Impact of Insulin-Treated and Noninsulin-Treated Diabetes Mellitus in All-Comer Patients Undergoing Percutaneous Coronary Interventions With Polymer-Free Biolimus-Eluting Stent (from the RUDI-FREE Registry)

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Patients with diabetes mellitus (DM) have worse outcomes after percutaneous coronary intervention (PCI). Recent evidences suggest a differential impact of insulin-treated and noninsulin-treated DM on prognosis. We evaluated the clinical outcome of diabetic patients after PCI with polymer-free biolimus-eluting stent from the RUDI-FREE Registry, investigating a possible different prognostic impact of insulin-treated and noninsulin-treated DM. A total of 1,104 consecutive patients who underwent PCI with polymer-free biolimus-eluting stent, enrolled in the RUDI-FREE observational, multicenter, single-arm registry, were stratified by diabetic status; diabetic population was further divided on the basis of insulin treatment. Primary end points of the study were target lesion failure (TLF; composite of cardiac death, target vessel myocardial infarction, target lesion revascularization) and major adverse cardiac and cerebrovascular events (composite of cardiac death, stroke, and myocardial infarction). Multiple ischemic adverse events were also single-handedly considered as secondary end points. At 1 year, TLF was significantly higher in the diabetic cohort, as compared with nondiabetic patients (6.0% vs 3.1%, p 0.022). None of the end points resulted significantly different between nondiabetics and noninsulin-treated diabetic patients. Divergently, compared with nondiabetic, insulin-treated diabetic patients faced significant higher rates of TLF (10.8% vs 3.1%, p 0.003), major adverse cardiac and cerebrovascular events (10.8% vs 3.4%, p 0.004), and of most of the analyzed adverse events. In conclusion, patients with DM had a higher risk of TLF compared with nondiabetics; nonetheless, the worse outcome of the diabetic population seems to be driven by the insulin-treated diabetic subpopulation. This finding suggests a different risk profile of insulin-treated and noninsulin-treated diabetic patients in the modern era of PCI. **(Am J Cardiol 2019;124:1518−1527)**

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Patients with diabetes mellitus (DM), as compared with nondiabetics, are at higher risk of developing cardiovascular events and present worse outcomes after percutaneous coronary interventions (PCI) for obstructive coronary artery disease (CAD).[1−3] Over the last years, the upgrading of implanted devices, from bare-metal stents (BMS) to first- and second-generation drug-eluting stents (DES), has driven an absolute improvement of post-PCI outcome; nevertheless DM remains an independent predictor of unfavorable clinical events.[4−9] Furthermore, recent evidences suggest a differential prognostic impact of insulin-treated and noninsulin-treated DM on both stent-related and patient-related adverse events.[3,10,11] This finding is anyway controversial, and the influence of insulin-treatment on diabetic patients' prognosis in the contemporary DES era is uncertain.[12,13] The polymer-free biolimus-eluting stent

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(PF-BES) is a very last generation DES thought for high bleeding risk patients not compliant with long-term dual antiplatelet therapy (DAPT). Devoid of a polymeric carrier, the PF-BES elutes the antirestenotic agent over a period of approximately 1 month. In the LEADERS FREE study, PF-BES showed to be safer and more effective than BMS in high bleeding risk patients treated with short DAPT.[14] In the large observational, multicenter, prospective, single-arm "PolymeR free biolimUs eluting stent implantation in all-comers population: analysis of DAPT cessation and clinical outcome after BioFREEdom stent implantation" (RUDI-FREE) study, PF-BES has demonstrated a favorable safety and efficacy profile in a cohort of real-world patients.[15] In this study, we sought to evaluate the clinical outcomes of diabetic patients from the RUDI-FREE Registry and to investigate if prognosis differs between the insulin-treated and noninsulin-treated diabetic subpopulations.

Methods

From January 2015 to May 2016, consecutive patients with CAD who underwent PCI with PF-BES implantation at 16 Italian centers were included in the RUDI-FREE observational, multicenter, prospective, single-arm study (ClinicalTrials.gov identifier: NCT02858739). A detailed study protocol was provided in the main publication.[15] Briefly, patients were eligible for enrolment if they were 18 years or older, had chronic stable CAD or acute coronary syndrome, and had ≥1 coronary lesion with diameter stenosis >50% and a reference vessel diameter of 2.25 to 3.5 mm. If multiple lesions were treated, the allocated study stent was used in all lesions. No limits were set for the number of treated lesions and vessels or lesions length, and no patients were excluded on the basis of co-morbid conditions or age, with exception for the following prespecified exclusion criteria: intolerance to any of the device components, in-stent restenosis as indication to PCI, and women with childbearing potential. All interventions were performed according to the standard clinical guidelines at the moment of enrollment. DAPT regimen was prescribed on the basis of patients' clinical presentation and treating physicians' preference; minimal recommended DAPT duration was 1 month. Use of GP IIb/IIIa receptor inhibitors was at the operators' discretion. The study protocol was approved by the ethics committee at each participating center and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent.

DM was defined as either known history of DM treated with pharmacological or nonpharmacological measures, or as a newly diagnosed DM according to the American Diabetes Association definition.[16] Diabetic patients were classified as "insulin-treated" if they were taking insulin, or "noninsulin-treated" if treated with oral hypoglycemic agents and/or therapeutic lifestyle modifications. Chronic kidney disease (CKD) was defined as an estimated Glomerular Filtration Rate <60 ml/min calculated by means of the Cockcroft-Gault formula; for estimated Glomerular Filtration Rate <30 ml/min CKD was defined severe. Complex PCI was defined as a procedure with at least 1 of the following angiographic characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with deployment of 2 stents, total stent length >60 mm, chronic total occlusion.[17]

The primary end points of the study were target lesion failure (TLF), defined as a composite of cardiac death, target vessel acute myocardial infarction (TV-AMI), and clinically indicated target lesion revascularization (TLR); major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of cardiac death, stroke, any AMI. The secondary end points were the RUDI-FREE primary end point, defined as a composite of cardiac death, AMI, and definite or probable stent thrombosis (ST); all-cause death, intended as cardiac and noncardiac death; AMI as a whole, TV-AMI, non−TV-AMI, and periprocedural AMI, all assessed according to the Fourth Universal Definition of Myocardial Infarction[18]; cerebrovascular events, intended as stroke and transient ischemic attack; any myocardial revascularization; TLR, defined as any repeated revascularization procedure (either percutaneous or surgical) performed on the target lesion; target vessel revascularization (TVR), defined as any repeated revascularization procedure (either percutaneous or surgical) performed on the target vessel; non-TVR, defined as any myocardial revascularization in other coronary vessels different from the target vessel; definite or probable ST, according to the Academic Research Consortium definition.[19,20]

The study model is observational prospective on historical cohort. The data were analyzed by STATA MP15 software (StataCorp LLC, College Station, Texas). Continuous variables were described as means ± standard deviations, categorical variables as proportions. The Skewness and Kurtosis test was used to evaluate the distribution of continuous variables and for not normally distributed variables a normalization model was set, when possible. The Student's *t* test for independent data (parametric) and the Wilcoxon's rank-sum test (not parametric) were used to compare continuous variables between diabetic and nondiabetic patients. The Kruskal-Wallis test (not parametric) was used to compare continuous variables among nondiabetic, insulin-treated diabetic patients, and noninsulin-treated diabetic patients; the Dunn test for multiple comparison with Bonferroni correction was used to compare single groups. The chi-square and exact Fisher tests were used to compare the proportions among groups.

The MACCE-free survival was evaluated as the time elapsed from the enrollment to the onset of the outcome or from the enrollment to the end of the study. The Kaplan-Meier curve was used to evaluate the MACCE-free survival and the log-rank test was used to evaluate the differences between groups (nondiabetic patients, insulin-treated and noninsulin-treated diabetic patients; Figure 1). The TLF-free survival was evaluated as the time elapsed from the enrollment to the onset of the outcomes or from the enrollment to the end of the study. To evaluate the determinants of the TLF-free survival, the univariate Cox semiparametric regression was used, considering as risk predictors other clinical, angiographic or procedural features; the hazard ratio was calculated, with the indication of 95% confidence interval. For the previous outcome, multivariate Cox semiparametric regression model was built, using as risk predictors the determinants associated in the univariate regression; the hazard ratios were calculated, with the

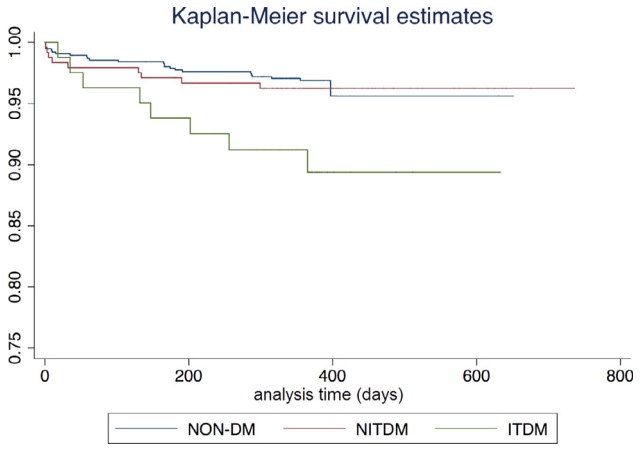

Figure 1. Kaplan-Meier MACCE-free survival* estimates in nondiabetic patients and diabetic patients divided according insulin treatment. Log-rank test = 9.3; p = 0.010.

*The MACCE-free survival was evaluated as the time elapsed from the enrollment to the onset of the outcome or from the enrollment to the end of the study. MACCE was defined as a composite of cardiac death, stroke, myocardial infarction.

ITDM = insulin-treated diabetes mellitus patients; MACCE = major adverse cardiac and cerebrovascular events; NITDM = noninsulin-treated diabetes mellitus patients; NON-DM = nondiabetes mellitus patients.

indication of 95% confidence interval. The Schoenfeld and scaled Schoenfeld residuals test was used to evaluate the proportionality assumption of the multivariate Cox semi-parametric regression models and the Gronnesby and Borgan test was used to evaluate the goodness of fit of the models. In addition, a survey Cox model was used as sensitivity analysis to account for patient multiplicity (i.e., the occurrence of multiple stents being implanted and lesions or vessels being treated in the same patient).

For all tests, a p value <0.05 was considered statistically significant.

Results

From January 2015 to June 2016, a total of 1,104 patients consecutively who underwent PCI with PF-BES in routine clinical practice were included at 16 Italian centers. The whole population was stratified by diabetic status into 773 nondiabetic (70.0%) and 331 diabetic (30.0%) patients. Diabetic population was further divided on the basis of the therapy in 83 insulin-treated (7.5%) and 248 noninsulin-treated diabetic patients (22.5%).

Baseline clinical, angiographic, and procedural characteristics of the population, taken as a whole and divided according to the presence or absence of DM and according to the insulin treatment are outlined in Tables 1 and 2. In summary, as compared with nondiabetic, diabetic patients were older, more often hypertensive, more often presented previous AMI, CKD, and lower left-ventricle ejection fraction at hospital admission. Most of these baseline differences were driven by the insulin-treated diabetic patients. Indeed, compared with nondiabetic patients, the insulin-treated diabetic patients presented a worse risk profile by reason of several parameters such as age, previous AMI, previous myocardial revascularization, peripheral artery disease, CKD, left-ventricle ejection fraction, and bleeding risk.

A total of 1,667 lesions, an average of 1.6 lesions per patient, were treated; in 54.6% of the patients a lesion located in the left anterior descending artery was treated. The complexity of the coronary arteries disease can be inferred by the following angiographic data: 64.1% of the whole population presented with type B2/C lesions according to the ACC/AHA classification, 46.5% with long lesions (≥20 mm), 15.4% with chronic total occlusion, and 12.1% with severely calcified stenoses. As regards procedural features, among diabetic patients reference vessel diameter was slightly smaller and severe calcifications were more frequent; a larger quote of bifurcations treated with 2 stents was observed only in the insulin-treated diabetic subpopulation. Conversely, no differences in terms of angiographic and procedural characteristics were detected between the nondiabetic and noninsulin-treated diabetic patients.

Medical therapy at discharge and at 1 year is summarized in Supplementary Table I. At discharge the recommended DAPT duration was similar in the nondiabetic and diabetic patients and, at 1 year, DAPT was ongoing in the 72.6% of the whole population with no differences related to the diabetic status.

Twelve-month follow-up was completed in 97.2% of patients, with a mean follow-up of 346 ± 29 days. Adverse clinical events during the follow-up period of the whole population and according to the DM status are shown in Table 3. The rate of TLF, 1 of the 2 primary end points, was significantly higher in the diabetic cohort, as compared with nondiabetic patients (6.0% vs 3.1%, p 0.022), as it was the rate of non−TV-AMI (1.2% vs 0.1%, p 0.030). In contrast, rates of MACCE, all-cause death, cardiac death, cerebrovascular events, any AMI, TV-AMI, TVR, and TLR were not significantly different. The incidence of definite or probable ST at 1 year was low and similar between the diabetic and nondiabetic patients (1.8% vs 0.8%, p 0.200).

As shown in Table 4, when the diabetic subpopulation was divided on the basis of the insulin treatment a stepwise increasing incidence of adverse clinical events was evident from the nondiabetic, through the noninsulin-treated diabetic, to the insulin-treated diabetic cohort. No significant differences were, in fact, found in any of the clinical end points between the nondiabetic and noninsulin-treated diabetic patients. Divergently, compared with nondiabetic, insulin-treated diabetic patients faced significant higher rates of TLF (10.8% vs 3.1%, p 0.003), MACCE (10.8% vs 3.4%, p 0.004), all-cause death, cardiac death, any AMI, non−TV-AMI, any revascularization. Conversely, definite or probable ST was low also in the insulin-treated diabetic patients and no threshold for significance was reached in the comparison with nondiabetic patients (1.2% vs 0.8%, p 0.512).

At univariate Cox semiparametric regression analysis, age, insulin-providing medications, severe CKD, and total stent length resulted predictors of TLF (Supplementary Table II). Using as risk predictors the determinants associated in the univariate regression, at multivariate Cox semi-parametric regression model only age and insulin-treated DM resulted predictors of TLF. These findings were confirmed at sensitivity analysis based on survey Cox

Table 1
Baseline clinical, angiographic, and procedural characteristics in diabetic and nondiabetic patients

Variable	Overall (n = 1,104)	Diabetes mellitus		p
		Yes (n = 331)	No (n = 773)	
Baseline characteristics				
Age (years)	68.7 ± 11.2	70.2 ± 10.0	68.1 ± 11.6	0.012
Men	853 (77.3%)	249 (75.2%)	604 (78.1%)	0.290
Hypertension	884 (80.1%)	286 (86.4%)	598 (77.4%)	0.001
Dyslipidemia	676 (61.2%)	206 (62.2%)	470 (60.8%)	0.736
Current smoker	492 (44.6%)	124 (37.5%)	368 (47.6%)	0.002
Family history of coronary artery disease	249 (22.6%)	75 (22.7%)	174 (22.5%)	0.651
Prior myocardial infarction	251 (22.7%)	89 (26.9%)	162 (21.0%)	0.033
Prior percutaneous coronary intervention	286 (25.9%)	97 (29.3%)	189 (24.5%)	0.096
Prior coronary bypass	74 (6.7%)	27 (8.2%)	47 (6.1%)	0.210
Prior stroke	33 (3.0%)	11 (3.3%)	22 (2.9%)	0.675
Left ventricular ejection fraction (%)	49.7 ± 10.8	48.1 ± 11.6	50.4 ± 10.4	<0.001
Severe left ventricular dysfunction (left ventricular ejection fraction <30%)	40 (3.6%)	15 (4.5%)	25 (3.2%)	0.290
High bleeding risk*	164 (14.9%)	59 (17. 8%)	105 (13.6%)	0.069
CRUSADE score	24.1 ± 13.1	25.6 ± 13.7	23.4 ± 12.8	0.010
Peripheral artery disease	97 (8.8%)	37 (11.2%)	60 (7.8%)	0.068
Carotid artery disease	63 (5.7%)	25 (7.6%)	38 (4.9%)	0.085
Chronic kidney disease	168 (15.2%)	69 (20.9%)	99 (12.8%)	0.001
Creatinine (mg/dl)	1.1± 0.7	1.2 ± 0.8	1.1± 0.7	0.136
eGFR (ml/min/1.73 m^2)	73.3 ± 24.6	71.1 ± 27.7	74.3 ± 23.2	0.027
Severe chronic kidney disease	50 (4.5%)	24 (7.3%)	26 (3.4%)	0.004
Chronic obstructive pulmonary disease	29 (2.6%)	9 (2.7%)	20 (2.6%)	0.898
Stable angina pectoris	514 (46.6%)	155 (46.8%)	359 (46.4%)	0.921
Silent ischemia	86 (7.8%)	26 (7.9%)	60 (7.8%)	0.962
Atypical symptoms	57 (5.1%)	16 (4.8%)	41 (5.2%)	0.810
Acute coronary syndrome presentation	447 (40.5%)	134 (40.5%)	313 (40.5%)	0.985
Unstable angina	136 (12.3%)	44 (13.3%)	92 (11.9%)	0.524
Non ST-elevation myocardial infarction	165 (15.0%)	53 (16.0%)	112 (14.5%)	0.521
ST-elevation myocardial infarction	146 (13.2%)	37 (11.2%)	109 (14.1%)	0.187
Angiographic and procedural characteristics				
Number of narrowings/pt	1.6 ± 0.9	1.6 ± 1.0	1.5 ± 0.9	0.280
Left main	45 (4.1%)	16 (4.8%)	29 (3.8%)	0.405
Left anterior descending	603 (54.6%)	175 (52.9%)	428 (55.4%)	0.445
Left circumflex	391 (35.4%)	122 (36.9%)	269 (34.8%)	0.512
Right	366 (33.2%)	119 (36.0%)	247 (32.0%)	0.196
Saphenous vein graft	20 (1.8%)	8 (2.4%)	12 (1.6%)	0.324
Bifurcations	237 (21.5%)	67 (20.2%)	170 (22.0%)	0.516
Tortuous lesions	21 (1.9%)	4 (1.2%)	17 (2.2%)	0.270
Long lesions (>20 mm)	513 (46.5%)	154 (46.5%)	359 (46.4%)	0.980
Calcified lesions	134 (12.1%)	52 (15.7%)	82 (10.6%)	0.017
B2/C lesions†	708 (64.1%)	209 (63.1%)	499 (64.6%)	0.654
Multilesion percutaneous coronary intervention	378 (34.2%)	120 (36.3%)	258 (33.4%)	0.356
Multivessel percutaneous coronary intervention	284 (25.7%)	91 (27.5%)	193 (25.0%)	0.379
Number of stents/pt	2.1 ± 2. 2	2.1 ± 2. 2	2.1 ± 2.2	0.758
Total stent length/pt (mm)	39.1 ± 32.8	40.8 ± 34.0	38.4 ± 32.4	0.285
Medium stent diameter (mm)	3.0 ± 0.4	2.9 ± 0.4	3.0 ± 0.4	0.002
Fractional flow reserve use	34 (3.1%)	12 (3.6%)	22 (2.9%)	0.492
Rotablator use	44 (4.0%)	18 (5.4%)	26 (3.4%)	0.106
Predilation	337 (30. 5%)	104 (31.4%)	233 (30.1%)	0.673
Postdilation	307 (27.8%)	92 (27.8%)	215 (27.8%)	0.995
Overlapping	234 (21.2%)	70 (21.2%)	164 (21.2%)	0.980
Complex percutaneous coronary intervention‡	299 (27.1%)	94 (28.4%)	205 (26.5%)	0.520
3 vessels percutaneous coronary intervention	72 (6.5%)	27 (8.2%)	45 (5.8%)	0.151
≥3 narrowings treated	51 (4.6%)	13 (3.9%)	38 (4.9%)	0.473
≥3 stents implanted	86 (7.8%)	24 (7.3%)	62 (8.0%)	0.662
≥60 mm total stent length	60 (5.4%)	18 (5.4%)	42 (5.4%)	0.997
Any chronic total occlusion lesion	170 (15.4%)	59 (17.8%)	111 (14. 4%)	0.144
Bifurcations treated with 2 stents	29 (2.6%)	9 (2.7%)	20 (2.6%)	0.900

* CRUSADE score >40.

† ACC/AHA (American College of Cardiology/American Heart Association) classification of coronary lesions.

‡ Complex percutaneous coronary intervention was defined as a procedure with at least one of the following angiographic characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with deployment of 2 stents, total stent length ≥60 mm, any chronic total occlusion lesion.

Table 2
Baseline clinical, angiographic, and procedural characteristics in nondiabetic patients and diabetic patients divided according insulin treatment

	NON-DM (n = 773)	NITDM (n = 248)	ITDM (n = 83)	NITDM vs ITDM vs NON-DM p*	NITDM vs ITDM p**	NITDM vs NON-DM p***	ITDM vs NON-DM p****
Baseline characteristics							
Age (years)	68.1 ± 11.6	69.2 ± 10.0	73.01 ± 9.7	0.001	0.013	0.392	0.001
Men	604 (78.1%)	188 (75.8%)	61 (73.5%)	0.520	0.673	0.444	0.334
Hypertension	598 (77.4%)	216 (87.1%)	70 (84.3%)	0.003	0.525	0.001	0.155
Dyslipidemia	470 (60.8%)	157 (63.3%)	49 (59.0%)	0.727	0.487	0.509	0.733
Current smoker	368 (47.6%)	97 (39.1%)	27 (32.5%)	0.019	0.284	0.018	0.008
Family history of coronary artery disease	174 (22.5%)	54 (21.8%)	21 (25.3%)	0.801	0.506	0.794	0.573
Prior myocardial infarction	162 (21.0%)	60 (24.2%)	29 (34.9%)	0.013	0.056	0.291	0.004
Prior percutaneous coronary intervention	189 (24.5%)	68 (27.4%)	29 (34.9%)	0.100	0.193	0.359	0.038
Prior coronary bypass	47 (6.1%)	14 (5.7%)	13 (15.7%)	0.003	0.004	0.795	0.001
Prior stroke	22 (2.9%)	7 (2.8%)	4 (4.8%)	0.598	0.477	0.980	0.308
Left ventricular ejection fraction (%)	50.4 ± 10.4	48.3 ± 11.6	47.5 ± 11.6	0.000	0.235	0.003	0.001
Severe left ventricular dysfunction (left ventricular ejection fraction <30%)	25 (3.2%)	11 (4.4%)	4 (4.8%)	0.488	1.000	0.372	0.516
High bleeding risk*	105 (13.6%)	37 (14.9%)	22 (26.5%)	0.007	0.017	0.597	0.002
CRUSADE score	23.4 ± 12.8	24.2 ± 13.3	29.7 ± 14.1	0.000	0.004	0.458	<0.001
Peripheral Artery Disease	60 (7.8%)	25 (10.1%)	12 (14.5%)	0.090	0.273	0.255	0.038
Carotid artery disease	38 (4.9%)	20 (8.1%)	5 (6.0%)	0.180	0.543	0.064	0.599
Chronic kidney disease	99 (12.8%)	41 (16.5%)	28 (33.7%)	0.000	0.001	0.142	<0.001
Creatinine (mg/dl)	1.1± 0.7	1.1 ± 0.5	1.4 ± 1.3	0.004	0.005	1.000	0.002
eGFR (ml/min/1.73 m^2)	74.3 ± 23.2	74.2 ± 27.1	61.5 ± 27.4	0.000	0.001	0.977	<0.001
Severe chronic kidney disease	26 (3.4%)	12 (4.8%)	12 (14.5%)	0.000	0.003	0.286	<0.001
Chronic obstructive pulmonary disease	20 (2.6%)	8 (3.2%)	1 (1.2%)	0.699	0.458	0.587	0.712
Stable angina pectoris	359 (46.4%)	119 (48.0%)	36 (43.4%)	0.763	0.466	0.684	0.587
Silent ischemia	60 (7.8%)	20 (8.1%)	6 (72.3%)	0.969	0.807	0.882	0.860
Atypical symptoms	41 (5.2%)	11 (4.4%)	5 (6.0%)	0.781	0.560	0.639	0.794
Acute coronary syndrome presentation	313 (40.5%)	98 (39.5%)	36 (43.4%)	0.825	0.535	0.774	0.618
Unstable angina	92 (11.9%)	34 (13.7%)	10 (12.1%)	0.754	0.700	0.455	0.972
Non ST-elevation myocardial infarction	112 (14.5%)	35 (14.1%)	18 (21.7%)	0.200	0.103	0.878	0.083
ST-elevation myocardial infarction	109 (14.1%)	29 (11.7%)	8 (9.6%)	0.373	0.607	0.331	0.259
Angiographic and procedural characteristics							
Number of narrowings/pt	1.5 ± 0.9	1.6 ± 0.9	1.7 ± 1.0	0.620	1.000	0.630	0.527
Left main	29 (3.8%)	9 (3.6%)	7 (8.4%)	0.144	0.134	0.929	0.074
Left anterior descending	428 (55.4%)	138 (55.7%)	37 (44.6%)	0.161	0.080	0.939	0.061
Left circumflex	269 (34.8%)	88 (35.5%)	34 (41.0%)	0.536	0.370	0.844	0.264
Right	247 (32.0%)	91 (36.7%)	28 (33.7%)	0.383	0.627	0.168	0.741
Saphenous vein graft	12 (1.6%)	5 (2.0%)	3 (3.6%)	0.269	0.419	0.577	0.171
Bifurcations	170 (22.0%)	49 (19.8%)	18 (21.7%)	0.756	0.705	0.456	0.949
Tortuous lesions	17 (2.2%)	3 (1.2%)	1 (1.2%)	0.701	1.000	0.435	1.000
Long lesions (>20 mm)	359 (46.4%)	119 (48.0%)	35 (42.2%)	0.655	0.358	0.672	0.458
Calcified lesions	82 (10.6%)	33 (13.3%)	19 (22.9%)	0.004	0.038	0.242	0.001
B2/C lesions†	499 (64.6%)	156 (62.9%)	53 (63.9%)	0.893	0.876	0.637	0.899

(*continued on next page*)

Table 2 (***Continued***)

	NON-DM (n = 773)	NITDM (n = 248)	ITDM (n = 83)	NITDM vs ITDM vs NON-DM p*	NITDM vs ITDM p**	NITDM vs NON-DM p***	ITDM vs NON-DM p****
Multilesion percutaneous coronary intervention	258 (33.4%)	90 (36.3%)	30 (36.1%)	0.653	0.981	0.400	0.612
Multivessel percutaneous coronary intervention	193 (25.0%)	69 (27.8%)	22 (26.5%)	0.660	0.816	0.370	0.759
Number of stents/pt	2.1 ± 2.2	2.0 ± 2.3	2.3 ± 2.3	0.429	0.255	0.580	0.501
Total stent lenght/pt (mm)	38.4 ± 32.4	40.3 ± 34.2	42.6 ± 33.7	0.423	0.668	0.791	0.327
Medium stent diameter (mm)	3.0 ± 0.4	2.9 ± 0.4	2.8 ± 0.4	0.001	0.042	0.107	0.001
Fractional flow reserve use	22 (2.9%)	9 (3.6%)	3 (3.6%)	0.703	1.000	0.532	0.727
Rotablator use	26 (3.4%)	14 (5.7%)	4 (4.8%)	0.227	1.000	0.107	0.523
Predilation	233 (30.1%)	77 (31.1%)	27 (32.5%)	0.886	0.801	0.787	0.653
Postdilation	215 (27.8%)	65 (26.2%)	27 (32.5%)	0.539	0.266	0.622	0.365
Overlapping	164 (21.2%)	51 (20.6%)	19 (22.9%)	0.904	0.653	0.827	0.723
Complex percutaneous coronary intervention [‡]	205 (26.5%)	66 (26.6%)	28 (33.7%)	0.366	0.213	0.977	0.161
3 vessels percutaneous coronary intervention	45 (5.8%)	19 (7.7%)	8 (9.6%)	0.293	0.569	0.301	0.171
≥3 narrowings treated	38 (4.9%)	9 (3.6%)	4 (4.8%)	0.764	0.744	0.400	1.000
≥3 stents implanted	62 (8.0%)	19 (7.7%)	5 (6.0%)	0.809	0.619	0.855	0.520
≥60 mm total stent length	42 (5.4%)	12 (4.8%)	6 (7.2%)	0.662	0.408	0.716	0.454
Any chronic total occlusion lesion	111 (14.4%)	42 (16.9%)	17 (20.5%)	0.255	0.465	0.323	0.137
Bifurcations treated with 2 stents	20 (2.6%)	3 (1.2%)	6 (7.2%)	0.022	0.009	0.203	0.033

* CRUSADE score >40.

[†] ACC/AHA (American College of Cardiology/American Heart Association) classification of coronary lesions.

[‡] Complex percutaneous coronary intervention was defined as a procedure with at least one of the following angiographic characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with deployment of 2 stents, total stent length ≥60 mm, any chronic total occlusion lesion.

DM = diabetes mellitus patients; ITDM = insulin-treated diabetes mellitus patients; NON-DM = nondiabetes mellitus patients; NITDM = noninsulin-treated diabetes mellitus patients

p* = p value between NITDM, ITDM and NON-DM.

p** = p value between NITDM e ITDM.

p*** = p value between NITDM e NON-DM.

p**** = p value between ITDM e NON-DM.

Table 3
Clinical outcomes at one year follow-up in diabetic and nondiabetic patients

	Overall (n = 1,104)	Diabetes mellitus		*P*
		Yes (n = 331)	No (n = 773)	
Target lesion failure*	44 (4.0%)	20 (6.0%)	24 (3.1%)	0.022
Major adverse cardiac and cerebrovascular events†	44 (4.0%)	18 (5.4%)	26 (3.4%)	0.106
RUDI-FREE primary end point‡	45 (4.1%)	19 (5.7%)	26 (3.4%)	0.067
All-cause death	43 (3.9%)	16 (4.8%)	27 (3.5%)	0.291
Cardiac death	26 (2.4%)	10 (3.0%)	16 (2.1%)	0.340
Noncardiac death	17 (1.5%)	6 (1.8%)	11 (1.4%)	0.630
Any myocardial infarction	22 (2.0%)	10 (3.0%)	12 (1.6%)	0.110
Target vessel-myocardial infarction	11 (1.0%)	5 (1.5%)	6 (0.8%)	0.321
Nontarget vessel-myocardial infarction	5 (0.5%)	4 (1.2%)	1 (0.1%)	0.030
Periprocedural myocardial infarction	6 (0.5%)	1 (0.3%)	5 (0.7%)	0.675
Cerebrovascular events	5 (0.5%)	3 (0.9%)	2 (0.3%)	0.162
Stroke	3 (0.3%)	1 (0.3%)	2 (0.3%)	1.000
Transient ischemic attack	2 (0.2%)	2 (0.6%)	0 (0.0%)	0.090
Any revascularization	24 (2.2%)	11 (3.3%)	13 (1.7%)	0.113
Target lesion revascularization	15 (1.4%)	8 (2.4%)	7 (0.9%)	0.083
Target vessel revascularization	20 (1.8%)	9 (2.7%)	11 (1.4%)	0.139
Nontarget vessel revascularization	4 (0.4%)	2 (0.6%)	2 (0.3%)	0.588
Definite or probable stent thrombosis	12 (1.1%)	6 (1.8%)	6 (0.8%)	0.200
Definite stent thrombosis	4 (0.4%)	1 (0.3%)	3 (0.4%)	1.000
Probable stent thrombosis	8 (0.7%)	5 (1.5%)	3 (0.4%)	0.057
BARC ≥3 bleeding§	13 (1.2%)	4 (1.2%)	9 (1.2%)	1.000

* Target lesion failure is defined as a composite of cardiac death, any myocardial infarction, target lesion revascularization.
† Major adverse cardiac and cerebrovascular events is defined as a composite of cardiac death, stroke, any myocardial infarction.
‡ RUDI-FREE primary end point is defined as a composite of cardiac death, myocardial infarction, definite or probable stent thrombosis.
§ BARC = Bleeding Academic Research Consortium classification of bleeding.

Table 4
Clinical outcomes at one year follow-up in nondiabetic patients and diabetic patients divided according insulin treatment

	NON-DM (n = 773)	NITDM (n = 248)	ITDM (n = 83)	NITDM vs ITDM vs NON-DM p*	NITDM vs ITDM p**	NITDM vs NON-DM p***	ITDM vs NON-DM p****
Target lesion failure*	24 (3.1%)	11 (4.4%)	9 (10.8%)	0.007	0.058	0.316	0.003
Major adverse cardiac and cerebrovascular events†	26 (3.4%)	9 (3.6%)	9 (10.8%)	0.011	0.022	0.842	0.004
RUDI-FREE primary end point ‡	26 (3.4%)	10 (4.0%)	9 (10.8%)	0.011	0.029	0.619	0.004
All-cause death	27 (3.5%)	9 (3.6%)	7 (8.4%)	0.110	0.134	0.919	0.039
Cardiac death	16 (2.1%)	5 (2.0%)	5 (6.0%)	0.089	0.129	0.959	0.044
Noncardiac death	11 (1.4%)	4 (1.6%)	2 (2.4%)	0.658	0.643	0.767	0.364
Any myocardial infarction	12 (1.6%)	5 (2.0%)	5 (6.0%)	0.036	0.129	0.577	0.018
Target vessel-myocardial infarction	6 (0.8%)	3 (1.2%)	2 (2.4%)	0.227	0.602	0.460	0.177
Nontarget vessel-myocardial infarction	1 (0.1%)	1 (0.4%)	3 (3.6%)	0.004	0.050	0.427	0.003
Periprocedural myocardial infarction	5 (0.7%)	1 (0.4%)	0 (0.0%)	1.000	1.000	1.000	1.000
Cerebrovascular events	2 (0.3%)	1 (0.4%)	2 (2.4%)	0.051	0.156	0.566	0.049
Stroke	2 (0.3%)	0 (0.0%)	1 (1.2%)	0.326	0.251	1.000	0.264
Transient ischemic attack	0 (0.0%)	1 (0.4%)	1 (1.2%)	0.039	0.439	0.243	0.097
Any revascularization	13 (1.7%)	5 (2.0%)	6 (7.2%)	0.014	0.032	0.782	0.007
Target lesion revascularization	7 (0.9%)	4 (1.6%)	4 (4.8%)	0.020	0.112	0.313	0.016
Target vessel revascularization	11 (1.4%)	5 (2.0%)	4 (4.8%)	0.077	0.236	0.557	0.049
Nontarget vessel revascularization	2 (0.3%)	0 (0.0%)	2 (2.4%)	0.036	0.062	1.000	0.049
Definite or probable stent thrombosis	6 (0.8%)	5 (2.0%)	1 (1.2%)	0.190	1.000	0.148	0.512
Definite stent thrombosis	3 (0.4%)	1 (0.4%)	0 (0.0%)	1.000	1.000	1.000	1.000
Probable stent thrombosis	3 (0.4%)	4 (1.6%)	1 (1.2%)	0.068	1.000	0.064	0.335
BARC ≥3 bleeding§	9 (1.2%)	2 (0.8%)	2 (2.4%)	0.440	0.262	1.000	0.290

* Target lesion failure is defined as a composite of cardiac death, any myocardial infarction, target lesion revascularization.
† Major adverse cardiac and cerebrovascular events is defined as a composite of cardiac death, stroke, any myocardial infarction.
‡ RUDI-FREE primary end point is defined as a composite of cardiac death, myocardial infarction, definite or probable stent thrombosis.
§ BARC = Bleeding Academic Research Consortium classification of bleeding.

DM = diabetes mellitus patients; ITDM = insulin-treated diabetes mellitus patients; NITDM = noninsulin-treated diabetes mellitus patients; NON-DM = nondiabetes mellitus patients.

p* = p value between NITDM, ITDM and NON-DM.

p** = p value between NITDM e ITDM.

p*** = p value between NITDM e NON-DM.

p**** = p value between ITDM e NON-DM.

modelling, highlighting the independent prognostic role of age and insulin treatment for TLF (Supplementary Table III).

Discussion

Aim of this analysis was to evaluate the safety and efficacy profile of the PF-BES in the diabetic subpopulation of the RUDI-FREE study, a large, real-world, observational, all-comers registry.

The main findings of the present study can be summarized as follows:

- diabetic patients as a whole showed a significantly higher risk of TLF compared with nondiabetic patients;
- stratifying the diabetic cohort according to insulin treatment, insulin-treated diabetic patients showed a significant higher occurrence of most of the adverse clinical events as compared with nondiabetics; moreover insulin-treated diabetic patients presented worse outcomes in terms of the RUDI-FREE primary end point, MACCE, non−TV-AMI, myocardial revascularization also when compared with noninsulin-treated diabetic patients;
- no significant differences were conversely detected between noninsulin-treated diabetic and nondiabetic patients in terms of any of the analyzed clinical outcomes;
- in regard to the definite or probable ST the incidence in the diabetic cohort resulted comparable to the nondiabetic subpopulation; this finding kept true also when the comparison was restricted to the insulin-treated diabetic patients.

The evidence that diabetic patients as a whole showed worse prognosis in terms of TLF compared with patients without DM was expected. Despite over the last years, the upgrade of devices from BMS to first- and second-generation DES has generated a stepwise absolute improvement in the outcome of patients who underwent PCI, at the same evolution stage DM has always represented an independent predictor of unfavorable clinical events.[4−8,21] Diabetic patients are more prone to repeated myocardial revascularization procedures, AMI, and death: adverse events that are expression of both the natural disease progression and stent failure, mainly in-stent restenosis.[4,8,9]

The main finding of our analysis is the differential prognostic impact of the 2 different forms of DM. The topic of the influence of insulin treatment on the outcome of diabetic patients who underwent PCI with DES appears relevant and still controversial. The literature in the field has traditionally considered diabetic status as whole with no distinction according to insulin therapy.[4] Some authors have supported the hypothesis that, when detected, worse clinical outcomes in insulin-treated diabetic patients can be nullified after risk adjustment, suggesting that concomitant risk factors, rather than insulin treatment, contribute to the increased risk.[13] Some recent reports are in agreement with our results. From the Global RESOLUTE Clinical Program, a significantly higher incidence of TLF emerged in the insulin-treated diabetic patients at 2 years from a zotarolimus-eluting stent implantation, whereas the prognosis of patients with noninsulin-treated DM was substantially equivalent to that of the nondiabetic population.[11] Tada et al also demonstrated a different outcome of insulin-treated and noninsulin-treated patients in terms of hard end points such as death, MI, and stroke.[22] The diabetes subanalysis of the FREEDOM trial evaluated the long-term clinical outcomes after myocardial revascularization (either percutaneous or surgical) in noninsulin-treated versus insulin-treated diabetic patients, documenting in the latter group worse outcomes.[23] Only few evidences on the outcome of diabetic patients who underwent PCI with last-generation DES are present in literature: Pi et al recently demonstrated, in a large cohort of diabetic patients treated with second-generation biocompatible and biodegradable polymer-coated DES taken together, an increased risk of cardiac death, any revascularization, and ST in the insulin-treated group.[24] Congruently, Konigstein et al confirmed a higher risk in the setting of insulin-treated DM in a subgroup analysis of the BIONICS randomized trial in which the effectiveness of the new generation ridaforolimus-eluting stent was tested.[3]

In accordance with the latest abovementioned findings, we documented that, when compared with nondiabetic patients, the insulin-treated cohort showed significant higher rates of most clinical outcomes including TLF, MACCE, all-cause death, cardiac death, any AMI, non−TV-AMI, cerebrovascular events, any revascularization, TLR, TVR, non-TVR. Moreover, for some of these end points the differences kept significant also between insulin-treated and noninsulin-treated diabetic patients. Two hypotheses can explain the association between insulin treatment and worse prognosis: insulin carries a direct adverse effect and/or is a mere innocent bystander marker of advanced and more aggressive diabetic disease. It is known that iatrogenic hyperinsulinemia may promote proinflammatory vascular state, neointimal tissue proliferation, augmented vulnerability of plaque, platelet dysfunction, resistance to antiplatelet agents, vascular smooth muscle cell proliferation.[25−27] At the same time, a role of ''high risk'' marker for insulin use cannot be ruled out. As widely reported in literature, an unequal distribution between the 2 different types of diabetes of cardiovascular risk factors and predictors of adverse outcome after PCI is evident also in the present analysis: insulin-treated patients were older and more frequently presented CKD and calcified lesions. The higher risk of insulin-treated patients is confirmed in our study by the augmented incidence of both “stent-related” and “patient-related” adverse events (i.e., non−TV-AMI and any myocardial revascularization), suggesting the importance of a careful secondary prevention and an integrated medical management of co-morbidities.

An additional key point is the absence of significant differences between the noninsulin-treated diabetic and nondiabetic subpopulations with reference to any of the analyzed clinical outcomes. The size and observational nature of the registry jeopardize reliability of this evidence. Nevertheless, it appears possible to hypothesize that, in the current era, careful PCI cases selection, more biocompatible and high-performance devices, more aggressive pharmacologic discharge therapies with “new” oral antiplatelet agents, and longer duration of DAPT, recently proved to be maximally beneficial especially in acute coronary syndrome setting,

might have together made the prognosis of noninsulin-treated diabetic patients approaching that of the nondiabetic population.[28] To this concern, some strengths of our study can licitly be recognized: firstly, the all-comers nature of the registry with no limitations related to either clinical presentation or lesions complexity, secondly the use in a relatively broad cohort of a single type of very last generation DES, and lastly the short enrollment time.

The newly introduced PF-BES differs in fact from other contemporary DES because of the absence of a polymeric carrier: from a stainless steel platform the antirestenotic agent is directly released over a period of approximately 1 month. The PF-BES ''revolution'' is based on the idea of eliminating the inflammatory and prothrombotic trigger of durable polymer coatings, whereas maintaining efficacy in terms of neointimal hyperplasia inhibition. The absolute performance of the PF-BES in all-comer patients is described in the RUDI-FREE main study and in other recent publications.[15,29,30] Despite only speculative, what seems nonetheless noteworthy to be highlighted is the comparable incidence of definite or probable ST between all groups (nondiabetic, noninsulin-treated diabetic, and insulin-treated diabetic patients). Within the limitations of the study, it seems fair to underline that this finding diverges from other recent evidences on second-generation DES.[3,24]

The present study should be interpreted in the light of some limitations. First of all, this was a nonrandomized study resulting in cohorts with differences in baseline, angiographic, and procedural characteristics. Second, detailed information on the patients' DM status are lacking: we could not account for the duration from onset or the degree of control of diabetes, the proportion of patients with type 1 and type 2 DM was not recorded, no detailed information about antidiabetic background medication (e.g., the type of oral hypoglycemic agent or the duration and amount of insulin therapy) were available. Third, the absence of a control group does not allow comparative evaluation of the PF-BES performance. Forth, the study size does not allow any inferential conclusion on the occurrence of rare adverse events.

In this real world, all-comers registry, DM resulted in a higher occurrence of TLF. After stratifying the diabetic cohort according to insulin treatment, the poorer prognosis of diabetic patients resulted to be substantially driven by the higher occurrence of adverse clinical events in the insulin-treated patients. The outcome of noninsulin-treated diabetic and nondiabetic patients was, conversely, comparable. Despite international guidelines do not differentiate diabetic patients according to insulin treatment, the results of the present study, in accordance with few other recent evidences, suggest that in the modern PCI era a further stratification of the diabetic population might be opportune and that randomized trials in this field are advocated.[2,31,32]

Disclosures

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Supplementary materials

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