ORIGINAL ARTICLE

Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk

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ABSTRACT

BACKGROUND

Patients at high risk for bleeding who undergo percutaneous coronary intervention (PCI) often receive bare-metal stents followed by 1 month of dual antiplatelet therapy. We studied a polymer-free and carrier-free drug-coated stent that transfers umirolimus (also known as biolimus A9), a highly lipophilic sirolimus analogue, into the vessel wall over a period of 1 month.

METHODS

In a randomized, double-blind trial, we compared the drug-coated stent with a very similar bare-metal stent in patients with a high risk of bleeding who underwent PCI. All patients received 1 month of dual antiplatelet therapy. The primary safety end point, tested for both noninferiority and superiority, was a composite of cardiac death, myocardial infarction, or stent thrombosis. The primary efficacy end point was clinically driven target-lesion revascularization.

RESULTS

We enrolled 2466 patients. At 390 days, the primary safety end point had occurred in 112 patients (9.4%) in the drug-coated–stent group and in 154 patients (12.9%) in the bare-metal–stent group (risk difference, −3.6 percentage points; 95% confidence interval [CI], −6.1 to −1.0; hazard ratio, 0.71; 95% CI, 0.56 to 0.91; P<0.001 for noninferiority and P=0.005 for superiority). During the same time period, clinically driven target-lesion revascularization was needed in 59 patients (5.1%) in the drug-coated–stent group and in 113 patients (9.8%) in the bare-metal–stent group (risk difference, −4.8 percentage points; 95% CI, −6.9 to −2.6; hazard ratio, 0.50; 95% CI, 0.37 to 0.69; P<0.001).

CONCLUSIONS

Among patients at high risk for bleeding who underwent PCI, a polymer-free umirolimus-coated stent was superior to a bare-metal stent with respect to the primary safety and efficacy end points when used with a 1-month course of dual antiplatelet therapy. (Funded by Biosensors Europe; LEADERS FREE ClinicalTrials.gov number, NCT01623180.)

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Among patients undergoing percutaneous coronary intervention (PCI), it is estimated that 15% or more are at high risk for bleeding.[1,2] Such patients are usually excluded from trials of stents and adjunctive therapy, and the default management of their care, supported by current guidelines,[3,4] favors the use of either a second-generation drug-eluting stent with a shortened course of dual antiplatelet therapy or a bare-metal stent followed by 1 month of dual antiplatelet therapy. The latter strategy, driven by the need to minimize the risk of bleeding, is associated with a higher risk of restenosis and reintervention than that observed with the use of a drug-eluting stent.[5]

A polymer-free and carrier-free drug-coated stent, the BioFreedom stent (Biosensors Europe), has been developed that transfers umirolimus (also known as biolimus A9), a highly lipophilic sirolimus analogue, into the vessel wall over a period of 1 month. In a preclinical study, the umirolimus-coated stent showed less neointimal proliferation and inflammation at 180 days than did a sirolimus-eluting stent.[6] In a first-in-human evaluation, the umirolimus-coated stent was noninferior to a paclitaxel-eluting stent with respect to in-stent late lumen loss at 12 months.[7] The Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) trial was designed to evaluate the efficacy and safety of the polymer-free umirolimus-coated stent as compared with a bare-metal stent in patients with increased bleeding risk, with a 1-month regimen of dual antiplatelet therapy in both groups.

METHODS

STUDY DESIGN AND ORGANIZATION

The LEADERS FREE trial is an ongoing randomized, double-blind clinical trial conducted at 68 sites in 20 countries on 4 continents (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The study design has been described previously.[2]

The trial was sponsored by Biosensors Europe (Morges, Switzerland). The sponsor approved the trial protocol, which was developed by the executive committee and is available at NEJM.org. The sponsor had no role in site monitoring, the collection, storage, or analysis of the data, or the decision to submit the manuscript for publication. Two members of the executive committee were employees of the sponsor and contributed to the writing of the manuscript. No agreement regarding data confidentiality was made between the sponsor and the executive committee.

The study was conducted in accordance with the trial protocol by Centre Européen de Recherche Cardiovasculaire (CERC; Massy, France), an independent research organization paid by the sponsor. The institutional review board at each site approved the study. The first six authors and last three authors wrote the manuscript, had full access to the data, and vouch for the completeness and accuracy of data and analyses and for the fidelity of this report to the trial protocol.

STUDY POPULATION

Eligible patients had coronary artery disease with a clinical indication for PCI. In addition, participants were required to meet one or more of the criteria listed in Table 1. These criteria were chosen to define a population of patients who had increased bleeding risk or who were otherwise considered by the investigator to be candidates for implantation of a bare-metal stent instead of a drug-eluting stent, owing to the perceived need to terminate dual antiplatelet therapy at 1 month. Detailed inclusion and exclusion criteria are listed in the Supplementary Appendix. All patients provided written informed consent.

STUDY PROCEDURES

Patients were randomly assigned in a 1:1 ratio to undergo PCI with the BioFreedom polymer-free umirolimus-coated stent or a similar bare-metal stent (the Gazelle stent, Biosensors Interventional Technologies, Singapore). Details of the design of both stents are provided in the Supplementary Appendix. Randomization was performed with the use of either a Web-based system or a telephone interactive voice-response system (both from Merge Healthcare) in blocks of 16 with no stratification. The patients, investigators, and members of the clinical-events committee and the executive committee were unaware of the study-group assignments.

Patients were enrolled after the guidewire had crossed the first target lesion, and PCI was performed according to standard techniques. Vascular access, periprocedural antithrombotic regimen, and lesion preparation were left to the operator's

Table 1. Baseline Patient Characteristics and Inclusion Criteria.*

Variable	Drug-Coated Stent (N=1221)	Bare-Metal Stent (N=1211)
Baseline characteristics		
Age — yr	75.7±9.4	75.7±9.3
Female sex — no. (%)	364 (29.8)	374 (30.9)
Body-mass index†	27.5±4.8	27.2±4.6
Diabetes — no./total no. (%)	414/1217 (34.0)	391/1210 (32.3)
Hypertension — no./total no. (%)	952/1219 (78.1)	961/1208 (79.6)
Hypercholesterolemia — no./total no. (%)	742/1197 (62.0)	746/1189 (62.7)
STEMI — no. (%)	57 (4.7)	48 (4.0)
NSTEMI — no. (%)	273 (22.4)	281 (23.2)
Unstable angina — no. (%)	177 (14.5)	193 (15.9)
Stable CAD — no. (%)	714 (58.5)	689 (56.9)
Multivessel disease — no./total no. (%)	755/1201 (62.9)	738/1198 (61.6)
Previous myocardial infarction — no./total no. (%)	237/1211 (19.6)	258/1203 (21.4)
Previous PCI — no./total no. (%)	270/1215 (22.2)	265/1208 (21.9)
Previous CABG — no./total no. (%)	115/1217 (9.4)	122/1209 (10.1)
Congestive heart failure — no./total no. (%)	175/1212 (14.4)	150/1211 (12.4)
Atrial fibrillation — no./total no. (%)	424/1215 (34.9)	418/1209 (34.6)
Previous stroke — no./total no. (%)	132/1212 (10.9)	110/1208 (9.1)
Peripheral vascular disease — no./total no. (%)	190/1208 (15.7)	190/1201 (15.8)
Chronic obstructive lung disease — no./total no. (%)	131/1207 (10.9)	141/1202 (11.7)
CRUSADE score‡	34.1±0.4	34.6±0.4
Inclusion criteria — no. (%)§		
Age ≥75 yr	788 (64.5)	776 (64.1)
Oral anticoagulation planned to continue after PCI	448 (36.7)	431 (35.6)
Hemoglobin <11 g/liter or transfusion within 4 wk before randomization	185 (15.2)	194 (16.0)
Platelet count <100,000/mm^3	20 (1.6)	18 (1.5)
Hospital admission for bleeding in previous 12 mo	46 (3.8)	33 (2.7)
Stroke in previous 12 mo	15 (1.2)	24 (2.0)
Previous intracerebral hemorrhage	14 (1.1)	19 (1.6)
Severe chronic liver disease	11 (0.9)	10 (0.8)
Creatinine clearance <40 ml/min	219 (17.9)	245 (20.2)
Cancer in previous 3 yr¶	119 (9.7)	120 (9.9)
Planned major surgery in next 12 mo	187 (15.3)	211 (17.4)
Glucocorticoids or NSAID planned for >30 days after PCI	38 (3.1)	34 (2.8)
Expected nonadherence to >30 days of dual antiplatelet therapy	41 (3.4)	47 (3.9)

* Plus–minus values are means ±SD. There were no significant differences (P<0.05) between the two groups in any of the baseline characteristics. CABG denotes coronary-artery bypass grafting, CAD coronary artery disease, NSAID nonsteroidal antiinflammatory drug, NSTEMI non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scores on the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) bleeding risk scale[8] range from 1 to 100, with higher scores indicating a higher risk of major bleeding.

§ These criteria were not mutually exclusive.

¶ Cancer excluded skin cancer.

preference. All target lesions were treated with at least one study stent. Staged procedures were permitted within 1 week after the index procedure; all the stents used were of the assigned type.

The protocol mandated that all patients receive both aspirin (75 to 250 mg once daily) and a $P2Y_{12}$ inhibitor (with clopidogrel, 75 to 150 mg once daily, being the preferred agent) for 30 days, followed by a single antiplatelet agent thereafter (aspirin preferred). Patients who were discharged while receiving a vitamin K antagonist could receive either triple therapy or the vitamin K antagonist plus clopidogrel (without aspirin) during the first 30 days.[9]

A patient follow-up visit was performed at the study center at 30 days (time window, 23 to 37 days), when the change from dual antiplatelet therapy to single antiplatelet therapy was prescribed, and again at 360 days. Further contacts, either on site or by telephone, were made at 60, 120, and 720 days. Ischemia testing and angiographic evaluation during follow-up were not mandated by the protocol and were left to the discretion of the investigator.

STUDY END POINTS

The primary safety end point was the cumulative incidence of a composite of cardiac death, myocardial infarction, or definite or probable stent thrombosis at 390 days. The primary efficacy end point was the incidence of clinically driven target-lesion revascularization at 390 days. Other end points included bleeding, target-vessel revascularization, and indexes of technical procedural success. Primary end-point events and bleeding events were recorded for up to 390 days in order to capture any events occurring soon after (and as a consequence of) the planned 1-year visit.

Myocardial infarction was defined according to the third universal definition of myocardial infarction,[10] stent thrombosis according to the Academic Research Consortium definitions,[11] and bleeding according to the Bleeding Academic Research Consortium (BARC) definitions.[12] Clinically driven target-lesion revascularization was defined as PCI or surgery either for an operator-defined restenosis in the treated lesion together with angina symptoms or documented ischemia or for a core-laboratory–defined restenosis of greater than 70% of the artery diameter when neither symptoms nor ischemia were present (see the Supplementary Appendix for detailed end-point definitions).

Data verification and core-laboratory angiographic assessment of all cases of stent thrombosis and revascularization were performed by CERC. An independent clinical-events committee adjudicated all components of both primary end points and all bleeding events.

STATISTICAL ANALYSIS

The composite primary safety end point was evaluated with the use of a noninferiority analysis. We predicted a 1-year incidence of 8% for this end point in the bare-metal–stent group. Noninferiority was to be declared if the upper limit of the one-sided 97.5% confidence interval of the difference in event rates between the two groups at 1 year was less than 3.2 percentage points. After allowing for a rate of loss to follow-up of up to 5% and for the censoring of data from up to 3% of patients owing to death from noncardiac causes, we determined that a sample size of 1228 patients per group would provide more than 80% power to detect noninferiority. If noninferiority were shown, the composite safety end point would then be tested for superiority.

For the primary efficacy end point of clinically driven target-lesion revascularization, we predicted an event rate of 10% at 1 year in the bare-metal–stent group. Using a two-sided type I error rate of 5% and allowing for a rate of loss to follow-up of up to 8%, we determined that 1228 patients per group would provide more than 80% power to detect an absolute difference of 3.3 percentage points in the rate of clinically driven target-lesion revascularization between study groups.

All primary results are based on a modified intention-to-treat analysis (i.e., after the exclusion of 34 patients who were mistakenly assigned before coronary angiography and were found not to have a suitable lesion for PCI). Secondary as-treated analyses were performed after the exclusion of a further 31 patients who received a nonstudy stent and the reassignment of the 9 patients who mistakenly received a study stent from the other group.

Time-to-event analyses were performed with the use of the Kaplan–Meier method, and the two stents were compared with the use of the log-rank test for the time to the first event after randomization. Risk differences at 390 days and their 95% confidence intervals were calculated with the use of these Kaplan–Meier estimates

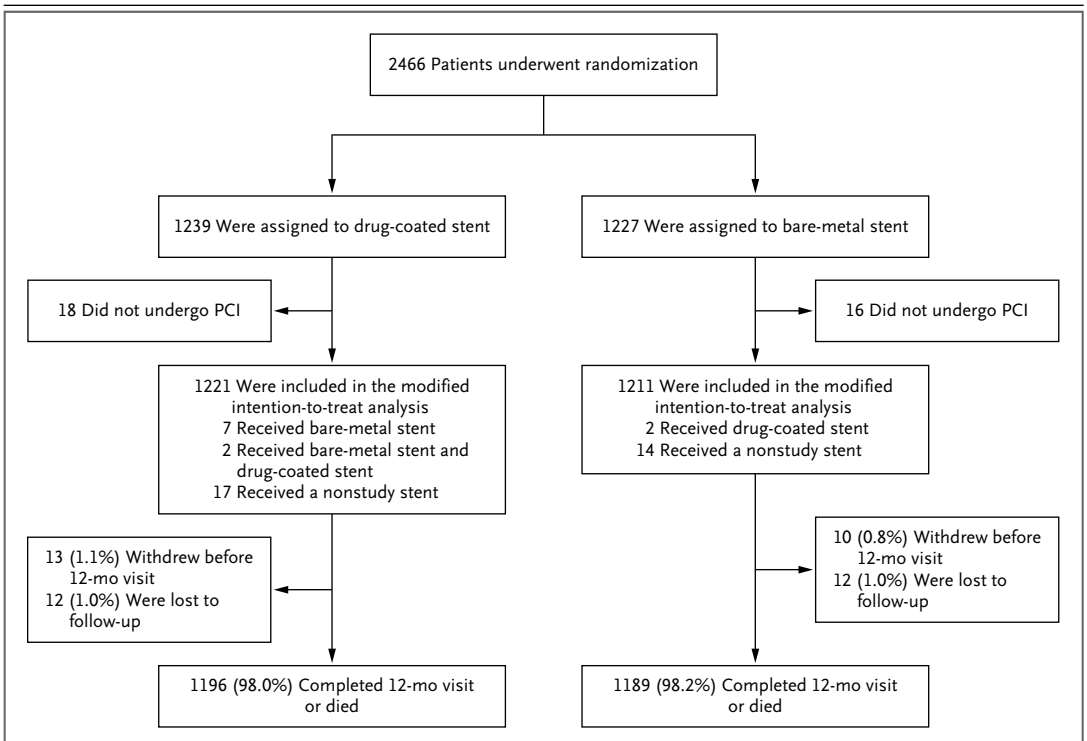

Figure 1. Randomization, Treatment, and Follow-up of the Patients.
PCI denotes percutaneous coronary intervention.

and their standard errors. Proportional-hazards models were used to estimate hazard ratios and their 95% confidence intervals. The consistency of treatment effects across prespecified subgroups was assessed with the use of proportional-hazards models with tests for interaction. All P values and 95% confidence intervals were two-sided except for the noninferiority analysis for the composite primary safety end point, for which a one-sided 97.5% confidence interval was used. Analyses were performed with Stata software, version 13.1 (StataCorp).

RESULTS

STUDY POPULATION AND PROCEDURES

A total of 2466 patients underwent randomization (1239 were assigned to the polymer-free umirolimus-coated stent and 1227 were assigned to the bare-metal stent) from December 2012 through May 2014. Of the 2432 patients who underwent PCI, 2385 (98.1%) were followed until death or 390 days (Fig. 1). The patient population was characterized by advanced age and major coexisting conditions indicative of increased bleeding risk. Patients had a mean of 1.7 inclusion criteria, and the two groups were well balanced with respect to baseline characteristics (Table 1).

A total of 60.7% of procedures in the drug-coated–stent group and 58.7% in the bare-metal–stent group were performed through a radial access, and 4.5% and 5.9% of procedures in the respective groups were staged. A total of 21.8% of procedures in the drug-coated–stent group and 21.4% in the bare-metal–stent group involved multivessel revascularization (Table S1 in the Supplementary Appendix). Dual antiplatelet therapy was being used by 96.5% and 96.9% of patients in the respective groups at discharge, by 95.2% and 94.7% at 23 days, and by 9.1% and 9.8% at 37 days (Table S2 in the Supplementary Appendix).

PRIMARY END POINTS

At 390 days, the primary safety end point (a composite of cardiac death, myocardial infarction, or stent thrombosis) had occurred in 112 patients (9.4%) in the drug-coated–stent group and in 154 patients (12.9%) in the bare-metal–stent

Table 2. Primary and Secondary End Points.*

End Point	Drug-Coated Stent (N=1221)	Bare-Metal Stent (N=1211)	Hazard Ratio (95% CI)	P Value
	no. of events (% of patients)			
Primary safety end point: cardiac death, myocardial infarction, or stent thrombosis	112 (9.4)	154 (12.9)	0.71 (0.56–0.91)	0.005†
Primary efficacy end point: clinically driven TLR	59 (5.1)	113 (9.8)	0.50 (0.37–0.69)	<0.001
Death				
From any cause	97 (8.0)	108 (9.0)	0.89 (0.67–1.17)	0.39
From cardiac causes	50 (4.2)	63 (5.3)	0.78 (0.54–1.14)	0.20
Myocardial infarction‡				
Any	72 (6.1)	104 (8.9)	0.68 (0.50–0.91)	0.01
Q-wave infarction	6 (0.5)	7 (0.6)	0.85 (0.29–2.53)	0.77
Non–Q-wave infarction	57 (4.8)	80 (6.9)	0.70 (0.50–0.98)	0.04
Undetermined type	10 (0.8)	25 (2.1)	0.39 (0.19–0.82)	0.01
Stent thrombosis‡				
Definite or probable	24 (2.0)	26 (2.2)	0.91 (0.53–1.59)	0.75
Definite	16 (1.3)	17 (1.4)	0.93 (0.47–1.84)	0.84
Probable	8 (0.7)	9 (0.8)	0.88 (0.34–2.28)	0.80
Possible	25 (2.2)	27 (2.3)	0.91 (0.53–1.57)	0.74
Acute	5 (0.4)	5 (0.4)	0.99 (0.29–3.43)	0.99
Subacute	7 (0.6)	10 (0.8)	0.69 (0.26–1.82)	0.45
Early: acute + subacute	12 (1.0)	15 (1.2)	0.79 (0.37–1.70)	0.55
Late	13 (1.1)	11 (1.0)	1.17 (0.52–2.61)	0.70
Revascularization				
Urgent TLR	39 (3.3)	67 (5.8)	0.57 (0.38–0.84)	0.004
Any TLR	60 (5.1)	115 (10.0)	0.50 (0.37–0.68)	<0.001
Clinically driven TVR	66 (5.7)	121 (10.5)	0.52 (0.39–0.71)	<0.001
Any TVR	67 (5.8)	125 (10.9)	0.51 (0.38–0.69)	<0.001
TVR by CABG	4 (0.3)	11 (1.0)	0.36 (0.11–1.12)	0.06
Any revascularization	97 (8.4)	141 (12.2)	0.67 (0.51–0.86)	0.002
Bleeding‡§				
BARC 1–5	215 (18.1)	225 (19.1)	0.95 (0.78–1.14)	0.56
BARC 2–5	166 (13.9)	172 (14.7)	0.96 (0.77–1.18)	0.68
BARC 3–5	85 (7.2)	85 (7.3)	0.99 (0.73–1.34)	0.96

* Percentages are Kaplan–Meier estimates at 390 days. TLR denotes target-lesion revascularization, and TVR target-vessel revascularization.
† P<0.001 for noninferiority comparison (primary analysis).
‡ Subcategories of myocardial infarction, stent thrombosis, or bleeding are not mutually exclusive, because patients could have more than one subtype of these events during follow-up.
§ Bleeding was defined according to the Bleeding Academic Research Consortium (BARC) definitions. BARC type 0 indicates no bleeding, and BARC type 5 indicates fatal bleeding.[12]

group (estimated absolute risk difference, –3.6 percentage points; 95% confidence interval [CI], –6.1 to –1.0; P<0.001 for noninferiority) (Table 2). A preplanned superiority analysis was then performed for the primary safety end point (hazard ratio, 0.71; 95% CI, 0.56 to 0.91; P=0.005 for

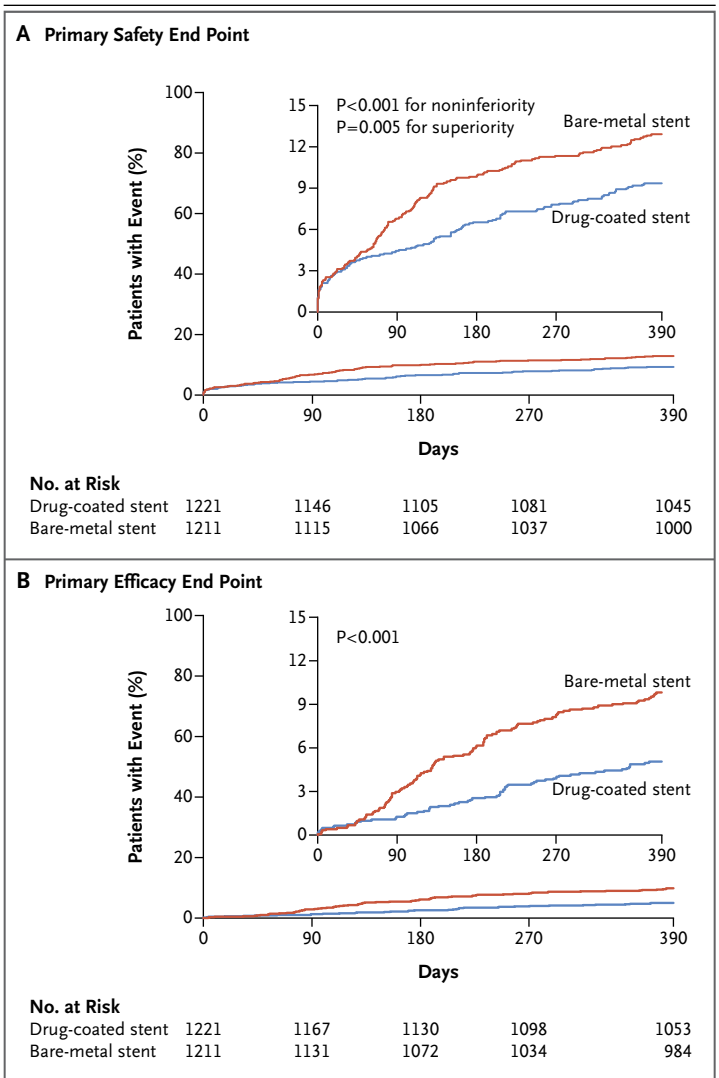

Figure 2. Time-to-Event Curves for the Primary End Points.

Kaplan–Meier time-to-event curves show the cumulative percentage of patients with the primary safety end point (a composite of cardiac death, myocardial infarction, or stent thrombosis) (Panel A) or the primary efficacy end point (clinically driven target-lesion revascularization) (Panel B). The inset in each panel shows the same data on an enlarged y axis.

superiority). The time-to-event curves for the primary safety end point are shown in Fig. 2A.

At 390 days, the primary efficacy end point (clinically driven target-lesion revascularization) had occurred in 59 patients (5.1%) in the drug-coated–stent group and in 113 patients (9.8%) in the bare-metal–stent group (estimated risk difference, −4.8 percentage points; 95% CI, −6.9 to −2.6; hazard ratio, 0.50; 95% CI, 0.37 to 0.69; P<0.001) (Table 2). The time-to-event curves for the primary efficacy end point are shown in Fig. 2B.

ADDITIONAL ANALYSES

Significant differences between the two groups were also observed with respect to other revascularization end points and with respect to myocardial infarction (Table 2, and Fig. S1 in the Supplementary Appendix). Among subtypes of myocardial infarction based on the third universal definition of myocardial infarction, type 1 (spontaneous myocardial infarction) and type 4c (myocardial infarction related to in-stent restenosis) occurred significantly less frequently in the drug-coated–stent group than in the bare-metal–stent group (Table S3 in the Supplementary Appendix). The rates of bleeding according to BARC criteria were similar in the two groups (Table 2, and Fig. S1 in the Supplementary Appendix). Results in the as-treated analysis were similar to those in the intention-to-treat analysis (Table S4 in the Supplementary Appendix).

Prespecified subgroup comparisons for the primary efficacy and safety end points are shown in Fig. 3; a post hoc subgroup analysis based on an age cutoff of 75 years is shown in Table S5 in the Supplementary Appendix. These analyses show a consistent treatment effect across most subgroups. However, interaction testing suggested heterogeneity of treatment effect with regard to the primary safety end point according to whether or not the patient presented with an acute coronary syndrome. Heterogeneity of treatment effect with regard to the primary efficacy end point was suggested in subgroups defined according to the presence or absence of renal failure on admission, the score on the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) bleeding risk scale,[8] and status with respect to anemia, transfusion, or bleeding leading to hospitalization.

DISCUSSION

In the LEADERS FREE trial involving patients at high risk for bleeding who underwent PCI, the rate of the composite primary safety end point of cardiac death, myocardial infarction, or stent thrombosis was significantly lower with the BioFreedom polymer-free and carrier-free umirolimus-coated stent than with a similar bare-metal stent. This result was driven mainly by a

Subgroup	No. of Patients	Drug-Coated Stent	Bare-Metal Stent	P Value for Interaction	Drug-Coated Stent	Bare-Metal Stent	P Value for Interaction
		no. of events (% of patients)			*no. of events (% of patients)*		
Age				0.86			0.17
≤80 yr	1602	65 (8.3)	92 (11.6)		31 (4.0)	72 (9.4)	
>80 yr	830	47 (11.5)	62 (15.5)		28 (7.1)	41 (10.6)	
Sex				0.59			0.92
Female	738	34 (9.6)	53 (14.4)		17 (5.0)	33 (9.3)	
Male	1694	78 (9.3)	101 (12.3)		42 (5.1)	80 (10.0)	
ACS at admission				0.04			0.55
No	1773	82 (9.4)	95 (10.9)		47 (5.5)	86 (10.1)	
Yes	659	30 (9.3)	59 (18.5)		12 (3.9)	27 (9.0)	
Diabetes				0.90			0.57
No	1622	65 (8.3)	93 (11.5)		40 (5.3)	74 (9.4)	
Yes	805	47 (11.5)	61 (15.9)		19 (4.7)	39 (10.7)	
Renal failure at admission				0.46			0.02
No	1754	73 (8.3)	89 (10.4)		42 (4.9)	88 (10.6)	
Yes	466	31 (14.7)	53 (22.2)		16 (7.9)	15 (6.7)	
OAC planned to continue after PCI				0.44			0.61
No	1553	66 (8.7)	100 (13.0)		39 (5.3)	80 (10.7)	
Yes	879	46 (10.5)	54 (12.8)		20 (4.7)	33 (8.2)	
CRUSADE score				0.86			0.02
≤35	1061	33 (6.4)	48 (9.1)		21 (4.1)	56 (10.7)	
>35	962	63 (13.6)	88 (18.6)		33 (7.5)	39 (8.7)	
Anemia, transfusion, or bleeding leading to hospitalization				0.63			0.03
No	2007	84 (8.5)	113 (11.4)		41 (4.2)	95 (9.9)	
Yes	425	28 (13.6)	41 (20.3)		18 (9.2)	18 (9.6)	0.43
Planned major surgery in next 12 mo				0.74			
No	2002	93 (9.4)	123 (12.7)		49 (5.1)	89 (9.5)	
Yes	404	16 (8.4)	27 (12.9)		8 (4.3)	23 (11.5)	0.59
Cancer in previous 3 yr				0.87			
No	2193	101 (9.3)	139 (12.9)		55 (5.2)	102 (9.8)	
Yes	239	11 (9.6)	15 (12.9)		4 (3.5)	11 (9.8)	0.64
Multivessel disease at admission				0.64			
No	906	24 (5.4)	39 (8.6)		12 (2.8)	28 (6.4)	
Yes	1493	84 (11.4)	112 (15.4)		46 (6.5)	84 (12.0)	0.48
Total stent length				0.19			
≤30 mm	1409	54 (8.0)	68 (9.6)		21 (3.2)	51 (7.4)	
>30 mm	999	56 (10.9)	82 (17.4)		38 (7.6)	61 (13.6)	0.26
Minimal stent diameter				0.33			
≥3 mm	1195	49 (8.3)	59 (10.1)		26 (4.5)	41 (7.2)	
<3 mm	1213	61 (10.2)	91 (15.3)		33 (5.7)	71 (12.4)	

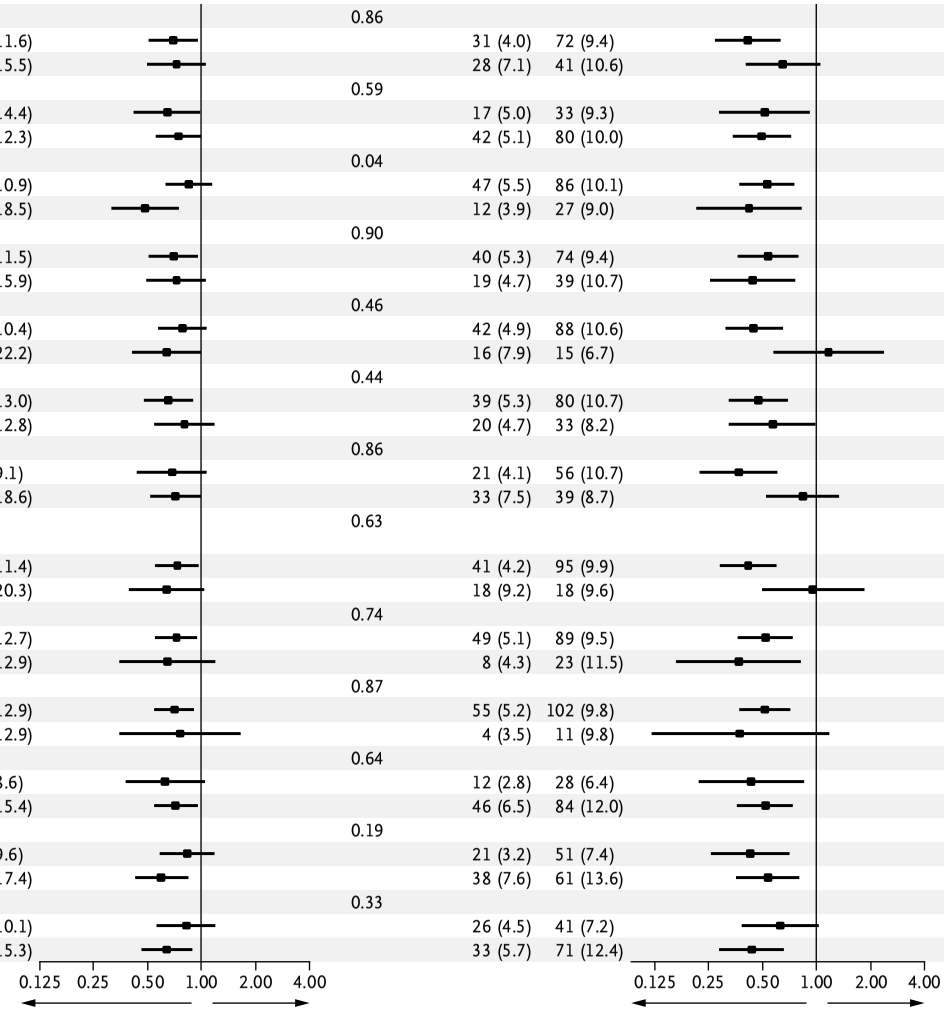

Figure 3. Subgroup Analyses for the Primary Safety and Efficacy End Points at 1 Year.

Scores on the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) bleeding risk scale[8] range from 1 to 100, with higher scores indicating a higher risk of major bleeding. The median score of 35 in our trial was chosen as the cutoff value. Cancer excluded skin cancer. ACS denotes acute coronary syndrome, and OAC oral anticoagulation.

lower rate of myocardial infarction. In addition, the rate of the primary efficacy end point of clinically driven target-lesion revascularization was significantly lower with the drug-coated stent than with the bare-metal stent.

The trial was designed with the intention of enrolling patients who were considered to be at high risk for bleeding or who were, for any reason, considered not to be candidates for prolonged use of dual antiplatelet therapy. As expected in this high-risk population, despite the short course of dual antiplatelet therapy, the rate of bleeding was high (with 7.2% of patients meeting criteria for BARC types 3 to 5 bleeding) and was similar in the two groups. In contrast, the rate of major bleeding ranged from 0.6% to 2.8% during the first year after PCI in trials that included patients at low-to-moderate risk who received dual antiplatelet therapy for longer durations.[13-15]

It is notable that 64% of the trial participants were regarded as being at high risk for bleeding specifically because of age; many such patients might not be regarded as requiring a shortened course of dual antiplatelet therapy in routine clinical practice. We chose the age of 75 years to define a population at increased risk for bleeding because this was a frequently used cutoff value in major trials of bleeding associated with antiplatelet treatment and in studies focusing on risk factors for bleeding after PCI.[16-18]

The rate of myocardial infarction was significantly lower in the drug-coated–stent group than in the bare-metal–stent group. Spontaneous myocardial infarction (type 1) and myocardial infarction related to in-stent restenosis (type 4c), as categorized according to the third universal definition of myocardial infarction,[9] occurred significantly less frequently among patients with a drug-coated stent. 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.

The rate of periprocedural myocardial infarction (type 4a) was low in both groups, which may be a consequence of the approach taken in our trial to detect such events. The protocol mandated at least one biomarker determination during a time window of 18 to 24 hours after PCI, or before discharge if this occurred earlier. We may have therefore underestimated the rate of periprocedural myocardial infarction, although this limitation applies equally to both treatment groups given the blinding of the trial.

Rates of definite or probable stent thrombosis in this study were high, although they are similar to those reported in some "all-comer" trials of drug-eluting stents[19-21] as well as in trials of triple therapy[9] or in trials involving patients who were considered to be uncertain candidates for drug-eluting stents.[22] The rate of stent thrombosis did not differ significantly between the two groups, and more than half the stent thromboses in both groups occurred during the first 30 days, when patients were prescribed dual antiplatelet therapy. These high rates of stent thrombosis may be a consequence of the high risk of bleeding among the trial participants, because patients at the highest risk for bleeding are often also at the highest risk for stent thrombosis.[23]

Current European guidelines[3] suggest the use of polymer-coated, new-generation drug-eluting stents with a 3-month course of dual antiplatelet therapy as an alternative option for PCI in patients at increased risk for bleeding, but they stress that this recommendation is based on only limited evidence. These guidelines were not available at the time of trial design, when the only reference treatment was a bare-metal stent with 1 month of dual antiplatelet therapy. Further evaluation is warranted of the use of the polymer-free drug-coated stent in comparison with currently available drug-eluting stents with a shortened course of dual antiplatelet therapy in patients at increased risk for bleeding.

In summary, patients at high risk for bleeding who underwent PCI received either a polymer-free umirolimus-coated stent or a bare-metal stent, with a 1-month course of dual antiplatelet therapy. Use of the drug-coated stent, as compared with the bare-metal stent, was associated with a lower rate of the composite primary safety end point of cardiac death, myocardial infarction, or stent thrombosis and a lower rate of the primary efficacy end point of clinically driven target-lesion revascularization.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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