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ORIGINAL STUDIES

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Polymer-free Biolimus-A9 coated thin strut stents for patients at high bleeding risk 1-year results from the LEADERS FREE III study

Franz R. Eberli MD[1] | Hans-Peter Stoll MD[2] | Philip Urban MD[3] | Marie-Claude Morice MD[3] | Philippe Brunel MD[4] | Luc Maillard MD[5] | Janus Lipiecki MD[6] | Stephane Cook MD[7] | Jacques Berland MD[8] | Thomas Hovasse MD[9] | Didier Carrie MD[10] | Diana Schütte PhD[2] | Sara Sadozai Slama MEng, MSc[2] | Philippe Garot MD[11]

[1]Cardiology Department, Triemli Hospital, Zurich, Switzerland

[2]Clinical Research, Biosensors Clinical Research, Morges, Switzerland

[3]Cardiovascular European Research Center (CERC), Massy, France

[4]Interventional Cardiology Unit, Clinique de Fontaine, Dijon, France

[5]Department of Cardiology, GCS ES Axium-Rambot, Aix-en-Provence, France

[6]Department of Cardiology, Pole Sante Republique, Clermont Ferrand, France

[7]Department of Cardiology, University Hospital Fribourg, Fribourg, Switzerland

[8]Department of Cardiology, Clinique Saint Hilaire, Rouen, France

[9]Department of Cardiology, Institut Cardiovasculaire Paris-Sud (ICPS), Ramsay-Santé, Hôpital Jacques Cartier, Massy, France

[10]Cardiology Department, Centre Hospitalier Universitaire Rangueil, Toulouse, France

[11]Ramsay-Santé, Hôpital Claude Galien, Institut Cardiovasculaire Paris-Sud (ICPS), Quincy, France

Correspondence
Prof. Franz R. Eberli, Stadtspital Triemli, Kardiologie, Birmensdorferstrasse 497, CH-8063 Zürich, Switzerland.
Email: franz.eberli@triemli.zuerich.ch

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Abstract

Background: In patients at high bleeding risk (HBR), the LEADERS FREE (LF) trial established the safety and efficacy of a polymer-free drug coated (Biolimus-A9) stainless steel stent (SS-DCS) with 30 days of dual antiplatelet treatment (DAPT). In LEADERS FREE III, we studied a new cobalt-chromium thin-strut stent (CoCr-DCS) in HBR patients.

Methods: The CoCr-DCS shares all of the design features of the SS-DCS but has a CoCr stent platform with strut thickness of 84–88 μm. The primary safety endpoint was a composite of cardiac death, myocardial infarction (MI), and definite/probable stent thrombosis. The primary efficacy endpoint was clinically indicated target lesion revascularization. Outcomes were compared to those of LF (non-inferiority to SS-DCS for safety and superiority to SS-BMS for efficacy). Additional propensity-matched comparisons were performed to account for baseline differences.

Results: We recruited 401 HBR patients using identical criteria to the LF trial. At 1 year, the primary safety endpoint was reached by 31/401 (8.0%) of patients treated with the CoCr-DCS versus 35/401 (8.9%) for the propensity-matched cohort (HR: 0.89, [0.55–1.44], $p < 0.001$ for non-inferiority, 0.62 for superiority). The efficacy endpoint was reached by 16/401 (4.2%) of CoCr-DCS patients versus 41/401 (10.6%) in the propensity-matched cohort (HR: 0.4 [0.2:0.7]) ($p = 0.007$ for superiority). There was no statistical difference between CoCr-DCS and SS-DCS in terms of efficacy (HR: 1.46 [0.68–3.15], $p = 0.33$).

Conclusions: The new thin-strut CoCr-DCS proved non-inferior to the SS-DCS for safety, and superior to the BMS for efficacy in HBR patients treated with 30 days of DAPT.

KEYWORDS

CLIN—clinical trials, PCI—percutaneous coronary intervention (PCI), DES—stent, drug eluting

1 | INTRODUCTION

Until recently, most patients at high bleeding risk (HBR) were excluded from interventional studies, even when "all comer" populations were recruited. These HBR patients were historically treated with bare-metal stents (BMS), since the consensus was that this allowed for a short duration of dual anti-platelet therapy (DAPT) of 30 days thereby minimizing the risk of bleeding and the associated increase in mortality.[1–4] The LEADERS FREE (LF) trial, as reported by Urban et al.,[5,6] was a prospective, double-blind, randomized multicenter trial, which focused exclusively on HBR patients and established that a stainless steel Biolimus-A9 drug-coated stent (SS-DCS) treated with 1 month of DAPT was more efficacious and safer than a bare-metal stent using the same stainless steel platform (SS-BMS).[6] These findings were reconfirmed recently in the LEADERS FREE II trial that generalized their applicability to patients and clinical practice in North America.[7] A thinner strut DCS built on a latest-generation cobalt-chromium stent platform (CoCr-DCS) with a strut thickness of 84 to 88 μm has recently become available. Thinner struts improve stent deliverability, reduce restenosis and may have a lower degree of thrombogenicity.[8] However, the thinner struts of this polymer-free design come with a reduced surface area and this may influence drug elution and diffusion. Accordingly, a study to confirm similar safety and efficacy outcomes was needed. The LEADERS FREE III (LF III) study was designed as a companion trial to LF and investigated the safety and efficacy of the next generation thin strut CoCr-DCS in HBR patients.

2 | METHODS

2.1 | Investigational device

The new CoCr-DCS (Biosensors International, Morges, Switzerland) shares with its predicate, the SS-DCS (BioFreedom™), the polymer-free design, the surface modification, the selective abluminal coating, the drug Biolimus-A9, and the dosage of 225 μg/14 mm stent length, but it is built on a state-of-the-art CoCr platform with a strut thickness of 84–88 μm. It has been established in preclinical studies (data on file at Biosensors) that drug content, drug transfer kinetics from the stent surface to the vessel wall, and drug tissue levels achieved in the vessel wall are similar between the SS-DCS and the new CoCr-DCS.

2.2 | Study design and organization

LF III is an international, single-arm, multicenter prospectively controlled trial. The study was performed according to the Declaration of Helsinki and ISO14155:2011 (ClinicalTrials.gov Identifier: NCT03118895). It was approved by the ethics committees of participating centers and all patients provided written informed consent. The first (F.E.) and last (P.G.) authors had full access to all the data in the study and take responsibility for its integrity and the data analysis. HBR selection criteria, other inclusion and exclusion criteria, abbreviated anti-platelet therapy (1 month of DAPT, followed by 11 months of single anti-platelet therapy), analytical endpoints, clinical follow-up, event adjudication, and the managing

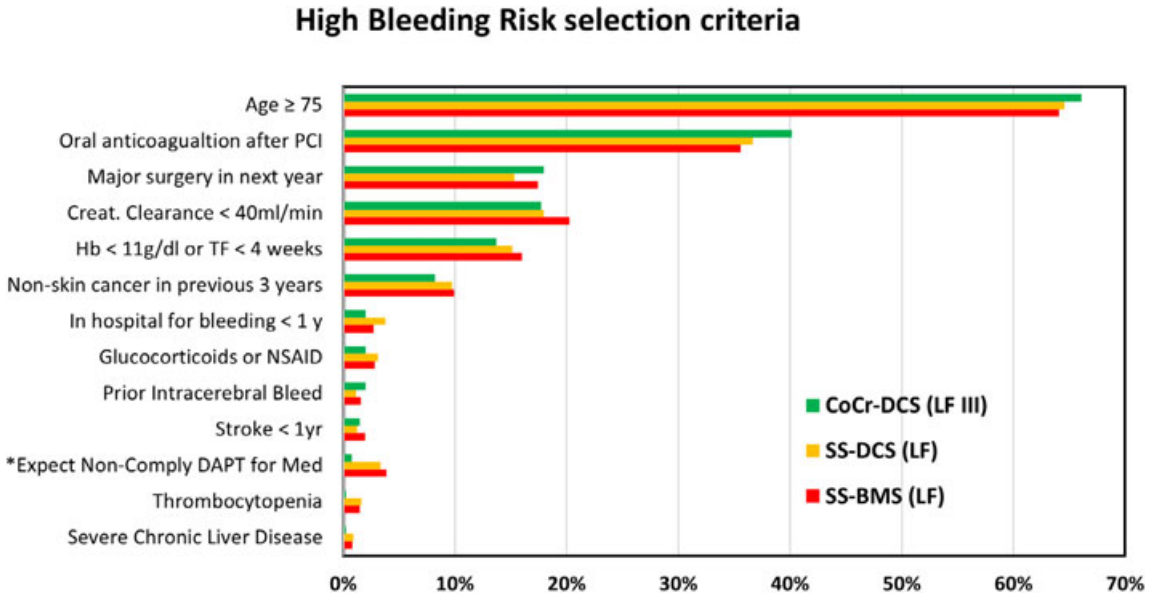

FIGURE 1 Use of clinical criteria to select high bleeding risk patients. Selection criteria for high bleeding risk are depicted for the LEADERS FREE III (LFIII) trial and the LEADERS FREE (LF) trial population. *There were no significant differences except for expected poor compliance for medication ($p > 0.05$). CoCr-DCS (LF III), thin-strut Biolimus-A9 drug-coated cobalt-chromium stent used in Leaders Free III; SS-DCS, stainless steel Biolimus-A9 drug-coated stent, used in Leaders Free; SS-BMS, Gazelle™ bare metal stent, used in Leaders Free; PCI, percutaneous coronary intervention; NSAID, non-steroidal anti-inflammatory drugs; DAPT, dual anti-platelet therapy [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline patient and procedural characteristics—comparison with full LF cohorts

Variable	Baseline characteristics CoCr-DCS (LF III) ($N = 401$)	SS-DCS (LF) full cohort ($N = 1221$)	*P*	SS-BMS (LF) full cohort ($N = 1211$)	*P*
Patient:					
Mean age (years)	76.5 ± 9.5	75.7 ± 9.4	0.14	75.7 ± 9.3	0.13
Female gender (%)	33.7	29.8	0.14	30.9	0.3
Body mass index	27.2 ± 5.1	27.5 ± 4.8	0.3	27.2 ± 4.6	1
STEMI presentation* (%)	2.2	4.7 *	0.028	4	0.09
NSTEMI presentation (%)	18.2	22.4	0.075	23.2*	0.04
Stable angina	32.2	39.4 *	0.01	37.6	0.05
Unstable angina	10.2	14.5*	0.03	15.9	0.05
Diabetes (%)	35.7	34	0.53	32.3	0.21
Previous MI* (%)	9.8	19.6*	<0.0001	21.4*	<0.0001
Previous PCI (%)	19.3	22.2	0.22	21.9	0.27
Previous CABG (%)	5.5	9.4*	0.015	10.1*	0.005
Current smoker (%)	12	11.1	0.62	11.4	0.74
Dyslipidaemia	54.1	62*	0.005	62.7*	0.002
Hypertension (%)	75.8	78.1	0.36	79.6	0.11
Congestive heart failure* (%)	8.8	14.4*	0.0038	12.4*	0.05
Atrial fibrillation (%)	36.3	34.9	0.61	34.6	0.54
Peripheral vascular disease* (%)	21.3	15.7*	0.01	15.8*	0.011
Renal insufficiency (%)	21.2	20.2	0.67	23.1	0.43
Mean number of HBR criteria	1.73	1.78	0.84	1.74	0.32
Procedure:					
Radial access (%)	79.9	60.7*	<0.0001	58.7*	<0.0001
Stent diameter (mm)	2.9 ± 0.4	3.0 ± 0.4	<0.0001	3.0 ± 0.4	<0.0001
Total stent length/patients* (mm)	38.9 ± 27.4	34.5 ± 23.1*	0.0016	33.4 ± 23.4*	0.0001
Number of stents/patients	1.9 ± 1.2	1.9 ± 1.1	1	1.8 ± 1.2	0.15
Bifurcation lesions (%)	16.2	14.9	0.53	16	0.92
Number of lesions	1.5 ± 0.8	1.51 ± 0.8	0.82	1.48 ± 0.8	0.65
Number of vessel	1.22 ± 0.5	1.25 ± 0.5	0.28	1.24 ± 0.5	0.47
Multi-lesion (%)	33.4	37.8	0.11	35.3	0.5
Target lesion coronary artery (%)			0.8		0.89
LAD	55.1	52.2		51.8	
LCX	24	29		28.9	
RCA	35	37.3		35.1	
LM	4.8	3		3.9	
In-stent restenotic lesions (%)	2.3	2.4	0.91	2.6	0.74
Chronic total occlusions (%)	3	5	0.094	4.4	0.22
Lesion success (%)	98.7	97.7	0.22	98	0.36
Device success (%)	98.9	97.7	0.14	97.6	0.11
Procedure success (%)	97	94.4	0.37	93.7	0.012

*Indicates significant difference.

TABLE 2 Baseline patient and procedural characteristics—comparison with LF propensity-matched cohorts

Variable	Baseline characteristics CoCr-DCS (LF III) ($N = 401$)	SS-DCS (LF) propensity matched ($N = 401$)	p	SS-BMS (LF) propensity matched ($N = 401$)	p
Patient:					
Mean age (years)	76.5 ± 9.5	76.6 ± 9.1	0.88	76.8 ± 8.7	0.59
Female gender (%)	33.7	34.2	0.38	31.9	0.77
Body mass index	27.2 ± 5.1	26.9 ± 4.6	0.84	27.1 ± 4.6	1
STEMI presentation (%)*	2.2	2	0.0024	2.2	0.08
Stable angina	32.2	43.1*	0.0015	36.4	0.21
Unstable angina	10.2	14	0.1	13.5	0.15
Previous MI* (%)	9.8	9.8	0.77	8.2	1
Previous PCI (%)	19.3	18.5	0.65	19.3	0.75
Current smoker (%)	12	12.1	0.97	11.6	0.86
Dyslipidaemia	54.1	53.6	0.89	51.8	0.51
Hypertension (%)	75.8	76.1	0.92	73.8	0.51
Peripheral vascular disease (%)	21.3	22.9	0.4	22.9	0.16
Renal insufficiency (%)	21.2	19	0.88	17.3	1
Mean number of HBR criteria	1.73	1.69	0.5	1.73	1
Procedure:					
Radial access (%)	79.9	82.6	0.33	83	0.26
Stent diameter (mm)	2.9 ± 0.4	2.9 ± 0.5	1	2.9 ± 0.5	1
Total stent length/patient (mm)*	38.9 ± 27.4	33.5 ± 22.2	0.0022	33.5 ± 22.5	0.0024
Number of stents/patients	1.9 ± 1.2	1.8 ± 1.1	0.22	1.8 ± 1.2	0.24
Bifurcation lesions (%)	16.2	15.8	0.87	15.9	0.91
Number of lesions	1.5 ± 0.8	1.41 ± 0.7	0.08	1.45 ± 0.8	0.35
Number of vessel	1.22 ± 0.5	1.19 ± 0.4	0.33	1.23 ± 0.5	0.77
Multi-lesion (%)	33.4	31.5	0.56	33.6	0.95
Target lesion coronary artery (%)			0.75		0.87
LAD	55.1	51.8		53	
LCX	24	24.2		28.3	
RCA	35	39		35	
LM	4.8	2.3		3.2	
In-stent restenotic lesions (%)	2.3	2.3	1	2.1	0.85
Chronic total occlusions (%)	3	5	0.15	4.4	0.29
Lesion success[a] (%)	98.7	97.6	0.25	96.8	0.07
Device success[b] (%)	98.9	97.4	0.12	97.3	0.09
Procedure success[c] (%)	97	96.3	0.58	95.4	0.24

Note: Data are presented as mean ± standard deviation.

Abbreviations: CABG, coronary artery bypass graft; CoCr-DCS, thin-strut Biolimus-A9 drug-coated cobalt-chromium stent; SS-DCS, Biolimus-A9 drug-coated stainless steel stent; SS-BMS, bare metal stainless steel stent; LF, LEADERS FREE Trial; LF III, LEADERS FREE III Trial; HBR, high bleeding risk; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

*Indicates significant difference.

[a]The attainment of <20% residual stenosis by visual estimate AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method.

[b]The attainment of <20% residual stenosis by visual assessment AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using the assigned device only.

[c]The attainment of <20% residual stenosis by visual estimate AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method without the occurrence of death, MI, or repeat revascularization of the target vessel during the hospital stay.

TABLE 3 Clinical endpoints (safety)

Safety endpoints: variable	CoCr-DCS (LF III) ($N = 401$)	SS-DCS (LF) full cohort ($N = 1221$)	*P1*[a]	SS-DCS (LF) propensity matched ($N = 401$)	*P2*[a]
Primary safety endpoint: cardiac death, myocardial infarction, or stent thrombosis—*N* (%)[b]	31 (8.0%)	110 (9.2%)	0.46	35 (8.9%)	0.62
All death—*N* (%)	25 (6.4%)	91 (7.5%)	0.46	33 (8.3%)	0.30
Cardiac death—*N* (%)	14 (3.7%)	49 (4.1%)	0.68	19 (4.9%)	0.41
Myocardial infarction—*N* (%)	17 (4.4%)	70 (5.9%)	0.27	22 (5.6%)	0.42
Definite/probable stent thrombosis—*N* (%)	4 (1.0%)	24 (2.0%)	0.20	7 (1.8%)	0.37
Bleeding (BARC 3–5)—*N* (%)	21 (5.4%)	85 (7.2%)	0.46	24 (6.2%)	0.68

[a]*P1*: *p*-value (superiority) CoCr-DCS versus SS-DCS full cohort ($N = 1221$); *P2*: *p*-value (superiority) CoCr-DCS versus SS-BMS propensity match cohort ($N = 401$).
[b]*p*-values for non-inferiority of the primary safety endpoint are $p = 0.0007$ for CoCr-DCS versus SS-DCS full cohort ($N = 12{,}221$), and $p = 0.0073$ for CoCr-DCS versus SS-DCS propensity match cohort, respectively (using a 3.92% non-inferiority margin).

Clinical Research Organization (CERC, Massy, France) were identical to the LF trial,[6] which served as historical reference for comparison.

2.3 | Study population

Patients included in this study were candidates for interventional treatment with stent implantation of atherosclerotic coronary artery lesions, and their HBR status was determined using the 13 HBR selection criteria defined for the LF trial[5,6] (Supporting Information, Table S1). With the aim of improving matching of trial cohorts and thus enhance the interpretability of outcomes, enrolment numbers for patients with acute myocardial infarction, expected low compliance to the prescribed DAPT, and age ≥75 years were prospectively capped to match the enrolment in the LF trial.

2.4 | Study procedures and endpoints

All patients were formally enrolled when the guidewire had crossed the target lesion and the intervention including stent placement was performed according to guidelines and local clinical practice. Choice of vascular access and peri-procedural drug regimen was left to operator's discretion. All target lesions were treated with the CoCr-DCS. Staged procedures were permitted within 1 week. The protocol-driven anti-platelet regimen included aspirin (75–250 mg/d) and a P_2Y_{12} inhibitor (preferably clopidogrel 75–150 mg/d) for 30 days. Thereafter, one drug had to be discontinued (preferably the P_2Y_{12} inhibitor) and single antiplatelet therapy was continued to the end of the study. Follow-up was planned for 1 month, 6 months and 1 year as clinical visits, and for 4 months, 24 and 36 months via telephone. There was no planned angiographic follow-up.

The primary safety endpoint was a composite of cardiac death, myocardial infarction (MI) and definite/probable stent thrombosis. Myocardial infarction was defined using the Third Universal Definition of MI.[9] The primary efficacy endpoint was clinically indicated target lesion revascularization (ci-TLR) at 1-year follow-up. The hypotheses formally tested were (1) that the new CoCr-DCS is non-inferior for safety compared to the stainless steel SS-DCS in LF and (2) that the CoCr-DCS is superior for efficacy compared to the bare-metal stent (SS-BMS, Gazelle™) in LF. Additionally, a post-hoc comparison was conducted to investigate if the CoCr-DCS was non-inferior in efficacy to the SS-DCS in LF.

2.5 | Statistical analysis

Based on a rate of 9.2% for the primary safety endpoint in the LF study, an α of 0.05, and a non-inferiority margin of 3.9%, a cohort of 340 evaluable patients would give >80% power to conclude non-inferiority for safety, and > 90% power to detect a 4% reduction in the primary efficacy endpoint to conclude superiority. Eventually, 401 patients were recruited to allow for dropouts and protocol deviations.

In the initial analysis the results of the patient population of LF III were compared to the entire study population of LF. Means and standard deviations are reported for continuous variables and counts, and percentages are reported for categorical variables. Baseline characteristics were compared using the Wilcoxon rank-sum test for continuous variables, and the chi-square test or Fisher exact test, as appropriate, for categorical variables.

Given the non-randomized design of the study we performed a propensity score analysis to adjust for discrepancies in patient baseline characteristics that might influence outcomes and attempted a quantification of the independent effects of stent type on outcomes. Forty baseline variables were used to calculate propensity scores (Table S2). We used multiple imputation from a logistic regression to obtain the propensity scores for each patient. We then weighted each patient by the reciprocal of their propensity score using stabilized inverse probability weighting to derive adjusted Kaplan–Meier estimates and hazard ratios. Hazard ratios and 95% confidence intervals were reported. Kaplan–Meier analysis and log-rank test were performed to compare the primary safety endpoint. The statistical

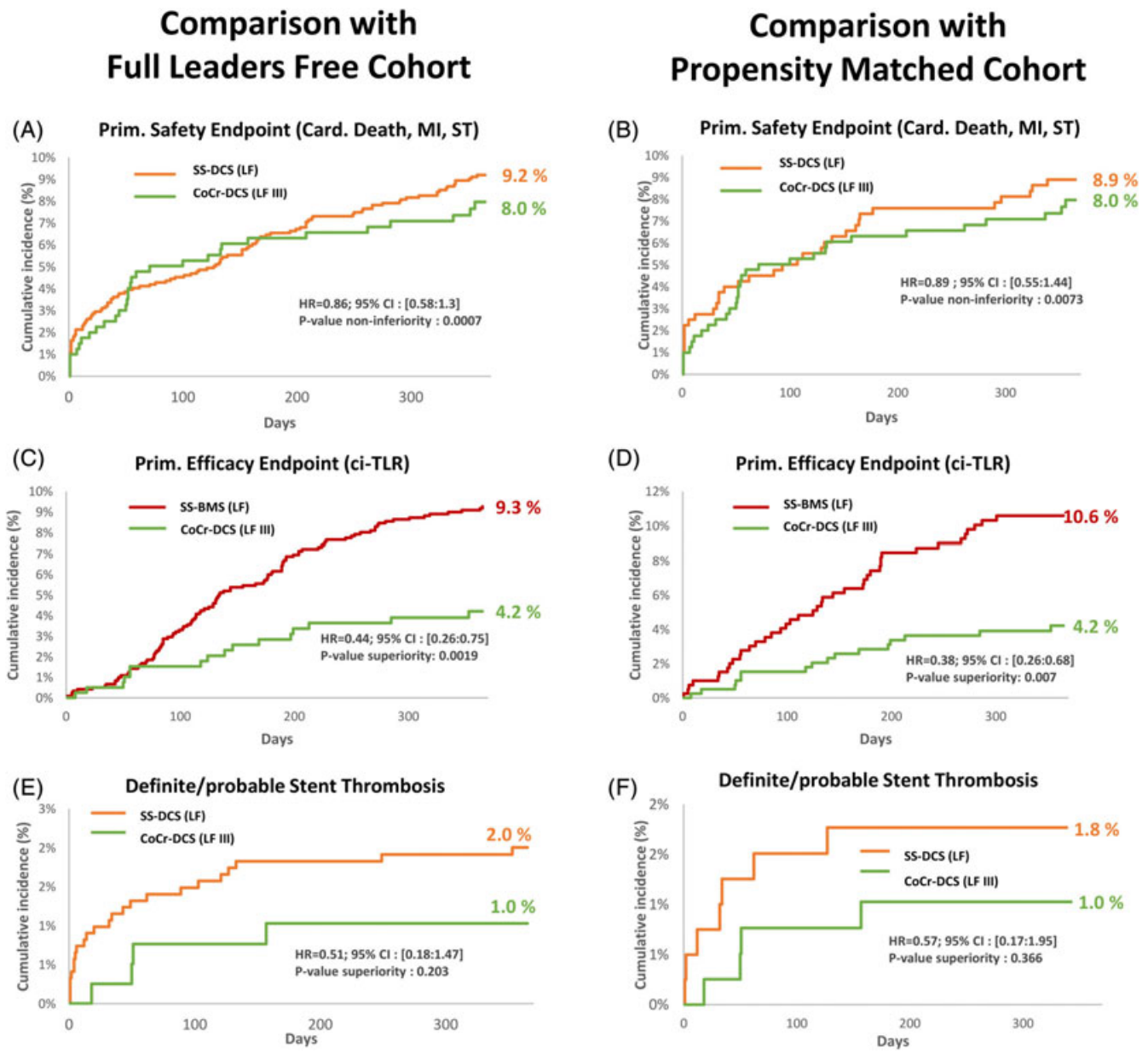

FIGURE 2 Clinical outcomes: Primary safety endpoint—(A) comparison with full LF cohort; (B) comparison with propensity matched cohort. Primary efficacy endpoint—(C) comparison with full LF cohort; (D) comparison with propensity-matched cohort. Definite/probable stent thrombosis; (E) comparison with full LF cohort; (F) comparison with propensity-matched cohort. CoCr-DCS (LF III), Thin-strut Biolimus-A9 drug-coated cobalt-chromium stent used in Leaders Free III; SS-DCS, stainless steel Biolimus-A9 drug-coated stent, used in Leaders Free; SS-BMS, Gazelle ™ bare metal stent, used in Leaders Free; MI, myocardial infarction; ST, stent thrombosis; ci-TLR, clinically indicated target lesion revascularization [Color figure can be viewed at wileyonlinelibrary.com]

analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) software.

The following comparisons with the LF reference data were conducted: (1) Non-inferiority comparison of the primary safety endpoint between the CoCr-DCS cohort (LF III) and the entire SS-DCS cohort in LF; (2) Superiority comparison of the primary efficacy endpoint between the CoCr-DCS cohort (LF III) and the entire SS-BMS (Gazelle™ stent) cohort in LF; (3) Post-hoc non-inferiority comparison of the primary efficacy endpoint between the CoCr-DCS cohort (LF III) and the entire SS-DCS cohort in LF. To better account for the non-randomized nature of the trial, all comparisons above were repeated using the propensity-matched populations from LF.

3 | RESULTS

LF III recruited a population of 401 HBR patients and the proportion of each HBR criterion was very similar to that of LF (Figure 1). On average, each patient fulfilled 1.73 HBR selection criteria. When baseline patient characteristics of the LF III cohort were compared with

TABLE 4 Clinical endpoints (efficacy)—superiority comparison with BMS

Efficacy endpoints: variable	CoCr-DCS (LF III) ($N = 401$)	SS-BMS (LF) full cohort ($N = 1211$)	*P1*	SS-BMS (LF) propensity matched ($N = 401$)	*P2*
Primary efficacy endpoint: clinically indicated TLR—*N* (%)	16 (4.2%)	107 (9.3%)	0.002	41 (10.6%)	0.007
Clinically driven target vessel revascularization—*N* (%)	19 (5.0%)	115 (10.0%)	0.003	45 (11.6%)	0.008

Note: P1: *p*-value (superiority) CoCr-DCS versus SS-BMS full cohort ($N = 1211$); *P2*: *p*-value (superiority) CoCr-DCS versus SS-BMS propensity match cohort ($N = 401$).

Abbreviations: CoCr-DCS, thin-strut Biolimus-A9 drug-coated cobalt-chromium stent; SS-DCS, Biolimus-A9 drug-coated stainless steel stent; SS-BMS, bare metal stainless steel stent; LF, LEADERS FREE trial; LF III, LEADERS FREE III trial; TLR, target lesion revascularization.

the full LF cohorts, small discrepancies were noted. Patients in LF III presented less frequently with STEMI and had a lower incidence of previous myocardial infarction, dyslipidemia, previous CABG, and previous congestive heart failure but a higher incidence of peripheral vascular disease. For the baseline procedural parameters, a significantly longer average stented length in LF III was noted, in comparison with both LF arms: 38.9 ± 27.4 mm (CoCr-DCS) versus 34.5 ± 23.1 mm (SS-DCS), $p = 0.0016$, and 33.4 ± 23.4 mm (SS-BMS), $i = 0.0001$, respectively. There were no discrepancies between trials in other procedural variables (Table 1) apart for a higher use of radial access in LF III. When the LF III cohort was compared with the propensity match cohorts from LF, no baseline patient discrepancies remained, except for the longer stented length in LF III (Table 2). Comparisons of baseline medications are provided in the supplemental Tables S3, S4, S5, S6.

After 1 year of follow-up, the primary safety endpoint was reached by 31/401 (8.0%) patients treated with the CoCr-DCS, versus 110/1221 (9.2%) of patients treated with the SS-DCS in the full LF cohort, ($p < 0.007$ for non-inferiority), and 35/401 (8.9%) in the propensity-matched cohort ($p = 0.007$ for non-inferiority). All other clinical safety endpoints including all death, cardiac death, myocardial infarction, and ARC definite/probable stent thrombosis were numerically lower for the CoCr-DCS in comparison with the SS-DCS in LF, albeit without statistical significance (Table 3) (Figure 2).

After 1 year of follow-up, the primary efficacy endpoint was reached by 16/401 (4.2%) patients treated with the CoCr-DCS, versus 107/1211 (9.3%) treated with the SS-BMS in the full LF cohort ($p = 0.002$ for superiority) and 41/401 (10.6%) patients in the LF propensity-matched cohort ($p = 0.007$ for superiority) (Table 4) (Figure 2).

In comparison to the SS-DCS, the CoCr-DCS was non-inferior for efficacy in both the full LF cohort (4.2% CoCr-DCS vs. 4.9% SS-DCS, $p = 0.0002$), and the propensity-matched cohort (4.2% CoCr-DCS vs. 2.8% SS-DCS), $p = 0.042$). Corresponding hazard ratios for the full and propensity matched cohort are 0.87 [0.50–1.51, $p = 0.61$ and 1.46 [0.68–3.15], $p = 0.33$ suggesting no benefit of CoCr-DCS over SS-DCS in terms of efficacy. Of note, the BARC 3–5 bleeding rate was non-significantly lower in LF III (5.4%) than in LF (7.2%), but still well above the threshold of 4.0% recently established by the Academic Research Consortium to characterize a HBR population.[10] The rate of procedural device success in LF III was 98.9% for the CoCr DCS vs 97.4% for the SS-DCS in LF ($p = 0.12$).

4 | DISCUSSION

Compared to the SS-DCS, a strut thickness reduction from 114–120 μm to 84–88 μm is the key improvement of the new CoCr-DCS, while all other design elements were kept the same. This multicenter, European, non-randomized study confirms non-inferiority for safety compared to the predicate stainless steel SS-DCS (BioFreedom™) and superiority for efficacy over the SS-BMS Gazelle™ studied in LF. In a population of HBR patients selected with the same inclusion exclusion criteria as LF, treated with an identical regimen, and studied using the same clinical follow-up and event adjudication process, the incidence of all clinical events was low, including the rate of definite/probable stent thrombosis. The trends towards lower clinical event rates in patients receiving the CoCr-DCS are in line with clinical evidence favoring thinner strut stents.[8]

In order to account for the non-randomized design of the trial, and the unavoidable baseline discrepancies in the absence of randomization, we conducted a propensity-matched analysis. The matching methodology used was developed earlier for the LF II trial in alignment with recommendations from the US Food and Drug Administration (FDA).[7] The 40 baseline covariates used to calculate propensity scores included clinical but not angiographic patient baseline conditions, as the focus of attention was on the high bleeding risk status of the patients, rather than on coronary anatomy. Patients in both the total LF population and the propensity-matched cohort had significantly shorter stented lengths than patients receiving the new CoCr-DCS in LF III. Despite this, procedure success rates were maintained (Tables 1 and 2) probably reflecting the improved deliverability of a thin strut platform and the new stent was non-inferior in safety and efficacy in all comparisons with the SS-DCS in LF.

The recently published ONYX ONE trial demonstrated non-inferiority of a thin-strut permanent polymer zotarolimus-eluting stent versus the BA9 SS-DCS in 1996 HBR patients.[11] These two stents differ in several ways (Platinum-Iridium vs. SS, thinner struts [81-91 μm vs.114-120 μm], zotarolimus vs. BA9, permanent polymer vs. polymer-free), but rates of death, MI and ci-TLR were almost identical in the two groups.

It is expected that a thin-strut stent should show advantages in deliverability and possibly lower rates of repeat revascularization and stent thrombosis.[8] Rates of lesion success, device success, and procedure success in LF III were 98.7%, 98.9%, and 97.0%, respectively.

While these rates are high and in line with current expectations towards a modern thin strut stent platform, there was no statistically significant advantage over the first-generation SS-DCS, most probably due to the sample size in LF III, which was not designed for such comparison.

In a post-hoc analysis of the STOPDAPT-2 trial,[12] a high bleeding risk cohort was identified using modified ARC-HBR criteria and compared to patients without high bleeding risk. At 1 year, the observed incidence of TIMI major/minor bleeding in this HBR population was 2.71% in the cohort treated with 12 months DAPT and 0.41% in the cohort treated with 1-month DAPT suggesting that the selection criteria used had not in fact identified a population at particularly high bleeding risk when treated with prolonged DAPT. The rate of the major secondary cardiovascular end point of cardiovascular death, myocardial infarction, definite stent thrombosis, and stroke in the HBR patients treated with 1-month DAPT was 3.07% at 1 year whereas in LEADERS FREE III, the rate of cardiovascular death, myocardial infarction and definite/probable stent thrombosis (without stroke) was 8.0% at 1 years. This most likely reflects a lower baseline ischaemic risk in STOPDAPT-2 with 70% of patients having stable coronary disease compared to only 32% of patients in LEADERS FREE III.

4.1 | Limitations

The key limitations of the LF III trial are the comparably small sample size and the single-arm design. This study is thus underpowered to show differences in several clinical outcome variables including stent thrombosis and repeat revascularization.

5 | CONCLUSIONS

Our study shows that the CoCr-DCS is associated with a low incidence of safety and efficacy endpoints at one-year follow-up. The results are non-inferior to the predicate SS-DCS and confirm superiority over a BMS in terms of efficacy. Overall, the results show that the thin strut Biolimus A9™ coated Cobalt Chromium coronary stent can be safely used in all comers HBR patients and confirm the good outcome for HBR patients treated with Biolimus-A9 drug coated stents followed by a 1-month DAPT regimen.

CONFLICT OF INTEREST

Hans-Peter Stoll, and Sara Sadozai Slama are employees of the trial sponsor (Biosensors, Morges Switzerland). Diana Schütte and Philip Urban are consultants to Biosensors. Philip Urban and Philippe Garot are shareholders of CERC, the CRO conducting the trial, Philip Urban is a shareholder of MedAlliance (Nyon, Switzerland). The other authors have no conflict of interest to report.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions

ORCID

Luc Maillard https://orcid.org/0000-0002-6898-3045

Sara Sadozai Slama https://orcid.org/0000-0002-0569-1491

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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