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2-Year Outcomes of High Bleeding Risk Patients After Polymer-Free Drug-Coated Stents

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ABSTRACT

BACKGROUND A 1-year follow-up, polymer-free metallic stent coated with biolimus-A9 followed by 1-month dual antiplatelet therapy is safer and more effective than a bare-metal stent (BMS) for patients with high risk of bleeding.

OBJECTIVES This study analyzed 2-year outcomes to determine whether these benefits are maintained.

METHODS In a prospective, multicenter, double-blind trial, we randomized 2,466 high bleeding risk patients to receive a drug-coated stent (DCS) or a BMS followed by 1-month dual antiplatelet therapy. The primary safety endpoint was a composite of cardiac death, myocardial infarction, or stent thrombosis. The primary efficacy endpoint was clinically driven target lesion revascularization.

RESULTS At 2 years, the primary safety endpoint had occurred in 147 DCS and 180 BMS patients (15.3%) (hazard ratio: 0.80; 95% confidence interval: 0.64 to 0.99; $p = 0.039$). Clinically driven target lesion revascularization occurred for 77 DCS and 136 BMS patients (12.0%) (hazard ratio: 0.54; 95% confidence interval: 0.41 to 0.72; $p < 0.0001$). Major bleeding occurred in 8.9% of DCS and 9.2% of BMS patients ($p = 0.95$), and a coronary thrombotic event (myocardial infarction and/or stent thrombosis) occurred in 8.2% of DCS and 10.6% of BMS patients ($p = 0.045$). One-year mortality was 27.1% for a major bleed and 26.3% for a thrombotic event. At 2 years, multivariate correlates of major bleeding were age >75 years, anemia, raised plasma creatinine, and planned long-term anticoagulation. Correlates of the primary safety endpoint were age, anemia, congestive heart failure, multivessel disease, number of stents implanted, and use of a BMS rather than a DCS.

CONCLUSIONS Safety and efficacy benefits of DCS over BMS were maintained for 2 years in high bleeding risk patients. Rates of major bleeding and coronary thrombotic events were no different and were associated with a substantial and comparable mortality risk. (A Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug Coated Stent Versus the Gazelle Bare Metal Stent in Patients With High Risk of Bleeding [LEADERS FREE]; NCT01623180) (J Am Coll Cardiol 2017;69:162–71) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Patients at high bleeding risk (HBR) who require percutaneous coronary intervention (PCI) are a challenging group who need careful evaluation of both their thrombotic and bleeding risks when selecting a stent and determining duration and intensity of antithrombotic management (1,2). Little evidence exists to aid such decisions, because HBR patients are mostly excluded from clinical trials of antithrombotics and PCI (3–6). Until recently, the perceived need for a very short course of dual antiplatelet treatment (DAPT) often led operators to prefer a bare-metal stent (BMS) to a drug-eluting stent (DES) for such patients (7,8).

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The LEADERS FREE (A Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug Coated Stent versus the Gazelle Bare Metal Stent in Patients With High Risk of Bleeding) trial recently showed that, together with a 1-month DAPT course, a polymer-free metallic drug-coated stent (DCS) was both safer and more effective than a BMS for patients at high risk of bleeding who were followed for 1 year (1). This DCS (BioFreedom, Biosensors Interventional Technologies, Singapore) transfers biolimus A9, a highly lipophilic sirolimus analog, into the vessel wall over a 1-month period (9). This is in contrast to currently available polymer-coated DES, which generally release the drug over a period of several months.

Limited encouraging 5-year data are available from the first-in-man evaluation of this DCS for 60 selected patients treated with DAPT for 6 to 12 months (10). For HBR patients with 1-month DAPT treatment, further evidence is needed to assess whether the first-year benefits of DCS over BMS are maintained in the long term. Also, because of the unique features of the LEADERS FREE design (i.e., unusual patient population, very short DAPT time) together with the observed high rate of major bleeding in both arms after 1 year (1), it is important to evaluate the balance of the 2-year risks and the baseline and procedure correlates of the primary safety endpoint and of major bleeding events.

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

BMS = bare-metal stents

CI = confidence interval

DAPT = dual antiplatelet therapy

DCS = drug-coated stent(s)

DES = drug-eluting stent(s)

HBR = high bleeding risk

HR = hazard ratio

PCI = percutaneous coronary intervention

METHODS

PATIENTS. Patient selection and study design of the LEADERS FREE trial have been described previously (1,11). Inclusion required a clinical indication for PCI together with 1 or more HBR criteria: most frequently age 75 or older, planned prolonged oral anticoagulation, renal insufficiency, planned major surgery, anemia or recent transfusion, and cancer. Such patients were potential candidates for a BMS instead of a DES, owing to their perceived need for only 1 month of DAPT.

STUDY DEVICE AND PROCEDURE. The BioFreedom polymer-free biolimus A9 coated stent, the control Gazelle BMS (Biosensors Europe, Morges, Switzerland; and Biosensors Interventional Technologies), and the PCI procedure have been described previously (1,11). A double-blind design was used. All patients were to receive DAPT including both aspirin (75 to 250 mg once daily) and a $P2Y_{12}$ inhibitor (with clopidogrel preferred) for 30 days followed by a single antiplatelet agent thereafter (aspirin preferred). Patients requiring a vitamin K antagonist could be treated either by triple therapy or a vitamin K antagonist plus clopidogrel only during the first 30 days. Patients had follow-up visits at 30 and 365 days and were contacted either on site or by telephone at 60, 120, and 730 days. Ischemia testing and angiographic evaluation during follow-up was left to the investigator's discretion.

STUDY DESIGN AND OVERSIGHT. A total of 2,466 patients from 68 sites were randomized to receive either the BioFreedom DCS or the Gazelle BMS. The study was sponsored by Biosensors Europe and conducted by the Cardiovascular European Research Center, an independent research organization paid by

Kingdom; [s]St. Thomas Hospital, London, United Kingdom; [t]Cardiovascular European Research Center, Massy, France; and the [u]Cardiovascular Department, Hôpital de la Tour, Geneva, Switzerland. All financial support for the trial was provided by the sponsor, Biosensors Europe. Dr. Pocock has received consulting fees from Biosensors. Dr. Meredith has received consulting fees, proctor fees, and honoraria from Boston Scientific; and has received consulting fees and honoraria from Medtronic. Dr. Abizaid has received research grants from Abbott Vascular, Medtronic, Elixir, and Riva. Dr. Menown has received grants to his institution from Biosensors, Boston Scientific, Meril Life, and Orbus Neich; and has received conference sponsorship from Biosensors. Dr. Christiansen has received grants to his institution from Biosensors. Dr. Gregson has received consulting fees and research grants from Biosensors. Drs. Copt and Stroll are full-time employees of Biosensors. Dr. Windhövel is a full-time employee of Cardiovascular European Research Center, the clinical research organization that ran the trial. Ms. Greene has received consulting fees from Biosensors. Dr. Urban has received consulting fees from Biosensors. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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the sponsor. The respective roles of the executive committee, the sponsor, Cardiovascular European Research Center, and authors have remained unchanged (1). The first author, statisticians (J.G., S.C.), and executive committee had unrestricted access to the data and prepared all drafts of the manuscript; they attest to the completeness and accuracy of all data and to the adherence to study protocol. The ethics committee at each site approved the trial, and written informed consent was obtained from all patients.

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. Pre-specified secondary endpoints included all-cause and cardiac mortality, bleeding (Bleeding Academic Research Consortium [BARC] definitions) (12), myocardial infarction (third universal definition) (13), stent thrombosis (Academic Research Consortium definitions) (14), and types of coronary revascularization. A clinical events committee adjudicated all components of the primary endpoints and all bleeding events, according to predefined criteria (1,11).

STATISTICAL ANALYSIS. All results are based on a modified intention-to-treat analysis after exclusion of 34 patients who had no suitable lesion for PCI (1). Continuous variables are presented as means, and categorical data as counts and percentages. Time-to-event analyses were performed using Kaplan-Meier plots, log-rank tests, and proportional-hazard models to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). Proportional hazard assumptions were checked using Schoenfeld residuals. Patients were censored at death, withdrawal from study, scheduled end of study, or 730 days post-randomization, whichever occurred first. We performed sensitivity analyses using the Fine and Gray method to estimate cumulative incidence of events while adjusting for the competing risk of mortality (15).

For major bleeding we used the BARC 3, 4, or 5 bleeding definition. To explore covariates associated with major bleeding and the primary safety endpoint, we performed multivariate analyses investigating the potential influence of 32 baseline and procedural variables (Online Table 1) by means of proportional hazard models. We selected a final model for each outcome by using forward stepwise variable selection on data with complete information on all covariates and an inclusion criterion of $p < 0.01$. Based on the trial results, we forced inclusion of BMS in the model for the primary safety endpoint. We used multiple imputations with chained equations to impute missing data on covariates when calculating HR. We used 10 imputed datasets and combined estimates and SE across studies using the Rubin rules (16). To calculate the HR for death following a thrombotic or major bleeding event, follow-up of each patient was divided into time spent before and after a major bleeding or thrombotic event. The association between these events and subsequent mortality was entered into a Cox-proportional hazards model as a time-updated categorical variable that enters the model on the day of the event (the methods in the Online Appendix). HR therefore compare the hazard of death after an event to the hazard before an event (which includes the hazard in patients who do not have an event during follow-up). We further broke each patient's follow-up after a thrombotic or major bleeding event into 3 time intervals (0 to 7, 8 to 30, and 31 to 365 days) based on similar analyses performed in other studies (17).

HR for death were adjusted for correlates of thrombotic or major bleeding events. Analyses were performed with Stata Software (version 14.1, Stata Corp., College Station, Texas) and SAS (version 9.3, SAS Institute, Cary, North Carolina), and all p values were calculated using 2-sided hypothesis tests.

RESULTS

PATIENTS. Of the 2,432 patients who underwent PCI, 2,386 (98.1%) were followed until death or 730 days (Online Figure 1). Only 9 patients in the DCS arm and 3 in the BMS arm were lost to follow-up before 2 years. Patients were included based on pre-defined criteria of an increased bleeding risk, mainly age ≥75 years (64.3%), prolonged oral anticoagulation (36.1%), renal failure (19.1%), planned major surgery (16.4%), hemoglobin <11 g/l or recent transfusion (15.6%), and cancer in the previous 3 years (9.8%). The DCS and BMS groups were well matched with regard to baseline characteristics (Online Table 2).

At 730 days, 78.8% of patients in the DCS group and 76.8% in the BMS group were receiving single antiplatelet therapy; 5.3% and 7.6%, respectively, had DAPT; 15.8% and 15.6%, respectively, were taking no antiplatelet drug; and 37.7% and 38.0%, respectively, were taking oral anticoagulants. Details regarding antithrombotic treatment are given in Online Table 3.

PRIMARY OUTCOMES AT 2 YEARS. We previously reported outcomes using a 390-day time point (1).

TABLE 1 Clinical Outcomes at 1 and 2 Years With a DCS or BMS

	1 Year			2 Years		
	DCS (n = 1,221)	BMS (n = 1,211)	p Value	DCS (n = 1,221)	BMS (n = 1,211)	p Value
Primary safety endpoint: cardiac death, MI, or stent thrombosis	110 (9.2)	151 (12.7)	0.006	147 (12.6)	180 (15.3)	0.039
Primary efficacy endpoint: clinically driven TLR	57 (4.9)	107 (9.3)	<0.001	77 (6.8)	136 (12.0)	<0.0001
Death						
From any cause	91 (7.5)	105 (8.7)	0.27	156 (13.1)	164 (13.8)	0.57
From cardiac causes	49 (4.1)	61 (5.1)	0.23	76 (6.6)	80 (6.9)	0.69
MI*						
Any	70 (5.9)	103 (8.7)	0.008	90 (7.4)	117 (10.1)	0.04
Q-wave infarction	6 (0.5)	7 (0.6)	0.77	6 (0.5)	10 (0.9)	0.31
Non-Q-wave infarction	55 (4.7)	78 (6.7)	0.04	67 (5.8)	86 (7.4)	0.09
Undetermined type	10 (0.8)	26 (2.2)	0.007	18 (1.6)	31 (2.7)	0.06
Stent thrombosis*						
Definite or probable	24 (2.0)	26 (2.2)	0.75	25 (2.1)	27 (2.3)	0.76
Definite	16 (1.3)	17 (1.4)	0.84	17 (1.4)	17 (1.4)	0.98
Probable	8 (0.7)	9 (0.8)	0.80	8 (0.7)	10 (0.9)	0.63
Possible	25 (2.2)	26 (2.2)	0.85	36 (3.2)	35 (3.1)	0.95
Early definite or probable (acute + subacute)	12 (1.0)	15 (1.2)	0.55	–	–	–
Late definite or probable	13 (1.1)	11 (1.0)	0.70	–	–	–
Very late definite or probable	–	–	–	1 (0.1)	1 (0.1)	0.99
Coronary thrombotic event*†	76 (6.4)	109 (9.3)	0.01	96 (8.2)	123 (10.6)	0.045
Bleeding*‡						
BARC 1-5	213 (17.9)	225 (19.1)	0.50	258 (22.0)	255 (22.3)	0.89
BARC 2-5	165 (13.9)	173 (14.8)	0.61	204 (17.4)	206 (17.9)	0.83
BARC 3-5	85 (7.2)	85 (7.3)	0.96	105 (8.9)	105 (9.2)	0.95
Revascularization						
Any TVR	65 (5.6)	119 (10.3)	<0.001	91 (8.1)	151 (13.3)	<0.0001
TVR by CABG	4 (0.3)	11 (1.0)	0.07	6 (0.5)	12 (1.1)	0.14
Any revascularization	94 (8.1)	134 (11.6)	0.003	129 (11.4)	180 (15.9)	0.001

Values are n (%). Percentages are Kaplan-Meier estimates at 365 (1 year) and 730 days (2 years). *Subcategories of MI, stent thrombosis, or bleeding are not mutually exclusive, because patients could have >1 subtype of these events during follow-up. †Any MI and/or definite or probable stent thrombosis. ‡Bleeding was defined according to the BARC definitions. BARC type 0 indicates no bleeding, and BARC type 5 indicates fatal bleeding (11).

BARC = Bleeding Academic Research Consortium; BMS = bare-metal stent(s); CABG = coronary artery bypass graft; DCS = drug-coated stent(s); MI = myocardial infarction; TLR = target-lesion revascularization; TVR = target-vessel revascularization.

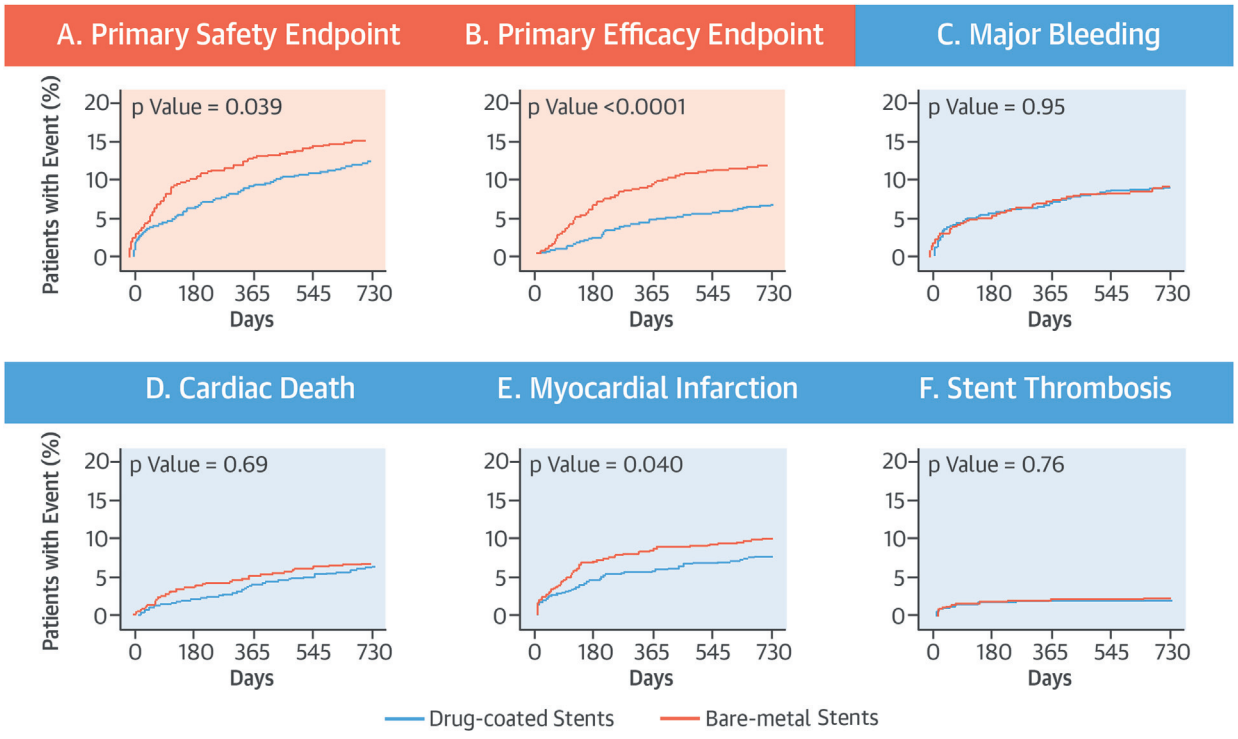
To facilitate comparisons between the first and second follow-up years, time points of 365 and 730 days were used for 1 and 2 years in the present analysis. Between 1 and 2 years, there were 53 new occurrences of a primary safety endpoint in 37 DCS patients and 44 in 29 BMS patients. The primary safety outcomes at 2 years occurred more frequently in the BMS than in the DCS group (15.3% vs. 12.6%; HR: 0.80; 95% CI: 0.64 to 0.99; p = 0.039) (Table 1, Central Illustration, Figure 1).

Between 1 and 2 years, there were 24 new clinically driven target lesion revascularizations (the primary efficacy endpoint) in 20 patients of the DCS group and 43 in 29 patients of the BMS group. Clinically driven target lesion revascularization was required at least once in 6.8% of DCS and 12.0% of BMS patients at 2 years (HR: 0.54; 95% CI: 0.41 to 0.72; p < 0.0001) (Table 1, Central Illustration, Figure 1).

OTHER CLINICAL OUTCOMES. Other clinical outcomes are summarized in Table 1. There were no significant differences in mortality between the DCS and BMS groups in either all-cause mortality (13.1% vs. 13.8%; HR: 0.94; 95% CI: 0.75 to 1.17; p = 0.57) or cardiac mortality (6.6% vs. 6.9%; HR: 0.94; 95% CI: 0.69 to 1.28; p = 0.69) (Table 1). Between the first and second years of follow-up, 48 myocardial infarctions occurred (25 in 20 patients of the DCS group, and 23 in 14 patients of the BMS group) and 2 very late definite or probable stent thromboses (1 in the DCS group and 1 in the BMS group).

The incidence of coronary thrombotic events from randomization to 2 years (defined as any myocardial infarction and/or definite or probable stent thrombosis) was significantly lower with DCS than with BMS (8.2% vs. 10.6%; p = 0.045) (Table 1). Major bleeding over 2 years occurred at a similar rate in both DCS and

CENTRAL ILLUSTRATION **HBR Patients After Polymer-Free DCS: Primary Safety Endpoint, Primary Efficacy Endpoint, Major Bleeding, and Individual Components of the Primary Safety Endpoint**



Garot, P. et al. J Am Coll Cardiol. 2017;69(2):162–71.

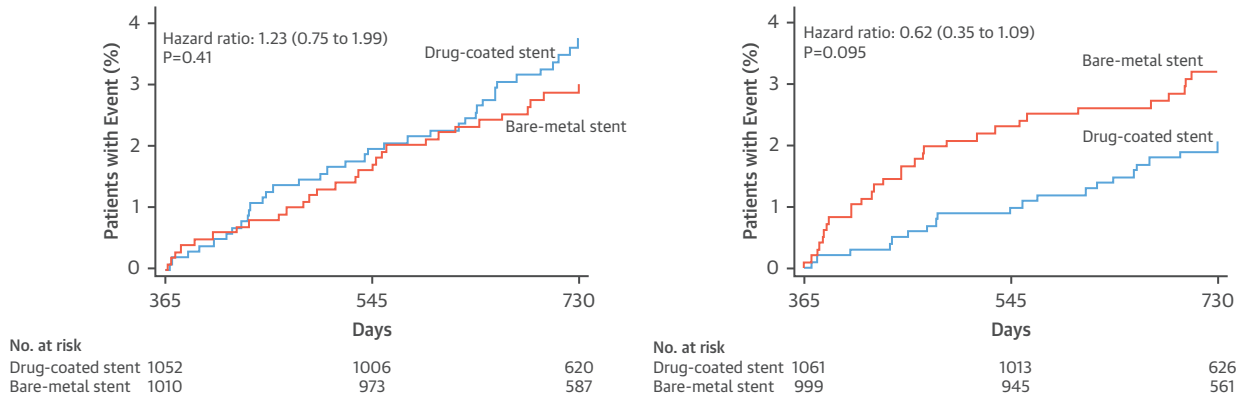
The Kaplan-Meier time-to-event curves show the cumulative percentage of patients with the primary safety endpoint (a composite of cardiac death, myocardial infarction, or stent thrombosis) **(A),** the primary efficacy endpoint (clinically driven target-lesion revascularization) **(B),** major bleeding **(C),** and the 3 components of the safety endpoint **(D to F)**. BMS = bare-metal stent(s); DCS = drug-coated stent(s); HBR = high bleeding risk.

BMS groups (8.9% vs. 9.2%; p = 0.95) (**Central Illustration**). Pre-specified subgroup comparisons for the primary efficacy and safety endpoints are shown in Online Figure 2. These analyses show a consistent treatment effect across most subgroups. However, interaction testing suggested heterogeneity of treatment effect with regard to the primary safety endpoint according to whether or not the patient presented with an acute coronary syndrome, and with regard to the primary efficacy endpoint in patients with a CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score >35. Both of these subgroups had already been identified at the 1-year follow-up (1).

We identified 8 baseline and procedural characteristics correlated with major bleeding and primary safety endpoint events at 2 years: 4 were related to the safety endpoint only (congestive heart failure, multivessel disease, number of stents and stent type); 2 to bleeding events only (planned oral anticoagulation and raised plasma creatinine); and 2 to both (age >75 years and low hemoglobin) (**Table 2**). Of note, use of a BMS had a 33% relative increase in the hazard for safety endpoint events (p = 0.04) compared with DCS after covariate adjustment.

The risks of all-cause death 1 year after a major bleed and 1 year after a coronary thrombotic event were 27.1% and 26.3%, respectively (**Figure 2**). Both show a similar pattern with very marked excess mortality risk within the first week after such events—especially for coronary thrombotic events—which then attenuates over time (**Table 3**). A major bleed remains associated with a significant excess mortality risk during 31 to 365 days after the event (adjusted HR: 2.54; p < 0.001). These mortality patterns were no different for both DCS and BMS groups, though the former has a reduced risk of a coronary thrombotic event (**Table 1**).

FIGURE 1 Landmark Analysis at 1 Year 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 **(left)** and the primary efficacy endpoint **(right)** for the first time between 365 and 730 days.

DISCUSSION

For HBR patients receiving a 1-month course of DAPT, 2-year follow-up in the LEADERS FREE trial demonstrates, for both efficacy and safety, the sustained superiority of the BioFreedom polymer-free biolimus A9-coated stent (DCS) compared with a similar BMS. In this patient population, both the risks of major bleeding and of a composite of cardiac death, myocardial infarction, or stent thrombosis were high. Both types of events were associated with several baseline and procedure characteristics, and when 2 of the components of the primary safety endpoint (myocardial infarction and/or stent thrombosis) were analyzed for their associated post-event 1-year all-cause mortality, this was high—26.3%—and comparable to that observed after major bleeding (27.1%).

TABLE 2 Multivariate Correlates of Primary Safety Endpoint and Major Bleeding

	HR (95% CI)	p Value
Primary safety endpoint*		
Age >75 yrs	1.56 (1.23–1.97)	<0.001
Hemoglobin (per 1 mmol/l <9)	1.32 (1.19–1.46)	<0.001
Congestive heart failure at baseline	1.61 (1.23–2.11)	0.001
Multivessel disease at baseline†	1.66 (1.27–2.18)	<0.001
Number of stents implanted (per additional stent)	1.13 (1.04–1.23)	0.005
BMS	1.28 (1.03–1.59)	0.027
Major bleeding event‡		
Age >75 yrs	1.52 (1.13–2.06)	0.006
Hemoglobin (per 1 mmol/l <9)	1.73 (1.52–1.96)	<0.001
Serum creatinine >150 μmol/l	1.58 (1.10–2.27)	0.012
Planned OAC use post-PCI	2.01 (1.51–2.68)	<0.001

*Primary safety endpoint: composite of cardiac death, myocardial infarction, and definite/probable stent thrombosis. †Multivessel disease includes patients with site-reported 2- or 3-vessel and/or left main disease. ‡BARC bleeding score 3 to 5.

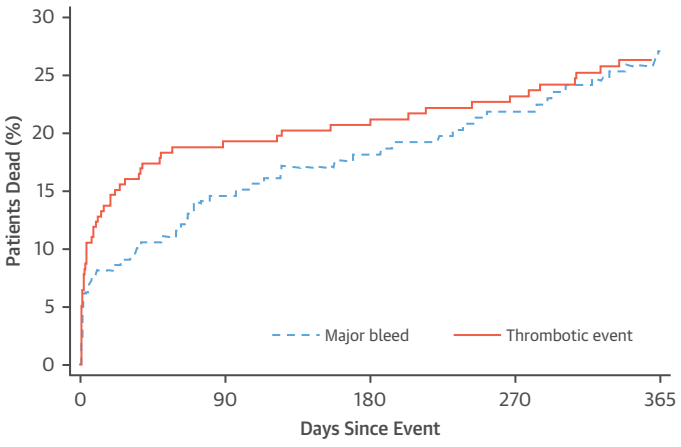
BMS = bare-metal stent(s); CI = confidence interval; HR = hazard ratio; OAC = oral anticoagulants; PCI = percutaneous coronary intervention.

Encouragingly for the DCS, no "catch-up" of target lesion revascularization was observed beyond 1 year. This is in keeping with studies of a polymer-free stent as well as a rapid-elution permanent polymer DES (18,19) and different from what has been seen with first generation DES (20). It is plausible that biolimus A9 is particularly well suited to rapid delivery into the vessel wall because of its marked lipophilicity (9). The low incidence of very late stent thrombosis in both trial arms (<0.1%) suggests that absence of any polymer on the DCS may contribute to its long-term safety despite the very short DAPT and compares favorably with stent thrombosis rates for polymer-coated DES, especially in this high risk population (21–26).

These data confirm the good long-term results of DCS observed in a previous study (10). However, HBR patients continue to suffer a high incidence of adverse events beyond the first year, most likely due to advanced age, major comorbidities, and possibly because of only partial revascularization in some patients (multivessel disease was reported in 62% of patients, but multivessel index revascularization was done in only 22%) (1). Two-year mortality was 13.1% for DCS versus 13.8% for BMS patients. This is higher than observed in all-comer trials and again points to the impact of comorbid conditions (23,26–29).

The ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates) trial randomized

FIGURE 2 1-Year Mortality Following a Major Bleed or a Coronary Thrombotic Event



Kaplan-Meier time-to-event curves show the cumulative percentage of patients who died within 1 year following a major bleed or a thrombotic event throughout the 2-year study period.

1,606 patients considered uncertain DES candidates to either a first-generation rapid-elution zotarolimus DES with a biocompatible permanent polymer or a thin-strut BMS (30). Among these patients, 52% had HBR, and their median DAPT duration was 30 days. The overall trial found better safety and efficacy for the DES, even more pronounced for HBR patients with substantial reductions in myocardial infarction and target vessel revascularization and a stent thrombosis rate of 2.6% versus 6.2% for DES and BMS, respectively (2,30). Two other randomized trials evaluated this rapid-elution zotarolimus-eluting DES in low bleeding risk patients and concluded that a 3-month course of DAPT was as safe and effective as a prolonged course of DAPT, but both were somewhat underpowered (5,6). The larger DAPT trial enrolled 9,961 low to medium bleeding risk patients after implantation of several slow-eluting DES and an uneventful first 12 months' period and evaluated prolonged DAPT. Rates of myocardial infarction and stent thrombosis were significantly lower with 30 than with 12 months' DAPT, but at the cost of an increase in bleeding (31).

The recent NORSTENT (Norwegian Coronary Stent Trial) randomized 9,013 patients to either a contemporary DES or a thin-strut BMS, and it found that with a 9-month DAPT course in both arms and after a 6-year follow-up, both stent types were equivalent for safety (cardiac death or myocardial infarction), whereas DES were superior in terms of need for repeat revascularization and a lower rate of stent thrombosis (32). Because both the DAPT duration and the patients' risk profiles were very different from those of LEADERS FREE, we believe that both trials complement rather than contradict each other. BMS design is unlikely to be a major factor, because the thin strut BMS used in NORSTENT were very similar to those used in ZEUS, where active stents were also both safer and more effective than BMS in HBR patients treated with a short course of DAPT (2,30).

Interest in shortening DAPT when needed is now considerable, and there are at least 9 randomized trials currently planned or ongoing to evaluate DAPT regimens of 3 months or less after coronary stenting. Some use stents with rapid drug transfer to the vessel wall, a logical feature when very short DAPT appears desirable, and others use stents coated with either a permanent or biodegradable polymer that delivers the antiproliferative drug over several months. Whether such strategies are safe remains to be demonstrated (33).

One important finding in our trial is that both bleeding and coronary thrombotic event rates (myocardial infarction and/or stent thrombosis) are high and similar in HBR patients. Although this balance has already been described for all-comer patients (34), both types of events are clearly more frequent in HBR patients. In the present trial, 8.2% of patients suffered a coronary thrombotic event (myocardial infarction and/or stent thrombosis) and 8.9% suffered a major bleeding event at 2 years in the DCS group, whereas these events occurred in 10.6% for thrombotic and 9.2% for bleeding events in the BMS group. In the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients) registry that analyzed 4,190 patients after coronary stenting, the majority of whom were maintained on DAPT for at least 1 year, coronary thrombotic events occurred in 3.8% and major BARC bleeding (BARC 3 or 5) in 3.3% (34-37). This difference is again most probably due to the more advanced age and greater comorbidity of HBR patients, compared with an all-comer population. Of interest is the fact that the ratio of thrombotic to bleeding events at 2 years was very similar in both trials (0.92 for the DCS arm and 1.15 for the BMS arm in LEADERS FREE, and 1.15 in PARIS).

The risk of ensuing mortality is also high, especially soon after the event. Of note is the persistently high excess mortality out to 1 year after a major bleed. These findings are similar to those of ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy Trial) (17), a trial focused on patients presenting with acute coronary syndrome, but the adjusted HR for mortality associated with major bleeding and thrombotic events were markedly

TABLE 3 1-Year Mortality Following a Major Bleed or Coronary Thrombotic Event

	Patients With Event	Deaths	Person-Time at Risk (yrs)	Rate (per Person-Year at Risk)	Adjusted HR Versus No Event (95% CI)
First year after event					
Thrombotic event					
No event or before event	2,432	256	4,137.3	0.06	1.00 (reference)
0–365 days	219	64	257.3	0.25	4.43 (3.24–6.04)
Major bleeding					
No event or before event	2,432	255	4,153.5	0.06	1.00 (reference)
0–365 days	210	65	241.1	0.27	3.43 (2.49 to 4.74)
Time since event					
Thrombotic event					
No event or before event	2,432	256	4,137.3	0.06	1.00 (reference)
0–7 days	219	24	3.9	6.22	77.96 (49.29–123.30)
8–30 days	195	11	11.8	0.93	11.51 (6.19–21.40)
31–365 days	183	29	241.6	0.12	1.53 (0.93–2.53)
Major bleeding					
No event or before event	2,432	255	4,153.5	0.06	1.00 (reference)
0–7 days	210	16	3.8	4.2	36.11 (20.82–62.64)
8–30 days	192	3	11.9	0.25	2.41 (0.76–7.65)
31–365 days	186	46	225.4	0.2	2.36 (1.60–3.48)

Abbreviations as in Table 2.

higher in LEADERS FREE, again suggesting that such events are of greater consequence for HBR than for younger patients with less comorbidity. The trade-off for any change in antithrombotic management may be finely balanced: a longer DAPT course might decrease thrombotic complications, but, most likely at the price of an increased risk of major bleeding (35,36). LEADERS FREE was designed to compare a new stent to a BMS using the accepted standard of 1 month DAPT in HBR patients, but the optimal duration of DAPT still remains to be determined in this high-risk population.

Among characteristics associated with either bleeding or the primary safety endpoint (Table 2), anemia, like age, was related to both. This stresses the limitations of using certain correlates to assess either bleeding or thrombotic risks in isolation when deciding about the intensity and duration of DAPT. As previously reported, anemia is a powerful prognostic indicator after PCI, more so for bleeding than for thrombosis in our series, and it has historically received insufficient attention (38–40). For avoidance of bleeding, the need for long-term oral anticoagulation should always be carefully reassessed after PCI (40). Renal insufficiency was correlated only with bleeding in our series, but it has also been reported as a predictor of thrombotic complications by others (34,37). It could either be that its thrombotic risk is of comparatively lesser importance for HBR patients who by definition often have other comorbid conditions, or that patients with the most severe renal dysfunction are already captured by their associated anemia.

STUDY LIMITATIONS. First, results are not directly applicable to non-HBR patients who are likely to tolerate longer courses of DAPT. For non-HBR patients, a 6- to 12-month course, perhaps longer, is associated with benefit (7,8,31) and a minimum of 12 months remains the guideline when such patients present with ACS (7,40). Second, our results cannot be generalized to other DES or DCS with different drugs or slower elution kinetics. Further evidence is needed, and those trials are currently underway.

CONCLUSIONS

The safety and efficacy benefits of a polymer-free biolimus A9-eluting stent versus a BMS together with a short 1-month DAPT course were maintained during 2 years of follow-up. The persistently high incidence of both bleeding and coronary thrombotic events in HBR patients needs wider recognition and deserves our full attention in future trials of antithrombotic therapy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: For patients at high risk of bleeding undergoing PCI followed by 1 month of DAPT, polymer-free DCS are both safer and more effective than BMS at 2 years' follow-up.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to define the optimum intensity and duration of DAPT for patients undergoing PCI characterized based on bleeding risk, coronary pathoanatomy and stability, procedural complexity, and the number and types of stents deployed.

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APPENDIX For supplemental material as well as tables and figures, please see the online version of this paper.