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Two-year outcomes of high bleeding risk patients with acute coronary syndrome after Biolimus A9 polymer-free drug-coated stents: a LEADERS FREE substudy

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Introduction

In patients with acute coronary syndrome (ACS) undergoing PCI, bleeding is associated with increased mortality[1]. An abbreviated dual antiplatelet therapy (DAPT) is recommended after drug-eluting or bare metal stent (BMS) implantation for patients at high bleeding risk (HBR)[2]. The LEADERS FREE trial[3] demonstrated superiority for safety and efficacy endpoints of a polymer-free Biolimus A9™ (BA9) drug-coated stent (DCS) over a similar BMS for patients at HBR treated with one-month DAPT. The one-year outcome of a pre-specified substudy of patients presenting with ACS has been reported[4].

The aim of this analysis was to evaluate whether the demonstrated superiority in safety and efficacy of the DCS compared to BMS at one year was sustained up to 24 months in HBR patients with ACS.

Methods

PATIENTS AND METHODS

The study includes all patients presenting with ACS at HBR from the modified intention-to-treat analysis of the LEADERS FREE trial[3,4], a randomised, double blind trial. Patients undergoing PCI were assigned to a polymer-free BA9 DCS (BioFreedom™; Biosensors Europe, Morges, Switzerland) or a similar BMS (Gazelle™; Biosensors Interventional Technologies, Singapore, Singapore). All patients were assigned to one month of DAPT only, followed by long-term single antiplatelet therapy (SAPT).

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STUDY ENDPOINTS

The primary safety endpoint consisted of cardiac death, myocardial infarction (MI), and definite or probable stent thrombosis (ST). The primary efficacy endpoint was defined as clinically driven target lesion revascularisation (TLR).

Results

PATIENTS AND PROCEDURES

Six hundred and fifty-nine patients[5] presenting with ACS (554 NSTEMI and 105 STEMI) were followed for two years after assignment to DCS (330 patients) or BMS (329 patients) treatment.

PRIMARY ENDPOINTS

At two years, the primary safety endpoint had occurred more frequently in the BMS than in the DCS group **(Figure 1)**. This difference was driven by events occurring within the first year. Between year one and year two, the primary safety endpoint occurred in 19 patients (DCS vs. BMS: 8 vs. 11 patients, p=0.560).

The primary efficacy endpoint was reached by 10.4% in the BMS and 5.0% in the DCS group **(Figure 1)**. This difference was driven by events occurring within the first year. Between year one and year two, the primary efficacy endpoint occurred in seven patients (DCS vs. BMS: 3 vs. 4 patients, p=0.152) **(Figure 2)**.

BLEEDING

The Bleeding Academic Research Consortium (BARC) 3-5 bleeding rates were high and similar between groups **(Table 1)**.

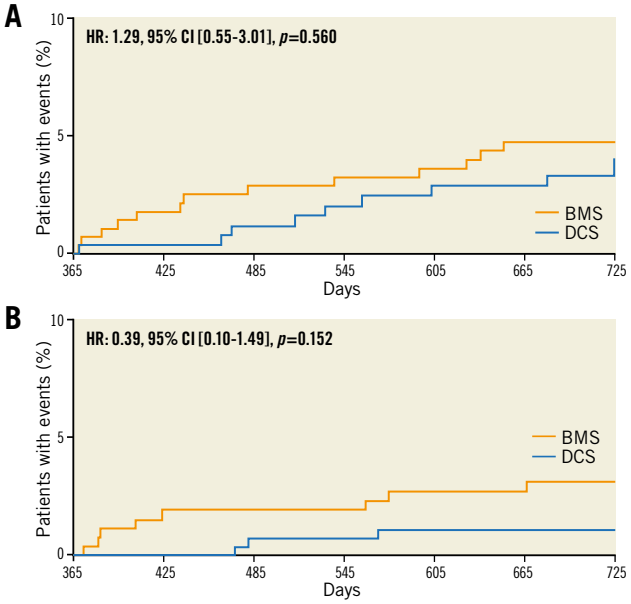

Figure 2. *Landmark analysis for the primary safety and primary efficacy endpoints. The Kaplan Meier time-to-event curves show the cumulative percentage of patients who reached the primary safety endpoint (A) and the primary efficacy endpoint (B) for the first time between day 365 and day 730 during follow-up.*

Details of antiplatelet and oral anticoagulation regimen adherence during follow-up are provided in the **Supplementary Appendix**, and in **Supplementary Table 1**.

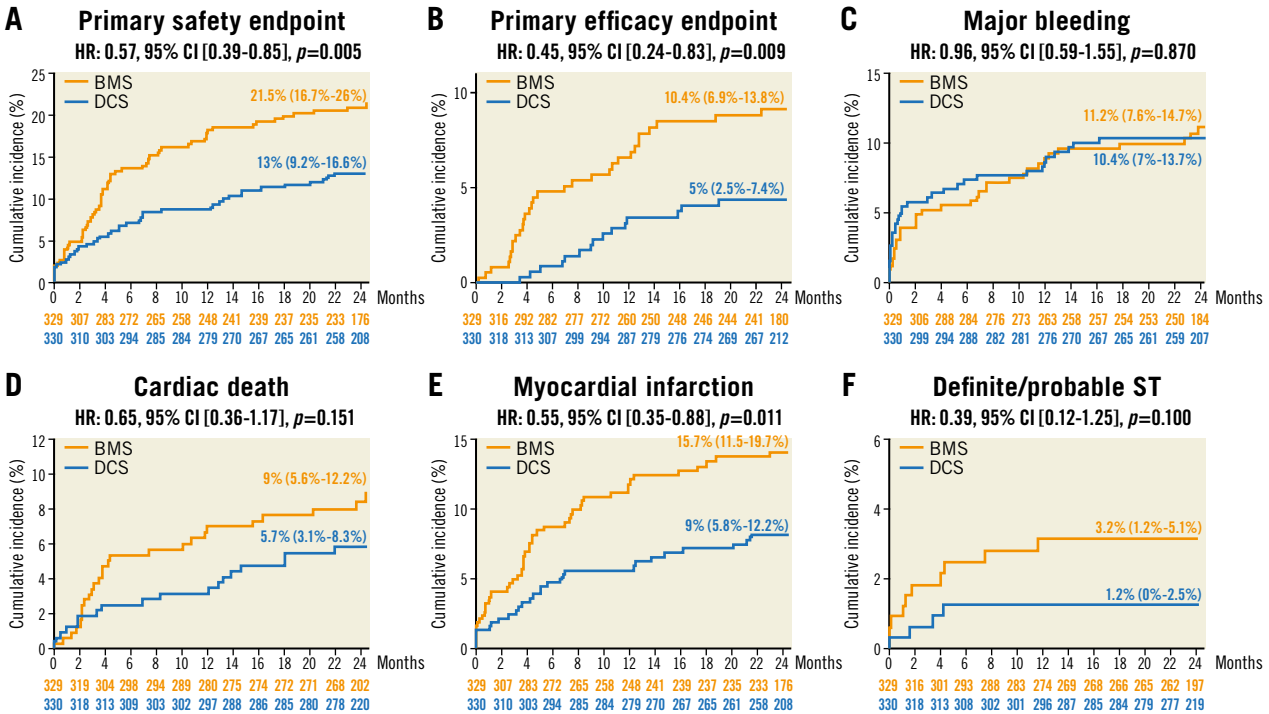

Figure 1. *Time-to-event analysis at two years. A) Primary safety endpoint. B) Primary efficacy endpoint. C) Major bleeding. D) Cardiac death. E) Myocardial infarction. F) Definite/probable ST.*

Table 1. Incidence of safety and efficacy endpoints at 1 and 2 years.

		1 year			2 years		
		Drug-coated stent (N=330)	Bare metal stent (N=329)	*p*-value	Drug-coated stent (N=330)	Bare metal stent (N=329)	*p*-value
Primary safety endpoint: cardiac death, MI or stent thrombosis		30 (9.3)	59 (18.5)	0.001	41 (13)	67 (21.5)	0.005
Cardiac death		11 (3.4)	22 (6.9)	0.049	18 (5.8)	27 (8.9)	0.151
Myocardial infarction		22 (6.9)	43 (13.8)	0.005	28 (9.0)	48 (15.7)	0.011
Definite or probable stent thrombosis		4 (1.2)	10 (3.1)	0.099	4 (1.2)	10 (3.1)	0.099
Primary efficacy endpoint: clinically driven TLR		12 (3.9)	27 (9.0)	0.009	16 (5.3)	32 (10.7)	0.010
Bleeding	BARC 1-5	65 (20.2)	67 (21.3)	0.860	78 (24.7)	73 (23.6)	0.720
	BARC 2-5	49 (15.2)	54 (17.2)	0.600	58 (18.3)	60 (19.5)	0.784
	BARC 3-5	29 (9.0)	29 (9.2)	0.990	33 (10.4)	34 (11.2)	0.870

Data are presented as n (%). BARC: Bleeding Academic Research Consortium; MI: myocardial infarction; TLR: target lesion revascularisation

Discussion

In this analysis of the LEADERS FREE ACS substudy of patients at HBR and with ACS who received only one month of DAPT, the superiority of the BA9 DCS over a BMS was preserved up to two years for both the primary efficacy and the primary safety endpoints. DCS treatment showed a lower rate of MI and a trend towards a lower ST rate, whereas cardiac death was not statistically different between treatment groups.

Short duration DAPT used to be considered a major advantage of using BMS. There are compelling data; however, this comes at the cost of reduced safety and efficacy. This study demonstrated safety and efficacy superiority of DCS compared to BMS at one year and two years. This was also true in patients receiving triple therapy compared to patients on DAPT.

Bleeding rates were high and the highest bleeding rates were observed during the first month while patients were on DAPT. This underlines the need for shortening the duration of DAPT. A prolonged DAPT regimen might have led to an even higher bleeding rate and a detrimental outcome. In fact, previous studies have suggested increasing mortality with prolonged DAPT especially in HBR patients[5].

Limitations

This predefined LEADERS FREE ACS substudy did not use a subrandomisation and is insufficiently powered for clinical endpoints.

– Given the unique properties of the studied DCS, our observations should not be extrapolated to other drug-eluting stents or DCS, or to stents with different drug-elution kinetics.
– The trial was designed to compare two strategies using a guideline-recommended minimal one-month DAPT course for BMS implantation and therefore no conclusions can be made concerning the optimal duration of DAPT for HBR patients after DCS implantation.

Conclusion

In HBR patients presenting with ACS undergoing PCI followed by one-month DAPT, the safety and efficacy benefits of a BA9 DCS compared to BMS were sustained up to 24 months. This study provides further evidence discouraging the use of BMS in HBR patients with ACS.

Impact on daily practice

This trial of HBR patients presenting with ACS undergoing PCI provides evidence that the use of BMS in ACS, in our view, can no longer be recommended. The BA9 DCS followed by one-month DAPT provides a safe and efficient treatment of ACS patients with HBR.

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Conflict of interest statement

C. Naber reports receiving personal fees from Abbott, Biosensors, Biotronik, Medtronic, Elixir, REVA and MicroPort, and is a shareholder of CERC, the contract research organisation (CRO) responsible for running the LEADERS FREE study. P. Urban reports receiving personal fees from Biosensors Europe, Edwards Lifesciences, Terumo, Abbott Vascular, Quest Medical, and is medical co-director and a shareholder of CERC. A. Abizaid reports receiving grants from Abbott, Medtronic, Elixir, and Riva. S. Pocock reports receiving personal fees from Biosensors Europe SA. C. Dubois reports receiving personal fees from Boston Scientific, Edwards Lifesciences, and Medtronic, and grants from Abbott Vascular and Biotronik. S. Copt and H.P. Stoll are employees of Biosensors International. M.C. Morice is the CEO of and a shareholder of CERC. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix. Methods, Results and Discussion.

Supplementary Table 1. Antithrombotic therapy during follow-up.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/131st_issue/316

Supplementary data

Supplementary Appendix. Methods, Results and Discussion

METHODS

Patients and methods

The patients, investigators, and clinical events committee members (CEC) were unaware of the study-group assignments.

Study endpoints

In our initial publication [6], we reported the primary endpoints at 390 days to make sure that all revascularisations scheduled were captured. In this analysis, cut-off time points at 365 and 730 days were chosen to compare event rate differences better between the first and second year.

Primary endpoint events and bleeding events were recorded up to two years post randomisation. A CEC adjudicated the primary endpoints and all bleeding events, according to predefined criteria.

Statistical analysis

Kaplan-Meier plots, log-rank tests, and proportional hazard models were performed to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs).

RESULTS

Antiplatelet and oral anticoagulation regimen adherence

Twenty-eight point five percent (28.5%) in the DCS versus 35.9% in the BMS arm (p=0.066) were on oral anticoagulation. Between one and two years, numerically more patients received

DAPT in the BMS compared to the DCS arm (BMS versus DCS at one year 9.7% versus 5.4%, at two years 6.1% versus 3.3%). These differences were not statistically significant **(Supplementary Table 1)**.

Supplementary Table 1. Antithrombotic therapy during follow-up.

Medication	**DCS, n (%)**	**BMS, n (%)**	***p*-value**
At discharge			
DAPT	324 (97.3)	334 (99.7)	0.011
SAPT	6 (1.8)	0 (0)	0.014
No APT	3 (0.9)	1 (0.3)	0.313
OAC	84 (25.2)	99 (29.6)	0.209
37 days			
DAPT	28 (8.7)	49 (15.2)	0.016
SAPT	289 (90.0)	263 (81.7)	0.003
No APT	4 (1.2)	10 (3.1)	0.179
OAC	79 (24.6)	97 (30.1)	0.139
12 months			
DAPT	16 (5.4)	27 (9.7)	0.052
SAPT	269 (90.9)	233 (83.5)	0.008
No APT	11 (3.7)	19 (6.8)	0.096
OAC	83 (28)	91 (32.6)	0.233
24 months			
DAPT	9 (3.3)	16 (6.1)	0.121

SAPT	240 (87.6)	207 (79)	0.008
No APT	25 (9.1)	39 (14.9)	0.039
OAC	78 (28.5)	94 (35.9)	0.066

Data are presented as n (%). APT: antiplatelet therapy; DAPT: dual antiplatelet therapy; OAC: oral anticoagulation; SAPT: single antiplatelet therapy

Triple therapy versus DAPT

One hundred and seventy-nine (179) patients received triple therapy and 470 patients received DAPT at hospital discharge. Subgroup analysis comparing primary endpoints, components thereof and bleeding rates showed no evidence that the advantage of DCS treatment varied between triple therapy and DAPT treatment groups (p for interaction >0.05).

DISCUSSION

Current guidelines recommend prolonged DAPT in patients with ACS for prevention of secondary events and ST, but the risk of bleeding increases with prolonged DAPT, and guidelines recommend shortening DAPT if bleeding risk is estimated to be high. The recently published OPTIMIZE trial in low-risk patients suggests that DAPT duration may be shortened to three months after implantation of fast-eluting zotarolimus-coated DES. The polymer-free design of the Biolimus-A9 DCS facilitates the delivery of Biolimus due to its marked lipophilicity. Therefore, this DCS should be particularly well suited for a short DAPT regimen.

Over the two-year period, MI occurred less frequently in DCS compared to BMS. This difference emerged entirely during the first year without further divergence in the second year, confirming the good results observed during the first year. There was a trend for higher ST rates at one year in the BMS compared to the DCS arm. No additional ST occurred beyond one year in either group. This suggests that very late ST will probably not be a problem with the polymer-free DCS, in contrast to previous DES. Moreover, after four months, no ST occurred in the DCS arm, whereas ST occurred in the BMS arm until 12 months post implantation. This could constitute a chance finding, but could also reflect the impact of Biolimus, since the drug is highly lipophilic and may effectively penetrate into lipid-rich plaque components. Further studies are needed to clarify the issue. There is no dedicated study on the optimal duration of DAPT in patients at HBR and with ACS. Previous studies showed that, in HBR patients, shortening of DAPT to six months reduced the risk of bleeding without increasing ischaemic events compared to 12 months of DAPT. The ZEUS and the LEADERS FREE studies proved superiority of the respective devices compared to BMS with DAPT of only one month. Further randomised studies are needed to assess the optimal duration of DAPT in ACS patients at HBR. It is not clear whether the specific design of the DCS used in this trial provides advantages over other second-generation DES. However, the rapid elution kinetics of the Biolimus DCS could be advantageous compared to other DES with slower drug-elution kinetics.