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One-year outcome of biolimus eluting stent with biodegradable polymer in all comers: The Italian Nobori Stent Prospective Registry☆

Cosmo Godino [a,*], Dennis Zavalloni Parenti [b], Damiano Regazzoli [a], David Rutigliano [c], Luigi Lucisano [d], Giacomo Maria Viani [a], Marco Spartera [a], Alaide Chieffo [a], Michael Donahue [e], Alberto Cappelletti [a], Nicola Locuratolo [c], Rosario Parisi [f], Rossella Fattori [f], Patrizia Presbitero [b], Alberto Margonato [a], Carlo Briguori [e], Gennaro Sardella [d], Antonio Colombo [a,g]
on behalf of the **I**talian **N**obori **S**tent **P**rospect**I**ve **RE**gistry-1 (**INSPIRE-1**) investigators

[a] San Raffaele Scientific Institute, Milan, Italy
[b] Humanitas Clinical Institute, Milan, Italy
[c] Ospedale San Paolo, Bari, Italy
[d] Policlinico Umberto I, "La Sapienza" University of Rome, Italy
[e] Clinica Mediterranea, Naples, Italy
[f] Ospedali Riuniti Marche Nord, Pesaro, Italy
[g] EMO-GVM Centro Cuore Columbus, Milan, Italy

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ABSTRACT

Objectives: INSPIRE-1 (Italian Nobori Stent ProspectIve REgistry-1) was designed and conducted to assess clinical performance of Nobori biolimus A9-eluting stent (BES) implantation in an unrestricted "real-world" cohort of patients.
Methods: Unrestricted consecutive high-risk patients treated with BES with biodegradable polymer (Nobori, Terumo, Tokyo, Japan) between February 2008 and July 2012 were prospectively enrolled in an independent multicenter registry and divided in two groups: complex and non complex lesions.
Results: 1066 patients (1589 lesions) treated with Nobori BES were analyzed. The majority of patients (57%) were treated for at least one complex lesion and presented a high-risk clinical profile (previous CABG 17.6%, diabetes mellitus 33.1%, chronic kidney disease 14.3%). Angiographic success rate was achieved in 96.2% cases. At 1 year, the primary endpoint, (composite of cardiac death, myocardial infarction, and clinically driven target vessel revascularization), occurred in 39 (4.0%) patients, and was higher in the complex lesions (5.2% vs. 2.5%, $P = 0.032$). Target lesion failure (TLF, secondary endpoint) occurred in 45 (4.6%) patients, and was more frequent in the complex lesions group (6.2% vs. 2.7%, $P = 0.011$), mainly due to a higher incidence of any target lesion revascularization (4.8% vs. 2.7%; $P = 0.095$). Definite and probable stent thrombosis (ST) rate was 0.6% and 0.5% respectively, with no difference between groups.
Conclusions: In unrestricted daily practice, BESs were implanted predominantly in high risk patients with complex lesions. Despite this, the Nobori BES was associated with a relatively low rate of primary endpoint and TLF, with a higher risk in patients with complex lesions.

1. Introduction

First generation drug-eluting stents (DESs) are better at preventing restenosis than bare metal stents; therefore, DESs represent the current standard of care for treatment of complex lesions. Nevertheless, DESs have been associated with impaired local coronary vasomotion, delayed endothelialization, and increased risk of late thrombosis [1–3]. This happens particularly when DESs are used in complex lesions or in high risk patients [4–6]. DESs using biodegradable polymers have been designed to overcome the long-term vascular adverse reactions related to durable polymers. The Nobori biolimus-eluting stent (BES, Terumo, Tokyo, Japan) is a stainless steel alloy stent with a strut thickness of 120 μm coated abluminally with a biodegradable polymer (polylactic acid that dissolves in 6–9 months) which elutes biolimus A9, a highly lipophilic analog of sirolimus [7,8]. All but one of the previous studies [9] demonstrated the non-inferiority of the Nobori BESs compared to first generation DESs [10–13] and to second generation DESs (everolimus eluting-stent, EES, with durable polymer) [14,15]. However, as with first-

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* Corresponding author at: Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. Tel.: +39 022643 3752; fax: +39 022643 7398.
E-mail address: cosmogodino@gmail.com (C. Godino).

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generation DESs, the clinical event rates are often higher in real world registries than in the randomized clinical trials [16]; therefore, concerns have been raised about the efficacy and safety of biodegradable polymer BES implantation in complex lesions. At the moment, only one study validates the clinical performance of the Nobori BES in high-risk patients with complex lesion anatomy [17]. Hence, we sought to confirm the clinical outcomes of unrestricted BES use in the contest of a large physician-initiated prospective multicenter registry.

2. Methods

2.1. Study design and patient population

This is a spontaneous Italian multicenter observational registry involving 7 centers (Appendix A). We prospectively enrolled all consecutive patients undergoing Nobori stent implantation between February 2008 and July 2012, including both elective and urgent procedures. The selection of the Nobori BES over another DES was performed without any specific preference and was not based on patient risk or lesion morphology. Patients undergoing primary angioplasty for ST-segment elevation myocardial infarction (STEMI) were also included. Exclusion criteria were contraindication to prolonged dual antiplatelet therapy (DAT), implantation of a combination of different types of DES or of BMS and DES. Due to the observational nature of the study, revascularization strategies (e.g., atherectomy, intravascular ultrasound guidance) as well as stent implantation technique (e.g., direct stenting) were left to the operator's choice. All patients were pretreated with aspirin and a second platelet inhibitor: clopidogrel was preferred over ticlopidine in elective patients, whereas, for urgent procedures, each center was allowed to choose between clopidogrel, prasugrel and ticagrelor, as well as to use glycoprotein IIb/IIIa inhibitors. In all the cases, aspirin was continued indefinitely and a second antiplatelet drug (clopidogrel, prasugrel or ticagrelor) was prescribed for at least 12 months.

2.2. End-points, definitions and data collection

The *primary endpoint* was a composite of *safety* (cardiac death and non-fatal myocardial infarction) and *efficacy* (clinically indicated target vessel revascularization, TVR) at 12 months (COMPARE II primary endpoint definition) [14]. *Secondary endpoint* was target lesion failure (TLF), defined as a composite of death from cardiac causes, any myocardial infarction attributable to the target vessel, or any target lesion revascularization (TLR) appraised at 12 months. The clinical outcome was monitored by phone interview or contact with referring physician or direct visit, specific hospital files was performed when needed. Angiographic follow-up was performed when clinically indicated. In a sensitivity analysis, we evaluated the cohort of patients who had received BES for complex lesions lesion treatment separately [18]. In the "*complex lesions*" group were included patients who received a BES in at least one coronary lesion that had one of the characteristics reported in Table 1. Procedural success was defined as angiographic success (thrombolysis in MI with flow grade 3 and angiographic residual stenosis <20%) without the occurrence of cardiac death, MI, and repeat TLR (percutaneous or surgical) during hospital stay. Cardiac death was defined as any death due to cardiac causes, procedure-related deaths, and death of unknown cause. Periprocedural MI was defined as any elevation of troponin or creatine kinase (CK) levels to >3 times the upper normal limit (Academic Research Consortium, ARC, definition) [19]. Non-procedural or after discharge MI was defined as an elevation of troponin or CK above the upper range limit in combination with symptoms of ischemia, electrocardiography changes indicative of new ischemia, or the development of pathological Q waves on electrocardiography. TLR was defined as any repeat PCI in the target segment or CABG of the target vessel performed for restenosis or other complications related to the target lesion. TVR was defined as any repeat intervention (PCI/CABG) within the treated vessels. Any revascularization was considered clinically indicated (clinically indicated TLR or TVR) according to the ARC definition [19]. Stent thrombosis (ST) rate was also defined according to the ARC criteria. *Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2.*

Table 1
Definition of complex lesions.

Lesions with thrombus present
Left main coronary artery lesion
Chronic total occlusion (>3 months)
Bifurcation lesion
Bypass graft lesion
BMS or DES restenosis
Small vessel (<2.5 mm)
Long lesion (>30 mm)
Lesions with excessive tortuosity
Ostial location
Lesions with mod/heavy calcification

A dedicated database for data entry and clinical-event committee-based end point adjudication was used; in order to avoid selection bias or incomplete data reports, every center was required to complete at least 95% of clinical forms.

2.3. Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range, IQR) and compared with Student's *t* test or Mann–Whitney or Wilcoxon tests, on the basis of the normality of the data (which was verified by Kolmogorov–Smirnov goodness-of-fit test). Categorical variables (such as frequencies or percentage) were compared with χ^2 test with Yates correction for continuity or the Fisher exact test as appropriate for the available data [20]. Event-free survival during follow-up was evaluated according to the unadjusted Kaplan–Meier method and survival among groups was compared using log-rank test (Cox–Mantel test). Clinical follow-up was censored at the date of the last follow-up or at 365 days, whichever came first. Data for patients lost to follow-up were censored at the time of the last contact. Cox proportional hazards methods were used to estimate the independent effect of multiple independent variables on the risk of primary endpoint and TLF (secondary endpoint). To avoid multi-collinearity, a "low-noise model" has been researched in which each predictor variable correlates at most just minimally with the others. Selection of the variables included in the multivariate model was done with backward elimination (Wald statistic, confirmed using forward and stepwise selection) based on covariates listed in Tables 2 and 3. Only the covariates that were significantly associated with the endpoint risk at univariate analysis ($p < 0.05$ for model inclusion and $p > 0.10$ for exclusion) were included, and the convention of limiting the number of independent variables to 1 for every 10 events was followed [21,22]. The proportional hazards assumption was checked both graphically and by hypothesis testing. The results are reported as adjusted hazard ratios (HRs) with associated 95% confidence intervals (CI). Two-side *p*-values <0.05 were considered statistically significant. The statistical analyses were performed using SPSS 16.0.2 (SPSS Inc., Chicago, IL, USA) and NCSS 2007 (NCSS, Kaysville, UT, USA). Kaplan–Meier survival curves were generated with GraphPad Prism software (version 4; GraphPad, Inc, San Diego, CA). The study was approved by the Hospital Ethics Committee and each patient provided written informed consent.

3. Results

Between February 2008 and July 2012, over a total of 16,355 PCI, a total of 1066 patients (7%) were treated with Nobori BES. Baseline clinical and lesion characteristics of the study population are summarized in Tables 2 and 3. According to the study definitions, Nobori BESs were

Table 2
Baseline patients' characteristics.

	Overall (1066)	Non complex lesions (458)	Complex lesions (608)	*P*-value
Clinical characteristics				
Age (years)	66.4 ± 10.7	66.2 ± 9.9	66.4 ± 11.2	0.796
Male gender	871 (81.7)	384 (83.8)	487 (80.1)	0.118
LVEF	51.8 ± 8.8	54.1 ± 6.6	50 ± 9.7	<0.001
LVEF <35%	78 (7.3)	0 (0)	78 (12.8)	<0.001
Chronic kidney disease*	106 (9.9)	19 (4.1)	87 (14.3)	<0.001
Hemodialysis	16 (1.5)	3 (0.7)	13 (2.1)	0.049
Prior myocardial infarction	335 (31.4)	136 (29.7)	199 (32.7)	0.291
Prior revascularization	506 (47.5)	227 (49.6)	279 (46)	0.234
Prior PCI	438 (41)	202 (44)	236 (38.8)	0.082
Prior CABG	162 (15.2)	55 (12)	107 (17.6)	0.012
Cardiac risk factors				
Hypertension	766(71.9)	325 (71)	441 (72.5)	0.572
Dyslipidemia	665 (62.4)	297 (64.8)	368 (60.5)	0.149
Smoker	322 (30.2)	119 (26)	203 (33.4)	<0.001
Previous smoke habit	265 (24.9)	140 (30.6)	125 (20.6)	0.009
Family history of CAD	359 (33.7)	167 (36.5)	192 (31.6)	0.095
NIDDM	232 (21.8)	85 (18.6)	147 (24.2)	0.028
IDDM	110 (10.3)	56(12.5)	54 (8.9)	0.075
Coronary vessel disease				
Single vessel disease	359 (33.7)	157 (34.3)	202 (33.2)	0.718
Two vessel disease	327 (30.7)	141 (30.8)	186 (30.6)	0.946
Three vessel disease	380 (35.6)	160 (34.9)	220 (36.2)	0.673
Clinical presentation				
Stable angina	648 (60.8)	345 (75.3)	303 (49.8)	<0.001
Unstable angina	221 (20.7)	113 (24.7)	108 (17.8)	0.006
NSTEMI	92 (8.7)	0 (0)	92 (15.1)	<0.001
STEMI	105 (9.8)	0 (0)	105 (17.3)	<0.001