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ORIGINAL ARTICLE

Merging the properties of a sirolimus coated balloon with those of a bioresorbable polymer sirolimus eluting stent to address the "diabetes issue"

Results from the En-Abl multicenter registry

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ABSTRACT

BACKGROUND: Patients with diabetes mellitus (DM) have poorer outcomes after percutaneous coronary intervention than patients without diabetes. The Abluminus DES+™ drug-eluting stent (DES) features a novel technology of fusion coating of PLLA bioresorbable polymer on both the abluminal surface of the stent and exposed parts of the balloon. The aim of this study was to evaluate the efficacy/safety profile of the Abluminus DES+ in an all-comers population with minimal exclusion criteria and with a specific focus on diabetic patients.

METHODS: Multicenter, prospective, all-comers registry performed in 31 centers in India. Patients were analyzed according to the diagnosis of DM and insulin dependency (ID or Non ID): non-DM (1256 patients), NIDDM (498 patients), IDDM (99 patients). The primary endpoint was a composite of device-oriented major adverse cardiac events (MACE): cardiac death, target vessel-related myocardial infarction (MI), and ischemia-driven target lesion revascularization (TLR)/ target vessel revascularization (TVR) at 1 year. Stent thrombosis (ST) at any time point was also recorded.

RESULTS: The MACE rate at 1 year in the overall population was 2.3% and it was mainly driven by a 1.57% rate of TLR/TVR. Although patients with IDDM showed slightly higher figures for MACE (non-DM 2.3%, NIDDM 2.8%, IDDM 4%, P=0.09), as well as for single end-points, none of them reached statistical significance. The rate of ST was 0.56%, 0.4%, 1% for non-DM, NIDDM and IDDM group, respectively (P=0.6).

CONCLUSIONS: The performance of the Abluminus DES+ is consistent among patients with or without diabetes, regardless the insulin dependency.

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KEY WORDS: Coronary artery disease - Diabetes mellitus - Drug-eluting stent - Percutaneous coronary intervention.

Compared to the previous generation of drug eluting stent (DES), the current one have shown to provide a better efficacy/safety profile in the treatment of simple as well as complex coronary disease by means of percutaneous coronary angioplasty (PCI).[1] Nevertheless, those improved results are still suboptimal for specific subset of high-risk patients, particularly for diabetic patients. The latter continue to have worse outcomes following PCI compared with patients without

diabetes.[1] This unmet clinical need spurred the introduction of new iterations of DES, theoretically able to overcome the "diabetic issue".

We indeed present the result of the En-Abl registry featuring the Abluminus DES+ (Envision Scientific, Surat, India). With its unique features it might provide diabetic patients with better short as well as long-term outcomes compared to current generation of DES.

Materials and methods

The Envision Abluminus DES+ registry (En-Abl registry) is a prospective, all comers, multicenter registry enrolling patients treated by means of PCI in 31 centers in India.

Clinical inclusion criteria were: indication to PCI following an acute coronary syndrome (ACS), stable angina or evidence of ischemia following a noninvasive stress test, patients willing to sign the consent form and have a life expectancy longer than 1 year. Women with childbearing potential, people younger than 18 year and those with known intolerance to antiplatelet agents or any component of the device were excluded.

Angiographic inclusion criteria included reference vessel diameter between 2.5 mm and 4 mm, single or multivessel disease. Angiographic exclusion criteria were: in-stent restenosis, saphenous vein graft disease and left internal mammary artery.

Procedural technique

All patients who were not already on chronic aspirin treatment received a loading dose of ≥250 mg of aspirin within 24 hours before the procedure. A loading dose of a P2Y12 receptor antagonist was administered before the procedure or within 1 hour after the procedure. Other medications were administered according to current guidelines.[2-4] The use of quantitative coronary angiography, optical coherence tomography (OCT) or intravascular ultrasound (IVUS) was left to operator's discretion, as well as the predilation or postdilation technique. A 30 seconds minimum inflation of the balloon during the deployment of the Abluminus DES+ was required to maximize the initial burst of drug release.

Dual antiplatelet therapy was recommended for 1 year in all patients, and aspirin (at a dose ≥100 mg daily) was continued indefinitely. Patients are followed-up with ambulatory visits or telephone contact at 30 days, 6 months, 1 year and yearly afterwards, up to 5 years after the index procedure to acquire information about clinical events, anginal status and use of medications. The Canadian Cardiovascular Society scores are used for the evaluation of angina symptoms. Follow-up coronary angiography was performed only if clinically indicated.

Study endpoints

The primary endpoint was a composite of device-oriented major adverse cardiac events (MACE): cardiac death, target vessel-related myocardial infarction (MI), and ischemia-driven target lesion revascularization (TLR)/target vessel revascularization (TVR) at 1 year. Myocardial infarction was always considered target vessel-related, unless angiography proved that it was not related to the vessel(s) treated with Abluminus DES+. The Stent Thrombosis (ST) rate was calculated at any time point. Endpoint definitions follow the criteria of the Academic Research Consortium (ARC).[5] Periprocedural MI was defined according to the Third Universal Definition of MI.[6]

Statistical analysis

Categorical variables are described as counts and percentages and were compared using Pearson's χ^2 test or Fisher's Exact Test. Continuous variables are described as mean±SD or as median and interquartile range (IQR) and compared using *t*-test or Mann-Whitney Test, as appropriate. Survival analyses were done graphically with Kaplan Meier Curve, and mathematically with the log-rank test. A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SPSS 20 software.

Results

Study population

Between January 2012 and September 2016, 1853 patients were been enrolled in 31 centers.

They were analyzed according to the presence and type (insulin dependent [IDDM], or non-insulin dependent [NIDDM]) of diabetes (Table I).

Patients with IDDM were more often hypertensive and had renal failure. The majority of the patients had single vessel disease, to the left anterior descending, however, IDDM patients had a higher rate of multivessel disease. In this group, there was also a higher prevalence of vessel smaller than 2.75 mm in diameter, and of a lesion longer than 28 mm (Table II).

Outcomes at 30 days

The MACE rate in the overall population was 0.75% (14 events: 7 cardiac death, 6 TV-MI, 1 TLR). Six definite stent thrombosis were been

TABLE I.—*Clinical features. P values refer to the three subgroups.*

	Overall (1853 patients)	Non-DM (1256 patients)	NIDDM (498 patients)	IDDM (99 patients)	P
Age, years	56±12	56±13	59±9	59±9	0.4
Male, N. (%)	1463 (79)	1012 (80.5)	392 (78.7)	77 (77)	0.6
Diabetes mellitus, N. (%)	597 (32.2)	-	-	-	-
Hypertension, N. (%)	814 (43.9)	451 (35.6)	297 (59.6)	66 (66)	0.04
Renal failure, N. (%)	37 (2)	18 (1.4)	10 (2)	9 (9)	0.03
Previous MI, N. (%)	260 (14.3)	169 (13.4)	77 (15)	14 (14)	0.5
Previous PCI, N. (%)	98 (5.3)	55 (4.3)	34 (6.8)	9 (9)	0.08
Previous CABG, N. (%)	35 (1.9)	19 (1.5)	12 (2)	4 (4)	0.6
SA N. (%)	709 (38)	527 (42)	201 (40)	41 (40)	0.6
ACS, N. (%)	1144 (62)	729 (58)	297 (60)	58 (60)	0.7
STEMI, N. (%)	384 (33)	233 (32)	92 (31)	17 (30)	0.6
NSTEMI, N. (%)	620 (54)	401 (55)	178 (60)	31 (54)	0.3
UA, N. (%)	140 (13)	95 (13)	26 (9)	10 (16)	0.07

ACS: acute coronary syndromes; CABG: coronary artery bypass graft; DM: diabetes mellitus; IDDM: insulin dependent DM; NIDDM: non-insulin dependent DM; MI: myocardial infarction; NSTEMI: non ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; SA: stable angina/inducible ischemia; STEMI: ST elevation myocardial infarction; UA: unstable angina.

TABLE II.—*Procedural features. P values refer to the three subgroups.*

	Overall (1853 patients)	Non-DM (1256 patients)	NIDDM (498 patients)	IDDM (99 patients)	P
N. of treated lesion per patients	1.2	1.1	1.2	1.2	0.2
N. of stents per patient	1.3	1.2	1.3	1.3	0.3
Extent of coronary artery disease					
1-vessel, N. (%)	1558 (84)	1078 (85.8)	404 (81.2)	71 (71)	0.03
2-vessel, N. (%)	265 (14)	157 (12.5)	87 (17.4)	21 (21)	0.05
3-vessel, N. (%)	30 (2)	21 (1.7)	7 (1.4)	7 (7)	0.02
Target vessels	2206	1486	599	121	
Left anterior descending, N. (%)	1081 (49)	802 (54)	287 (48)	55 (45)	0.07
Left circumflex, N. (%)	456 (21)	283 (19)	120 (20)	32 (26)	0.08
Right coronary artery, N. (%)	594 (27)	356 (24)	167 (28)	35 (29)	0.09
Ramus, N. (%)	29 (1.3)	15 (1)	12 (2)	0	0.7
Left main coronary artery, N. (%)	37 (1.7)	30 (2)	12 (2)	0	0.8
Predilatation, N. (%)	1391 (63)	936 (63)	381 (63.6)	74 (61.5)	0.5
Thrombus aspiration, N. (%)	80 (3.6)	50 (4)	18 (3)	4 (3)	0.7
Postdilatation, N. (%)	828 (37.5)	559 (44)	235 (39)	48 (40)	0.6
Vessel ≤2.75 mm, N. (%)	944 (42.8)	569 (45)	315 (52.5)	75 (62)	0.04
Long lesion (≥28 mm), N. (%)	1044 (47.3)	695 (46.7)	313 (52)	80 (66)	0.03
Device details					
Mean stent diameter (mm)	2.93±0.43	2.9±0.43	2.83±0.40	2.83±0.38	0.5
Mean stent length (mm)	26.3±8.76	26.4±8.77	26.66±8.77	25.87±8.66	0.6

DM: diabetes mellitus; IDDM: insulin dependent DM; NIDDM: non-insulin dependent DM. NSTEMI: non ST-elevation myocardial infarction; STEMI: ST elevation myocardial infarction.

TABLE III.—*Thirty-day follow-up. P values refer to the three subgroups.*

	Overall (1853 patients)	Non-DM (1256 patients)	NIDDM (498 patients)	IDDM (99 patients)	P
MACE, N. (%)	14 (0.75)	10 (0.8)	3 (0.6)	1 (1)	0.09
Death, N. (%)	7 (0.38)	5 (0.4)	2 (0.4)	0	0.8
TV-MI, N. (%)	6 (0.32)	4 (0.3)	1 (0.2)	1 (1)	0.07
TLR/TVR, N. (%)	1 (0.05)	1 (0.08)	0	0	-
ST, N. (%)	9 (0.49)	6 (0.48)	2 (0.4)	1 (1)	0.6
Definite, N. (%)	6 (0.32)	4 (0.32)	1 (0.2)	1 (1)	0.09
Acute, N. (%)	1 (0.05)	1 (0.08)	0	0	-
Sub-acute, N. (%)	5 (0.27)	3 (0.2)	1 (0.2)	1 (1)	0.7
Probable, N. (%)	3 (0.1)	2 (0.1)	1 (0.2)	0	0.8
Acute, N. (%)	3 (0.1)	2 (0.1)	1 (0.2)	0	0.7
Sub-acute, N. (%)	0 (0)	0 (0)	0 (0)	0 (0)	-

DM: diabetes mellitus; IDDM: insulin dependent DM; MACE: major adverse cardiovascular events; NIDDM: non-insulin dependent DM; NSTEMI: non ST-elevation myocardial infarction; STEMI: ST elevation myocardial infarction; ST: stent thrombosis; TV-MI: target vessel myocardial infarction; TLR/TVR: target lesion/vessel revascularization.

TABLE IV.—*Clinical events at 1 year. P values refer to the three subgroups.*

	Overall (1853 patients)	Non-DM (1256 patients)	NIDDM (498 patients)	IDDM (99 patients)	P
MACE, N. (%)	44 (2.3)	26 (2.07)	14 (2.8)	4 (4)	0.09
Death, N. (%)	8 (0.43)	5 (0.4)	3 (0.6)	0	0.8
TV-MI, N. (%)	7 (0.38)	5 (0.4)	1 (0.2)	1 (1)	0.07
TLR/TVR, N. (%)	29 (1.57)	16 (1.27)	10 (2.02)	3 (3)	-
ST, N. (%)	10 (0.54)	7 (0.56)	2 (0.4)	1 (1)	0.6
Definite, N. (%)	7 (0.38)	5 (0.4)	1 (0.2)	1 (1)	0.09
Acute, N. (%)	1 (0.05)	1 (0.08)	0	0	-
Sub-acute, N. (%)	6 (0.32)	4 (0.32)	1 (0.2)	1 (1)	0.7
Late, N. (%)	0	0	0	0	-
Probable, N. (%)	3 (0.16)	2 (0.16)	1 (0.2)	0	0.8
Acute, N. (%)	3 (0.16)	2 (0.16)	1 (0.2)	0	0.7
Sub-acute, N. (%)	0	0	0	0	-
Late, N. (%)	0	0	0	0	-

DM: diabetes mellitus; IDDM: insulin dependent DM; MACE: major adverse cardiovascular events; NIDDM: non-insulin dependent DM; NSTEMI: non ST-elevation myocardial infarction; STEMI: ST elevation myocardial infarction; ST: stent thrombosis; TV-MI: target vessel myocardial infarction; TLR/TVR: target lesion/vessel revascularization.

observed (0.32%). No differences were observed for the 3 subgroups in any of the single end-points (Table III).

Primary end point

The MACE rate at 1 year in the overall population was 2.3% and it was mainly driven by a 1.57% rate of TLR/TVR. Of note, no differences were observed across the 3 subgroups, although patients with IDDM showed slightly higher figures for MACE as well as for single end-points: none of them reached statistical significance (Table IV). Figure 1 shows the cumulative hazard function for MACE in patients with *versus* without diabetes and Figure 2 shows single end-points hazard function.

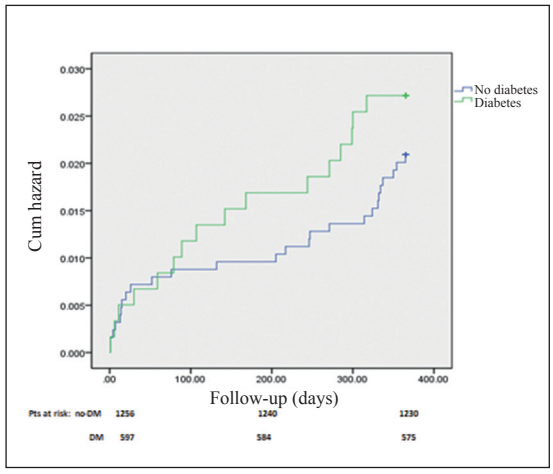

Figure 1.—Cumulative hazard for MACE in patients with *versus* without diabetes.

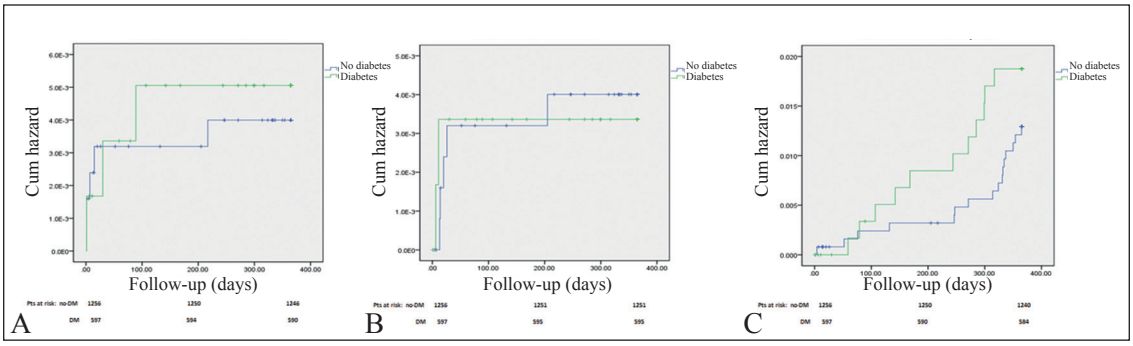

Figure 2.—Cumulative hazard for cardiac death (A), TV-MI (B) and TLR/TVR (C) in patients with *versus* without diabetes.

Discussion

The results of the present manuscript assessing the performance of the Abluminus DES+ can be summarized as follows:

- in a large unselected population with minimal exclusion criteria, the efficacy/safety profile of the Abluminus DES+ is confirmed by very low rates of events at 1 year follow-up;
- these results are consistent across the prespecified groups according to the presence of diabetes and the insulin dependency.

Nowadays, more than 400 million adults have diabetes worldwide[7] and this figure is destined to further increase. Moreover, it is estimated that there are around 190 million people worldwide with undiagnosed diabetes.[7]

Overall, more than 25% of patients referred for PCI or coronary artery bypass graft (CABG) procedures have diabetes. Compared to patients without diabetes, such patients have a poorer long-term prognosis in terms of restenosis, stent thrombosis, myocardial infarction (MI) and all-cause as well as cardiovascular death.[8-12]

Clinical outcomes in diabetic patients treated with DES *versus* bare-metal stents, as well as the comparative performance of several DES, have been assessed in randomized trials and large observational registries.[13] The 300-patient randomized ESSENCE-DIABETES trial succeeded in showing non-inferiority of everolimus-eluting stents (EESs) compared to first-generation sirolimus-eluting stents with respect to angiographic late lumen loss (LLL) at 8 months with no significant difference in clinical outcomes at 1 year, although the trial was not powered to show a statistical difference with respect to the latter.[14]

A pooled analysis of 6780 patients treated with second-generation EES *versus* first generation paclitaxel-eluting stents enrolled in the SPIRIT II, SPIRIT III and SPIRIT IV and COMPARE randomized trials showed that, despite improved safety and efficacy of EES in non-diabetic patients at 2 years, there was no difference between the devices with respect to outcomes in diabetic patients (N.=1869).[15]

Furthermore, different second-generation DES devices — utilizing permanent or bioresorbable polymers — have not demonstrated differential efficacy in patients with diabetes.[16, 17]

The Abluminus DES+™ (Envision Scientific Pvt. Ltd., India) has an abluminal coating of PLLA/PLGA (50:50 lactide-co-glycolide) poly-

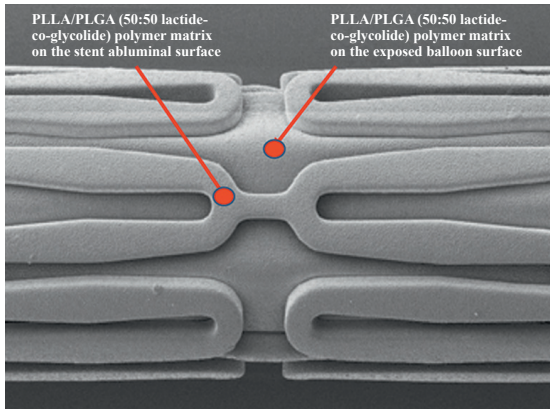

Figure 3.—Scanning Electron microscopy specimen of the Abluminus DES+. The PLLA/PLGA (50:50 lactide-co-glycolide) polymer is spray-coated with 1% solution of sirolimus with polymers in dichloromethane.

mer matrix on the stent abluminal surface and exposed balloon surface in precrimped configuration (Figure 3). The stent is spray-coated with 1% solution of Sirolimus and polymers mixture in dichloromethane. The stent is made of chromium-cobalt (L605 alloy) with a strut thickness of 73 micron.

These features, along with a required prolonged inflation up to 30 seconds during the implantation, ensure a biphasic drug release: an initial burst of 40-50% of the drug release during the first 3-4 days, and then a controlled release up to 48 days.[18] The exposed parts of the balloon actually work as a drug coated balloon (DCB), perhaps releasing sirolimus instead of paclitaxel as most of the DCB commercially available. At present, sirolimus and its derivatives are largely applied to stent technology. Evidence suggests that sirolimus inhibits Nuclear Factor-kappaB (NF-kB). NF-kB is key inflammatory substance which releases upon device originated injury by balloon or stent. On the other hand, muscle cells in diabetic patients are relatively resistant to the effect of sirolimus, *i.e.* they need a higher dose to be inhibited.[19]

Indeed, these kinetic of initial burst followed by a controlled release of sirolimus could actually explain the consistent results observed in the present registry across the different subgroups of patient with or without diabetes.

According to this hypothesis, a large international registry on diabetic patients is actively enrolling (The DEDICATE study: Drug Eluting Stent For Diabetic Patients In Coronary Artery Disease Treatment) targeting 5000 patients in Europe and Asia, as well as a randomized controlled trials comparing the angiographic and clinical performance of Abluminus DES+ *versus* Everolimus eluting stents at 6 month (ABILITY: A Randomized clinical trial of Abluminus DES+ Sirolimus eluting stent *versus* Everolimus-eluting DES for Percutaneous Coronary Intervention in patients with Diabetes Mellitus: an Investigator-initiated pilot study).

Limitations of the study

Patients were temporally consecutive, however as the participating centers performed a much larger volume of procedure, a certain degree of selection bias cannot be ruled out. Events were reported by the participating centers, there was no Clinical Event Committee. The relatively small population of patients with IDDM may confound the statistical analysis.

Conclusions

The results of the En-Abl multicenter registry supports the hypothesis that the Abluminus DES+ could provide consistent result in patients with as well as without diabetes. To the best of our knowledge, this is the first 3rd generation DES having achieved such results. The ongoing clinical program will provide more evidence.

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Conflicts of interest.—Mainish Doshi, Prakash Sojitra, Poonam Chodvadiya and Gopee Dutta are employee of the manifacturer.

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