	0.57
Hospital admission for bleeding in previous 12 months	23 (7.0)	15 (4.6)	0.18
Stroke in previous 12 months	6 (1.8)	5 (1.5)	0.77
Previous intracerebral bleed	7 (2.1)	7 (2.1)	0.99
Severe chronic liver disease	4 (1.2)	4 (1.2)	0.99
Creatinine clearance < 40 mL/min	62 (18.8)	80 (24.3)	0.08
Cancer (non-skin) in the previous 3 years	35 (10.6)	37 (11.2)	0.79
Planned major surgery in next 12 months	38 (11.5)	36 (10.9)	0.82
Glucocorticoids or NSAID planned for > 30 days after PCI	14 (4.2)	12 (3.6)	0.70
Expected non-adherence to > 30 days of dual antiplatelet therapy	18 (5.5)	19 (5.8)	0.86

STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-segment myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

<sup>a</sup>Either presented as n (%) or mean ± SD.

continued in significantly more patients in the BMS arm (Table 2). This had no significant effect on the primary endpoints.

## Primary endpoints

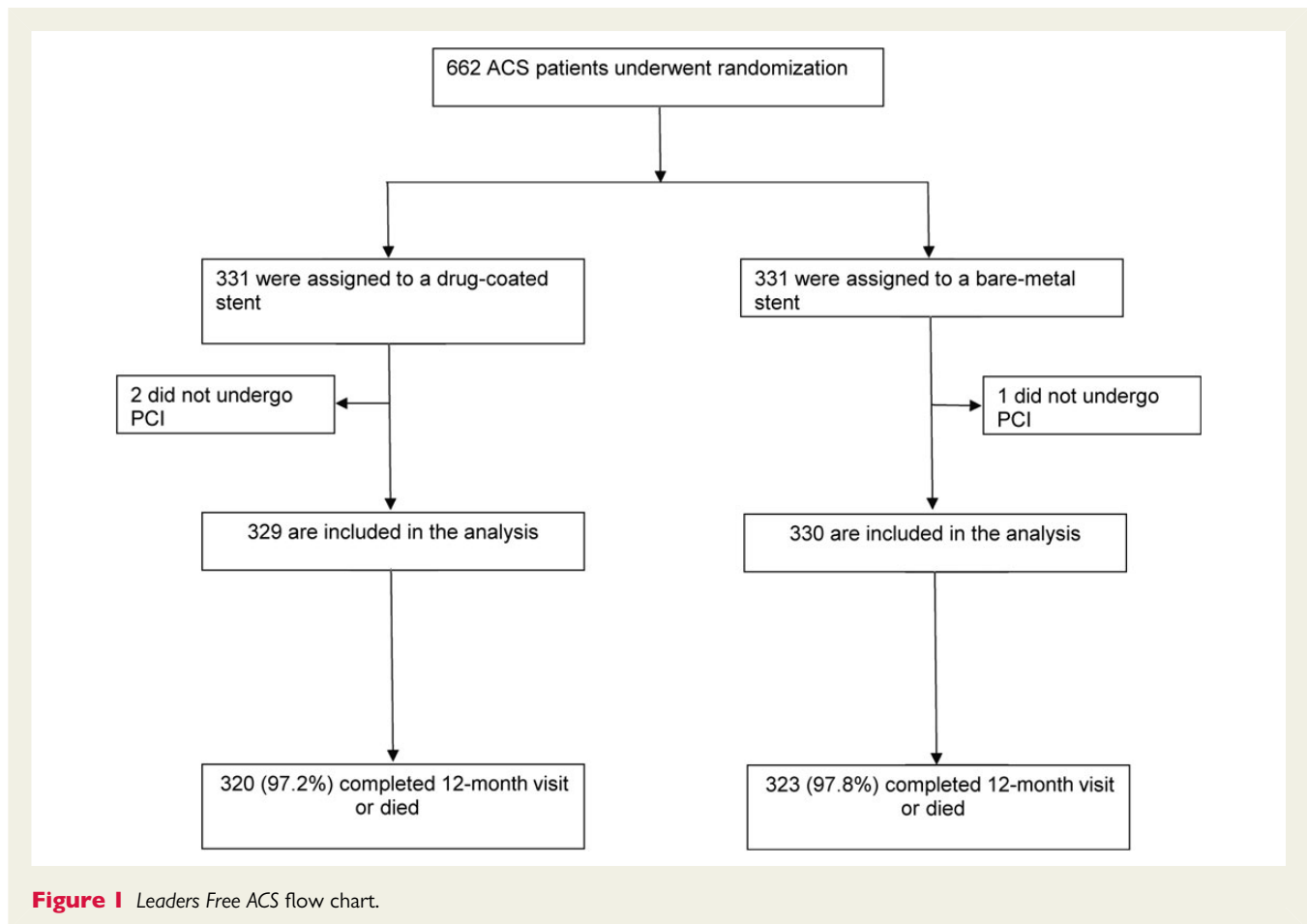
At 390 days, the primary efficacy endpoint (clinically driven target-lesion revascularization) had occurred in 12 patients (3.9%) in the DCS group and 27 patients (9.0%) in the BMS group (HR 0.41; 95% CI 0.21–0.82;  $P = 0.009$ ) (Table 3).

At 390 days, the primary safety endpoint (composite of cardiac death, myocardial infarction, or definite or probable

stent thrombosis) had occurred in 30 patients (9.3%) in the DCS group and in 59 patients (18.5%) in the BMS group (HR 0.48; 95% CI 0.31–0.75;  $P = 0.001$ ). The time-to-event curves for the primary efficacy and safety endpoints are shown in Figure 2.

## Additional analyses

Significant differences between the treatment groups were also observed for cardiac death (DCS 3.4%; BMS 6.9%; HR 0.49; 95% CI 0.23–1.01;  $P = 0.049$  and myocardial infarction (DCS 6.9%; BMS



13.8%; HR 0.48; 95% CI 0.29–0.81;  $P = 0.005$ ). There were numerically fewer definite and probable stent thromboses in the DCS group (1.2 vs. 3.1%; HR 0.39, 95% CI 0.12–1.24;  $P = 0.099$ ). Rates of bleeding according to BARC criteria were high and similar in the two groups (Table 3).

We analyzed if the treatment effects on the primary endpoints were comparable between patients with and without an ACS and with NSTEMI or STEMI, respectively. These analyses show that while the efficacy benefit of the treatment is consistent across all subgroups, the safety benefit in the *Leaders Free* population is mainly driven by the ACS subgroups (Figure 3).

## Discussion

At 390 days follow-up, *Leaders Free ACS* demonstrates that a polymer-free BA9-coated stent with 1-month DAPT is significantly more effective and safe than a BMS in high bleeding risk patients presenting with an ACS. The BA9-coated stent not only reduced the re-intervention rate and the incidence of the composite safety endpoint but also significantly reduced rates of cardiac mortality and myocardial infarction. These findings were not dependent on the post-procedural DAPT scheme, the oral anti-coagulation regimen, or imbalances at baseline.

There are two reasons why patients with an ACS receive prolonged DAPT: first for the prevention of secondary events,

which is currently recommended for 12 months or beyond after the event,<sup>1–3</sup> second for the prevention of stent thrombosis if they undergo PCI with stent implantation. With stable CAD, DAPT is currently recommended for at least 4 weeks after BMS—and 6 months after DES implantation.<sup>2,13</sup>

The bleeding risk induced by the prolonged DAPT in ACS patients is usually considered to be more than balanced by the benefits of a reduction of secondary thrombotic events,<sup>14</sup> however, this has never been specifically studied in ACS patients with an increased risk of bleeding.<sup>15–18</sup> Current guidelines suggest in this scenario the implantation of a DES with shortened DAPT or a BMS with 1-month DAPT.<sup>1–3</sup> The use of BMS for ACS patients increases the rate of target-lesion revascularization and carries a significant risk for increasing major adverse cardiac events.<sup>19,20</sup>

The guideline's recommendations regarding shortening of DAPT are, besides the results of a network meta-analysis<sup>21</sup> mainly based on the OPTIMIZE<sup>22</sup> and RESET<sup>23</sup> trials which assessed clinical non-inferiority of 3 months vs. 12 months of DAPT. The results of both trials suggest that it may be suitable to shorten DAPT after implantation of a fast-eluting Zotarolimus-eluting DES in selected patients at low-risk of bleeding, with no detectable benefit, but no significant trade off regarding clinical events. Observational data from new-generation Zotarolimus- and Everolimus-eluting stents have also raised the possibility that DAPT interruption may be safe in selected low-risk patients.<sup>24–26</sup>

**Table 2** Procedure details and medication<sup>a</sup>

	Drug-coated stent (N = 330)	Bare-metal stent (N = 329)	P-value
Procedure details			
Radial access	218 (63.6)	231 (64)	0.91
Staged procedure	13 (3.8)	32 (8.9)	0.01
Multi-lesion procedure	113 (32.9)	133 (36.8)	0.28
Multi-vessel procedure	64 (18.7)	83 (23.0)	0.16
LAD	175 (51.0)	193 (53.6)	0.52
LCX	113 (32.9)	114 (31.7)	0.64
LM	8 (2.3)	15 (4.2)	0.16
RCA	110 (32.1)	122 (33.9)	0.17
SVG	5 (1.5)	6 (1.7)	0.93
Bifurcation	43 (12.5)	59 (16.4)	0.15
ISR	5 (1.5)	5 (1.4)	0.94
CTO	26 (7.6)	24 (6.7)	0.64
Mean stent diameter	2.90 ± 0.48	2.90 ± 0.50	0.93
Total stent length	32.20 ± 22.1	33.4 ± 23.3	0.50
Number of stent	1.70 ± 1.0	1.79 ± 1.1	0.27
Lesion success	468 (96.9)	533 (97.4)	0.60
Device success	560 (96.9)	613 (96.7)	0.97
Procedural success	326 (95.0)	341 (94.7)	0.85
Medication			
DAPT at Day 23	311 (95.6)	317 (97.8)	0.18
DAPT at Day 37	28 (8.7)	49 (15.2)	0.01
UFH	282 (82.2)	280 (77.6)	0.12
LMWH	28 (8.2)	34 (9.4)	0.56
Bivalirudin	7 (2)	16 (4.4)	0.07
GPIIb/IIIa antagonist	7 (2)	5 (1.4) <sup>b</sup>	0.50

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; SVG, saphenous vein graft; ISR, in-stent restenosis; CTO, chronic total occlusion; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

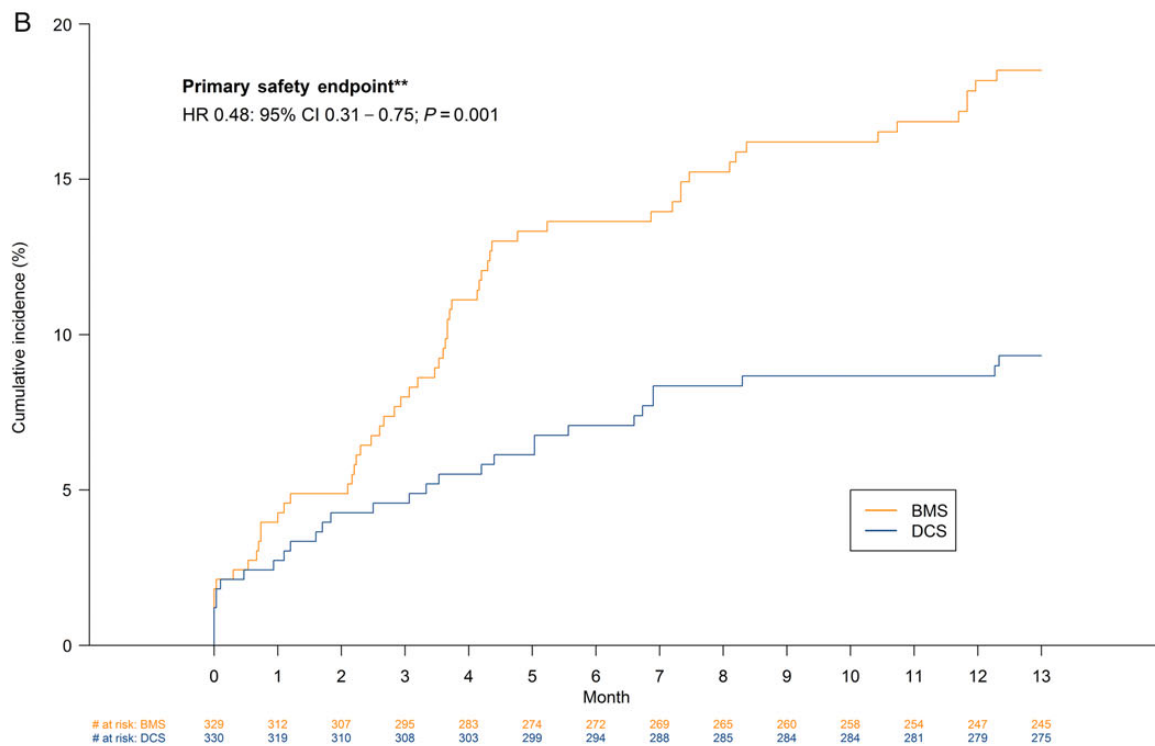
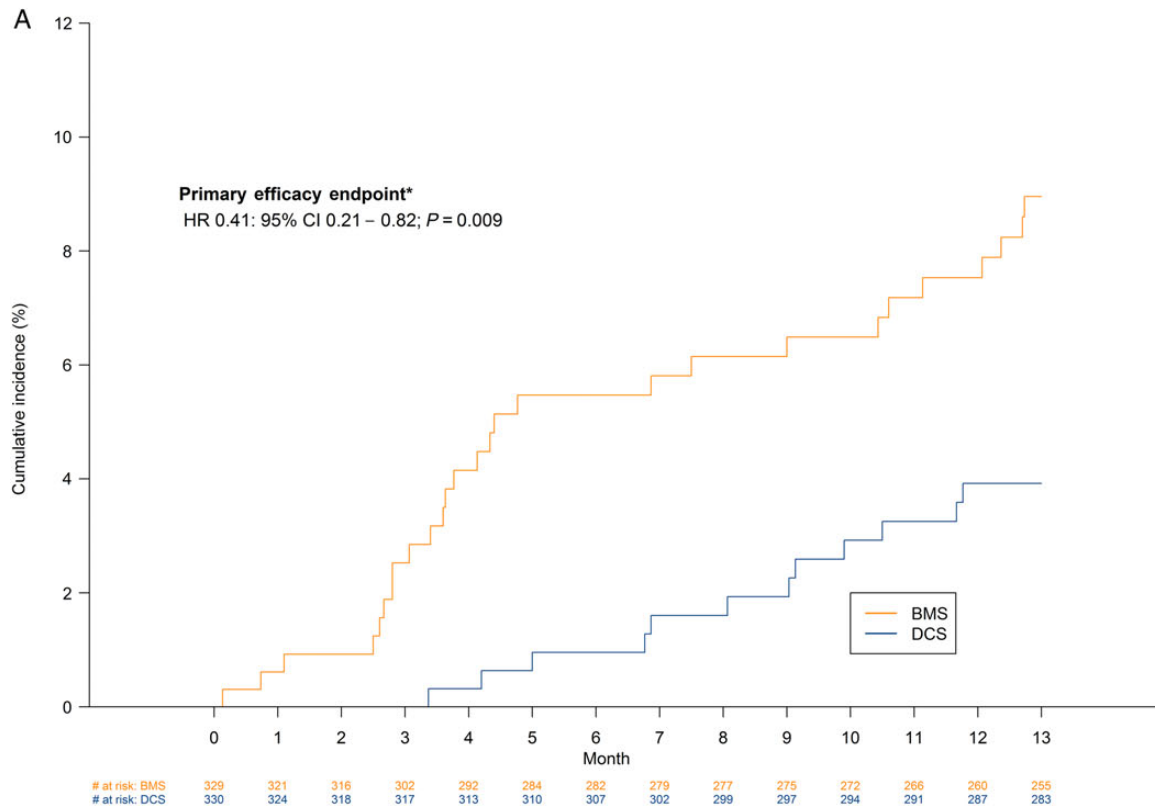
<sup>a</sup>Either presented as n(%) or mean ± SD.

<sup>b</sup>Following the *Leaders Free* report, medication is reported at Day 23 post-PCI.

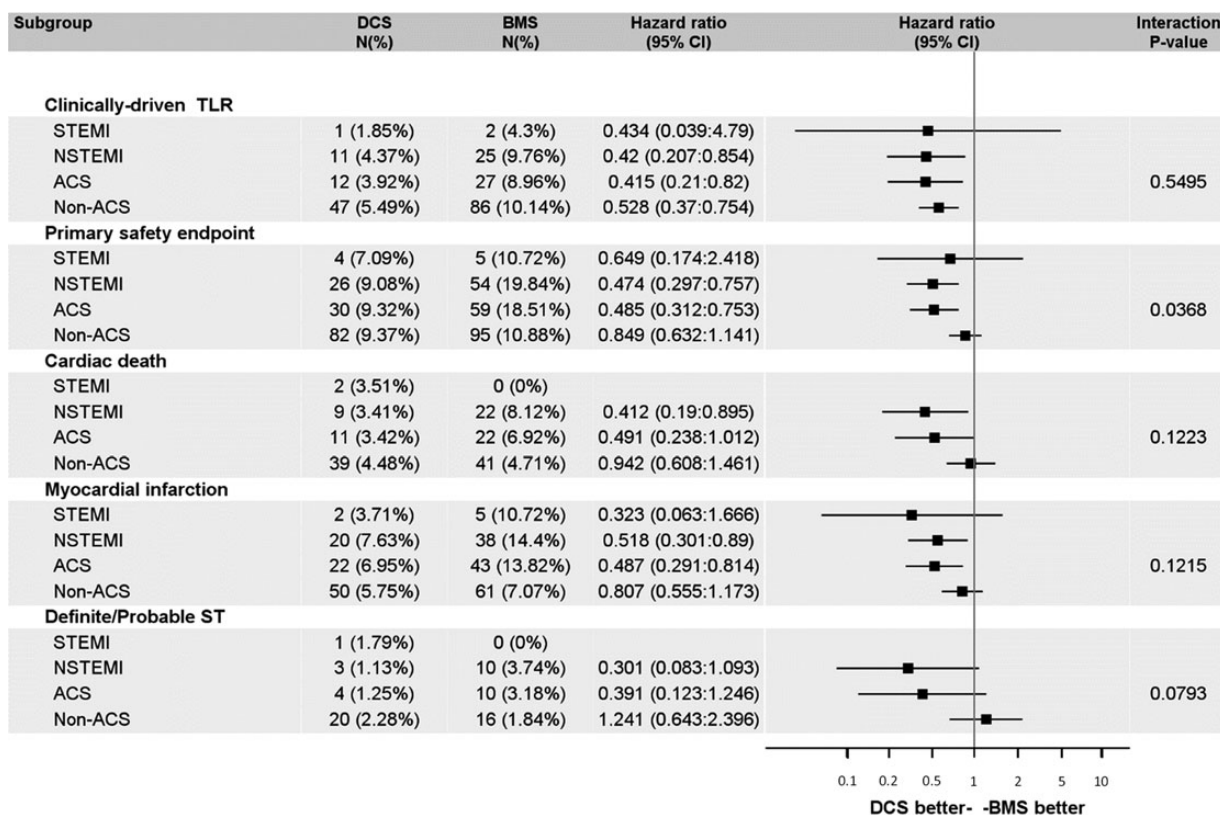
**Table 3** Incidence of safety and efficacy endpoints at 390 days, presented as n (%) of patients affected

Endpoint	Drug-coated stent (N = 330)	Bare-metal stent (N = 329)	Hazard ratio (95% CI)	P-value
<i>Primary safety endpoint:</i> cardiac death, myocardial infarction, or definite/probable stent thrombosis	30 (9.3)	59 (18.5)	0.48 (0.31–0.75)	0.001
Cardiac death	11 (3.4)	22 (6.9)	0.49 (0.23–1.01)	0.049
Myocardial infarction	22 (6.9)	43 (13.8)	0.48 (0.29–0.81)	0.005
Definite or probable stent thrombosis	4 (1.2)	10 (3.1)	0.39 (0.12–1.24)	0.099
<i>Primary efficacy endpoint:</i> clinically driven TLR	12 (3.9)	27 (9.0)	0.41 (0.21–0.82)	0.009
<i>Bleeding</i>				
BARC 1–5	65 (20.2)	67 (21.3)	0.97 (0.69–1.36)	0.86
BARC 2–5	49 (15.2)	54 (17.2)	0.90 (0.61–1.32)	0.60
BARC 3–5	29 (9.0)	29 (9.2)	0.99 (0.59–1.66)	0.99

TLR, target-lesion revascularization; BARC, bleeding according to Academic Research Consortium definition.



**Figure 2** Time-to-event curves for the primary efficacy and safety endpoints \*primary efficacy endpoint (clinically driven target-lesion revascularization) \*\*primary safety endpoint (cardiac death, myocardial infarction, or definite and probable stent thrombosis).



Percentages are Kaplan-Meier estimates  
Interaction p-value is for ACS versus non-ACS

**Figure 3** Forest plot of *Leaders Free* for the primary efficacy and safety endpoints and components by acute coronary syndrome status.

A very recent sub-analysis of the ZEUS trial included patients with pre-defined risk factors for bleeding. Similar to *Leaders Free*, this analysis found a significant disadvantage regarding safety and efficacy in patients receiving a thin-strut BMS when compared with a fast-eluting Zotarolimus-eluting stent.<sup>27</sup>

Despite the fact that patients with a BMS in our analysis had a higher rate of DAPT use when compared with DCS patients at 37 days, definite and possible stent thrombosis tended to be lower in the DCS group, while both myocardial infarction and cardiovascular death were significantly less frequent in the DCS group at follow-up.

The fact that not only the primary efficacy endpoint but also stent thrombosis and ischaemic events are reduced in the DCS group is compelling. Spontaneous myocardial infarction (type 1), and myocardial infarction related to stent thrombosis (type 4b), as categorized according to the third Universal Definition of Myocardial Infarction, occurred significantly less frequent among patients with a drug-coated stent (see Appendix, Table A1). A comparable, however, non-significant trend was seen for myocardial infarction related to in-stent restenosis (type 4c). Because routine angiography was not systematically performed, it is likely that many of the spontaneous myocardial infarctions were also related to in-stent restenosis, although this uncertainty does not affect the comparison between treatment groups.

As demonstrated above, in *Leaders Free* this superior safety effect was mainly driven by the ACS subgroups. A similar effect has also been demonstrated in other studies of BA9 stents. Superior safety was also observed in the COMFORTABLE AMI study.<sup>19</sup> The study, compared the same drug on the same stent platform as investigated in this trial, albeit with a biodegradable polymer, with the same BMS in the setting of acute myocardial infarction. Finally interaction testing in the LEADERS trial<sup>28</sup> demonstrated heterogeneity of treatment effects in regards to the primary endpoint in the BA9 STEMI sub-group.

It is therefore tempting to speculate about a benefit for this type of therapy in the acute setting that is conferred by BA9. The high lipophilicity of this drug which may allow it to penetrate into lipid rich plaques more effectively than other drugs may explain part of the superior outcomes in the ACS population. This also means that our findings may not be extendable to polymer-coated DES or other polymer-free drug-coated stent designs.

In an ACS population at high risk of bleeding, our data show for the first time that it is possible to clinically reproduce an efficacy similar to that of current DES together with a significant safety benefit when compared with BMS implantation with only 1 month DAPT duration. Of note, despite a course of only 1 month DAPT, the incidence of any reported bleeding events was similar and >20% in



both groups and the rate of severe bleeding was >9% during the 390 days follow-up. These figures are higher by one order of magnitude than those reported during the first year for several of the DAPT duration trials,<sup>22,23</sup> underlining that a longer course of DAPT would be expected to be poorly tolerated in this high bleeding risk cohort.

## Implications

Although the data presented herein are the result of a sub-analysis from the *Leaders Free* trial, and should be, thus, regarded as hypothesis generating, we believe that they are likely to significantly impact clinical practice for high bleeding risk patients presenting with an ACS: the use of a BMS can, in our view, no longer be recommended, and, given the paucity of available data for second-generation DES with shortened DAPT in these patients, the BA9-DCS should currently be considered as the device with the strongest evidence to support its use for this indication.

## Limitations

Although pre-defined, *Leaders Free ACS* is a sub-study of *Leaders Free* and was, thus, not powered to detect clinical differences between the groups.

This pre-defined ACS sub-analysis was not intended to include unstable angina, since Troponin negative unstable angina was not thought to be precisely enough defined to serve as discriminator for an outcome analysis in a randomized trial. Therefore, these patients were not included in the analysis.

Despite the fact that observed effects tended to be similar in all groups, the number of STEMI patients in this analysis was limited and the ACS group consisted mainly of patients with NSTEMI.

In this analysis, we compared the combination of 1 month DAPT with implantation of a BA9-DCS or with implantation of a BMS only. Our results cannot be extended to other device or treatment regimens.

## Authors' contributions

S.C., S.J.P. performed statistical analysis. P.U., S.G., M.-C.M. handled funding and supervision. C.K.N., P.U., P.J.O., M.V.-C., F.F., C.D.,

M.-C.M., A.A.A. acquired the data. P.U., M.-C.M., C.K.N., A.A.A. conceived and designed the research. P.U., M.-C.M., S.P., S.C., C.K.N. drafted the manuscript. C.K.N., P.U., P.J.O., M.V.-C., A.A.A., S.J.P., F.F., C.D., S.C., S.G., M.-C.M. made critical revision of the manuscript for key intellectual content.

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## Appendix

**Table A1** Myocardial infarction stratified by 3rd universal definition of myocardial infarction (6)

Parameter	Statistics	Drug-coated stent (N = 330)	Bare-metal stent (N = 329)	Total (N = 659)	Hazard ratio	P-value
Myocardial infarction	n (%)	22 (6.95%)	43 (13.85%)	65 (10.37%)	0.487 (0.291:0.814)	0.005
Myocardial infarction—type 1	n (%)	14 (4.49%)	26 (8.46%)	40 (6.46%)	0.515 (0.269:0.987)	0.04
Myocardial infarction—type 2	n (%)	4 (1.27%)	5 (1.66%)	9 (1.46%)	0.784 (0.211:2.921)	0.72
Myocardial infarction—type 3	n (%)	0 (%)	0 (%)	0 (%)	N/A	—
Myocardial infarction—type 4a	n (%)	5 (1.52%)	6 (1.84%)	11 (1.68%)	0.83 (0.253:2.719)	0.76
Myocardial infarction—type 4b	n (%)	0 (0%)	8 (2.52%)	8 (1.26%)	N/A	0.004
Myocardial infarction—type 4c	n (%)	2 (0.65%)	5 (1.66%)	7 (1.15%)	0.385 (0.075:1.983)	0.24
Myocardial infarction—type 5	n (%)	0 (%)	0 (%)	0 (%)	N/A	—

Given that many patients did not undergo control angiography when readmitted during follow-up, a definite distinction between Types I, 4b and 4c was sometimes difficult to establish.

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