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Abluminal biodegradable polymer biolimus-eluting versus durable polymer everolimus-eluting stent in patients with diabetes mellitus 5 years follow-up from the COMPARE II trial

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ABSTRACT

Background: Drug eluting stents with biodegradable polymers have been developed to address the risk of very late adverse events. Long-term comparison data between the biodegradable polymer-coated biolimus-eluting stent (BES; Nobori®) and the second-generation durable polymer-coated everolimus-eluting stent (EES; XIENCE V® or XIENCE PRIME® or PROMUS™) in diabetic patients are scarce.
Methods: The COMPARE II trial was an investigator-initiated, multicenter, open-label, randomized, all-comers trial which assigned patients undergoing percutaneous coronary intervention (PCI) in a 2:1 fashion to either BES or EES. We analyzed the safety and efficacy outcomes in diabetic patients at 5 year follow-up. The primary pre-specified composite endpoint major adverse cardiac event (MACE) was defined as cardiac death, non-fatal target-vessel myocardial infarction (TV-MI), or clinically indicated target vessel revascularization (CD-TVR).
Results: Out of 2707 study patients, 588 were diabetics (21.7%) of whom 391 were treated with BES and 197 with EES. At 5 years follow-up, MACE occurred in 87 patients (22.2%) in the BES group and in 34 patients (17.2%) in the EES group ($p = .34$). Other safety and efficacy endpoints did not differ between stent groups.
Conclusions: At 5 years follow-up, no differences in terms of MACE as well as all analyzed safety and efficacy measures, including stent thrombosis, between the biodegradable polymer-coated BES and the durable polymer-coated EES in diabetic patients were observed.

1. Introduction

Diabetic patients account for approximately 20–30% of all patients undergoing percutaneous coronary interventions (PCI) and experienced higher rates of adverse events when compared to non-diabetics.

New-generation drug eluting stents (DES) have improved clinical outcomes of patients undergoing PCIs compared to bare-metal stents (BMS) and early generation DES and are, indeed, strongly recommended in this high-risk subgroup. However, diabetes mellitus (DM) still remains a powerful predictor of adverse clinical outcomes after PCI with significant late catch-up in major adverse cardiac events (MACE) and target lesion revascularization (TLR) [1].

Small calibers of the target vessels, exuberant neointimal proliferation, prothrombotic state and diffuse vascular inflammation associated with diabetic status have been advocated as the main drivers of recurrent ischemic events [2].

Permanent polymer of first- and second-generation DES has been suggested as a trigger for chronic inflammatory response and biodegradable polymers third-generation DES have been conceived to overcome the safety issues of durable polymer comparators.

Recently, an ultra-thin struts biodegradable polymer sirolimus-eluting stent has shown to have a similar efficacy and safety profile as the current standard durable fluoropolymer-coated everolimus-eluting stent (EES) in this high-risk population [3]. However, these results were obtained at 1 year follow-up and potential benefits of the biodegradable polymer DES are expected at long-term follow-up.

The multicenter randomized COMPARE II trial has compared the safety and efficacy outcomes of the new-generation durable polymer-coated everolimus-eluting stent (EES; XIENCE V® or XIENCE PRIME® or PROMUS™) with biodegradable polymer-coated biolimus-eluting stent (BES; Nobori®) in a population-based all comer setting. Up to

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5 years the clinical outcomes of the whole population have been found to be similar between the two groups. Nevertheless, little is known about very-long term outcomes of biodegradable polymer DES in diabetic patients.

The present subgroup analysis, according to diabetic status, displays the five-years results of COMPARE II trial in this high-risk population.

2. Methods

The COMPARE II trial was an investigator-initiated, multicenter, open-label, randomized, all-comers trial which assigned patients undergoing PCI in a 2:1 fashion to either BES or EES. Details of the main study with its inclusion and exclusion criteria as well as description of study device and procedural methodologies have been previously published [4]. All patients with medical treatment for diabetes were included in this analysis and 5 year follow-up safety and efficacy outcomes were analyzed. The primary pre-specified composite endpoint major adverse cardiac event (MACE) was defined as cardiac death, non-fatal myocardial infarction (MI), or clinically indicated target vessel revascularization (CD-TVR).

The device-oriented endpoint of target lesion failure (TLF) was a composite of cardiac death, non-fatal target vessel-related myocardial infarction (TV-MI), and clinically driven target lesion revascularization (CD-TLR). Stent thrombosis (ST) was defined as ARC definition [5]. Patients were evaluated at 1, 6, 12, 24, 36 and 60 months at the outpatient clinic or by telephone, post or email. All sites were independently monitored and reportable clinical events were adjudicated by an independent committee. The study complied with the Declaration of Helsinki and the institutional ethics committees of each participating institution approved the protocol. All enrolled patients provided informed consent before inclusion. The sponsor had no role in the study design, data collection, data monitoring, data analysis or writing of the report.

2.1. Statistical analysis

The main study was designed as a non-inferiority trial at one year. On the basis of other all-comer stent DES trials with a non-inferiority design, such as LEADERS (delta <4•0%) and the RESOLUTE AC trial (delta <3•5%), a non-inferiority margin of 4•0% was considered an acceptable difference between the biolimus-eluting stent and everolimus-eluting stent [6,7]. With a one-sided type 1 error of 0•05% and 5% lost at follow-up, we calculated that 2700 patients would yield at least 90% power to detect non-inferiority, according to the Newcombe-Wilson score method.

The current analysis compared clinical outcomes according to diabetic status and stent type. Continuous variables are presented as mean ± SD and binary variables as number and percentage. *p* values for baseline characteristics were calculated with Chi-square or Fisher exact test. Cumulative events rates were analyzed using the Kaplan-Meier method. Hazard ratios were calculated using Cox regressions and reported with 2-sides 95% confidence intervals (CI). The interaction between diabetic status and stent type was tested using Cox regressions. Significance level was set at $p < .05$. All analyses were performed as intention-to-treat principle. Statistical analysis was performed with SPSS version 20.0 (IBM, Armonk, New York).

3. Results

Out of 2707 patients enrolled in the Compare II trial and randomized 2:1 to BES or EES, 588 (21.7%) were diabetics. Among them, 391 patients and 593 lesions received BES and 197 patients and 332 lesions received EES. At 5 years follow-up, 6 patients (3%) in the EES group and 7 patients (1.8%) in the BES group were lost to follow-up or withdrew consent (Fig. 1 Suppl).

As shown in Table 1, baseline characteristics were well balanced between the two treatment arms. Insulin dependent requiring diabetes mellitus (IDDM) was present in 115 patients (29.4%) allocated to BES treatment and 55 patients (27.9%) allocated to EES treatment and the rest of the patients were on oral hypoglycemic agents. Half of the patients presented with acute coronary syndrome (ACS) with a similar distribution between the two groups. Angiographic and procedural characteristics are shown in Table 2 and no significant differences between BES and EES groups were detected.

Five-year clinical events rate are summarized in Table 1 Suppl and shown in Fig. 1. The composite primary endpoint of cardiac death, TV-MI and CD-TVR occurred in 87 patients (22.2%) in the BES group and 34 patients (17.2%) in the EES group (relative risk 1.12 [95% CI: 0.82, 1.55], p: 0.34) (Fig. 1). In ACS subgroup the rates of composite primary endpoint in the BES and EES group were 20.3% and 20.2% (p: 0.65). In non ACS subgroup MACE occurred in 46 (24.3%) patients of the BES group and in 14 (14.3%) of the EES group (p: 0.24) (Table 1 Suppl, Figs. 2,3,4 Suppl). Rates of device-oriented endpoint of TLF occurred in 75 patients (19.2%) in the BES group and in 32 (16.2%) in EES group (relative risk 1.18 [95% CI: 0.78, 1.79], p: 0.38.

Stent thrombosis rates up to 5 years were similar between groups at all timepoints (Table 2 Suppl).

The Kaplan–Meier estimates showing the interplay between insulin-requiring status and stent type are shown in Fig. 2. IDDM patients showed higher rates of MACE compared to non IDDM patients, but no significant *p* of interaction has been found between the two factors.

Table 1
Baseline characteristics.

	BES (391)	EES (197)	*p* value
Age (mean age-yr)	69.55 ± 10.68	70.14 ± 10.89	0.53
Male n, (%)	273 (69.8)	141 (71.5)	0.66
Insulin treatment n, (%)	115 (29.4)	55 (27.9)	0.69
Hypertension n, (%)	282 (72.1)	140 (71.0)	0.78
Dyslipidemia n, (%)	279 (71.3)	146 (74.1)	0.48
Smoking n, (%)	252 (64.4)	118 (59.8)	0.38
Previous PCI/CABG n, (%)	114 (29.1)	56 (28.4)	0.94
Previous stroke (CVA/TIA/RIND) n, (%)	31 (7.9)	10 (5.0)	0.16
Chronic renal failure n, (%)	27 (6.9)	15 (7.6)	0.95
COPD n, (%)	35 (8.9)	23 (11.6)	0.38
ACS presentation n, (%)	202 (51.6)	99 (50.2)	0.74

Table 2
Procedural characteristics.

	BES (391)	EES (197)	*p* value
Multivessel treatment n, (%)	77 (19.6)	38 (19.2)	0.74
Number of lesions treated	1.39 ± 0.73	1.48 ± 0.87	0.17
At least 1 RVD ≤ 2.75 mm n, (%)	151 (38.6)	84 (42.6)	0.75
At least 1 lesion length > 20 mm n, (%)	265 (67.7)	116 (58.8)	0.29
	Lesions (593)	Lesions (332)	*p* value
Target vessel			
RCA	321 (54.2%)	166 (50.2%)	
LAD	141 (23.8%)	69 (20.8%)	
LCX	115 (19.4%)	87 (26.4%)	
LM	13 (2.3%)	8 (2.5%)	
SVG	5 (0.8%)	3 (0.9%)	
CTO n, (%)	12 (2.0)	9 (2.7)	0.32
In stent restenosis n, (%)	17 (2.8)	10 (3.0)	0.48
B2/C lesions n, (%)	274 (46.2)	142 (42.7)	0.75
Calcification moderate or severe n, (%)	201 (33.8)	107 (32.2)	0.56
Thrombus n, (%)	92 (15.5)	40 (12.0)	0.51
Ostial lesion n, (%)	86 (14.5)	38 (11.4)	0.72
Bifurcation n, (%)	32 (5.3)	25 (7.5)	0.74
Provisional	19 (60.0%)	13 (52%)	0.67
2 stents technique	13 (40.0%)	12 (48%)	0.58
Direct stenting n, (%)	205 (34.5)	115 (34.6)	0.11
Number of stents/lesion	1.44 ± 0.75	1.48 ± 0.87	0.49

RCA: Right coronary artery; LAD: Left descending artery; LCX: Left circumflex; LM: Left Main; SVG: saphenous vein graft.

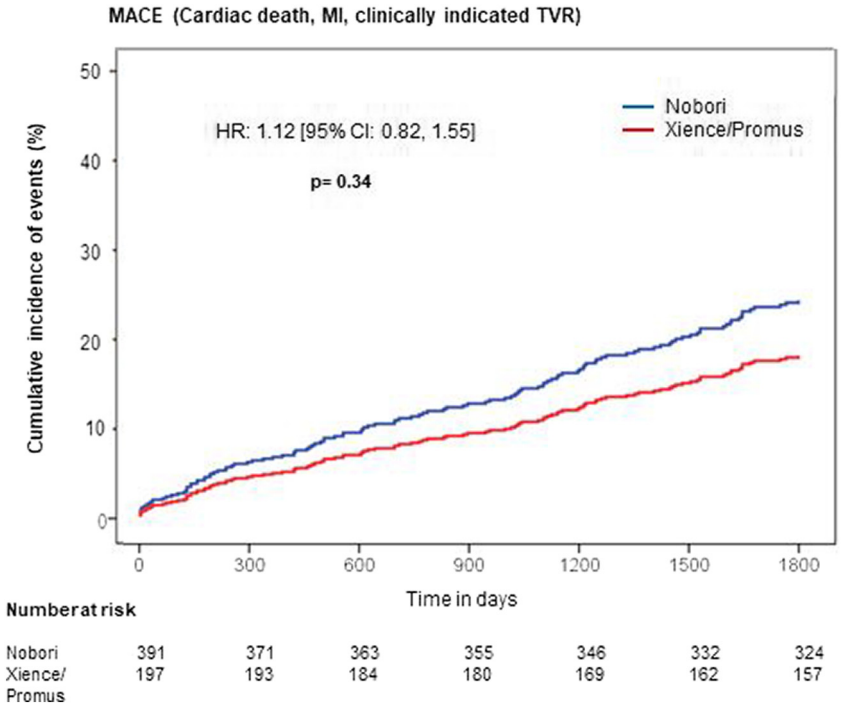

Fig. 1. Kaplan-Meier for the composite primary endpoint.

4. Discussion

The main findings of the current sub-analysis of the Compare II trial according to diabetic status are: 1) the biodegradable polymer coated BES (Nobori) has a similar efficacy and safety profile as the durable polymer coated EES (Xience or Promus) at 5 year follow up, 2) clinical outcomes of diabetic patients, especially in the subset of insulin-treated DM patients, continue to be worse compared to non-diabetics.

It is known that the diabetic status is associated with a higher risk of both stent- and patient-related adverse events after PCI [8–10]. Several mechanisms are involved in this pathophysiological process: decreased insulin level combined with hyperglycemia may accelerate oxidative stress, platelet activation, inflammation, apoptosis and endothelial dysfunction and ultimately lead to progression of atherosclerotic lesions [11]. The use of second-generation DES has shown promising results in terms of target vessel and target lesion revascularization and ST, when compared to first generation DES even in this high-risk subgroup of patients [11]. However, the event rates of diabetic patients remain considerably higher compared to the general population.

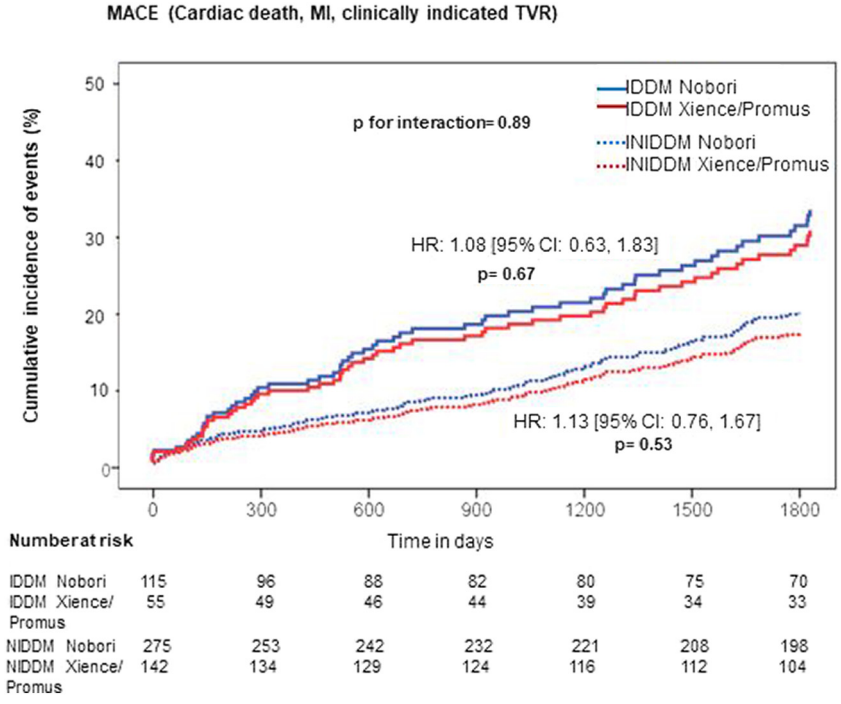

Fig. 2. Kaplan Meier cumulative event curves of primary composite endpoint according to stent type and insulin-requiring status.

In this peculiar clinical subset, biodegradable polymer-coated DES have been conceived to mitigate the device-related risk of recurrent events. By avoiding the persistent vascular injury related to polymer remnants within the arterial wall, newer-generation DES may offer potential advantages over durable polymer DES.

To date, long term follow-up data comparing biodegradable polymer with durable polymer-coated first-generation DES in diabetic patients are available from a pooled analysis of three randomized trials (ISAR-TEST 3, ISAR-TEST 4 and LEADERS) [12]. At 4 years, biodegradable polymer DES were associated with similar incidence of primary endpoint of first generation durable polymer coated sirolimus eluting stent but a statistically significant reduction in stent thrombosis occurred in the former group after one year. However, second generation durable polymer DES with new platform design, more biocompatible polymer coating, thinner struts and different antiproliferative agents have significantly lowered the incidence of adverse events, including ST, also in diabetic patients [13–15].

Five years results in the general population of the Compare II trial showed similar clinical outcomes between the newer-generation durable polymer-coated EES and biodegradable polymer-coated BES. Promising benefits of the biodegradable polymer DES were expected at long term follow and potentially magnified in diabetic patients. Nevertheless, in our analysis no differences between the two treatment arms in the diabetic subgroup have been detected. Overall, our results were obtained in the context of rather large percentage of IDDM patients, ACS presentation and multivessel treatment, providing remarkable evidence of the comparable efficacy and safety of the two devices in a population with high-risk profiles and complex lesion characteristics. Indeed, despite the low percentages of bifurcations lesions treated known to be responsible for higher rates of TLR at long term follow-up, almost half of the lesions included were classified B2/C according to AHA/ACC definition [16].

The present study represents the first analysis on long-term outcomes of diabetic patients treated with biodegradable polymer DES compared to newer generation durable polymer DES. Moreover the relevant number of enrolled patients allowed a further analysis according to insulin-requiring diabetic status. In line with previous results, we found that insulin-treated diabetic patients experienced higher adverse event rates than non-insulin requiring diabetic patients. However, we failed to prove an interplay between DES type and insulin treatment; thus confirming a worse clinical outcomes in IDDM patients irrespective of stent type.

Nevertheless, biodegradable polymer DES are differentiated by strut thickness, polymer composition, distribution and load as well as the time course for polymer resorption. Thick-struts devices have been associated with higher rates of luminal flow turbulence and thrombus formation compared to thin-struts devices [12,17]. Factors, other than polymer may indeed play a role in the risk of ST. Subgroup analysis of diabetic patients in the BIOSCIENCE trial showed similar clinical outcomes between ultrathin struts polymer sirolimus eluting stents and durable polymer EES at 1 year follow up, thus challenging the concept of biodegradable polymer coated even with the newer ultrathin struts devices [3].

However, the cumulative pathophysiological sequelae of DM on cardiovascular event rates highlight the caveat of assessing short-term PCI outcomes in these high-risk group patients. Hence, longer follow up are needed to confirm the absence of benefits of newer biodegradable polymer devices.

5. Study limits

Despite being rigorously conducted, this analysis has important limitations.

First, the diabetic status was not a pre-specified parameter for randomization. Although baseline and procedural characteristics were not statistically significant different between the two stent types in the diabetic subpopulation, no correction for differences in this analysis were made. Therefore, the results of the subgroup analysis should be considered as hypothesis-generating and require further investigation in a properly powered and prospectively randomized trial.

Second, this trial aimed to compare the Nobori biodegradable polymer-coated BES compared to the permanent polymer-coated EES. Recent trials have investigated very-thin struts biodegradable polymer coated DES but have failed to find significant differences between the currently available devices in terms of angiographic and clinical outcomes. However potential benefits of more recent devices could emerge at longer follow-up.

6. Conclusions

This is the first analysis on long-term outcomes between the Nobori biodegradable polymer-coated BES compared to the current standard permanent polymer-coated EES in medically-treated diabetic patients. At 5 years follow-up, no difference in terms of MACE and other efficacy and safety measures were detected between the BES and EES groups.

Our data confirmed higher rates of adverse events in diabetic patients and, therefore, there is a continuing need for the most effective coronary stent in this high-risk population.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.054.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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