

Randomized Comparison of the Nobori Biolimus A9-Eluting Coronary Stent With the Taxus Liberté Paclitaxel-Eluting Coronary Stent in Patients With Stenosis in Native Coronary Arteries

The NOBORI 1 Trial—Phase 2

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Background—The newly developed Nobori coronary stent coated with a bioresorbable polymer, polylactic acid, and the antiproliferative agent Biolimus A9 has the potential to reduce restenosis by suppressing neointima formation.

Methods and Results—We conducted a randomized (2:1), controlled trial comparing the Biolimus A9-eluting stent Nobori and the paclitaxel-eluting stent Taxus Liberté, in 243 patients (153 Nobori and 90 Taxus) at 29 centers in Europe, Asia, and Australia. Patients with previously untreated lesions in up to 2 native coronary arteries were considered for enrollment. The primary end point was in-stent late loss at 9 months, whereas secondary end points included other quantitative coronary angiography parameters, such as in-segment late loss and the rate of restenosis as well as key intravascular ultrasound parameters. Clinical secondary end points were stent thrombosis and composite of major adverse cardiac events comprising death, myocardial infarction, and target vessel revascularization. At 9 months, the in-stent late loss was significantly lower in the Nobori group compared with the Taxus group (0.11 ± 0.30 mm versus 0.32 ± 0.50 mm) reaching both the primary hypothesis of noninferiority of Nobori stent versus Taxus Liberté stent ($P < 0.001$) and the secondary hypothesis of superiority ($P = 0.001$). This finding was confirmed by a significant reduction in binary restenosis from 6.2% in Taxus to 0.7% in Nobori ($P = 0.02$) and neointimal volume obstruction, detected by intravascular ultrasound, from $5.5 \pm 7.2\%$ in Taxus to $1.8 \pm 5.2\%$ in Nobori ($P = 0.01$). The major adverse cardiac events rate was 4.6% in the Nobori and 5.6% in the Taxus cohort of patients. The stent thrombosis rate was 0% in the Nobori arm and 4.4% in the Taxus arm.

Conclusions—The NOBORI 1 clinical trial confirmed its primary hypothesis—noninferiority of the Nobori Biolimus A9-eluting stent versus the Taxus Liberté stent in reducing neointimal proliferation. Both stents showed a low major adverse cardiac events rate in the studied population. (*Circ Cardiovasc Intervent.* 2009;2:188-195.)

Key Words: drug eluting stent ■ angioplasty ■ Biolimus A9 ■ paclitaxel ■ randomized trial

Drug-eluting stents (DES) have transformed the landscape of interventional cardiology on the basis of evidence showing a reduction in angiographic and clinical restenosis without increasing adverse events.¹⁻⁷ However, longer

follow-up and treatment of more complex patient populations have revealed higher frequency of late stent thrombosis, delayed vessel healing, and hypersensitivity on polymer carriers, prompting new developments in this field.⁸⁻¹⁵ Be-

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cause durable polymers used in first-generation DESs are suspected to be responsible for some of the observed pathological changes, numerous efforts have concentrated on drug release via bioresorbable polymers.^{5,16,17} The newly developed Nobori coronary stent system uses a bioresorbable polymer (polylactic acid), coated only on the abluminal side of stent surface from which Biolimus A9, an analogue of sirolimus, is eluted. Biolimus A9 is expected to prevent coronary stent restenosis by interrupting smooth muscle cell migration and proliferation. A similar drug-polymer combination is used in BioMatrix (Biosensors International, Singapore) and in the development of specific devices for bifurcation stenting (AXXESS System, Devax, Inc, Lake Forest, Calif) or long lesions (Custom NX, XTENT, Inc, Menlo Park, Calif).

NOBORI 1 phase 1 was the first-in-man experience with the Nobori stent (Terumo Corporation, Tokyo, Japan) where it was randomized versus the Taxus Express paclitaxel-eluting stent.¹⁷ This study is the second phase of NOBORI 1 clinical trial differing from the first phase by a substantially improved Nobori stent and replacement of Taxus Express by Taxus Liberté (Boston Scientific Corporation, Natick, Mass).

Methods

Patient Population

Patients, at least 18 years old, with stable or unstable angina, or provokable ischemia, indicated to undergo percutaneous coronary intervention of de novo lesions in up to 2 native coronary arteries were considered for enrollment. Angiographic inclusion criteria were a reference vessel diameter of 2.5 to 3.5 mm and a lesion length of ≥ 5 mm and ≤ 25 mm. Clinical exclusion criteria included left ventricular ejection fraction $< 30\%$, myocardial infarction (MI) within 48 hours before enrollment, intolerance to aspirin, heparin, clopidogrel bisulfate, ticlopidine, drugs similar to biolimus A9 (sirolimus, tacrolimus, everolimus, and zotarolimus), paclitaxel, contrast media, and stainless steel; platelet count $< 100\,000$ – $> 700\,000$ cells/mm³ or a WBC < 3000 cells/mm³, serum creatinine level > 2.0 mg/dL (or > 150 μ mol/L); current participation in other investigational trials; any coronary interventional procedure within 30 days before or planned within 60 days after the study stent implantation; planned surgery within 6 months; stroke or transient ischemic attack in the previous 3 months; and gastrointestinal bleeding. Main angiographic exclusion criteria were significant ($> 50\%$) stenosis proximal or distal to the treated lesion; previous stenting anywhere in the territory of treated vessel; total occlusion (TIMI flow 0 and I), left main or ostial target lesion, severe calcification; and evidence of thrombus or severe tortuosity.

The patients were enrolled in 29 hospitals (listed in the Appendix) from May to October 2006. The study was conducted according to the Declaration of Helsinki, ISO 14155 and respecting all country-specific regulatory requirements. The protocol was reviewed and approved by the ethics committee of each participating hospital, and all patients gave written informed consent. An automated telephone randomization system was used to assign eligible patients to treatment with Nobori or Taxus stent in a 2:1 ratio before the stent implantation.

The Nobori Biolimus A9-Eluting Stent

The Nobori DES system comprises 4 components: the bare metal stent platform, the delivery catheter, a drug carrier (polylactic acid), and an antiproliferative substance, Biolimus A9 (Biosensors International). Contrary to other DES, the drug polymer matrix (15.6 μ g drug per mm stent length in 1:1 ratio with polymer) is applied only abuminally (ie, toward the vessel wall) and is designed to allow for rapid initial elution of $\approx 40\%$ of drug from the stent, ensuring its distribution into the target tissue at the time of procedure-induced

vessel wall injury. The initial burst is followed by sustained drug release and polymer degradation over the period of 6 to 9 months (data on file of Terumo).

The Biolimus A9 is an analogue of rapamycin that binds to FK binding protein 12 and subsequently to the mammalian target of rapamycin. The formed complex inhibits smooth muscle cells proliferation by blocking the cell cycle progression between the G1 and S phase. The main difference between Biolimus A9 and rapamycin is replacement of hydrogen by alkoxy-alkyl group at 40-O position, increasing its lipophilicity. The coating design of Nobori stent combined with the lipophilicity of the drug is expected to optimize the drug distribution and to reduce its release into the peripheral circulation. The additional potential benefit of Nobori stent is a biocompatible and biodegradable polymer that degrades primarily by hydrolysis. The degradation product is water-soluble lactic acid, which is converted to carbon dioxide and water.

In this study, the second generation of polymer-based paclitaxel-eluting stent Taxus Liberté (Boston Scientific Corporation) was used as comparator. Safety and efficacy of the Taxus Liberté eluting stent have been studied in several registries.¹⁸

Coronary Stent Procedure

At least 100 mg of aspirin was administered daily to all patients before the procedure and indefinitely thereafter. A loading dose of 300 mg of clopidogrel was recommended if administered more than 6 hours before the procedure or 600 mg if administered periprocedurally. Clopidogrel was further given at 75 mg/day for at least 6 months to all patients receiving stents. During the procedure, intravenous heparin boluses were administered per standard hospital practice and use of intravenous glycoprotein IIb/IIIa inhibitors was at the physician's discretion.

Both Nobori and Taxus stents were available in length from 8 to 28 mm and in diameters of 2.5, 3.0, and 3.5 mm. After mandatory predilatation, an appropriately sized stent was implanted. Additional study stents were permitted for edge dissection or otherwise suboptimal results.

Preprocedural and postprocedural ECGs were obtained and cardiac enzymes were measured at baseline, 8 to 12 hours, and 18 to 24 hours after the procedure or at discharge, whichever came first.

Patient Follow-Up

All patients were scheduled to undergo a repeat angiography at 9 months ± 30 days along with an intravascular ultrasound (IVUS) study at prespecified study sites. Clinical follow-up was scheduled at 30 days, 4, 9, and 12 months, and annually up to 5 years.

Study Management

A data safety and monitoring board was responsible for the review of data and identification of potential safety issues. The members of this board were not affiliated with the study sponsor and were not participating in the trial.

An independent clinical event committee reviewed and adjudicated all major adverse cardiac events.

Independent study monitors (Cardialysis, Rotterdam, The Netherlands) verified all case report forms data onsite and data were stored and maintained in a central database of the same organization. The Statistical Department of Cardialysis was responsible for data analysis. The sponsor of this study contributed to study design, but did not have any role in data collection, data monitoring, or analysis. The corresponding author had full access to all data in the study and takes final responsibility for the decision to submit for publication.

End Points and Definitions

The primary end point was angiographic in-stent late loss at 9 months postprocedure defined as the difference between the postprocedure minimal lumen diameter and the minimal lumen diameter at follow-up angiography. Secondary end points were major adverse cardiac events, a composite of cardiac death (a death in which cardiac cause could not be excluded), MI (Q-wave and non-Q-wave), emergent cardiac bypass surgery, and target vessel revascu-

larization at 30 days, 4, 9, and 12 months, and yearly up to 5 years; target vessel failure defined as target vessel revascularization, recurrent MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel; and target lesion revascularization at 9 months postprocedure and stent thrombosis at 30 days and 9 months. Secondary end points included in-segment late loss, in-stent and in-segment binary restenosis rate (defined as $\geq 50\%$ diameter stenosis), in-stent, in-segment, proximal, and distal minimal lumen diameter as measured by offline quantitative coronary angiography, and neointimal hyperplasia volume at 9 months postprocedure as measured by offline IVUS.

Definitions: MI was defined either as the development of pathological Q-waves in at least 2 contiguous leads or as an elevation in creatinine phosphokinase concentration to more than double normal, in the presence of an elevated level of creatine kinase-MB isoenzyme (CK-MB) fraction. Target vessel (or lesion) revascularization was considered clinically driven if prompted by a positive functional study, by ischemic ECG changes at rest in a distribution consistent with the target vessel or by ischemic symptoms with an in-lesion diameter stenosis $\geq 50\%$ by quantitative coronary angiography, or if the lesion diameter stenosis was $>70\%$ at follow-up. Stent thrombosis was defined as confirmed thrombus within the stented vessel at the time of the clinically driven angiographic restudy for documented ischemia (chest pain and ECG changes), representing abrupt or subabrupt closure. Any death (without other obvious cause) or any Q-wave MI in the territory of the stented segment within the first 30 days was considered surrogate for stent thrombosis when angiography was not available. It was classified as acute if it occurred within the first 24 hours, subacute up to 30 days, and late after 30 days. Late thrombosis was defined as MI attributable to the target vessel with angiographic documentation of thrombus or total occlusion at the target site more than 30 days after the index procedure in the absence of an interim target vessel revascularization. Besides the adjudication of stent thrombosis according to the protocol definition, all events except periprocedural MIs were readjudicated according to the new definition proposed by Academic Research Consortium.¹⁹

Quantitative Coronary Angiography and IVUS Evaluation

An independent angiographic and IVUS core laboratory (Cardialis, Rotterdam, The Netherlands) analyzed all angiographic and IVUS recordings. All pre-, peri-, and postprocedural angiographic images were analyzed using edge detection technique (CAAS II, Pie Medical, Maastricht, The Netherlands) of stented segment and the persistent segments (defined as the length of 5 mm proximal and distal to the stent edges).

In 11 prespecified sites, stented vessel segments (including 5 mm proximal and distal to the stent edges) were examined postprocedure and at 9 months follow-up with intravascular ultrasound using automated pullback at 0.5 mm per second. A computer-based contour detection program (Curad BV, Wijk bij Duurstede, The Netherlands) was used for automated 3D reconstruction of the stented and the persistent segments. The lumen, stent boundaries, and external elastic membrane were detected using a minimum cost algorithm.²⁰ The stent volume and lumen volume were calculated according to Simpson's rule.²¹ Feasibility, reproducibility, and inter- and intraobserver variability of this system have been validated in vitro and in vivo.²⁰

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Statistical Analysis

This study was powered for noninferiority for the primary end point of in-stent late loss at 9 months. The noninferiority would be declared if the upper limit of 1-sided 97.5% confidence interval of difference did not exceed a δ of 0.20 mm from the observed in-stent late loss of Taxus stent. Assuming a late loss of 0.39 ± 0.50 mm for the Taxus stent and 0.34 ± 0.50 mm for the Nobori stent, with angiographic follow-up in 192 patients (128 in Nobori and 64 in

Taxus arm) the study would have 90% power to demonstrate noninferiority for in-stent late loss. The total sample size was increased to 240 patients to accommodate for $\approx 80\%$ compliance with 9-month angiographic follow-up. Sequential superiority testing was prespecified if noninferiority was met. The possibility to treat up to 2 lesions per patient gave additional power to the study.

All trial end points, including the primary end point, were analyzed on the intent-to-treat population. Angiographic end points were analyzed on a per lesion basis. For the calculation of late loss, only lesions having the same orthogonal projection postprocedure and at follow-up were taken into consideration. Clinical events including death, MI, and revascularization are reported on a per patient basis. For continuous variables, differences between the treatment groups were examined by analysis of variance, whereas Fisher's exact test was used for categorical variables. All statistical analyses were performed using SAS statistical software, version 8 (SAS Institute Inc, Cary, NC).

Results

Between May and October 2006, 243 patients were randomly assigned in a 2:1 ratio to receive either the Nobori Biolimus A9-eluting stent or the Taxus Liberté Paclitaxel-eluting stent. There were 153 patients (174 lesions) assigned to treatment with Nobori stents and 90 patients (98 lesions) assigned to Taxus stent. The groups were well matched with no significant differences in frequency of cardiac risk factors except for diabetes mellitus (Table 1).

Procedural Results and Angiographic Outcomes

The treated vessel distribution was similar between the groups with a somewhat higher percentage of more complex lesions in Nobori arm (Table 1). Both stents had similar success rates for lesion (100%), device (98.8% and 100% for Nobori and Taxus, respectively) and procedure (96.7% for Nobori and 95.6% for Taxus stent). Preprocedural angiographic lesion characteristics were similar between the 2 groups (Table 2).

Angiographic follow-up at 9-months was completed in 210 (86%) patients with 233 (86%) lesions. The primary null hypothesis of inferiority was rejected at the favor of the alternative hypothesis, noninferiority with an in-stent late loss in the Nobori group compared with the Taxus group, 0.11 ± 0.30 versus 0.32 ± 0.50 (95% upper confidence limit of the difference [Nobori-Taxus] was -0.12 mm; $P < 0.001$). The secondary null hypothesis of no effect was also rejected and superiority was concluded by $P = 0.001$. The cumulative frequency distribution of in-stent late loss for the 2 stents is shown in the Figure. Although all relevant angiographic parameters were similar in the 2 groups at postprocedure, significantly better results were achieved with the Nobori stent at 9 months with respect to in-stent late loss and minimal lumen diameter and diameter stenosis in-stent and in-segment (Table 2). This resulted in significant reduction ($P = 0.02$) in binary in-stent restenosis with the Nobori stent compared with the Taxus stent.

Intravascular Ultrasound Evaluation

Intravascular ultrasound was used to assess vessel, stent, and lumen volume, plaque volume, and in-stent volume obstruction after stent implantation in 95 lesions (35% of all cases, 59 in Nobori and 36 in Taxus arm). The vessel volume within the stented segment, stent volume, and lumen volume were

Table 1. Baseline Patient and Lesion Characteristics

Patient Characteristics	Nobori Stent Group (N=153)	Taxus Stent Group (N=90)	P
Age, y	62.7	63.2	0.74
Male sex, %	74.5	68.9	0.37
Diabetes mellitus	16.3	27.8	0.05
Insulin dependent, %	7.2	2.2	0.01
Hyperlipidemia, %	66.7	72.2	0.39
Hypertension, %	62.7	64.4	0.89
Family history of CAD, %	40.5	40.0	1.00
Previous myocardial infarction, %	19.6	27.8	0.16
Previous coronary artery bypass surgery, %	3.9	3.3	1.00
Previous coronary angioplasty, %	20.3	21.1	0.87
Current smoking, %	21.6	20.0	0.51
Unstable angina pectoris, %	29.4	25.6	0.11
Multivessel coronary artery disease, %	27.5	27.8	1.00
Target lesion coronary artery, %			0.19
Left anterior descending artery	35.6	46.9	
Left circumflex artery	23.6	19.4	
Right coronary artery	40.8	33.7	
No. of lesions stented, %			0.31
1	86.3	91.1	
2	13.7	8.9	
Lesion Characteristics	Nobori Stent Group (N=174)	Taxus Stent Group (N=98)	P
Reference vessel diameter, mm	2.72	2.73	0.90
Lesion length, mm	10.56	10.84	0.62
Lesion class*			
Type A/B1 lesions (%)	50.6	55.1	
Type B2/C lesions (%)	49.4	44.9	

*AHA/ACC, American Heart Association/American College of Cardiology; CAD, coronary artery disease.

not different between the Nobori and Taxus groups, neither at baseline nor at follow-up. However, mean plaque volume and area, and in-stent volume obstruction, were all significantly lower in Nobori stent at 9 months follow-up (Table 3).

Clinical Outcomes

In-Hospital

During the index hospitalization, 4 (2.6%) patients treated with the Nobori stent suffered non-Q-wave MI. In the Taxus arm, 4 (4.4%) patients suffered MI, 3 patients had a Q-wave MI, and 1 patient had a non-Q-wave MI. The overall rate of in-hospital major adverse cardiac events was 2.6% for the Biolimus A9-eluting stent group versus 4.4% for the paclitaxel-eluting stent group (Table 4).

Clinical Follow-Up

Clinical follow-up at 30 days was completed for 100% of Nobori- and 98% of Taxus-treated patients. No further adverse events were recorded in the Nobori arm, whereas 1 patient died in the Taxus arm (sudden cardiac death 5 days

after procedure) and 1 patient had 2 occurrences of stent thrombosis both followed by target lesion revascularizations. The later patient finally underwent coronary bypass surgery and withdrew consent for further participation in the study. At 9 months, 96.3% of the patients were available for clinical follow-up (99.3% in Nobori arm and 91.1% in Taxus arm). Between 30 days and 9 months (300 days) 4 patients died. Three deaths (2 in Taxus arm and 1 in Nobori arm) were adjudicated as noncardiac, whereas 1 death in Nobori arm was a cardiac death. The patient suffered a Q-wave MI due to stent thrombosis (confirmed by autopsy) in a nontarget vessel treated with Taxus stent several months before the patient's enrollment in the NOBORI 1 study. The autopsy report described the Nobori stent as fully patent. Two patients in Nobori arm and 4 patients in Taxus arm underwent target lesion revascularization whereas 1 patient in Nobori arm underwent target vessel revascularization. All these events were adjudicated as nonclinically driven. Three patients in Nobori arm had clinically driven percutaneous revascularization of target vessel. During the revascularization, 1 patient suffered non-Q-wave MI. Up to 300 days, major adverse cardiac events rate was 4.6% in Nobori and 5.6% in Taxus cohort. There were no stent thromboses in the Nobori arm, whereas there were 5 stent thromboses in 4 patients (4.4%) in the Taxus arm when analyzed by the prespecified protocol definitions. Three stent thromboses were acute and 2 were subacute. An additional analysis of stent thrombosis using the Academic Research Consortium definition confirmed 2 stent thromboses in the Taxus arm (1 definitive and 1 probable), both early, whereas there was no stent thrombosis in the Nobori arm. The difference derives from the exclusion of periprocedural MI by Academic Research Consortium definition.

At 9 months, 55.9% and 57.8% of patients in Nobori and Taxus arms, respectively, were still on dual antiplatelet therapy.

Discussion

In this prospective, randomized, multicenter, controlled trial of patients undergoing stented angioplasty for de novo lesions (up to 2 lesions located in different epicardial vessels), the implantation of Nobori Biolimus A9-eluting stent markedly reduced the in-stent late loss at 9 months confirming the primary hypothesis, the noninferiority of the Nobori versus the Taxus Liberté stent. Moreover, the a priori defined secondary hypothesis of superiority of the Nobori stent versus the Taxus Liberté stent for the same end point was also established. The clinical efficacy and safety of the Nobori stent were evidenced by the absence of both clinically driven target lesion revascularization and stent thrombosis up to 9 months follow-up. Patients treated with the Taxus Liberté stent in this trial also had good outcomes that are either equivalent or superior to previously reported results of paclitaxel-eluting stent.^{3,4}

The efficacy of locally delivered Biolimus A9 has been confirmed in this trial by significant and concordant improvements in the quantitative coronary angiography and IVUS parameters such as late loss, minimal lumen diameter, diameter stenosis, plaque area, plaque volume, and volume obstruction at 9 months when compared with locally delivered

Table 2. Results of Quantitative Coronary Angiography Analysis

	In-Stent			In-Segment		
	Nobori Stent (N _{lesions} = 143, N _{patients} = 128)	Taxus Stent (N _{lesions} = 76, N _{patients} = 70)	P	Nobori Stent (N _{lesions} = 143, N _{patients} = 128)	Taxus Stent (N _{lesions} = 76, N _{patients} = 70)	P
Reference vessel diameter, mm						
Preprocedure	na	na	na	2.72±0.53	2.73±0.52	0.90
Postprocedure	2.94±0.48	2.94±0.48	0.96	2.86±0.50	2.88±0.50	0.75
At 9 months	2.89±0.47	2.82±0.50	0.35	2.84±0.49	2.79±0.52	0.47
MLD, mm						
MLD preprocedure	na	na	na	1.11±0.33	1.00±0.37	0.031
Acute gain before	1.48±0.36	1.56±0.42	0.14	1.16±0.44	1.27±0.45	0.08
MLD postprocedure	2.59±0.41	2.57±0.42	0.67	2.27±0.48	2.27±0.46	0.95
MLD at 9 months	2.48±0.48	2.25±0.62	0.005	2.17±0.52	2.09±0.59	0.31
Late loss						
Late loss, mm	0.11±0.30	0.32±0.50	0.001	0.10±0.35	0.18±0.44	0.16
Late loss index %	0.07±0.21	0.20±0.36	0.004	0.04±0.47	0.14±0.46	0.12
Diameter stenosis, %						
Preprocedure	na	na	na	59.0±9.7	63.0±11.8	0.011
Postprocedure	11.4±5.9	12.5±7.4	0.28	13.3±5.5	14.3±6.1	0.21
At 9 months	14.1±8.5	20.7±15.2	0.001	15.7±8.8	20.7±15.1	0.009
Binary restenosis at 9 months, %						
Binary restenosis	0.7	6.2	0.02	0.7	6.2	0.02

MLD indicates minimal luminal diameter; N_{lesion}, No. of lesions with 9 months angiography in the same orthogonal projection as baseline and postprocedure except for binary restenosis calculated for all lesions at follow-up (N=152 for Nobori and N=81 for Taxus stent).

paclitaxel from Taxus Liberté stent. As a result, even though the trial was not powered for a reduction in binary angiographic restenosis, a significant difference ($P=0.02$) was found favoring Nobori stent. Approximately 10% of the patients in this study had 2 lesions treated and the per-lesion analysis and a mixed-effects analysis gave nearly identical results with modest intraclass correlation. Therefore, we decided to present all the results based on per-lesion analysis.

Although there is considerable debate concerning the use of primary surrogate angiographic, rather than primary clinical end points in trials, the latest statistical meta-analysis²² of

individual patient level data from 11 trials confirmed a correlation between angiographic findings and clinical efficacy reflected by target lesion revascularization. The report identified late loss and diameter stenosis as the most predictive parameters allowing to differentiate the efficacy of various stents. The low rates of target lesion revascularization achieved by the majority of DESs require large trials to prove noninferiority or superiority of each individual device, whereas use of a reliable angiographic surrogate makes such comparisons less cumbersome and more affordable.

By applying the formulas given by Pocock et al²² to NOBORI 1 individual patient's data, lower target lesion revascularization rates were predicted for the Nobori stent using either in-stent late loss (1.9% for Nobori versus 5.5% for Taxus) or in-stent diameter stenosis (0.7% for Nobori versus 3.5% for Taxus). These numbers support our findings

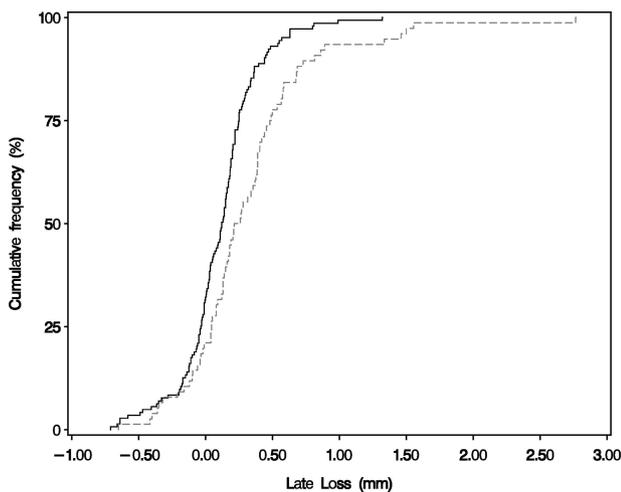


Figure. Late loss—cumulative frequency distribution.

Table 3. Serial IVUS Results at 300 Days

IVUS Data	Nobori Stent (N=43)	Taxus Stent (N=29)	P
Vessel volume, mm ³	332.9±136.5	387.1±195.6	0.20
Stent volume, mm ³	161.0±67.1	185.5±97.4	0.24
Mean lumen area, mm ²	7.35±1.84	7.74±2.42	0.45
Minimum lumen area, mm ²	5.99±1.73	6.08±2.43	0.88
Lumen volume, mm ³	158.4±66.9	173.0±81.5	0.41
Mean plaque area, mm ²	0.12±0.41	0.43±0.57	0.017
Plaque volume in-stent, mm ³	2.59±6.81	12.59±22.71	0.028
Volume obstruction, %	1.75±5.23	5.50±7.18	0.012

Table 4. Clinical Outcomes at 300 Days

All Events	Nobori Stent Group (N=153)		Taxus Stent Group (N=90)	
	N	%	N	%
Death	2	1.3	3	3.3
Cardiac death	1	0.7	1	1.1
MI	6	3.9	5	5.6
Q-wave	1	0.7	3	3.3
Non-Q-wave	5	3.3	2	2.2
TLR	2	1.3	6	6.7
Percutaneous	2	1.3	5	5.6
Surgical	0	0.0	1	1.1
Clinically indicated TLR	0	0.0	2	2.2
Percutaneous	0	0.0	2	2.2
Surgical	0	0.0	0	0.0
TVR	4	2.6	0	0.0
Percutaneous	4	2.6	0	0.0
Surgical	0	0.0	0	0.0
Clinically indicated TVR	3	2.0	0	0.0
Percutaneous	3	2.0	0	0.0
Surgical	0	0.0	0	0.0
MACE	7	4.6	5	5.6
Stent thrombosis	0	0.0	4*	4.4
Acute	0	0.0	3	3.3
Subacute	0	0.0	2	2.2
Late	0	0.0	0	0.0

TLR indicates target lesion revascularization; TVR, target vessel revascularization; MACE, cardiac death, myocardial infarction, clinically driven target vessel revascularization.

*One patient had 2 episodes of stent thrombosis.

(Table 4: clinically and nonclinically indicated target lesion revascularization for Nobori 1.3% and for Taxus 5.6%).

Overall, major adverse cardiac events rate in this trial is remarkably low, but the study was not powered to allow comparison of the 2 stents for clinical end points. The stent thrombosis rate in the Taxus arm was higher than previously reported for this type of stent, but the patient number was small and the confidence intervals are wide. The absence of stent thrombosis in the Nobori arm is particularly promising and deserves further evaluation in larger cohorts of patients with long-term follow-up.

Stent thrombosis has become one of the most critical issues in the daily use of DES.^{8–10} Delayed healing, hypersensitivity reaction to polymer carriers, and insufficient restoration or nonfunctional endothelium, along with specific patient/lesion characteristics have been implicated in the development of stent thrombosis.^{8–15} Several recently published studies have demonstrated long-term coronary endothelial dysfunction after implantation of sirolimus- or paclitaxel-eluting stents, without such observations for bare metal stents.^{23–25} However, the link between adverse clinical outcomes and abnormal vessel wall motion is yet to be established. Contrary to the findings with other DES, another study, comparing the sirolimus-eluting stent Cypher to the Biolimus A9-eluting

stent Nobori, reported almost completely preserved endothelium-dependent vasomotion in adjacent stent segments after implantation of a Nobori stent with impaired response of vessels treated with a Cypher stent.²⁶ Considering that sirolimus and Biolimus A9 belong to the same family and share the common mechanism of action, it could be speculated that either the biodegradable polymer coating only on the outer surface of the stent or better drug release kinetics could have contributed to this finding.

The neointimal volume suppression recorded for the Biolimus-A9 eluting stent in this trial resembles the efficacy previously reported for sirolimus- and everolimus-eluting stents, whereas it seems superior to zotarolimus- and paclitaxel-eluting stents.^{1–7,27,28} Our results add further evidence to Biolimus A9 efficacy confirming the findings of NOBORI 1 phase 1 and of recently published LEADERS trials that studied similar stent platform.^{17,29} The target vessel failure rate of 4.6% with Nobori stent compares favorably with the recently reported results of the most contemporary DESs.^{27,28} The LEADERS clinical trial that enrolled complex patients population representing routine clinical practice reported acceptable low target vessel failure rate indicating that Biolimus A9-eluting stents could present a valuable alternative to currently available DES.²⁹

Study Limitations

Although this study was a prospective, multicenter, randomized, controlled trial, some limitations remain. The trial was powered to detect differences in angiographic end point and, as such, does not allow drawing any definite conclusions concerning clinical outcomes. Also, it is important to note that the results from this trial are specific to the patient population studied and cannot be generalized to the much broader population of patients with more complex lesions. Further studies enrolling larger number and higher risk patients with clinical end points are either ongoing or planned to answer those questions.

Conclusions

In this head-to-head comparison with an established DES as a reference, the Nobori Biolimus A9-eluting stent showed a significantly greater degree of neointimal hyperplasia inhibition that was translated into a significant reduction of angiographic restenosis and the absence of clinically driven target lesion revascularization. In addition to its excellent efficacy, the Nobori stent seemed safe in the studied population with a very low rate of adverse cardiac event and no stent thrombosis up to 9 months follow-up. The results of our study suggest that the Nobori stent might represent a critical step toward achieving an optimal balance between preserved efficacy and improved safety.

Appendix

NOBORI 1 Principal Investigator

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The NOBORI 1 Steering Committee

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B. Chevalier received a consulting fee because he is the principal investigator of the study. H. Nagai, D. Detiege, and D. Paunovic are employees of the study sponsor. None of the other authors have declared any conflict of interests related to the content of this manuscript.

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SUPPLEMENTAL MATERIAL

**A SAS PROC MIXED analysis with a compound symmetry correlation structure
for the covariance matrix on the primary endpoint (i.e. in-stent late loss)**

NOBORI vs Taxus stent

Analysis of primary endpoint with and without taking into account the within and between Patient Correlation Structure (PCS)

Results of the ITT analysis

Absolute loss [mm]	Nobori		Taxus	
	With PCS	Without PCS	With PCS	Without PCS
Estimated treatment effect	0.1069	0.11	0.3295	0.3185
Standard error	0.0335	0.0248	0.0455	0.0578

Treatment effect (Nobori – Taxus) [mm]		Standard error		95% upper confidence limit	
With PCS	Without PCS	With PCS	Without PCS	With PCS	Without PCS
-0.2225	-0.209	0.0565	0.0541	-0.1292	-0.119

Conclusions for the interim analysis (N=219 evaluable lesions)
ITT population

Test for non-inferiority based on the one-sided confidence interval for the difference in late loss (Nobori – TAXUS)
Equivalence limit: ≥ 0.2 mm

Analysis	Location	95% Upper confidence limit	Conclusion
Matched data	STENT	-0.13	Non-inferior

The above conclusions do not include corrections for non-evaluable lesions.

The p-value for non-inferiority is $p < 0.001$

The upper limit of the confidence interval does not cross the non-inferiority limit

SUPPLEMENTAL MATERIAL

**A SAS PROC MIXED analysis with a compound symmetry correlation structure
for the covariance matrix on the primary endpoint (i.e. in-stent late loss)**

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