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ORIGINAL PAPER

Polymer-free drug-coated coronary stents in diabetic patients at high bleeding risk: a pre-specified sub-study of the LEADERS FREE trial

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Abstract

Objective Diabetics are at increased risk after stent implantation and potentially sensitive to the type of stent and dual antiplatelet therapy (DAPT). The randomized, double-blind LEADERS FREE trial compared 2432 patients at high bleeding risk (HBR) receiving either a polymer-free BA9-coated stent (DCS) or a bare metal stent (BMS) with 1 month of DAPT, and showed superior safety and efficacy of the DCS at 2 years. We report outcomes at 2 years of the pre-specified diabetic subgroup.

Methods and results The diabetic sub-group comprised 805 (33.1%) patients; 262 (10.8%) were insulin-dependent (IDDM). Compared to non-diabetics, diabetics were younger and had more risk factors and multi-vessel disease. They suffered higher rates of death (15.6 vs. 12.2%, $p=0.01$), cardiac death (8.3 vs. 5.9%, $p=0.02$), myocardial infarction (MI) (11.1 vs. 7.8%, $p=0.009$) and definite/probable stent thrombosis (3.1 vs. 1.7%, $p=0.01$), but rates of clinically-indicated TLR (9.1 vs. 9.5%, $p=0.93$) and BARC 3–5 bleeding (10.2 vs. 8.4%, $p=0.20$) were comparable. Compared to diabetic patients treated with a BMS, diabetic DCS recipients required less clinically driven TLR (6.3 vs. 12.2%, $p=0.006$). The primary safety endpoint (cardiac death, MI, definite/probable stent thrombosis) occurred numerically less frequently in the DCS group (14.9 vs. 19.7%, p = 0.10), and was significantly lower in IDDM patients (13.8 vs. 25.4%, $p=0.03$). BARC 3–5 was similar for patients treated with DCS (9.9%) and BMS (10.5%, $p=0.84$).

Conclusions In diabetic HBR patients, DCS significantly reduced re-intervention rates over BMS, and showed a strong trend towards a safety benefit at 2 years.

Clinical trial registration ClinicalTrials.gov number: NCT01623180.

Keywords: Diabetes mellitus · Bleeding · Drug-coated stents

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Introduction

Patients with diabetes mellitus (DM) have more ischemic events after percutaneous coronary intervention (PCI) including cardiac death, myocardial infarction, stent thrombosis and restenosis [1]. Poorer outcomes of diabetics after PCI is possibly due to a higher level of underlying vascular inflammation, presence of a pro-thrombotic state, as well as a more complex clinical and angiographic presentation [2]. Moreover, both acute and long-term adverse events of diabetic patients correlate with the severity of the diabetes as reflected by insulin dependence [3]. Whether the presence of diabetes mellitus differentially affects the clinical outcomes after implantation of specific stent types is a matter of debate [4, 5].

The randomized LEADERS FREE trial compared high bleeding risk (HBR) recipients of either a polymer-free BA9-coated stent (DCS) or a bare metal stent (BMS) with only 1 month of dual antiplatelet therapy (DAPT) and showed superior safety and efficacy of the DCS up to 2-year follow-up [6–8]. The LEADERS FREE trial was unique in several aspects. The study had a double blind design, and thus the operators did not know the stent type. Furthermore, the study intentionally enrolled only HBR patients, a group of patients that had been excluded or underrepresented in most stent trials. In consequence of these inclusion criteria, any subgroup of the LEADERS FREE trial will have particular qualities. We report characteristics and outcomes of the pre-specified subgroup of patients with DM.

Methods

Patient selection and study design of the LEADERS FREE trial have been previously described [6, 7]. Inclusion required a clinical indication for PCI together with one or more of 13 pre-defined HBR criteria. Those most frequently used were age ≥ 75 years, planned prolonged oral anticoagulation, renal failure, planned major surgery, anemia or recent transfusion, and cancer.

Patients were randomly assigned in a 1:1 ratio to undergo PCI with a polymer-free BA9-coated stent or a similar bare metal stent (BioFreedom and Gazelle stents, respectively, Biosensors Europe, Morges, Switzerland, SA). All patients were to receive only 1 month of DAPT. Patient visits were performed at 30 days and 1 year, and telephone contact at 2 and 4 months and at 2 years. Target lesion revascularization (TLR) was defined as the primary efficacy endpoint of the study, while a composite of cardiac death, myocardial infarction (MI) and stent thrombosis was defined as the primary safety endpoint. Both primary endpoints as well as bleeding according to the Bleeding Academic Research Consortium (BARC) definition were recorded and adjudicated up to 730 days. The trial was sponsored by Biosensors Europe (Morges, Switzerland) and was conducted in accordance with the trial protocol by Centre European de Recherche Cardiovasculaire (CERC; Massy, France). The institutional review board at each site approved the study.

Among the 2,432 patients in the modified ITT population [7], diabetic status at baseline was missing for 5 patients (4 DCS and 1 BMS). From the remaining 2,427 patients, 805 were diagnosed with DM at baseline, 262 of which were insulin dependent. The presence of diabetes mellitus was identified by the local investigators according to the patients' history and was entered as such in the case report forms. Randomization was not stratified according to the presence or absence of diabetes. For the purpose of this pre-specified subgroup analysis, clinical events were compared in diabetic vs. non-diabetic patients and in DCS vs. BMS recipients among the diabetic population. Patient disposition is described in Fig. 1.

Statistical analysis

For continuous variables (such as age), mean and standard deviations are reported. For categorical variables (such as number of lesions), counts and percentages are displayed. For comparing characteristics on patient level for continuous variables, a non-parametric Wilcoxon rank-sum test was used. Categorical variables were compared via a chi-square test. Whenever appropriate a Fisher's exact test was used instead. For time-dependent variables, hazard ratios (HR), 95% confidence intervals (CI) or both were calculated from an unadjusted Cox proportional hazard model. The cumulative incidence of events was calculated using Kaplan–Meier statistics and compared using the log-rank test. Proportional hazard assumptions were verified using Schoenfeld residuals. We made no adjustment for covariates or imputation for missing data. For clinical events according to diabetic status

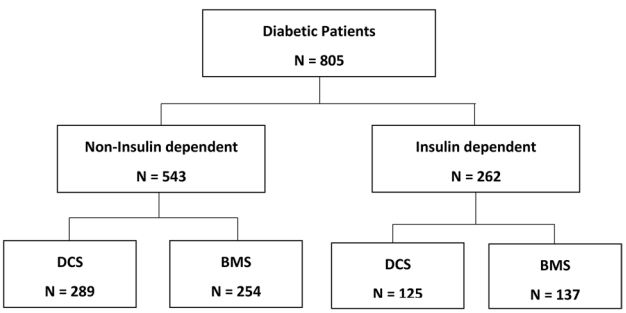

Fig. 1 Patient disposition

and stent type, an interaction variable was added in the Cox proportional hazard model to test for a potential subgroup by stent-type interaction. A p-value < 0.05 was considered statistically significant. All data were analyzed using the SAS V.9.3 statistical package (SAS Institute, Cary, NC).

Results

Diabetic compared to non-diabetic patients

Compared to non-diabetic HBR patients at baseline, diabetic patients were younger and had a higher BMI. They had more frequently a history of high blood pressure, hypercholesterolemia, renal failure and previous coronary interventions. Anemia and multivessel disease were more frequent at baseline than in non-diabetic patients (Table 1). Diabetics presented more often with acute non-ST-segment elevation MI. Lesion length (median 15 mm) and reference vessel diameter (median 3 mm) were similar in diabetic and non-diabetic patients. Most of the patients in both cohorts were treated with one stent for one lesion. Regarding HBR inclusion criteria, diabetic patients were less often enrolled for age ≥ 75 years, but more often for anemia and renal failure (Table 2).

Compared to NIDDM patients, IDDM were more frequently female and had a higher BMI (29.4 ± 5.4 vs. 28.1 ± 4.7, $p < 0.0008$). IDDM patients also had a higher prevalence of renal and heart failure. Lesion characteristics and procedural details revealed no major differences between the NIDDM and IDDM subgroups. IDDM patients

Table 1 Baseline characteristics and medical history

Parameter	Diabetic ($N=805$)	Non-diabetic ($N=1622$)	P
Age, years (mean ± SD)	74.4 ± 9.1	76.3 ± 9.4	< 0.0001
Female, N (%)	246 (30.6)	490 (30.2)	0.86
Body mass index, (mean ± SD)	28.5 ± 5.0	26.8 ± 4.5	< 0.0001
Hypertension, N (%)	694 (86.2)	1,215 (75.1)	< 0.0001
Hypercholesterolemia, N (%)	549 (69.2)	939 (59.1)	< 0.0001
STEMI presentation, N (%)	28 (3.4)	77 (4.7)	0.18
NSTEMI presentation, N (%)	191 (23.7)	361 (16.1)	< 0.0001
Multivessel disease, N (%)	556 (69.7)	935 (58.5)	< 0.0001
Atrial fibrillation, N (%)	277 (34.5)	562 (34.8)	0.90
Previous PCI, N (%)	193 (24.1)	304 (21.0)	0.08
Previous MI, N (%)	186 (23.3)	308 (19.1)	0.02
Previous CABG, N (%)	104 (13.0)	131 (8.1)	< 0.0001
Previous congestive heart failure, N (%)	120 (15.0)	204 (12.6)	0.11
Previous stroke, N (%)	90 (11.2)	151 (9.4)	0.16
Peripheral vascular disease, N (%)	130 (16.3)	249 (15.5)	0.60
Chronic obstructive lung disease, N (%)	101 (2.7)	171 (10.6)	0.13

Table 2 High-bleeding risk criteria diabetic vs. non-diabetic

Parameter	Diabetic ($N=805$)	Non-Diabetic ($N=1622$)	P
Patient > 75 years old, N (%)	460 (57.1)	1,100 (67.8)	< 0.0001
OAC needed after PCI, N (%)	307 (38.1)	570 (35.1)	0.15
Impaired renal function (CCR < 40), N (%)	191 (23.7)	272 (16.8)	< 0.0001
Low Hemoglob./recent transfusion, N (%)	183 (22.7)	196 (12.1)	< 0.0001
Planned major surgery < 1 year	124 (15.4)	273 (16.8)	0.37
Cancer, N (%)	69 (8.6)	170 (10.5)	0.14
Hospitalized for bleeding < 1 year, N (%)	28 (3.5)	51 (3.1)	0.66
Likely non-compliant for DAPT, N (%)	25 (3.1)	63 (3.9)	0.33
Non-aspirin NSAID needed > 30 days, N (%)	24 (3.0)	48 (3.0)	0.98
Stroke < 1 year, N (%)	17 (2.1)	22 (1.4)	0.16
Thrombocytopenia, N (%)	14 (1.7)	24 (1.5)	0.63
Prior intra-cranial bleed, N (%)	13 (1.6)	20 (1.2)	0.44
Severe chronic liver disease, N (%)	11 (1.4)	10 (0.6)	0.06

were more commonly included for planned surgery and for renal failure compared to those without insulin dependence.

Clinical events depending on diabetic status

At 2-year follow-up, diabetics had higher rates of all-cause death (15.6 vs. 12.2%, $p=0.01$), cardiac death (8.3 vs. 5.9%, $p=0.02$), myocardial infarction (11.1 vs. 7.8%, $p=0.009$) and definite or probable stent thrombosis (3.1 vs. 1.7%, $p=0.001$). Major bleeding rates (BARC 3–5) were similar in DM compared to non-DM patients (10.2 vs. 8.4%, $p=0.20$). The event rates were even higher for IDDM patients: all-cause death (19.9%, $p=0.0003$), cardiac death (10.9%, $p=0.0015$) and myocardial infarction (11.5%, $p=0.059$) (p-value for comparison with non-diabetic patients).

Clinically-driven target vessel and target lesion revascularization rates were comparable to the non-DM population (10.3 vs. 10.5%, $p=0.92$ and 9.1 vs. 9.5%, $p=0.93$, respectively). Even in the IDDM cohort, target-vessel and target-lesion revascularization rates were comparable to the non-DM patients (11.5 vs. 10.5%, $p=0.64$ and 10.2 vs. 9.5%, $p=0.73$, respectively).

Clinical events in diabetic patients according to stent type

Although randomization was not stratified depending on the diabetes status, both stent cohorts had largely similar baseline characteristics (Table 3). Among the 805 patients with DM, the combined primary safety endpoint (cumulative incidence of cardiac death, MI, or definite or probable stent thrombosis) at 2 years was numerically less frequent in the DCS group than in the BMS group (14.9 vs. 19.7%, $p=0.10$). A 28% risk reduction with DCS was observed already after 1 year ($p=0.09$) (Fig. 2). For the primary safety endpoint, the p-value for interaction with the

Table 3 Baseline characteristics in diabetics by stent group

Parameter	BMS ($N=391$)	DCS ($N=414$)	P
Age, years (mean ± SD)	73.98	74.81	0.17
Female, N (%)	118 (30.2%)	128 (30.9%)	0.82
Body mass index, (mean ± SD)	28.51 ± 4.76	28.52 ± 5.19	0.83
Hypertension, N (%)	343 (87.7%)	351 (84.8%)	0.23
Hypercholesterolemia, N (%)	265 (68.7%)	284 (69.8%)	0.73
ACS presentation, N (%)	108 (27.6%)	111 (26.8%)	0.26
Multivessel disease, N (%)	272 (69.7%)	284 (69.6%)	0.97
Atrial fibrillation, N (%)	134 (34.4%)	143 (34.6%)	0.94
IDDM, N (%)	137 (35%)	125 (30.2%)	0.88
Previous MI, N (%)	100 (25.7%)	86 (21%)	0.11
Previous congestive heart failure, N (%)	55 (14.1%)	65 (15.8%)	0.49
Previous stroke, N (%)	32 (8.2%)	58 (14%)	0.01
Peripheral vascular disease, N (%)	54 (13.9%)	76 (18.6%)	0.07
Chronic obstructive lung disease, N (%)	57 (14.7%)	44 (10.8%)	0.10

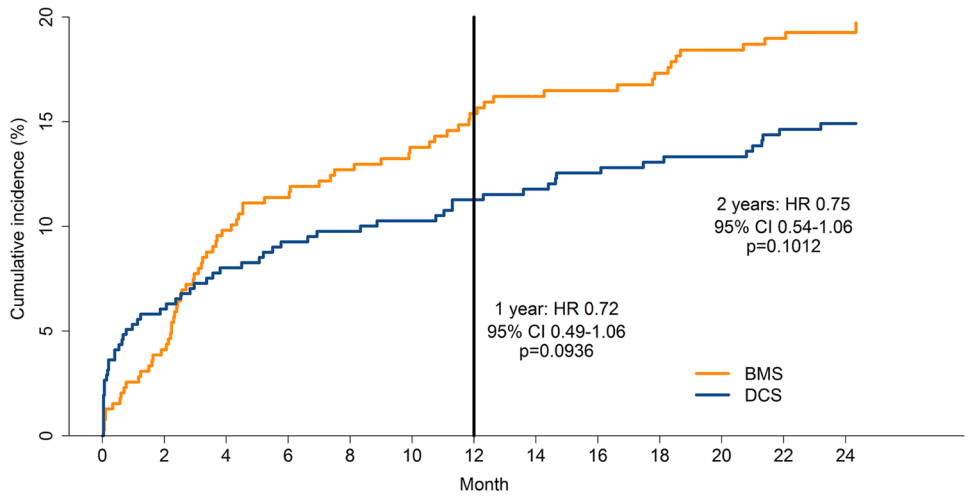

Fig. 2 Primary safety endpoint (cardiac death, myocardial infarction and definite/probable stent thrombosis)—diabetic patients ($N=805$)

Table 4 Clinical events in diabetics by stent group

Parameter	BMS ($N=391$)	DCS ($N=414$)	P
All death, N (%)	65 (17.1)	59 (14.4)	0.30
Cardiac death, N (%)	35 (9.5)	29 (7.3)	0.28
Myocardial infarction, N (%)	45 (12.3)	40 (10.1)	0.37
Definite or probable stent thrombosis, N (%)	12 (3.2)	13 (3.2)	0.95
Very late def. or probable stent thrombisis, N (%)	1 (0.3)	1 (0.3)	0.94
Any revascularisation, N (%)	63 (17.5)	42 (10.8)	0.0086
BARC bleeding 2–5, N (%)	78 (21.4)	71 (17.9)	0.27
BARC bleeding 3–5, N (%)	38 (10.5)	39 (9.9)	0.84

diabetes status was 0.70. The event rates for all death, cardiac death, and MI were also numerically lower in the DCS group (Table 4). We observed no difference in the occurrence of definite or probable stent thrombosis between the treatments arms. Notably, only one patient in each group developed a very late stent thrombosis (Table 4). Importantly, the antithrombotic treatment was not significantly different between the DCS and BMS group. The proportion of patients on dual antiplatelet therapy was similar in both groups throughout the time points of follow-up (DCS vs. BMS: discharge 96.5 vs. 97%, $p=0.68$; 1 month 74.8 vs. 71.1%, $p=0.41$; 2 months 7.3 vs. 6.6%, $p=0.74$; 24 months 4.9 vs. 7.9%, $p=0.11$).

For diabetics, treatment with DCS was more effective than treatment with BMS with a roughly 50% reduction of clinically driven TLR after 1 year, and this reduction was persistent up to 2 years (6.3 vs. 12.2%, $p=0.006$) (Fig. 3). For the efficacy endpoint, the p-value for interaction with the diabetes status was 0.75. Moreover, the need for any revascularization was significantly reduced in the DCS group (Table 4).

Bleeding rates for diabetic patients were high at 18.5% for BARC 2–5 and 9.5% for BARC 3–5, and were similar in both stent groups (Table 3).

In the analysis by IDDM status, the combined safety endpoint was significantly lower with DCS in patients with IDDM (13.8 vs. 25.4%, $p=0.03$). While the effect of the DCB on the safety endpoint was small after 1 year, the significant difference developed in year 2 after stent implantation (Fig. 4).

In IDDM patients, the efficacy benefit of DCS was unchanged, with a nearly 50% reduction of clinically driven target-lesion revascularisations vs. BMS, but it no longer reached statistical significance, likely due to small numbers (6.9 vs.13.2%, $p=0.13$) (Fig. 5).

Discussion

The recently published 2-year outcome data of the LEADERS FREE trial document that the superior safety and efficacy advantage of the DCS over a bare metal stent is maintained 24 months after stent implantation [8]. The principal

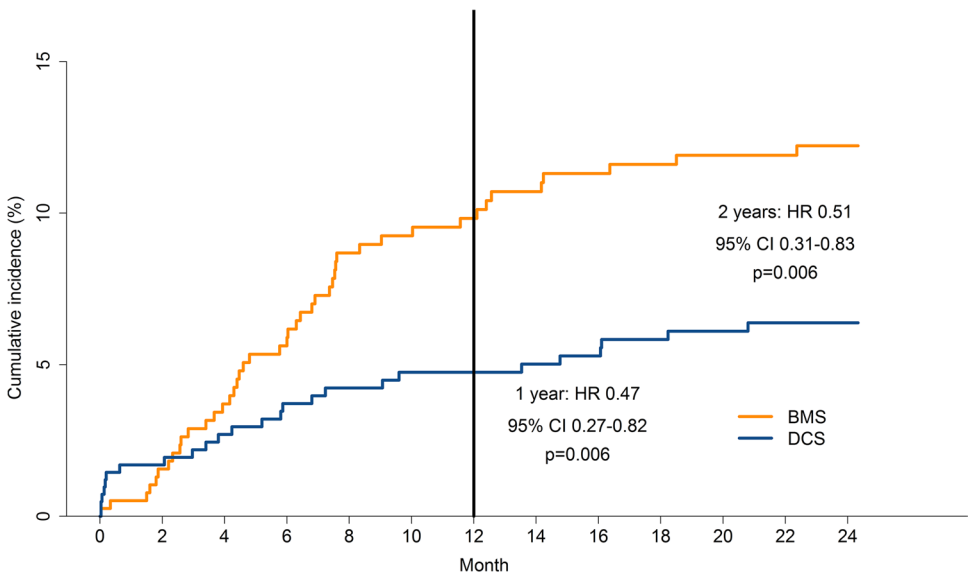

Fig. 3 Primary efficacy endpoint (clinically indicated target lesion revascularization)—diabetic patients ($N=805$)

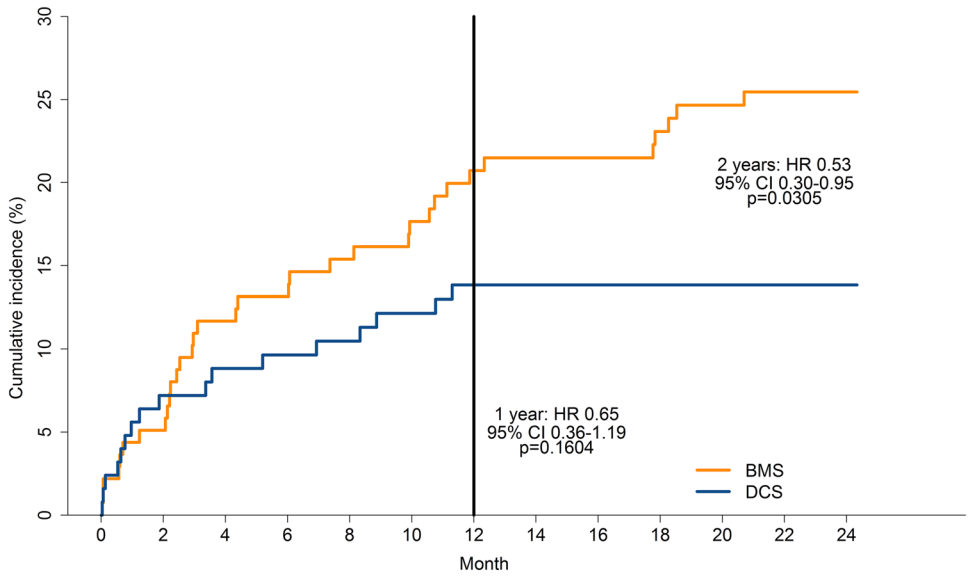

Fig. 4 Primary safety endpoint (cardiac death, myocardial infarction and definite/probable stent thrombosis)—insulin-dependent diabetic patients ($N=262$)

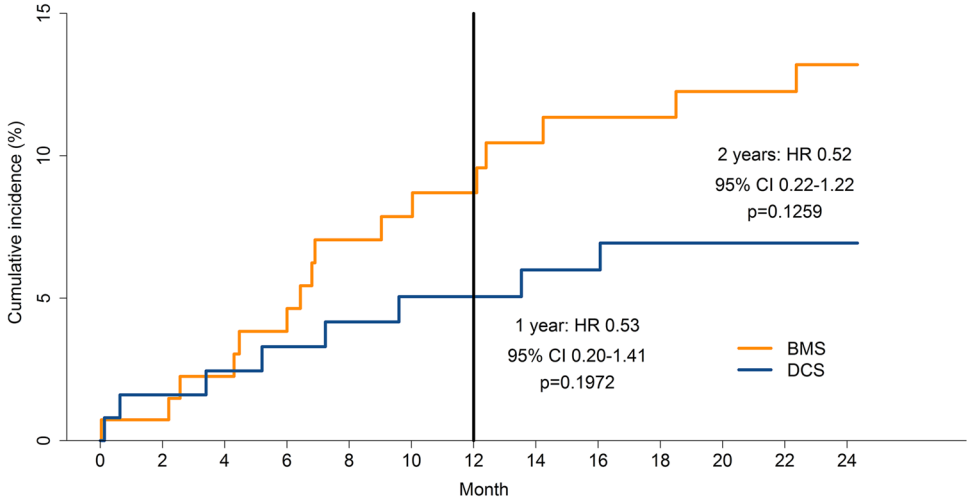

Fig. 5 Primary efficacy endpoint (clinically indicated target lesion revascularization)—insulin-dependent diabetic patients ($N=262$)

finding of the present pre-specified subgroup analysis is that the DCS shows similar benefits in diabetic patients at HBR.

Diabetic patients

Diabetic patients accounted for nearly one-third of the LEADERS FREE population [7]. The HBR diabetes subgroup of LEADERS FREE is different from diabetes subgroups in other studies, which often excluded HBR patients. Typically, the proportion of diabetic patients is lower, and the diabetes subgroups are on average older and more often female compared to the corresponding non-diabetic populations [9].

Whether DM by itself affects the outcome after coronary revascularization or whether it is the associated complex anatomy, mode of clinical presentation, and co-morbidities that are the major determinants remains a matter of debate [9, 10]. Interestingly, in LEADERS FREE, diabetes was a significant predictor for the primary safety endpoint in the univariate analysis (hazard ratio: 1.44 p-value = 0.001), while in the multivariate model the p-value for diabetes was no longer significant [8].

Efficacy of the DCS in diabetes

In the DM subgroup of the LEADERS FREE trial, DCS treatment led to significantly less clinically driven target lesion re-interventions than BMS treatment. The DCS transfers Biolimus A9 into the vessel wall over a period of 1 month. This is in contrast to the majority of currently available DES using a polymer, which generally releases the drug over a substantially longer period. Since patients with diabetes have higher levels of underlying vascular inflammation, concern was expressed that a short exposition to an

anti-proliferative agent could be insufficient. The clinical data gathered in diabetic patients at HBR suggest, however, that this is not the case in this population, and the presence of diabetes did not interact with the treatment effect of DCS. A possible explanation may be derived from the unique property of Biolimus-A9: owing to its high lipophilicity, drug residence in the vessel wall is prolonged compared to other sirolimus analogues. In consequence, despite complete drug transfer within a month, the anti-proliferative effect is sustained over a longer period of time [11].

PCI, as well as CABG studies, have generally reported an increased need for repeat revascularizations in the subgroups of patients with diabetes, some of which can be ascribed to the complexity of the coronary anatomy, i.e. longer lesions, smaller reference diameter, poor run-off, more calcifications, etc. [9, 10]. In the present series, it appears from the site-reported lesion characteristics that some degree of patient selection may have occurred, since the treated lesions were of relatively large diameter (3.0 mm) and short length (15 mm), and were not significantly different from non-diabetic patients. Kedhi et al. previously showed that TLR and TVR within 1 year following PCI with DES were more frequent in diabetic than in non-diabetic patients, but only in complex target lesions, without differences when simple lesions were treated [12].

Safety of DCS in diabetes

For diabetic patients at HBR, treatment with the DCS vs. BMS was associated with a non-significant trend towards a safety benefit. This finding is reassuring, since diabetes is a known risk factor for stent thrombosis and the potential risks of a 1-month DAPT strategy with an active stent were undetermined at the time when the LEADERS FREE trial was designed [13]. While the occurrence of ST was nearly identical for DCS and BMS, the unadjusted definite and/or probable stent thrombosis rate was nearly doubled in diabetic vs. non-diabetic patients, when both stents were considered together. Regarding the other components of the safety endpoint, cardiac death and myocardial infarction were numerically lower with DCB implantation. Because routine angiography was not systematically performed, it is likely that many of the myocardial infarctions adjudicated as "spontaneous" were in fact related to restenosis.

DCS implantation was associated with a significant reduction of the primary safety endpoint in IDDM. It has been questioned whether DES can provide more than a symptomatic improvement compared to BMS treatment in coronary artery disease [14, 15]. In the overall LEADERS FREE trial, however, the rate of myocardial infarction was reduced by DCS [7, 8]. We assume that this is due to the high-risk population in the trial, since high-bleeding risk patients are also at a high risk for ischemic events. The contention that the benefit of the DCS increases with the patient risk is substantiated by a significant reduction of the primary safety endpoint in the small subgroup of diabetics depending on insulin.

Limitations

Although diabetic patients were a predefined subgroup, the trial was neither designed nor powered to detect differences between patients with and without diabetes, and there was no sub-randomization for diabetic patients. Moreover, we have no information about the quality of glucose control such as fasting glucose or HbA1C levels, as well as the detailed anti-diabetic background medication, which might influence the outcome [16]. Consequently, our encouraging results should only be regarded as hypothesis generating.

Conclusions

In diabetic patients at HBR, treatment with DCS significantly reduced clinically driven target lesion revascularizations and showed a strong trend towards a safety benefit compared to BMS treatment.

Given the lack of available data for current-generation DES with abbreviated DAPT regimens in diabetic patients at HBR, DCS should currently be considered as the device with the strongest clinical evidence to support its use in this complex group of patients.

Compliance with ethical standards

Conflict of interest M.-C. Morice is the chief executive officer and a shareholder of the Cardiovascular European Research Center (CERC). S. Copt and H.-P. Stoll are full-time employees of the sponsor company (Biosensors). P. Urban is a consultant to Biosensors and has received honoraria from Terumo, Sinomed, Astra-Zeneca, and Edwards Lifesciences during the past 12 months. All other authors have no conflict of interest to disclose.

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