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Safety and Efficacy of Polymer-Free Biolimus A9–Coated Versus Bare-Metal Stents in Orally Anticoagulated Patients

2-Year Results of the LEADERS FREE Oral Anticoagulation Substudy

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ABSTRACT

OBJECTIVES The aim of this study was to compare the performance of drug-coated stents (DCS) versus bare-metal stents (BMS) in patients who are candidates for long-term oral anticoagulation (OAC) after percutaneous coronary interventions.

BACKGROUND The randomized controlled LEADERS FREE (A Randomized Clinical Evaluation of the BioFreedom™ Stent) trial demonstrated the superior safety and efficacy of a polymer-free biolimus A9 DCS compared with a similar BMS used with 1 month of dual antiplatelet therapy in 2,466 patients at high bleeding risk.

METHODS The 2 stents were compared in a pre-specified analysis of the 879 LEADERS FREE patients (35.6%) scheduled to remain on OAC after percutaneous coronary intervention. The primary safety endpoint was a composite of cardiac death, myocardial infarction, and stent thrombosis. The primary efficacy endpoint was the incidence of clinically driven target lesion revascularization.

RESULTS Baseline characteristics of 448 DCS and 431 BMS recipients were similar, 78.8% had histories of atrial fibrillation, and 21% presented with acute coronary syndromes. Four hundred patients in the DCS group and 376 in the BMS group were discharged on OAC after percutaneous coronary intervention. At 2 years, for the DCS and BMS recipients, respectively, the incidence of clinically driven target lesion revascularization was 7.5% versus 11.2% (hazard ratio: 0.63; 95% confidence interval: 0.40 to 1.01; p = 0.0514), the safety endpoint was reached by 14.4% and 15.0% (p = NS), and the rates of major bleeding events (Bleeding Academic Research Consortium 3 to 5) were 10.7% and 12.9% (p = NS).

CONCLUSIONS The efficacy advantage of DCS over BMS up to 2 years appears confirmed in patients on long-term OAC. Despite the very short course of dual antiplatelet therapy, both the DCS and BMS groups experienced similarly high rates of major bleeding. (A Randomized Clinical Evaluation of the BioFreedom™ Stent [Leaders Free]; NCT01623180) (J Am Coll Cardiol Intv 2017;10:1633–42) © 2017 by the American College of Cardiology Foundation.

Patients treated with long-term oral anticoagulation (OAC) who undergo percutaneous coronary intervention (PCI) are often prescribed triple-antithrombotic therapy, which usually includes aspirin and clopidogrel (1). However, the optimal duration of triple therapy after PCI remains to be determined, particularly for patients at high risk for bleeding. Largely on the basis of level C expert

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

DAPT = dual antiplatelet therapy

DCS = drug-coated stent(s)

DES = drug-eluting stent(s)

MI = myocardial infarction

OAC = oral anticoagulation

PCI = percutaneous coronary intervention

TLR = target lesion revascularization

VKA = vitamin K antagonist

consensus, current recommendations for chronically anticoagulated patients vary between 1 and 12 months after PCI, depending on the clinical presentation, perceived relative risks for thrombosis and bleeding, and type of stent used (2–4). The issue is very significant, because it has been estimated that 5% to 7% of patients undergoing PCI are also candidates for long-term anticoagulation (2,3).

SEE PAGE 1643

The LEADERS FREE (A Randomized Clinical Evaluation of the BioFreedom™ Stent) trial (5–7) was designed to compare the safety and efficacy of 1 month of dual antiplatelet therapy (DAPT) after the implantation of a polymer-free, biolimus A9-coated stent versus a bare metal stent (BMS) in patients presenting with 1 or more risk factors for bleeding, such as advanced age, long-term OAC, recent hemorrhage, anemia, chronic renal failure, or cancer. In these patients, drug-coated stents (DCS) were superior to BMS both at 390 days and at 2 years with respect to clinically driven target lesion revascularization (TLR) as well as for a composite safety endpoint including: 1) cardiac death; 2) myocardial infarction (MI); and 3) definite or probable stent thrombosis. All patients who participated in LEADERS FREE and whose treatment with OAC was planned to continue after PCI were included in this pre-specified LEADERS FREE OAC substudy.

METHODS

The objectives, design, and methods of the trial have been described in detail elsewhere (5,6). In brief, patients were randomly assigned 1:1 in a double-blind fashion to undergo PCI and implantation of either a polymer-free BioFreedom DCS (Biosensors Europe, Morges, Switzerland) or a Gazelle BMS (Biosensors Interventional Technologies, Singapore, Singapore). The patients were assigned in blocks of 16, using an Internet-based or a telephone interactive system (Merge Healthcare, Chicago, Illinois) with no further stratification. All patients included in this analysis were scheduled at the time of enrollment to receive long-term OAC after PCI. Per protocol, they received either clopidogrel plus aspirin or clopidogrel alone for 1 month, followed by long-term single-antiplatelet therapy, preferably aspirin.

STUDY PROCEDURES. PCI was performed according to standard techniques. The site of vascular access, periprocedural antithrombotic regimen, and lesion preparation were left to the operator's discretion. All target lesions were treated with ≥1 study stent. Staged procedures were permitted within 1 week after the index procedure. The patients were seen for follow-up visits at 30 days and 1 year and contacted by telephone at 2 and 4 months and 2 years after their discharge from the hospital. Choice, duration, and dose of OAC, as well as decisions regarding coronary angiography and other investigations to document myocardial ischemia developing during follow-up, were left to the discretion of the treating physicians.

STUDY ENDPOINTS. The primary efficacy endpoint was the incidence of clinically driven TLR. The primary safety endpoint was the cumulative incidence of a composite of cardiac death, MI, and definite or probable stent thrombosis. These endpoints were recorded up to 2 years after the index PCI. MI was defined according to the third universal definition (8), stent thrombosis according to the Academic Research Consortium (9) and bleeding according to the Bleeding Academic Research Consortium definitions (10). Clinically driven TLR was defined as PCI or surgery for: 1) restenosis of the treated lesion associated with angina or documented myocardial ischemia; or 2) a core laboratory–diagnosed >70% angiographic restenosis of the treated artery with or without myocardial ischemic manifestations. The primary study endpoints and all bleeding events were adjudicated by an independent clinical events committee.

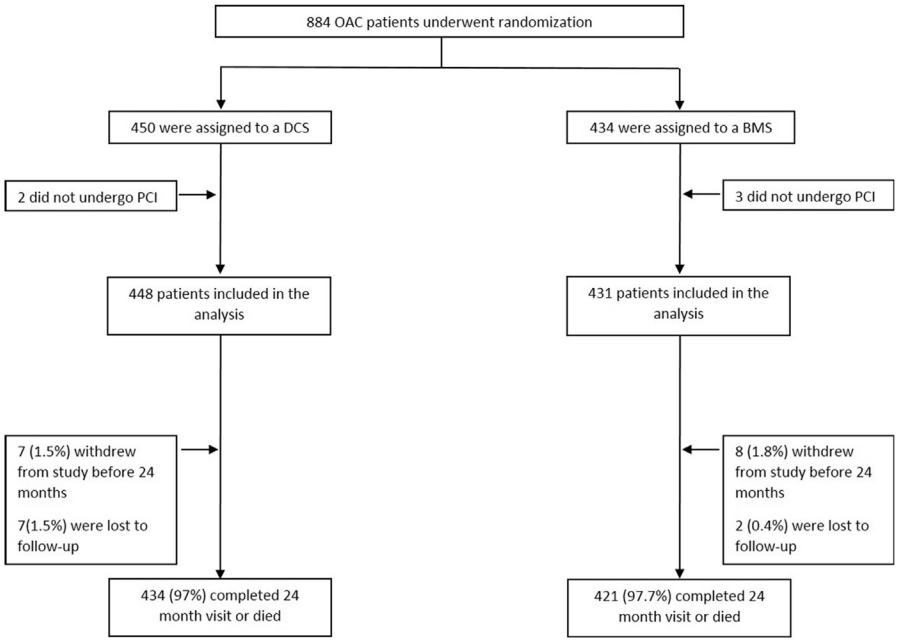
STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD and categorical variables as counts and percentages. Categorical variables were compared using the chi-square test, and continuous variables were compared using a 2-sample Student *t* test or the Fisher exact test when appropriate. For time-dependent variables, hazard ratios, 95% confidence intervals, or both, were calculated from an unadjusted Cox proportional hazards model. The cumulative incidence of events was calculated using Kaplan-Meier statistics and compared using the log-rank test. Proportional hazards assumptions were verified using Schoenfeld residuals.

We made no adjustment for covariates or imputation for missing data. A p value <0.05 was considered to indicate statistical significance. All data were analyzed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENT AND PROCEDURAL CHARACTERISTICS. The LEADERS FREE trial enrolled 2,466 patients, of whom 35.6% (448 recipients of DCS and 431 recipients

FIGURE 1 Flow of Study Groups Between Random Assignment and 2-Year Follow-Up



BMS = bare-metal stent(s); DCS = drug-coated stent(s); OAC = oral anticoagulation; PCI = percutaneous coronary intervention.

of BMS) were planned to receive long-term OAC following the index PCI (Figure 1). The general characteristics of both study groups, including age, sex distribution, prevalence of diabetes, congestive heart failure and atrial fibrillation, presentation with acute MI, and histories of stroke and previous myocardial revascularization, were similar (Table 1). Three or more of the criteria for high bleeding risk were met in 216 patients (24.6%), 2 criteria in 387 (44.0%), and a single criterion (planned OAC after PCI) in 276 patients (31.4%).

Procedural and lesion characteristics are shown in Table 2. DCS and BMS were similarly implanted through a radial artery in more than 60% of procedures. In both groups, <5% of the procedures were staged. Multiple vessels were revascularized in slightly more than 20% and multiple lesions in approximately one-third of the procedures in both study groups. The mean number of stents implanted per patient was 1.8 ± 1.1, and mean total stent length was 32.5 ± 21.7 mm. The overall procedural success was >97% in both groups.

ANTITHROMBOTIC THERAPY. The antithrombotic regimens prescribed to both study groups before the stent implantation procedure and at various time points, up to the last follow-up, are shown in Table 3. Ultimately, 776 of the 851 survivors (91.2%) at the time of discharge from the hospital were treated with OAC, including 716 (84.1%) with a vitamin K antagonist (VKA), clopidogrel, and aspirin (triple therapy); 56 (6.6%) with a VKA plus clopidogrel alone (WOEST [What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting] regimen); and 4 (0.5%) with other combinations of VKA and antiplatelet agents. The new non-antivitamin K oral anticoagulants rivaroxaban and dabigatran were prescribed to <9% of patients. Except for a greater prescription of dabigatran of borderline significance in the BMS group at 4-month follow-up, the distribution of these antithrombotic regimens was similar in both study groups.

ADVERSE CLINICAL EVENTS. The adverse clinical events observed in the entire study sample and in each antithrombotic treatment subgroup at 1 and 2 years of follow-up are summarized in Table 4.

PRIMARY SAFETY ENDPOINT. The overall cumulative incidence of cardiac death, MI, and definite or probable stent thrombosis at 1 and 2 years (Table 4) was 10.3% and 14.4%, respectively, in the DCS group and 12.3% and 15.0%, respectively, in the BMS group (Figure 2). None of these differed significantly between the 2 groups, and neither did any of the 3 components of the primary safety endpoint.

TABLE 1 Baseline Characteristics of 879 Candidates for Long-Term Anticoagulation After Percutaneous Coronary Intervention and Trial Inclusion Criteria

	Stent Recipients	
	Drug Coated (n = 448)	Bare Metal (n = 431)
General characteristics		
Age (yrs)	74.7 ± 8.9	74.7 ± 8.7
Female	128/448 (29)	111/431 (26)
Body mass index (kg/m^2)	28.4 ± 5.0	28.3 ± 4.8
Diabetes	153/447 (34)	154/430 (36)
Hypertension	356/448 (80)	343/428 (80)
Hypercholesterolemia	280/432 (65)	271/422 (64)
Angina		
Stable	194/448 (43)	184/431 (43)
Unstable	72/448 (16)	65/431 (15)
Silent ischemia	103/448 (23)	81/431 (19)
Myocardial infarction	79/448 (18)	101/431 (23)
ST-segment elevation	9/79 (11)	9/101 (9)
Non-ST-segment elevation	70/79 (89)	92/101 (91)
Disease of multiple coronary arteries	270/444 (61)	248/427 (58)
Congestive heart failure	90/447 (20)	88/431 (20)
Atrial fibrillation	356/447 (80)	336/431 (78)
History of		
Myocardial infarction	93/444 (21)	99/428 (23)
Percutaneous coronary intervention	120/446 (27)	97/430 (23)
Coronary artery bypass graft	57/447 (13)	61/430 (14)
Cerebral vascular accident	54/445 (12)	52/430 (12)
Peripheral vascular disease	72/445 (16)	63/423 (15)
Chronic obstructive pulmonary disease	48/441 (11)	52/425 (12)
Inclusion criteria		
Planned long-term oral anticoagulation	448 (100)	431 (100)
Age >75 yrs	242 (54)	240 (56)
Anemia or blood transfusion in 4 weeks before randomization	50 (11)	46 (11)
Intracerebral hemorrhage	2 (0.4)	6 (1.4)
Stroke in past 12 months	9 (2)	10 (2)
Hospitalization for bleeding in past 12 months	10 (2)	5 (1)
Noncutaneous cancer in past 3 yrs	24 (5)	22 (5)
Anti-inflammatory* therapy planned for ≥30 days after stent implantation	11 (3)	10 (2)
Planned surgery with interruption of DAPT in next 12 months	29 (7)	41 (10)
Creatinine clearance <40 ml/min	69 (15)	49 (11)
Platelet count <100,000/mm^3	6 (1)	2 (0.5)
Advanced, chronic hepatic insufficiency	1 (0.2)	1 (0.2)
Expected noncompliance with DAPT	2 (0.4)	4 (0.9)

Values are mean ± SD, n/N (%), or n (%). *Other than aspirin. All between-group differences are statistically nonsignificant.

DAPT = dual antiplatelet therapy.

TABLE 2 Procedures and Lesions Characteristics

	Stent Recipients	
	Drug Coated (n = 448)	Bare Metal (n = 431)
Number of lesions treated	687 (100)	639 (100)
Number of stents implanted		
Total	785	737
Mean per lesion	1.2 ± 0.5	1.1 ± 0.4
Reference vessel diameter, mm	3.0 ± 0.5	3.0 ± 0.5
Estimated percentage diameter stenosis		
Pre-procedural	80.7 ± 12.6	81.3 ± 11.9
Post-procedural	1.1 ± 6.9	1.0 ± 5.7
Estimated lesion length, mm	17.5 ± 10.0	17.2 ± 8.6
Total stent length per patient, mm	33.7 ± 22.7	31.3 ± 20.5
Target coronary artery		
Left anterior descending	281 (40.9)	272 (42.6)
Left circumflex	155 (22.6)	145 (22.7)
Right	214 (31.1)	182 (28.5)
Others	37 (5.3)	40 (6.3)
Bifurcation lesion	66 (9.6)	96 (15.0)
Chronic total occlusion	24 (3.5)	24 (3.8)
Vascular access		
Femoral	172 (37.1)	180 (39.9)
Radial	291 (62.9)	271 (60.1)
Procedures		
Staged	15 (3.2)	10 (4.4)
Multiple lesions	169 (36.5)	147 (32.6)
Multiple vessels	100 (21.6)	90 (20.0)
Success		
Lesion	670 (98.7)	624 (98.7)
Device	779 (99.2)	723 (98.1)
Procedure	455 (98.3)	439 (97.3)

Values are n (%) or mean ± SD. All between-group differences are statistically nonsignificant.

PRIMARY EFFICACY ENDPOINT. The overall cumulative incidence of clinically driven TLR at 1 and 2 years (Table 4) was 4.7% and 7.9%, respectively, in the DCS group and 7.5% and 11.2%, respectively, in the BMS group. The between-group difference was statistically significant at 1 year (hazard ratio: 0.57; 95% confidence interval: 0.33 to 0.99; p = 0.0425) and was borderline at 2 years (hazard ratio: 0.63; 95% CI: 0.40 to 1.01; p = 0.0514) (Figure 3).

Treatment efficacy appeared similar in the subgroups treated with the WOEST regimen or with non-antivitamin K oral anticoagulant agents plus DAPT, though the small number of observations precluded meaningful statistical comparisons. It is, however, noteworthy that at 2 years, the difference in the primary efficacy endpoint between the groups treated with VKA, clopidogrel, and aspirin (triple therapy) (Table 4), was significantly in favor of DCS recipients. Finally, in all analyses, the rate of Bleeding Academic Research Consortium 3 to 5 events was high in both study groups, with a 2-year incidence of 10.7% and 12.9%, respectively, for the DCS and BMS groups (Table 4, Figure 4). Of note, 49% of Bleeding Academic Research Consortium 3 to 5 events were gastrointestinal, and 51% of all patients were discharged on proton pump inhibitors, with no significant differences between the DCS and BMS groups.

TABLE 3 Antithrombotic Therapy

	Stent Recipients	
	Drug Coated (n = 448)	Bare Metal (n = 431)
At baseline		
Aspirin	233 (52)	209 (49)
Clopidogrel	139 (31)	130 (30)
Antiplatelet therapy		
None	184 (41)	197 (46)
Single	150 (34)	121 (28)
Dual	114 (25)	113 (26)
Oral anticoagulation	351 (78)	343 (80)
Antivitamin K	295 (66)	290 (67)
Plus clopidogrel	21 (5)	13 (3)
Plus dual antiplatelet therapy	65 (15)	71 (17)
Non-vitamin K oral anticoagulant agents	49 (11)	45 (10)
Rivaroxaban	22 (5)	23 (5)
Dabigatran	24 (5)	20 (5)
Apixaban	3 (0.7)	2 (0.5)
Other	9 (2)	9 (2)
At discharge from hospital		
Aspirin	403 (93)	386 (93)
Clopidogrel	429 (99)	406 (98)
Antiplatelet therapy		
None	1 (0.2)	2 (0.5)
Single	33 (8)	28 (7)
Dual	401 (92)	386 (93)
Oral anticoagulation	400 (92)	376 (90)
Antivitamin K	357 (82)	342 (82)
Plus aspirin only	1 (0.2)	0
Plus clopidogrel only	29 (7)	27 (7)
Plus dual antiplatelet therapy	327 (75)	315 (76)
Non-vitamin K oral anticoagulant agents	43 (10)	34 (8)
Rivaroxaban	21 (5)	17 (4)
Dabigatran	20 (5)	15 (4)
Apixaban	2 (0.5)	2 (0.5)
Other	0	0
1-month follow-up (37 days)*		
Aspirin	319 (74)	314 (75)
Clopidogrel	119 (28)	105 (25)
Antiplatelet therapy		
None	27 (6)	23 (6)
Single	369 (85)	372 (89)
Dual	36 (8)	24 (6)
Oral anticoagulation	388 (90)	371 (89)
Antivitamin K	339 (79)	336 (80)
Plus aspirin only	1 (0.3)	0
Plus clopidogrel only	72 (17)	72 (17)
Plus dual antiplatelet therapy	17 (4)	12 (3)
Non-vitamin K oral anticoagulant agents	49 (11)	35 (8)
Rivaroxaban	25 (6)	18 (4)
Dabigatran	22 (5)	14 (3)
Apixaban	2 (0.5)	3 (1)
Other	0	1 (0.2)
1-yr follow-up		
Aspirin	266 (67)	263 (69)
Clopidogrel	84 (22)	87 (23)
Antiplatelet therapy		
None	65 (17)	55 (14)
Single	310 (79)	303 (80)
Dual	22 (6)	25 (7)
Oral anticoagulation	354 (89)	341 (89)
Antivitamin K	295 (74)	294 (77)
Plus aspirin only	1 (0.3)	0
Plus clopidogrel only	10 (3)	51 (13)
Plus dual antiplatelet therapy	59 (15)	12 (3)
Non vitamin-K oral anticoagulant agents	28 (7)	47 (12)
Rivaroxaban	24 (6)	25 (7)
Dabigatran	7 (2)	16 (4)
Apixaban	0	6 (2)
Other	0	0
2-yr follow-up		
Aspirin	223 (61)	211 (59)
Clopidogrel	40 (11)	40 (11)
Antiplatelet therapy		
None	117 (32)	114 (32)
Single	239 (65)	229 (64)
Dual	12 (3)	13 (4)
Oral anticoagulation	320 (87)	314 (88)
Antivitamin K	260 (71)	267 (75)
Plus aspirin only	1 (0.3)	0
Plus clopidogrel only	21 (6)	22 (6)
Plus dual antiplatelet therapy	7 (2)	6 (2)
Non-vitamin K oral anticoagulant agents	60 (16)	47 (13)
Rivaroxaban	24 (7)	26 (7)
Dabigatran	18 (5)	14 (4)
Apixaban	18 (5)	7 (2)†
Other	0	0

Values are n (%). *37 days is the upper limit of the 1-month visit as defined in the protocol (30 ± 7 days). †$p < 0.05$; all other between-group differences are statistically nonsignificant.

DISCUSSION

The LEADERS FREE OAC substudy is the first randomized comparison of 2 different stents in a large sample of OAC patients. Our main findings confirm the results of the overall trial with superior efficacy (4.7% clinically driven TLR for DCS vs. 7.9% for BMS; $p < 0.05$) and a trend toward greater safety (10.3% for DCS vs. 12.3% for BMS; p = NS) at 1-year follow-up (6,7). Similar trends persisted to 2 years, but without statistical significance, probably because the size of this subgroup, limited to one-third of the main trial sample, conferred insufficient statistical power. As previously reported, no significant interaction was found when patients with or without OAC were compared (6). The biolimus A9 DCS is, therefore, the only active stent whose performance currently

TABLE 4 Study Endpoints and Other Adverse Events at 1 and 2 Years of Follow-Up in the Entire Study Sample and in Each Antithrombotic Therapy Subgroup

	Stent		
	Drug Coated (n = 448)	Bare Metal (n = 431)	Hazard Ratio (95% CI)
1-yr follow-up			
Entire sample			
Primary endpoints			
Safety: cardiac death, MI, and definite/probable stent thrombosis	45 (10.3)	52 (12.3)*	0.80 (0.54-1.19)
Efficacy: clinically driven TLR	20 (4.7)	32 (7.9)†	0.57 (0.33-0.99)
Cardiac death	27 (6.2)	25 (5.9)	1.04 (0.60-1.79)
MI	21 (5.2)	31 (7.5)	0.67 (0.39-1.15)
Definite or probable stent thrombosis	10 (2.3)	13 (3.1)	0.74 (0.32-1.70)
BARC			
1-5	95 (21.9)	105 (25.5)	0.85 (0.64-1.12)
2-5	74 (16.5)	87 (21.2)	0.80 (0.59-1.09)
3-5	35 (8.1)	43 (10.4)	0.77 (0.50-1.21)
Subgroup treated with antivitamin K plus clopidogrel plus aspirin (triple therapy)	(n = 368)	(n = 348)	
Primary endpoints			
Safety: cardiac death, MI, and definite/probable stent thrombosis	35 (10.0)	38 (11.1)	0.85 (0.54-1.35)
Efficacy: clinically driven TLR	18 (5.1)	26 (7.8)	0.64 (0.35-1.16)
Cardiac death	20 (5.6)	16 (4.7)	1.18 (0.61-2.28)
MI	16 (4.5)	23 (6.8)	0.64 (0.34-1.21)
Definite or probable stent thrombosis	8 (2.2)	8 (2.4)	0.94 (0.35-2.51)
BARC			
1-5	78 (21.7)	91 (27.0)	0.79 (0.58-1.06)
2-5	65 (18.1)	73 (21.7)	0.83 (0.59-1.16)
3-5	31 (8.6)	36 (10.7)	0.80 (0.50-1.30)
2-yr follow-up			
Entire sample	(n = 448)	(n = 431)	
Primary endpoints			
Safety: cardiac death, MI, and definite/probable stent thrombosis	62 (14.4)	63 (15.0)	0.93 (0.65-1.32)
Efficacy: clinically driven TLR	30 (7.5)	44 (11.2)	0.63 (0.40-1.01)
Cardiac death	39 (9.1)	32 (7.6)	1.17 (0.74-1.87)
MI	32 (7.7)	35 (8.6)	0.86 (0.53-1.39)
Definite or probable stent thrombosis	11 (2.6)	13 (3.1)	0.81 (0.36-1.82)
BARC			
1-5	115 (27.1)	121 (29.8)	0.89 (0.69-1.15)
2-5	94 (22.3)	104 (25.8)	0.85 (0.64-1.13)
3-5	45 (10.7)	52 (12.9)	0.82 (0.55-1.23)
Subgroup treated with antivitamin K plus clopidogrel plus aspirin (triple therapy)	(n = 368)	(n = 348)	
Primary endpoints			
Safety: cardiac death, MI and definite/probable stent thrombosis	48 (13.5)	45 (13.2)	0.99 (0.66-1.48)
Efficacy: clinically driven TLR	24 (7.0)	59 (10.8)	0.63 (0.38-1.10)
Cardiac death	29 (8.2)	20 (5.9)	1.38 (0.78-2.43)
MI	24 (7.0)	26 (7.8)	0.85 (0.50-149)
Definite or probable stent thrombosis	9 (2.5)	8 (2.4)	1.06 (0.41-2.75)
BARC			
1-5	96 (27.3)	102 (30.6)	0.87 (0.66-1.14)
2-5	83 (23.6)	85 (25.7)	0.91 (0.68-1.24)
3-5	41 (11.7)	81 (12.1)	0.96 (0.62-1.49)

Values are n (%) (Kaplan-Meier estimates). *p = 0.0280 and †p = 0.0425; all other between-group differences are statistically nonsignificant.

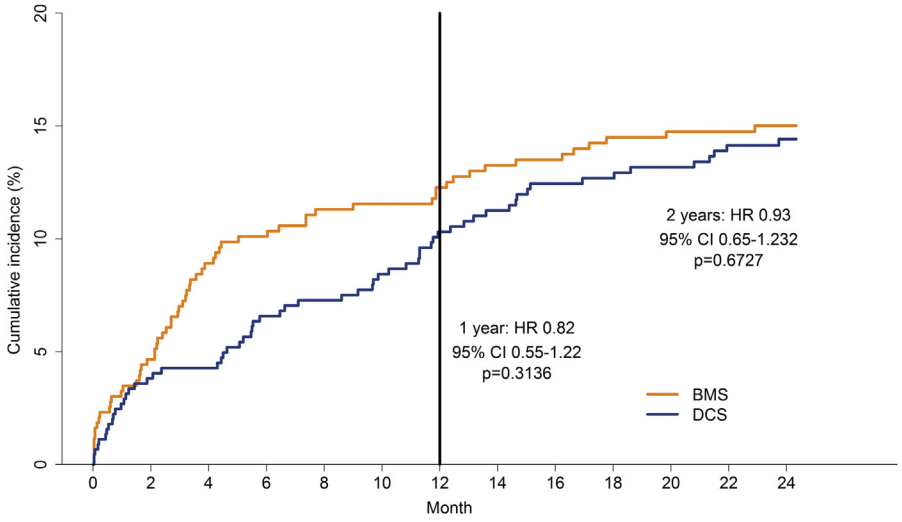
BARC = Bleeding Academic Research Consortium; CI = confidence interval; MI = myocardial infarction; TLR = target lesion revascularization.

supports limiting DAPT to 1 month in patients requiring OAC.

Three other randomized clinical trials of PCI and OAC have been published (11-14). ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen—Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting) included nearly 99% of drug-eluting stent (DES) recipients, whereas the WOEST and PIONEER AF (Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation) trials included patients treated with approximately one-third BMS and two-thirds DES, though the results were not analyzed according to the stent type. WOEST, which compared triple versus dual therapy, and PIONEER AF, which compared: 1) rivaroxaban 15 mg/day plus a $P2Y_{12}$ inhibitor alone; versus 2) rivaroxaban 2.5 mg twice daily plus DAPT; versus 3) a VKA plus DAPT, used bleeding as a primary endpoint, whereas ISAR-TRIPLE compared triple therapy (VKA plus DAPT) for 6 weeks versus 6 months with a composite endpoint of death, MI, definite stent thrombosis, stroke, or major bleeding. On the basis of a combined assessment of bleeding and thrombotic risks for patients at high risk for bleeding the use of BMS and triple therapy for ≥1 month, followed by OAC plus single-antiplatelet therapy for 12 months has been recommended (2,3). For patients presenting with acute coronary syndrome treated with DAPT after DES implantation, who are at high risk for bleeding (e.g., treated with OAC or in need of major surgery) or who experience major hemorrhage, treatment with a $P2Y_{12}$ inhibitor may be discontinued after 6 months. A distinction between BMS or DES is not systematically made, and the recommendations are mostly level C. A more recent North American consensus, based on a similar balanced estimation of bleeding risk, thromboembolic risk, and clinical presentation, recommends several different durations of triple therapy or the prescription of the WOEST regimen (4). Of note, although the randomized OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor) and RESET (Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation) trials documented the safety of 3 months of DAPT with the same first-generation rapid-elution DES, both enrolled selected patients who were at low risk for bleeding and were not on OAC (15,16).

Clopidogrel is widely considered the $P2Y_{12}$ inhibitor of choice for patients on OAC, and the latest

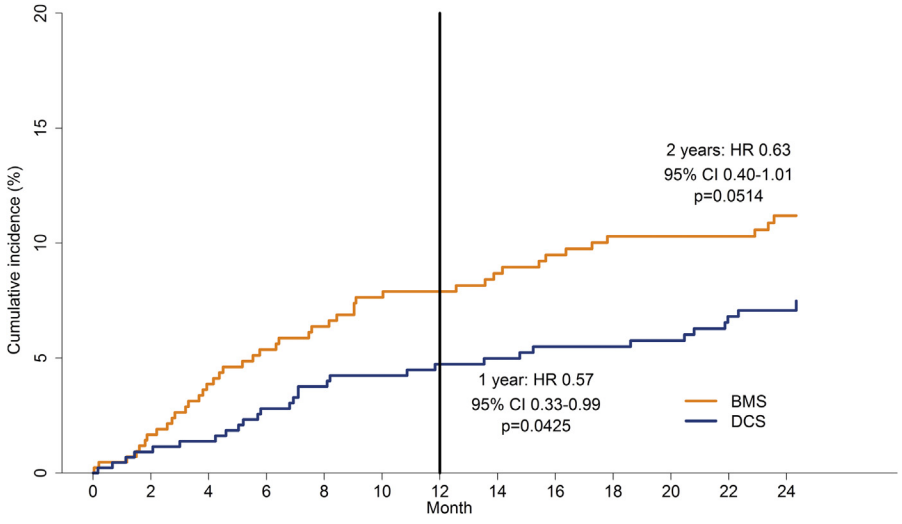
FIGURE 2 Primary Safety Endpoint



Two-year cumulative incidence of primary safety endpoint (composite of cardiac death, myocardial infarction, and definite or probable stent thrombosis) in the bare-metal stent (BMS) **(orange line)** and drug-coated stent (DCS) **(blue line)** groups. One-year follow-up is indicated by the **black vertical line**. CI = confidence interval; HR = hazard ratio.

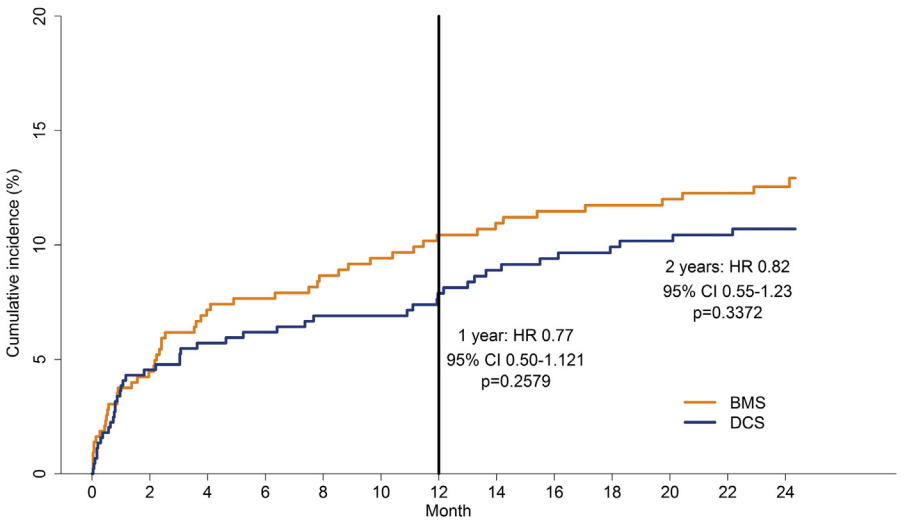
clinical practice guidelines issued by the European Society of Cardiology for the management of atrial fibrillation discourage the use of ticagrelor and prasugrel combined with OAC (17). In this study, more than 98% of patients were discharged from the hospital on clopidogrel, and <1% were discharged on other $P2Y_{12}$ inhibitors. Aspirin is generally recommended, except in the WOEST regimen (11). This was used in only 6.6% of our patients, suggesting that it was not widely adopted at the time of enrollment in

FIGURE 3 Primary Efficacy Endpoint



Two-year cumulative incidence of primary efficacy endpoint (clinically driven target lesion revascularization) in the bare-metal stent (BMS) **(orange line)** and drug-coated stent **(blue line)** groups. One-year follow-up is indicated by the **black vertical line**. CI = confidence interval; HR = hazard ratio.

FIGURE 4 Bleeding Events



Two-year cumulative incidence of Bleeding Academic Research Consortium 3 to 5 bleeding events in the bare-metal stent (BMS) **(orange line)** and drug-coated stent (DCS) **(blue line)** groups. One-year follow-up is indicated by the **black vertical line**. CI = confidence interval; HR = hazard ratio.

this trial. New non-antivitamin K oral anticoagulant agents were used in <9% of our patients; however, following the recent report of a low rate of bleeding complications in the PIONEER AF trial, rivaroxaban will probably be used increasingly in patients requiring OAC and undergoing PCI. Beyond the first year after PCI, the North American and European clinical practice guidelines recommend OAC alone for most patients. It is noteworthy that only approximately one-third of our patients were off all antiplatelet therapy at 2 years after PCI, whereas more than 90% remained on OAC, indicating that the recommendations of recent practice guidelines are only partially followed. Of note, the rapidly accumulating amount of medical information means that physicians may now choose from a confusing total of 1,683 drug combinations when choosing a periprocedural antithrombotic regimen (18).

Despite the very short duration of DAPT, the rate of major bleeding complications was high, and somewhat higher than the 8.9% and 9.2%, respectively, observed at 2 years with DCS and BMS in the main LEADERS FREE trial. Our results are concordant with the bleeding rates observed at 9 months in ISAR-TRIPLE and at 1 year in WOEST (11,12). More recently, PIONEER AF reported markedly lower bleeding rates at 1 year, but its population consisted entirely of patients presenting with AF and was highly selected by the application of several exclusion criteria known to increase the risk for bleeding (13). In contrast, LEADERS FREE did not exclude these patients. Two other ongoing randomized trials are currently testing other combinations together with dabigatran or apixaban in patients with AF (19,20).

Finally, in view of the high risk for bleeding in this typically elderly patient population, shortening DAPT or using a single-antiplatelet agent may not always be sufficient. Further developments of alternatives to long-term OAC are needed, including closure of the left atrial appendage for patients with nonvalvular AF, which may enable clinicians to avoid the potentially dangerous combination of anticoagulant and antiplatelet agents.

STUDY LIMITATIONS. LEADERS FREE compared a DCS with a BMS using DAPT for 1 month, a recommended standard when the trial was designed. Whether a longer course of DAPT, a different drug combination, or both would have modified the outcomes is unknown. Furthermore, our observations cannot be extrapolated to other DES or DCS or to stents with different drug elution kinetics. Finally, no information was collected concerning international normalized ratio values or the indications for OAC. Although most patients presented with atrial fibrillation at baseline and the mean $CHADS_2VASc_2$ scores were similar in both groups, some patients were likely anticoagulated for other indications, such as prosthetic valves or venous thromboses, introducing some heterogeneity in this population.

CONCLUSIONS

For patients requiring OAC and treated with a single month of DAPT, the LEADERS FREE OAC substudy confirmed the significantly higher efficacy and showed a trend toward greater safety for DCS compared with BMS, up to 1 year, as was observed in the main trial (6,7). Similar trends persisted to 2 years but without reaching statistical significance. Although this DCS is thus the only active stent with a proven track record for a single month of DAPT in orally anticoagulated patients, the high incidence of major bleeding suggests that further work is needed to optimize the care of these high-risk patients.

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PERSPECTIVES

WHAT IS KNOWN? Patients treated with long-term OAC who undergo PCI and receive DAPT are at high risk for bleeding. Shortening the duration of triple therapy appears desirable, but only BMS have been commonly used with an ultrashort 1-month course of DAPT.

WHAT IS NEW? Together with a DAPT course of only 1 month, a new polymer-free biolimus A9 DCS was more effective and safer than a BMS in a general population of patients at high bleeding risk in the LEADERS FREE trial. The current prespecified subset analysis suggests that similar benefits are also present for patients on OAC.

WHAT IS NEXT? Although a DCS is the only active coronary stent shown to be superior to a BMS with a 1-month DAPT course, defining the optimal duration and combination of antithrombotic agents deserves further studies for patients on long-term OAC.

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