Bionert Stent Angiographic Study

a report by

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Drug-eluting stents (DES) have demonstrated their efficacy in reducing restenosis and repeated revascularisation.[1–4] Some concerns related to DES safety (increased late stent thrombosis, difficulties with antiplatelet therapy compliance) and cost restrictions have encouraged interventional cardiologists to be selective in the use of DES and bare-metal stents (BMS).[5–8] The latest generation of BMS have been successful in the treatment of anatomically favourable lesions with a low incidence of major adverse cardiac events (MACEs) at short- and mid-term follow-up. Some practitioners prefer using BMS when facing lesions with low risk of restenosis or problems with antiplatelet therapy compliance. This selection of a BMS is especially important in cases of scheduled or probable extracardiac surgery, or when there is no history of clear antiplatelet therapy adherence; therefore, it is important to have an effective BMS to successfully treat these cases.

This study aims to evaluate the short- and mid-term results of the Oxygen Ion Bombarded Stents (Bionert) stent in the treatment of lesions with low to medium risk of restenosis located in native coronary arteries, and to compare these results with those obtained by the reference cobalt–chromium alloy stents (Driver®, Guidant Corporation and Vision®, Medtronic) and other BMS. It is a prospective, observational, multicentre study that has included 298 patients treated with the Bionert stent in European and South American hospitals.

Description of the Stent

The Bionert stent is a stainless steel stent, the surface of which has been modified by oxygen ionic implantation. This technology makes the stent extremely biocompatible because the oxygen ions immobilise the heavy metal ions and prevent them from being released into the bloodstream. As a consequence, the nickel, chromium and molybdenum ions are encapsulated into the structure of the stainless steel and kept inside. During *in vitro* studies the release of these heavy metal ions decreased three-fold. The surface modification is not a coating but a deep implantation and therefore the stent does not lose its configuration, does not delaminate in expansion and does not crack while being crimped onto the balloon. This prevents thrombus formation. The Bionert stent is a laser-cut tube with open-cell design, and is flexible with a big radial force and minimal recoil.

Methods

Patient Selection

Patients included in the study presented stable or unstable angina or silent ischaemia, and were scheduled for percutaneous coronary intervention of *de novo* or restenotic lesions after balloon angioplasty. All of the lesions were treated with a Bionert stent. To be included as a candidate in the study the patient had to be over 18 years of age, with one or two *de novo* restenotic lesions after balloon angioplasty located in vessels with a reference diameter by visual estimation of 3–4.5mm and a length of up to 15mm. Diabetic patients and those with coronary total occlusion were excluded from the study. Hypersensitivity or allergies to aspirin, heparin or clopidogrel were criteria for exclusion. Also excluded were those with thrombocytopenia or leucopenia, patients with ST-segment elevation myocardial infarction (MI) diagnosed within 24 hours of the intervention and those with severe hepatic and renal disease. Angiographic exclusion criteria included lesions located in the left main trunk, those located at the ostium of the left anterior descending and circumflex arteries and those containing thrombus or with severe calcification.

Stent Procedure

Percutaneous procedures for stent implantation were performed using the femoral or radial approaches, according to the protocols of each centre. The choice of pre-dilatation or direct stenting technique was left to the operator's discretion. Nevertheless, direct stenting was not recommended in cases of calcified lesions, in lesions located distal to severe tortuosity or if the vessel was nearly occluded (lesion severity >90%). When pre-dilatation was required, it was advocated to use a balloon shorter than the stent to be used. The minimal pressure recommended for stent deployment was 10 atmospheres. Post-deployment dilatation at high pressure was left to the judgement of the operator, but was recommended in cases of stent underexpansion suggested by angiographic and/or intravascular ultrasound findings. Available stent sizes for the patients included in the study were 2.75, 3, 3.5, 4 and 4.5mm in diameter and 9, 14 and 18mm in length. Intravenous or intra-arterial sodium heparin at a dose of at least 5,000IU was administered before the procedure. They were also treated with acetylsalicylic acid (ASA) 100–325mg, which was continued for life. Before, during or immediately after the stent implantation, the patients were also treated with at least 300mg of clopidogrel as a loading dose, followed by 75mg/day for at least one month.

Follow-up

Post-procedure cardiac enzymes and surface electrocardiogram were monitored at least once in the first 24 hours, and repeated if the patient had chest pain or any other symptom suggestive of myocardial ischaemia. Patients were discharged the day after the procedure if there were no

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Table 1: Baseline Clinical Characteristics

Age 63±11 years
Male gender 243 (81%)
Hypertension 179 (60%)
Hypercholesterolaemia 181 (61%)
Current smoker 100 (34%)
Ex-smoker 84 (28%)
Clinical Indication
Stable angina 27%
Unstable angina 54%
Silent ischaemia 12%
Others 7%
Recent ST-segment elevation myocardial infarction 27%

Table 2: Baseline Angiographic Characteristics

Lesion Location
Left anterior descending–diagonal 34.7%
Left circumflex artery–obtuse marginal 24.7%
Right coronary artery–patent ductus arteriosus–paramedian pontine infarct 40.6%
Type of Lesion
A 18.7%
B1 39.9%
B2 33.3%
C 8.1%
Calcifications 17%
Thrombus 12%

Table 3: Procedural Characteristics

Stent Diameter
2.75mm 0.4%
3mm 57.2%
3.5mm 32.8%
4mm 9.6%
Stent Length
9mm 6.3%
14mm 42.8%
18mm 50.6%
19mm 0.4%
Moderate–severe tortuosity 35%
Glycoprotein IIb/IIIa 8%
Ejection fraction 60±11%

adverse events. After discharge, patients were clinically and electrocardiographically evaluated at one month and six months. In 30% of pre-specified patients a repeat coronary angiogram for angiographic evaluation was performed at six months.

Quantitative Coronary Angiography

Three sets of coronary angiograms (pre- and post-procedure and at six-month follow-up) were recorded. Before the procedure, a minimum of three projections (two orthogonal) were obtained for the left coronary and two for the right. The same projections were performed post-procedure and an angiographic evaluation was carried out at six months. A 6F guiding catheter or bigger was recommended to minimise the error of angiographic measurements. Intra-coronary nitroglycerine (200µg) was injected prior to each set of angiographies. The coronary angiograms were recorded on CD dicom. At the beginning of the injection, a big enough segment of catheter filled with contrast media was recorded to be used as a reference point. Quantitative analyses of the coronary angiograms were performed in a core angiographic laboratory through automatic borders detection (CMS version 5.0). The following values were analysed at the index procedure: reference vessel diameter, per cent diameter stenosis, minimal vessel diameter, lesion length and acute gain. At six-month angiographic evaluation, the values analysed were: reference vessel diameter, per cent diameter stenosis, minimal vessel diameter (including 5mm pre- and post-stent), late loss and loss index.

End-points

Primary End-point

The study primary end-point was the cumulative incidence of MACEs at six months: death, Q and non-Q MI and target lesion revascularisation (TLR).

Secondary End-points

There were several secondary end-points: binary angiographic restenosis (in a pre-specified group [30%] of patients included in the study), procedural and device success and MACEs at 30 days.

Data Collection and Statistical Analysis

Clinical and angiographic data were collected at the Cardiovascular Research Foundation (CRF) and forwarded to the data co-ordinating centre for statistical analysis. Data are presented by the mean and standard deviation (SD), median and interquartile range (IQR) or the total number of patients (n) and its proportion in relation to the total (%) as the variable characteristics. The statistics analysis was performed by the SPSS version 13.0 program.

Patient and Angiographic Characteristics

A total of 298 patients (324 lesions) were enrolled in 23 hospitals in Europe and South America (see end of article for participating centres and the number enrolled by each centre). The baseline clinical and angiographic characteristics are shown in *Tables 1* and *2*. The mean age was 63 years and 81% of the patients were male. The indication to begin the revascularisation procedure was mostly acute coronary syndrome (54% unstable angina and 27% recent ST-elevation MI). The majority of lesions (81.3 %) were complex: type B or C according to the American College of Cardiology/American Heart Association (ACC/AHA) classification. The location of the lesions was 40% in the right coronary artery or branches, 35% in the left anterior descending artery and 25% in the circumflex. Calcification was observed in 17% of the lesions and thrombus in 12%. Moderate tortuosity proximal to the lesion was observed in 35% of the cases. Mean left ventricular ejection fraction was 60±11% (see *Table 3*).

Procedural Characteristics

In 66% of the patients, the procedure was performed by direct stenting without prior balloon pre-dilation. The mean stent deployment pressure was 14.4 atmospheres. In 23% of the patients a high-pressure balloon was used after stent deployment, and the main procedural characteristics can be seen in *Table 3*. The most common stent diameters used were 3mm (57%) and 3.5mm (33%), and stent lengths were 18mm (51%) and 14mm. Additional stents were used in nine of the patients (3.3%): in eight cases because the lesion was not completely covered and in one case because of intimal dissection. Glycoprotein IIb/IIIa inhibitors were used in 8% of the patients.

Quantitative Coronary Angiographic Analysis

Angiographic data of the index procedure and six-month follow-up of 83 pre-specified patients who underwent angiographic evaluation were available for analysis (*see Table 4*). The reference vessel diameter before the

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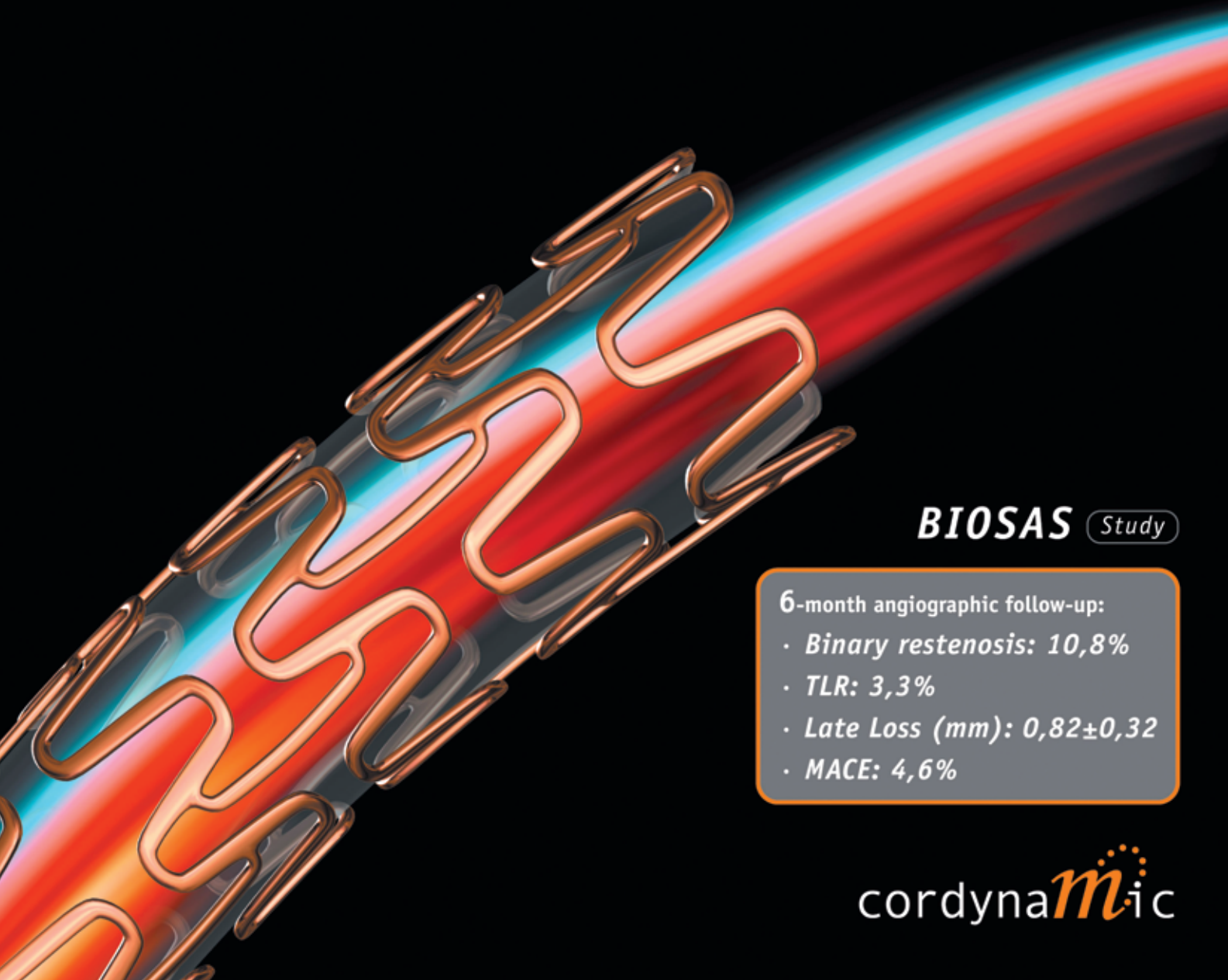

BIOSAS Study

6-month angiographic follow-up:

- *Binary restenosis: 10,8%*
- *TLR: 3,3%*
- *Late Loss (mm): 0,82±0,32*
- *MACE: 4,6%*

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Table 4: Quantitative Coronary Angiography

	Pre	Post	Follow-up
Reference diameter (mm)	2.98±0.47	3.09±0.5	2.98±0.42
Minimal lumen diameter (mm)	1.15±0.41	2.82±0.52	1.99±0.41
Lesion length (mm)	10.8±0.45		
% diameter stenosis	61.3	8.7	32
Late loss (mm)	0.82±0.32		
Binary restenosis (>50%)			9 (10.8%)

Table 5: In-hospital Results

Procedural success 99%
Death 0.6%
Myocardial infarction 0%
Stroke 0%
Target lesion revascularisation 0%
Subacute thrombosis 0%
Clinical Outcome at Six-month Follow-up
Death 3 (1%)
Myocardial infarction 1 (0.3%)
Target lesion revascularisation 10 (3.3%)
Target lesion revascularisation–coronary artery bypass graft 2 (0.6%)
Target lesion revascularisation–percutaneous coronary intervention 8 (2.7%)
Major adverse cardiac events 4.6%

procedure was 2.98±0.47mm, which increased to 3.09±0.5mm and returned to 2.98±0.42mm at six-month follow-up. The lesion length was 10.8±0.48mm. The minimal luminal diameter was 1.15±0.41mm, increasing to 2.82±0.52mm, and was maintained at 1.99±0.41mm at six months. Diameter stenosis was 61% pre-procedure, 8% post-procedure and 32% at follow-up. Late loss was 0.82±32mm. Binary angiographic restenosis at six months was observed in nine patients (10.8%). Severe restenosis (>70%) was observed in one patient only (1.2%) and there were no cases of total occlusion angiographic evaluation at six months.

In-hospital Results

The results of the 298 patients in the study were available for analysis (see *Table 5*). The procedure was successful in 297 patients (99%). Device success (successful procedure using only the index device) was achieved in 290 of the patients (97%). One patient (0.6%) died after emergency surgery and there were no incidences of MI, stroke, TLR or stent thrombosis.

Follow-up Results

Clinical data from the 297 discharged patients (99%) were available for analysis at one month and from 297 at at six-month follow-up. At one month, one more patient (0.3%) had died after a probable stent thrombosis, one patient suffered an MI and four patients (1.3%) underwent TLR – one (0.3%) by surgical bypass and three (1%) by percutaneous procedure. In summary, the cumulative incidences of MACEs at one month were mortality 0.6%, MI 0.3% and TLR 1.3%. The incidence of acute/subacute thrombosis was 0.3%. At the end of the observation period (six months) three patients had died (1%), one patient (0.3%) had suffered an MI and 10 patients (3.3%) underwent repeat TLR (two [0.6%] surgical and eight [2.7%] percutaneous). The cumulative incidence of MACEs at six months was 4.6%.

Discussion

DES have dramatically changed the landscape of interventional cardiology, and have been demonstrated to be efficient in reducing angiographic restenosis and TLR.[9] Safety concerns related to late and very late stent thrombosis, difficulty or uncertainty in patient compliance with prolonged dual antiplatelet therapy[10] and doubts related to cost-effectiveness in short lesions located in non-small vessels have shifted interest towards finding efficient and dependable BMS to be used in such scenarios. The Bionert Stent Angiographic Study (BIOSAS) demonstrates that a modern, well-designed BMS can be efficient in the treatment of low- to medium-risk lesions with low incidence of angiographic restenosis (<10.8%) and a low incidence of TLR (3.3%).

In a recent multicentre registry by Marzocchi et al.,[11] the multivariate analysis did not show any benefit of DES over BMS in low-risk patients. Patients with diabetes and those with long lesions or small reference diameter were excluded from the BIOSAS study.[12] The potential impact of oxygen ion bombardment in reducing restenosis isolating the heavy metals is an attractive hypothesis that seems to be working in these low- to medium-risk lesions. The high rate of successful direct stenting (66%) highlights the good performance of the Bionert stent. There was only one case of probable subacute stent thrombosis following one-month clopidogrel therapy. There are limited data on angiographic restenosis of the new alloy cobalt chromium BMS, but the reported data pertain to the incidence of angiographic restenosis and TLR observed in the present study. ■

Centres Participating in the Study

Nuestra Senora del Mar (n=20); Clinic i Provincial (n=20); De Galdakao (n=20); Gregorio Marañón (n=17); General de Valencia (n=4); De Navarra (n=4); Complejo Hospital de León (n=10); Txagorritxu (n=4); Josep Trueta (n=19); Juan Ramón Jiménez (n=16); Virgen de la Salud (n=4); Virgen de las Nieves, all Spain (n=13); University Hospital Vienna (n=13); Krankenanstalt Rudolfstiftung (n=11); Wiener Neustadt, all Austria (n=16); CHU Toulouse (n=30); Clinique Clairval (n=7); Clinique de la Casamance, all France (n=17); Instituto Cardiología y Cirugía Vascular, Cuba (n=18); Hospital Italiano, Argentina (n=11); San Borja Arriarán, Chile (n=18); Militar, Colombia (n=5); and Interbalkan Medical Centre, Greece (n=11).

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