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ORIGINAL ARTICLE

Safety and efficacy of the latest generation biodegradable polymer-coated ultrathin sirolimus-eluting stent in the treatment of coronary artery disease in a European all-comer population with or without high bleeding risk: The Cruz HBR Registry

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ABSTRACT

BACKGROUND: The latest generation ultrathin Supraflex Cruz (Sahajanand Medical Technologies Limited, Surat, India) sirolimus-eluting stent (SES) has shown early healing properties and represents an attractive percutaneous coronary intervention (PCI) device in a high bleeding risk (HBR) population. The aim of this Cruz HBR registry was to assess safety and efficacy of the Supraflex Cruz SES in a large cohort of all-comer patients, of whom about one third were patients at HBR.

METHODS: Patients undergoing PCI were enrolled in this prospective, multi-centre, open label registry and stratified into non-HBR and HBR groups. The primary endpoint was a device-oriented composite endpoint (DOCE), a composite of cardiovascular death, myocardial infarction not clearly attributable to a non-target vessel and clinically driven target lesion revascularization within 12 months after PCI. The predefined aims were to show non-inferiority of the non-HBR group to the Supraflex arm of the TALENT Trial, and of the HBR group to polymer-free biolimus-coated stent arm of LEADERS FREE Trial.

RESULTS: A total of 1203 patients were enrolled across 26 European centers, including a significant proportion (38.7%; N.=466) of HBR patients. A total of 1745 lesions were treated in 1203 patients and 2235 stents were implanted. The

DOCE occurred within the total cohort in 5.8% of patients with a significant difference between HBR patients and non-HBR patients (8.1% *vs.* 4.4%; P<0.001). All-cause mortality at 12 months was significantly (P<0.0001) different among HBR (9.0%) and non-HBR patients (1.7%), respectively. At 12 months, the overall incidence of definite and probable stent thrombosis was 1.0%. Major bleeding occurred in 5.9% patients of the HBR group. These results met the non-inferiority criteria with respect to the TALENT trial for the non-HBR group (P<0.0001), and the LEADERS FREE trial for the HBR group (P<0.0001).
CONCLUSIONS: The Cruz HBR registry confirms that PCI with the Supraflex Cruz SES is associated with a favorable clinical outcome in an all-comer population, including complex patients with HBR.

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KEY WORDS: Hemorrhage; Drug-eluting stents; Dual anti-platelet therapy; Percutaneous coronary intervention; Sirolimus.

The evolution of stent technology has resulted in better clinical outcomes in patients with coronary artery disease over time. Contemporary drug-eluting stents (DES) allow successful treatment even in challenging lesions and complex patient subgroups. Supraflex (Sahajanand Medical Technologies Limited, Surat, India) is a novel ultrathin sirolimus-eluting stent (SES), which has recently shown non-inferiority to the Xience everolimus-eluting stent in the TALENT trial.[1] Recent real-world registries[2, 3] suggest favourable safety and clinical performance after percutaneous coronary intervention (PCI) using Supraflex Cruz SES with a low adverse event rate at 12 months. Additionally in the T-FLEX registry,[2] Supraflex Cruz showed favorable rates of clinical outcomes in high risk-subgroups such as patients with diabetes, small coronary vessel disease, ST-segment elevation myocardial infarction (STEMI), as well as chronic total occlusions (CTO). Moreover, the FIRE Trial,[4] published in 2023, focused on older patients (≥75 years) with myocardial infarction (MI) and multivessel disease undergoing PCI with Supraflex Cruz, either for only the culprit lesion or complete revascularization. The trial reported that those who underwent physiology-guided complete revascularization had a reduced risk of a composite of death, myocardial infarction, stroke, or ischemia-driven revascularization at one-year compared to those who received only culprit-lesion revascularisation.[4] However, there are limited data on the performance of Supraflex Cruz in patients at high bleeding risk (HBR).

Earlier, bare metal stents (BMS) were preferred for the PCI in HBR patients, in order to limit the duration of dual-antiplatelet therapy (DAPT). However, BMS consistently showed higher rates of restenosis and MI compared to DES.[5] The randomized LEADERS FREE trial (BioFreedom Biolimus A9 drug-coated stent versus the Gazelle bare metal stent in Patients at High Bleeding Risk) used a polymer-free drug-coated stent (PF-DCS) with one month of DAPT in a HBR patient cohort and revealed superior clinical outcomes of PF-DCS as compared to BMS.[6] Subsequently, several studies were performed using different DES platforms in HBR populations, but the use of DES in these patients is still challenging, as the optimal duration of DAPT required to reduce ischemic events while minimizing bleeding has not been completely clarified.[7] Moreover, available guidelines permit one to six months DAPT in selected HBR patients; however, these recommendations are derived from expert consensus or observational data rather than prospective randomized controlled trials.[8] In fact, in most clinical trials, HBR patients are either excluded or under-represented,[9-11] thus, limiting the evaluation of the clinical outcomes after PCI using DES in HBR patients. Of note, intravascular imaging studies suggested that implantation of Supraflex Cruz may be associated with early healing and low inflammatory burden, making this device particularly attractive for use in a HBR group.[12, 13]

Therefore, the Cruz HBR registry was designed to confirm the safety and efficacy of the novel Supraflex Cruz in a large unselected real-world all-comer cohort. The study had two main objectives: firstly, to demonstrate non-inferiority to the Supraflex arm of the TALENT trial for non-HBR patients, and secondly, to demonstrate non-inferiority of Supraflex Cruz in a subset of HBR

patients to the BioFreedom biolimus-coated stent arm of the LEADERS FREE trial, both with respect to a clinical device-oriented outcome.

Materials and methods

Study design and population

The Cruz HBR registry was a prospective, multicentric, open label registry conducted at 26 sites across 3 European countries (Switzerland, Germany and France). The population consisted of patients presenting with acute coronary syndromes (ACS) (unstable angina and NSTEMI) and chronic coronary syndrome (CCS). Initially, 1213 patients were included in the study, but nine of them did not receive the study stent and one informed consent form was not confirmed. Therefore, there were a total number of 1203 patients enrolled. The study flowchart is shown in Figure 1. Target lesions with a diameter between 2.0 mm and 4.5 mm and a lesion length between 15 mm and 120 mm were included. A staged procedure was allowed within three months and mandated the use of the Supraflex Cruz stent. For more detailed inclusion and exclusion criteria see Supplementary Digital Material 1, Supplementary Text File 1. All patients were followed up at six and 12 months either by telephone contact or an on-site visit. The patients were categorized into two groups – non-HBR and HBR patients after assessment of their bleeding risk according to recommendations from the Academic Research Consortium (ARC) for HBR consensus document.[14] Patients were considered to be at HBR if at least one major or two minor criteria were met. The study was performed in accordance with the principles set in the Declaration of Helsinki and was registered at ClinicalTrials.gov (Identifier: NCT04138238). All patients provided full informed written consent to participate in this registry, which was approved by the ethics committees of the study centers.

Description of the study device

Supraflex Cruz, the ultrathin SES coated with biodegradable polymer, has the latest-generation Tetrinium (Sahajanand Medical Technologies Limited, Surat, India) as stent platform. Tetrinium consists of a L-605 cobalt-chromium alloy.

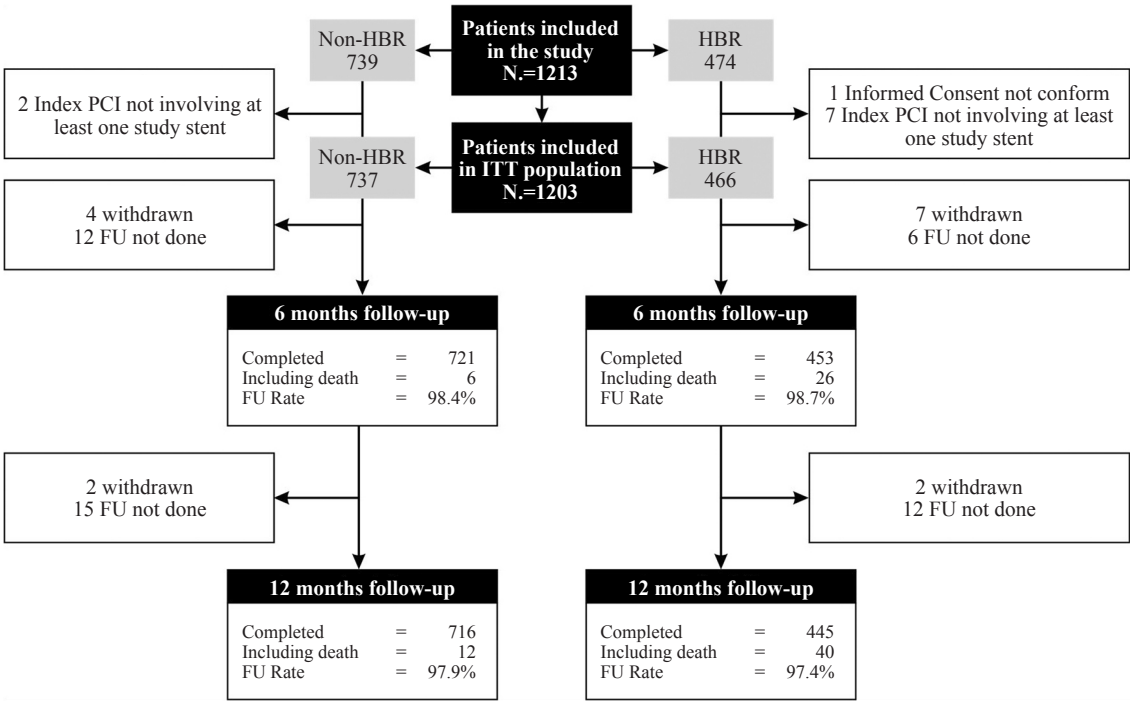

Figure 1.—Study flow chart.

The conformal multi-layer coating contains 1.4 μg/mm^2 of sirolimus mixed with a biodegradable polymeric matrix containing a combination of hydrophilic and hydrophobic polymers, containing poly (L-lactide), poly (L-lactide-co-caprolactone), and polyvinylpyrrolidone. Almost 80% of the drug is released within four weeks in biological media. The remaining drug is programmed to be released at a slow rate in approximately three months. The average coating thickness of Supraflex Cruz SES is between 4 and 6 μm. Further details of the stent characteristics are described elsewhere.[2]

Endpoints and definitions

The primary endpoint of the registry was a device oriented composite endpoint (DOCE), a composite of cardiovascular death, MI not clearly attributable to a non-target vessel and clinically driven target lesion revascularization (TLR) at 12 months. The secondary endpoints included rates of any MI, any death (both cardiovascular and non-cardiovascular), any revascularization, stent thrombosis (ST) and major bleeding (Bleeding Academic Research Consortium [BARC] (BARC 3, 4 or 5 for HBR patients) at six and 12 months.

Device success was defined as the deployment of stents without system failure or device-related complication. Procedural success was defined as successful treatment of all lesions without the occurrence of a DOCE event during the patient's hospital stay following the procedure. Lesion success was defined at the attainment of <50% residual stenosis after PCI and ST (definite or probable) was defined according to ARC-2.[15] Cardiovascular death was defined as death resulting from cardiovascular causes, as per the ARC-2 definition. The following categories were collected: death caused by acute myocardial infarction; death caused by sudden cardiac, including unwitnessed death; death resulting from heart failure; death caused by stroke; death caused by cardiovascular procedures; death resulting from cardiovascular hemorrhage; death resulting from other cardiovascular cause. Acute MI was defined as a rise of cardiac biomarker levels with at least one value above the 99th percentile upper reference limit and at least one of the following: ischemic symptoms, evidence of new ischemic changes on electrocardiogram or echocardiogram or identification of intracoronary thrombus at angiography. TLR was defined as any repeat PCI of the target lesions including 5 mm on either side of the implanted stent or surgical bypass of the target vessel for restenosis or other complication involving the target lesion. Target vessel revascularization (TVR) was defined as any repeat PCI or surgical bypass of any segment of the target vessel.

An independent Clinical Events Committee adjudicated all endpoint-related adverse events.

Statistical analysis

The sample size of the non-HBR group was chosen to replicate that of the TALENT trial.[1] The expected primary endpoint was estimated to be 6.6% at 12 months and the non-inferiority margin set at 3%. Accounting for an attrition rate of 10%, we estimated that 800 patients would be required to demonstrate non-inferiority with a power of 80% using a one-sided significance level of 0.05. The sample size for the HBR group was based on published event rates in the BioFreedom arm of the LEADERS FREE trial.[6] The non-inferiority margin was set at 6%. With an expected primary endpoint of 11.5% at 12 months and a 10% lost to follow-up rate, we estimated that 400 patients would be required to demonstrate non-inferiority with a power of 90% using a one-sided significance level of 0.05. Continuous variables are presented as mean±standard deviation and categorical variables as number and percentages. Patient characteristics of the HBR and non-HBR groups were analyzed using *t*-tests or χ^2 tests (whichever was applicable) for comparison on a patient level or a generalized estimating equation model using an independent working correlation matrix was applied for analyses on stent or procedure level. Endpoints were compared between the two groups using a Z-test.

The primary endpoint was estimated by means of a Kaplan-Meier curve. The non-HBR and HBR group were first analyzed separately and then in combination for the total cohort. For non-HBR patients, the results of the TALENT trial were considered to be confirmed, and non-inferiority met, if the upper limit of the one-sided 95% confidence interval (CI) was lower than 9.6% (expected event rate of 6.6%+non-inferiority mar-

gin of 3%). For the HBR group, non-inferiority to the BioFreedom stent was considered to be demonstrated if the upper limit of the one-sided 95% CI was lower than 17.5% (expected event rate of 11.5%+non-inferiority margin of 6%). Subgroup analyses of the primary endpoint in the total cohort were conducted according to a set of pre-specified parameters which consisted of the presence of diabetes mellitus, ACS, small vessel diseases (≤2.75 mm), multi-vessel treatment, long lesions (>18 mm), in-stent restenosis, previous coronary artery bypass grafting,left main stem treatment, bifurcation treatment, overlapping stents and age (>80 years).

Results

Between 26th February 2020 and 22nd October 2020, a total of 1203 patients were recruited in this registry. Of these, 466 of the participants were deemed to be at high risk of bleeding and comprised the HBR group.

The patient characteristics and procedural details are presented in Table I, II. Mean age of patients in the cohort was 69.3±10.9 years and 71.1% were male. The main indication for PCI was CCS (44.3%) while the NSTEMI population comprised 15.9% of the cohort.

In line with contemporary practice, the radial approach was used in most of the procedures (72.0%). A total of 1745 lesions were treated in 1203 patients and 2235 stents were implanted. A wide spectrum of lesions with different levels of complexity were treated, including 13.7% bifurcation lesions of which about a third were Medina type 1,1,1 classification. Left main PCI accounted for 3.0% of procedures. Device success, lesion success, and procedural success were achieved in 99.5%, 99.7%, and 98.6% of the cases, respectively. At six months, 89.7% and 48.8% of patients were on DAPT in the non-HBR and HBR groups respectively (P<0.001), while at 12 months, the percentage decreased to 52.3% and 23.8% (P<0.001), respectively.

The Kaplan-Meier curves for the primary endpoint in both groups are shown in Figure

TABLE I.—*Baseline characteristics of population.*

Variables	Non-HBR (N.=737)	HBR (N.=466)	Total (N.=1203)	P value
Characteristics				
Age (yrs)	64.8 (±9.9)	76.5 (±8.5)	69.3 (10.9)	<0.0001
Male	556 (75.4%)	299 (64.2%)	855 (71.1%)	<0.001
BMI (kg/m²)	[733] 28.6 (±5.0)	[458] 27.2 (±5.0)	[1191] 28.1 (±5.0)	<0.0001
Previous MI	159 (21.6%)	79 (17.0%)	238 (19.8%)	0.05
COPD	45 (6.1%)	56 (12.0%)	101 (8.4%)	<0.001
Previous PCI	298/736 (40.5%)	215 (46.1%)	513/1202 (42.7%)	0.054
Previous CABG	38 (5.2%)	44 (9.4%)	82 (6.8%)	0.004
PVD	59 (8.0%)	79 (17.0%)	138 (11.5%)	<0.001
Current Smoker	203 (27.5%)	50 (10.7%)	253 (21.0%)	<0.001
Diabetes Mellitus	195 (26.5%)	170 (36.5%)	365 (30.3%)	<0.001
Dyslipidemia	534 (72.5%)	321 (68.9%)	855 (71.1%)	0.183
Hypertension	601/736 (81.7%)	425/465 (91.4%)	1026/1201 (85.4%)	<0.001
Family History*	212 (28.8%)	62/465 (13.3%)	274/1202 (22.8%)	<0.001
Hemoglobin (g/L)£	[800] 144.5 (±12.6)	[505] 128 (±19.7)	[1305] 138.1 (±17.7)	<0.0001
Hematocrit (%)£	[800] 42.8 (±3.7)	[504]38.5 (±5.7)	[1304] 41.1 (±5.0)	<0.0001
Ejection Fraction£	[488] 56.0 (±9.2)	[302] 50.4 (±11.8)	[790] 53.9 (±10.6)	<0.0001
Indication for PCI£				
Stable angina	394/848 (46.5%)	214/525 (40.8%)	608/1373 (44.3%)	0.0001
Silent ischemia	225/848 (26.5%)	197/525 (37.5%)	422/1373 (30.7%)	
Unstable angina	84/848 (9.9%)	41/525 (7.8%)	125/1373 (9.1%)	
NSTEMI	145/848 (17.1%)	73/525 (13.9%)	218/1373 (15.9%)	

Data are presented as mean (±standard deviation) or numbers and percentages. In case of missing data, the available number of patients with data are reported between brackets or as denominators, respectively.
BMI: Body Mass Index; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; HBR: high bleeding risk; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease.
*Family history of premature <60 years coronary artery disease; £denominator are the number of procedures with data available.

TABLE II.—*Lesion and procedural characteristics.*

Variable	Non-HBR	HBR	Total	P value
Total number of procedures	851	527	1378	
Radial access	634/850 (74.6%)	357 (67.7%)	991/1377 (72.0%)	0.011
Index procedure	737 (86.6%)	466 (88.4%)	1203 (87.3%)	0.522
Staged procedure	114 (13.4%)	61 (11.6%)	175 (12.7%)	
Total number of lesions	1071	674	1745	
LMS lesions	30/1067 (2.8%)	23/672 (3.4%)	53/1739 (3.1%)	0.470
In-stent restenosis	44 (4.1%)	40 (5.9%)	84 (4.8%)	0.109
Total occlusion	113 (10.6%)	43 (6.4%)	156 (8.9%)	0.008
Bifurcation	159 (14.9%)	80/273 (11.9%)	239/1744 (13.7%)	0.102
SB diameter in bifurcation (mm)	[134] 2.5 (±0.5)	[68] 2.7 (±0.5)	[202] 2.6 (±0.5)	0.097
Medina 1,1,1	45/143 (31.5%)	22/72 (30.6%)	67/215 (31.2%)	0.892
Lesion length (mm)	[1057] 23.3 (±13.8)	[665] 23.5 (±14.1)	[1722] 23.4 (±13.9)	0.786
RVD (mm)	[1058] 3.0 (±0.5)	[667] 2.9 (±0.5)	[1725] 3.0 (±0.5)	0.267
Severe calcification	110/1058 (10.4%)	80/669 (12.0%)	190/1727 (11.0%)	0.313
Total number of Supraflex Cruz stents implanted	1367	868	2235	
Predilatation	1114 (81.4%)	771 (88.8%)	1885 (84.3%)	<.0001
Use of stent ≥40 mm	[1364] 98 (7.2%)	[866] 51 (5.9%)	[2230] 149 (6.7%)	0.072
N. of patients with TVD	707/737 (95.9%)	449/466 (96.4%)	1156/1203 (96.1%)	0.7126
N. of stents per patient	[737] 1.9 (±1.26)	[466] 1.9 (±1.16)	[1203] 1.9 (±1.22)	0.58
N. of stents per lesion				0.6860
0	19/1070 (1.78%)	19/674 (2.82%)	38/1744 (2.18%)	
1	802/1070 (74.95%)	487/674 (72.26%)	1289/1744 (73.91%)	
2	199/1070 (18.60%)	130/674 (19.29%)	329/1744 (18.86%)	
3	36/1070 (3.36%)	31/674 (4.60%)	67/1744 (3.84%)	
4	11/1070 (1.03%)	7/674 (1.04%)	18/1744 (1.03%)	
5	3/1070 (0.28%)	0/674 (0.00%)	3/1744 (0.17%)	
Total stent length per patient (mm)	[737] 42.1 (±30.1)	[466] 40.7 (±28.9)	[1203] 41.6 (±29.7)	0.427
Total stent length per lesion (mm)	[1047] 29.6 (±17.9)	[654] 29.0 (±17.8)	[1701] 29.4 (±17.9)	0.520
Average stent length (mm)	[1364] 22.7 (±9.53)	[866] 21.9 (±9.28)	[2230] 22.4 (±9.44)	0.086
Average stent diameter (mm)	[1366] 3.0 (±0.48)	[867] 2.9 (±0.47)	[2233] 3.0 (±0.48)	0.039
Procedural complications	15/851 (1.8%)	19/527 (3.6%)	34/1378 (2.5%)	0.046
Dissection not covered by stent at end of procedure	3 (0.4%)	4 (0.8%)	7 (0.5%)	
Permanent vessel or SB occlusion	2 (0.2%)	0	2 (0.1%)	
Arterial access site requiring intervention	2 (0.2%)	1 (0.2%)	3 (0.2%)	
Antithrombotic regime post procedure	N.=737	N.=466	N.=1203	
Aspirin	597 (81%)	220 (47.2%)	817 (67.9%)	<.001
Clopidogrel	233 (31.6%)	134 (28.8%)	367 (30.5%)	0.304
Prasugrel	35 (4.8%)	2 (0.4%)	37 (3.1%)	<.001
Ticagrelor	48 (6.5%)	17 (3.7%)	65 (5.4%)	0.036
Warfarin	0	34 (7.3%)	34 (2.8%)	<.001
NOAC	2 (0.3%)	153 (32.8%)	155 (12.9%)	<.001

Data are presented as mean (±standard deviation) or numbers and percentages. In case of missing data, the available number of patients with data are reported between brackets or as denominators, respectively.
HBR: high bleeding risk; LMS: left main stem; NOAC: new oral anticoagulants; RVD: reference vessel diameter; SB: side branch; TVD: triple vessel disease.

2. At 12 months, 97.9% and 97.4% follow-up was achieved in the non-HBR and HBR group, respectively. The primary endpoint occurred in 4.4% (32/737) of patients in the non-HBR group. The upper limit of the one-sided 95% CI was 5.9%, which met the requirement for non-inferiority compared to the Supraflex arm of the TALENT trial (P<0.0001). In the HBR group, the primary endpoint occurred in 8.1% (36/466) patients with an upper limit of the one-sided 95% CI of 11%. This was below the pre-specified 17.5% required to demonstrate non-inferiority to BioFreedom stent arm (P<0.0001) in the LEADERS FREE trial.

Table III shows the primary and secondary endpoints at six and 12 months. At 12 months,

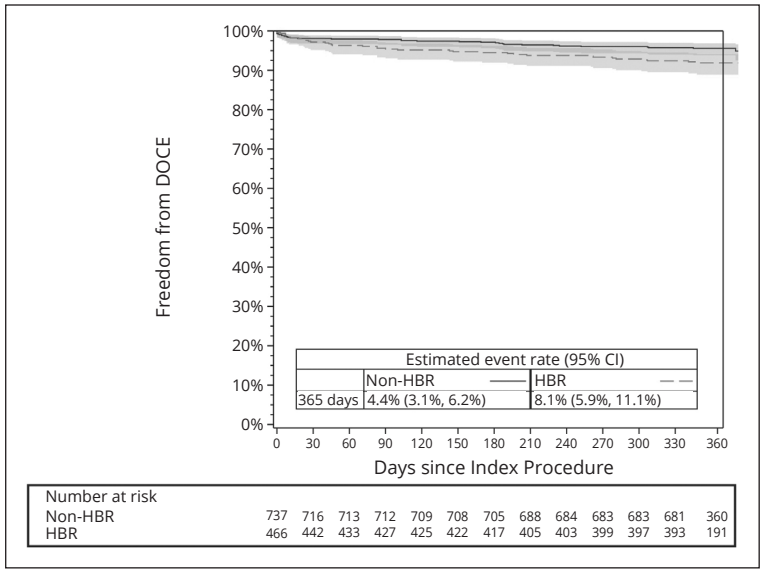

Figure 2.—Kaplan-Meier curve demonstrating freedom from the primary endpoint (DOCE).

TABLE III.—*Comparison of outcomes between non-HBR and HBR patients.*

Variable	6 months				12 months			
	Non-HBR (N.=737)	HBR (N.=466)	P value	Total (N.=1203)	Non-HBR (N.=737)	HBR (N.=466)	P value	Total (N.=1203)
Primary endpoint								
CV death, MI not clearly attributable to non-target vessel, clinically driven TLR					32 (4.4%)	36 (8.1%)	<0.0001	68 (5.8%)
Secondary endpoints								
CV death, MI not clearly attributable to non-target vessel, clinically driven TLR, MB, ST	24 (3.3%)	45 (9.9%)	<0.0001	69 (5.8%)	35 (4.8%)	59 (13.2%)	<0.0001	94 (8.0%)
Mortality								
All-cause mortality	6 (0.8%)	26 (5.7%)	<0.0001	32 (2.7%)	12 (1.7%)	40 (9.0%)	<0.0001	52 (4.5%)
CV mortality	5 (0.7%)	14 (3.1%)	0.006	19 (1.6%)	7 (1.0%)	22 (4.9%)	0.0003	29 (2.5%)
Non-CV mortality	1 (0.1%)	12 (2.6%)	0.001	13 (1.1%)	5 (0.7%)	18 (4.1%)	0.0007	23 (2.0%)
Myocardial Infarction								
MI	15 (2.0%)	13 (2.8%)	0.40	28 (2.3%)	21 (2.9%)	18 (3.9%)	0.33	39 (3.3%)
TV-MI and MI not clearly attributable to non-target vessel	10 (1.4%)	11 (2.4%)	0.21	21 (1.8%)	13 (1.8%)	11 (2.4%)	0.48	24 (2.0%)
Revascularization								
Clinically indicated TLR	12 (1.6%)	9 (2.0%)	0.68	21 (1.8%)	21 (2.9%)	12 (2.6%)	0.78	33 (2.8%)
All TLR	12 (1.6%)	9 (2.0%)	0.68	21 (1.8%)	23 (3.2%)	12 (2.6%)	0.57	35 (3.0%)
All TVR	15 (2.1%)	11 (2.4%)	0.69	26 (2.2%)	33 (4.6%)	14 (3.1%)	0.18	47 (4.0%)
All revascularization	25 (3.4%)	13 (2.8%)	0.57	38 (3.2%)	58 (8.1%)	21 (4.8%)	0.03	79 (6.8%)
Stent thrombosis								
Definite+probable	4 (0.5%)	5 (1.1%)	0.33	9 (0.8%)	7 (1.0%)	5 (1.1%)	0.83	12 (1.0%)
Definite	3 (0.4%)	5 (1.1%)	0.21	8 (0.7%)	6 (0.8%)	5 (1.1%)	0.65	11 (0.9%)
Probable	1 (0.1%)	0	n/a	1 (0.1%)	1 (0.1%)	0	NA	1 (0.1%)
MB (BARC 3-5)	4 (0.5%)	24 (5.2%)	<0.0001	28 (2.4%)	5 (0.7%)	27 (5.9%)	<0.0001	32 (2.7%)

Data are presented as number of events and the percentages are Kaplan-Meier estimates at 6 or 12 months, respectively.
CV: cardiovascular; HBR: high bleeding risk; MI: myocardial infarction; MB: major bleed; ST: stent thrombosis; TLR: target lesion revascularization; TVR: target vessel revascularization; NA: not available.

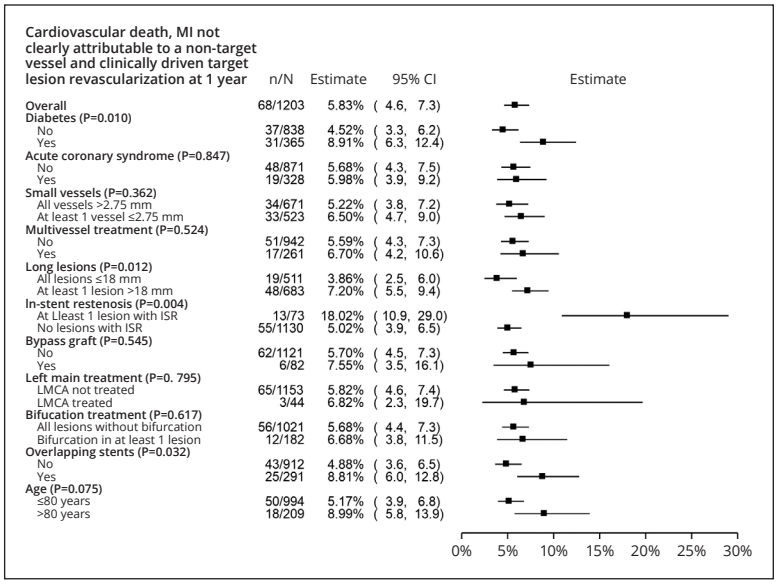

Figure 3.—Subgroup analyses for the primary endpoint at 12 months.

the overall incidence of definite and probable ST was 1.0%. Major bleeding occurred in 5.9% patients of the HBR group. The pre-specified subgroup analyses of the primary endpoint are shown in Figure 3. In the stratified analyses, the presence of diabetes, treatment of long lesions, overlapping stents and in-stent restenosis were associated with worse outcomes.

Discussion

The main findings of our registry were as follows: 1) Supraflex Cruz was associated with low adverse clinical events in an all-comer population at 12 months; 2) Supraflex Cruz showed non-inferiority in non-HBR patients for the primary endpoint compared to the Supraflex arm from the TALENT Trial; 3) in the treatment of patients at HBR, Supraflex Cruz was non-inferior for the primary endpoint compared to the BioFreedom stent at 12 months; 4) subgroups with worse outcomes included patients with diabetes, long lesions, overlapping stents and in-stent restenosis.

Progress in stent design and technology has allowed the production of stents with thinner struts and better biocompatibility, resulting in improved clinical outcomes; one-year major adverse cardiovascular event rates range around 5% with the latest generation of DES.[16] The safety and efficacy of the contemporary Supraflex stent was demonstrated in an all-comer population in the TALENT Trial, at 12 months[1] as well as 3 years.[17] In this prospective, multi-center (23 centers in 7 European countries), randomized, all-comer trial, Supraflex was shown to be non-inferior (P<0.001) to the Xience stent (Abbott, USA) for DOCE at 12 months. The target lesion failure (TLF) rate at 12 months was 4.9% with Supraflex *vs.* 5.3% with Xience, with a significantly lower rate of TLR with Supraflex, 1.2% *vs.* 3.1% with Xience (P=0.021). The non-HBR group of the Cruz HBR registry adds further supportive evidence on the safety and efficacy of Supraflex Cruz in an all-comer population. The rates of DOCE among the non-HBR group of this registry and Supraflex arm of the TALENT Trial (4.8% *vs.* 4.9%) were similar with numerically lower rates of all-cause mortality (1.7% *vs.* 2.0%) and any MI (2.9% *vs.* 3.1%) in the non-HBR group compared to Supraflex arm of the TALENT Trial.

The percutaneous treatment of patients at high risk of bleeding is challenging. Over the past decade, a substantial amount of research has been devoted to producing stent platforms that combine the low ischemic risk of a DES and the low bleeding risk of a BMS.[18, 19] Moreover, a review of recent DES trials has pointed out that the current goal is to hit two targets with one arrow, *i.e.*, bleeding attenuation by restricting duration of DAPT in the effort to improve safety while

preserving efficacy.[20] In optical coherence tomography studies, Supraflex Cruz was associated with rapid endothelialization and neointimal coverage[12, 13] which can potentially allow the duration of DAPT to be shortened safely. Interestingly, the percentage of major bleeding (BARC 3-5) was numerically lower in the HBR group of Cruz HBR registry than the BioFreedom arm of the LEADERS FREE trial (5.9% *vs.* 7.2%) despite a longer DAPT duration. Table IV compares populations and outcomes of both the cohorts, *i.e.*, HBR group from present registry and Biofreedom group from LEADERS FREE Trial. Unlike the latter study where a month of DAPT was mandated, the length of DAPT in the HBR group of Cruz HBR registry was left to the discretion of the treating physician. Under half of the HBR cohort was still on DAPT at 6 months. This would suggest that taking an individualized approach to DAPT duration based on the careful assessment of bleeding and ischemic risk on a case-by-case basis may be more beneficial than adopting a "blanket" approach to the treatment of patients with HBR. The ischemic endpoints of MI (3.9% *vs.* 6.1%), TLR (2.6% *vs.* 5.1%), TVR (3.1% *vs.* 5.8%) and ST (1.1% *vs.* 2.0%) were all numerically lower in the HBR group of our registry compared to the BioFreedom arm of the LEADERS FREE Trial. The longer duration of DAPT in our registry may partly explain this trend. Another potential explanation may relate to the differences in stent architecture. Computational fluid dynamic studies have shown that thick struts can perturb laminar blood flow and adversely affect wall shear stress, both of which can lead to progression of native atherosclerosis and in-stent restenosis.[21] With a thickness of 60 μm compared to the 112 μm of BioFreedom stent, Supraflex Cruz may generate a better hemodynamic profile and consequently be less atherogenic.

The BioFreedom France Study was a recent study with similar aims to the current registry. It was an all-comer study, which included patients who underwent PCI with BioFreedom PF-DCS at 25 centers in France and compared outcomes in patients with or without HBR. The study reported that HBR patients, as compared to non-HBR patients, had a higher risk of cardiac death (4.4% *vs.* 1.4%, P=0.0005) and MI (2.9% *vs.* 0.6%, P=0.0003), and also had increased rates of BARC 3-5 bleeding (6.2% *vs.* 1.4%, P<0.0001).[22] Recently, the ReCre8 sub analysis, evaluated clinical outcomes in patients with and without HBR according to the ARC-HBR criteria at one and three years. A higher TLF rate among HBR patients at long-term follow-up was observed (13.3% *vs.* 9.1%; P=0.013), highlighting the challenge in treatment of HBR patients. In contrast to our registry, there was no statistically significant difference in BARC 3-5 bleeding between patients with and without HBR regardless of DAPT duration.[23]

There have been several non randomized trials that compared performance of DES in patients at HBR with the historical data on cohorts or applied objective performance goal as a control: these in-

TABLE IV.—*Comparison of HBR populations and outcomes of Cruz HBR registry and LEADERS FREE Trial.*

	Cruz HBR Registry (HBR Group) (N.=466 patients)	LEADERS FREE Trial (Biofreedom Group) (N.=1221 patients)
Age, years (mean±SD)	76.5±8.5	75.7±9.4
Male, %	64.2%	70.2%
BMI (kg/m²) (mean±SD)	27.2±5.0	27.5±4.8
Diabetes, %	36.5%	34.0%
Hypertension, %	91.4%	78.1%
Stable angina, %	40.8%	58.5%
Previous MI, %	17.0%	19.6%
Previous PCI, %	46.1%	22.2%
All-cause mortality, N. (%)	40 (9.0%)	97 (8.0%)
Any MI, N. (%)	18 (3.9%)	72 (6.1%)
Clinically indicated TLR, N. (%)	12 (2.6%)	59 (5.1%)
Definite+probable ST, N. (%)	5 (1.1%)	24 (2.0%)
Major bleeding (BARC 3-5), N. (%)	27 (5.9%)	85 (7.2%)

BARC: Bleeding Academic Research Consortium; BMI: Body Mass Index; HBR: high bleeding risk; MI: myocardial infarction; PCI: percutaneous coronary intervention; ST: stent thrombosis; TLR: target lesion revascularization.

clude the XIENCE 28, XIENCE 90, Onyx ONE Clear, EVOLVE Short DAPT, MODEL-U SES, and LEADERS FREE 2 trials.[24] All these trials had set varying limits of discontinuing DAPT, either one month, three months or 12 months and, in each case, the study arm was either non-inferior or superior to the comparator arm. It is thus possible to attain a balance between two opposing risks of bleeding and ischemia in stented patients; adapting the treatment strategy by individualizing risk in each patient may be a crucial step in reducing overall adverse events.

Limitations of the study

The current study has a few limitations: 1) it was designed as a registry and statistical comparisons were made to historical data; 2) the patients included in this registry were not consecutively enrolled; and 3) the goal of this registry was to examine the clinical outcomes in routine practice in both non-HBR and HBR patients, and then make comparisons to historical data. Thus, differences between groups in patient characteristics and medical therapy are expected, since these are not randomized comparisons. Furthermore, the choice of DAPT duration was decided by the treating physician depending upon the clinical presentation of the patient, rather than by randomization.

Conclusions

The Cruz HBR study confirms favorable clinical outcomes after PCI using the ultrathin Supraflex Cruz SES to treat coronary artery disease in a large all-comer population. In addition, its use in a subset of patients at high risk of bleeding is safe and efficacious with results being non-inferior to biolimus PF-DCS, suggesting that the use of Supraflex Cruz may be a novel valuable option in HBR patients undergoing PCI.

Key messages

- The percutaneous treatment of coronary artery disease in patients with a HBR is challenging.
- The Supraflex ultrathin SES has previously shown non-inferiority to the Xience everolimus-eluting stent. Its current iteration, Supraflex Cruz, is associated with early healing and low inflammation, which may be beneficial in the treatment of HBR patients.
- The use of the ultrathin Supraflex Cruz SES to treat coronary artery disease in an all-comer population is associated with good clinical outcomes. Moreover, its 12 months outcomes in patients at HBR are comparable to that of polymer-free drug-coated stent.

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Conflicts of interest

All authors declare no conflict of interest, except Krishnankutty Sudhir who serves as Chief Medical Officer of Sahajanand Medical Technologies Limited.

Authors' contributions

Conception or design of the work and critical revision of the article: Christoph Naber (lead principal investigator [PI]), David M. Leistner (coordinating investigator); data collection: Rajiv Rampat; data analysis and interpretation: Kris Bogaerts, Christoph Naber (Lead PI), David M. Leistner (Coordinating Investigator); drafting the article: Christoph Naber (lead PI), David M. Leistner (coordinating investigator), Krishnankutty Sudhir (Chief Medical Officer, sponsor's representative); final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: David M. Leistner (coordinating investigator), Rajiv Rampat, Thomas Schmitz (site investigator), Abdelhakim Allali (site investigator), Helge Möllmann (site investigator), Barbara E. Stähli (site investigator), Tanja K. Rudolph (Site Investigator), Alexander Lauten (site investigator), René Koning (Site Investigator), Kris Bogaerts, Krishnankutty Sudhir (Chief Medical Officer, sponsor's representative) and Christoph Naber (lead PI). All authors read and approved the final version of the manuscript.

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History

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SUPPLEMENTARY DIGITAL MATERIAL 1

Inclusion and exclusion criteria

Inclusion criteria:

1. Patients ≥ 18 years old
2. De novo or restenotic significant stenosis in at least one native coronary artery
3. Patients with silent ischemia, stable angina, unstable angina or non STEMI eligible for PCI (no limitation of the number of treated lesions and vessels, except higher tercile of Syntax score assessed by the site)
4. Target lesions suitable for PCI with Drug Eluting Stent (DES) diameter between 2.00 and 4.50 mm
5. Total lesion length should be from 15 to 120 mm
6. Patient is willing and capable to sign the written informed consent and comply with all requirements of the registry
7. Planned staged procedures are allowed within 3 months using Supraflex Cruz™ stent only

Exclusion criteria:

1. SYNTAX Score > 32
2. Hemodynamic instability or cardiogenic shock
3. Known hypersensitivity or contraindication to any component of the study stent or the eluting drug, to media contrast, to dual antiplatelet therapy (DAPT) medication required by current practice
4. Subject is pregnant, nursing or is a woman with childbearing potential

5. Any co morbid condition with life expectancy < 1 year or that may result in protocol non compliance
6. Patients who are participating in another drug or device investigational study, which has not reached its primary endpoint
7. Patients under judicial protection, tutorship or curatorship