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A novel nanocarrier sirolimus-coated balloon for coronary interventions: 12-Month data from the Nanoluté Registry☆

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ABSTRACT

Background: The aim of the Nanoluté registry was to observe the clinical performance of a novel sirolimus coated balloon (SCB) (Concept Medical Research Private Limited, India) for the treatment of coronary de-novo and restenotic lesions.
Methods: All patients treated with SCB between July 2012 and September 2015 were enrolled at Indian centres and clinically followed for 1, 3, 6 and 12 months post-procedure. Primary endpoints were procedural success and device-oriented adverse cardiac events (DOCE) at 12 months. DOCE were defined as a composite of cardiac death, target lesion revascularization (TLR) and target vessel-myocardial infarction.
Results: A total of 394 SCB were used in 332 patients to treat 356 lesions. In-stent restenosis and small coronary vessel disease occurred in 46% and 43% of the patients respectively. Mean balloon length and diameter (average ± SD) were 21.83 ± 6.70 mm and 2.69 ± 0.45 mm respectively. All patients with 1 year follow-up were included. Overall DOCE rate was 4.2% (n = 14) which included death 0.3% (n = 1), TLR 3.6% (n = 12) and myocardial infarction 0.3% (n = 1).
Conclusion: The Nanoluté prospective registry, is the first clinical evidence of the safety and feasibility of this type of SCB, both in patients with in-stent restenosis or de novo lesions.

1. Introduction

In the last decades, the use of coronary stents experienced an exponential growth, also caused by the technical improvements of the latest generations, which resulted in a widespread adoption as the standard of care for percutaneous coronary interventions (PCI). However, the long-term outcome of stent implantation remains significantly constrained by the occurrence of in-stent restenosis (ISR) or stent thrombosis over time. While many factors such as stent malapposition and stent fracture have been shown to be contributory, the fundamental mechanism of ISR relate to the progressive increase in cellularity from either neointimal formation, neoatherosclerosis, or their combination. The use of bare metal stents (BMS) has been associated with a 16–44% incidence of ISR [1–3], and although drug-eluting stents (DES) reduced the risk, its incidence remained clinically significant (5–15%) [3,4]. Furthermore, the increasing use of DES in more complex patients, namely those with small arteries, long lesions, diabetes and history of bypass surgery, is associated with a higher risk of ISR.

While DES is used routinely for the treatment of ISR [5] drug-coated balloons (DCB) therapy has emerged as a reasonable alternative in this setting, and they are increasingly used for small vessel and bifurcation management thanks to their anti-proliferative properties, without the need for permanent implants [6,7].

To date, all DCB elute paclitaxel due to its favorable pharmacokinetic properties. However, its efficacy has been sometimes questioned, especially when a drug carrier is not used and due to the limited therapeutic window. In 2016 the first sirolimus-eluting DCB (SCB) has obtained the CE mark and has been marketed in Europe. We here present the 12-month results of the first study performed with this device.

☆ All the authors have no conflicts of interest to declare.
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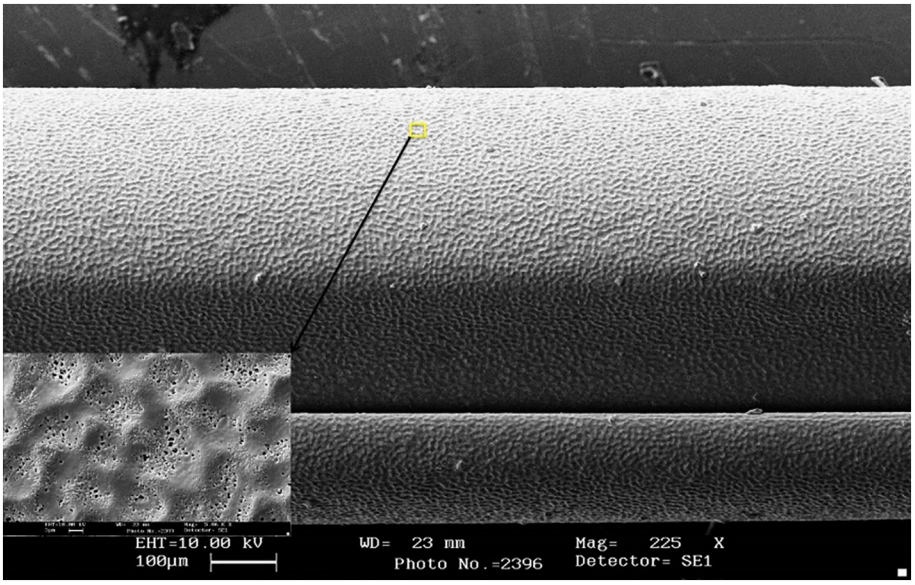

Fig. 1. Scanning electron microscope images of SCB.

2. Methods

2.1. Device description

Magic Touch – SCB (Concept Medical Research Private Limited, India) is the only CE approved device which elutes the drug sirolimus thanks to a nanocarrier technology (Fig. 1). Drug nominal dose on a 3.00/15 mm balloon is 180 µg (~1.27 µg/mm^2); sirolimus is encapsulated in a phospholipid bi-layer as drug carrier and in nanocarriers configuration. The device is available in lengths from 10 to 40 mm and diameters from 1.50 to 4.00 mm. The delivery system is a semi-compliant coronary balloon with low tip profile and nanocarriers are coated on hydrophilic coated surface of balloon. Hydrophilic surface of the balloon on contact with blood forms micro-channel by a wetting mechanism, which upon inflation of balloon delivers drug faster. Preliminary bench-test and animal data show how SCB due to its coating uniqueness neither leaves particulates to downstream nor determines distal embolization [5] [8,9].

2.2. Study design and population

The Nanoluté registry is a prospective, multicenter clinical registry and post market clinical follow up evaluation that enrolled a real world, all-comer patient population at various interventional cardiology centers in India.

Inclusion criteria were patients with age > 18 years, coronary artery disease including chronic stable angina, silent ischemia, and acute coronary syndromes. ISR, small coronary vessel disease, bifurcation lesions, multi-vessel disease and hybrid strategies were included. Allowed reference vessel diameters were 1.50–4.00 mm.

Exclusion criteria were patients with known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, sirolimus or sensitivity to

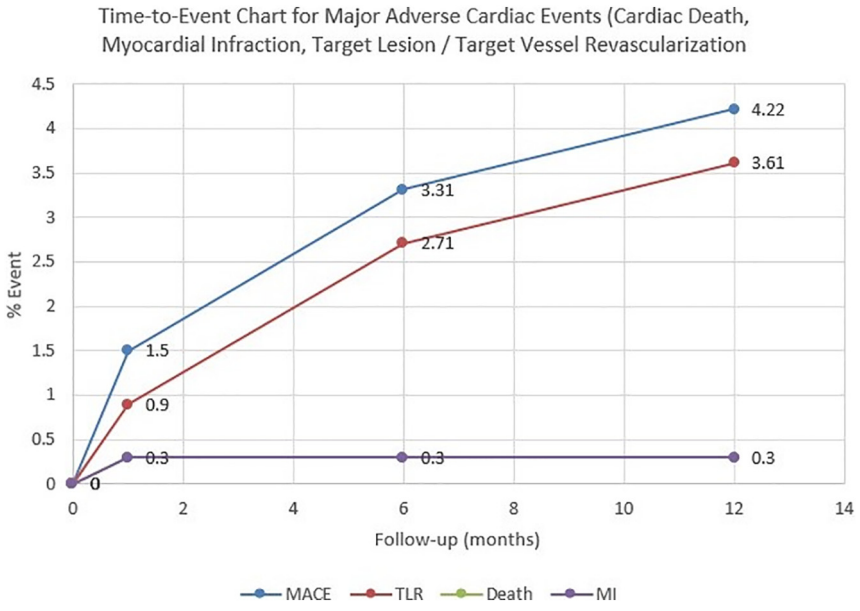

Fig. 2. Time-to-event chart for device-oriented adverse cardiac events (DOCE) and their single determinants.

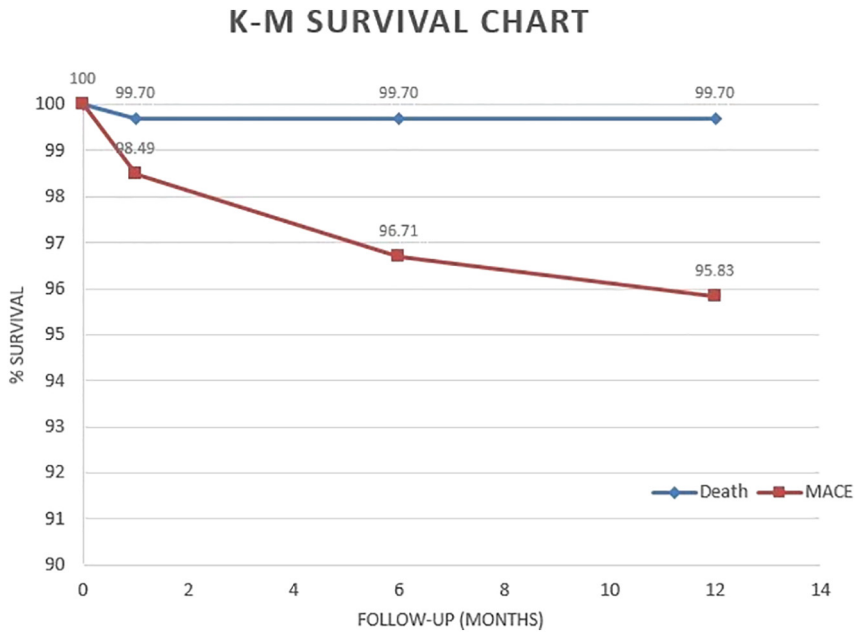

Fig. 3. Survival curve at 1-year follow-up by Kaplan–Meier method (total death and DOCE).

contrast media which could not be adequately pre-medicated; patients already participating in another clinical evaluation; visible thrombus at lesion which was not treatable with aspiration, target lesion/vessel where pre-dilatation was not performed or not successful, heavy calcification of the target lesion or greater than mild calcification in the proximal vessel and highly tortuous lesions which could impair the access of device to treatment site (Figs. 2–7).

For the purpose of this analysis, only patients with complete 12-month follow up were included. Therefore, we excluded patients that were lost at follow up (12).

2.3. Procedure

PCI procedure was performed according to current standard international guidelines. During procedure, intravenous heparin (70–100 units/kg) was administered after sheath insertion to maintain an activated clotting time > 250 s (or >200 s if glycoprotein IIb/IIIa inhibitors were used, at the operator's discretion). Regarding dual antiplatelet treatment, aspirin 100–325 mg was given prior to procedure; a loading dose of clopidogrel 300 mg was administered prior to procedure (600 mg in case the procedure was scheduled within 2 h). After the procedure, all patients received aspirin (100–325 mg) daily indefinitely; clopidogrel 75 mg was prescribed for 6 months. Lesion pre-dilatation with either a semi-compliant or non-compliant balloon was mandatory. SCB were inflated for at least 45 s if clinically tolerated.

2.4. End points and clinical follow-up

Primary study endpoints were procedural success at discharge, defined as angiographic success without the occurrence of adverse events during hospitalization, and device-oriented adverse cardiac events (DOCE) at 12 months. DOCE were defined as a composite of cardiac death, target lesion revascularization (TLR) and target vessel-myocardial infarction (MI). Secondary endpoints were the single determinants of DOCE at 6 and 12 months. MI was defined as the presence of pathological and new Q-waves on the ECG, or an increase in creatinine kinase-myocardial band level to >5× the upper limit of the normal range.

All patients had a clinical (visit or phone call) follow-up at 1, 6, and 12 months. Angiographic follow up was not recommended unless clinically indicated. All device-related events were adjudicated by a Clinical Event Committee that consisted of cardiologists not participating in the registry.

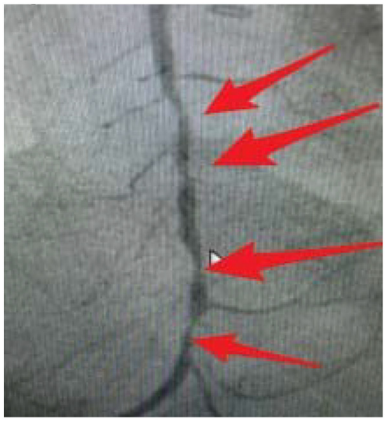

Fig. 4. Pre-treatment angiography showing diffuse narrowings of the distal left anterior descending artery.

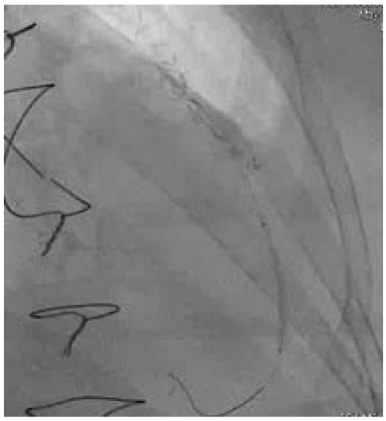

Fig. 5. Magic Touch SCB delivery (2.5/30 mm).

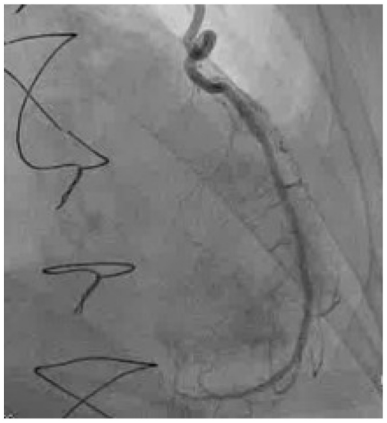

Fig. 6. Post treatment, final angiographic result.

2.5. Statistical analysis

Continuous variables were expressed as mean values ± standard deviation (SD), values were reported as numbers with relative percentages of standard deviation. P values < 0.05 were considered statistically significant. Cumulative event rates were analyzed using the Kaplan-Meier methods, and the rate differences among the groups estimated using the log-rank test. All analyses were performed using the SPSS 21.0 software package (SPSS, Chicago, IL, USA).

3. Results

Between July 2012 and September 2015 a total of 332 patients with 356 lesions were treated with 394 SCB and enrolled in the study. The baseline demographics of the patients are shown in Table 1. There was a history of diabetes in 154 (46.4%) patients. Baseline lesion characteristics are shown in Table 2. Patients with in-stent restenosis were 153 (46.1%), whereas 143 (43.1%) had small vessel disease (diameter < 2.75 mm). Table 3 shows the type of restenosis.

Pre-dilatation, recommended by protocol, was performed in 348 lesions, including the use of scoring balloon in 5 lesions. Procedural characteristics are described in Table 3. Notably, angiographic success was obtained for all the lesions, and in only 6.6% of the cases a BMS was implanted after SCB use because of a flow-limiting dissection.

Procedural success, primary study endpoint, was obtained in 331 (99.7%) patients.

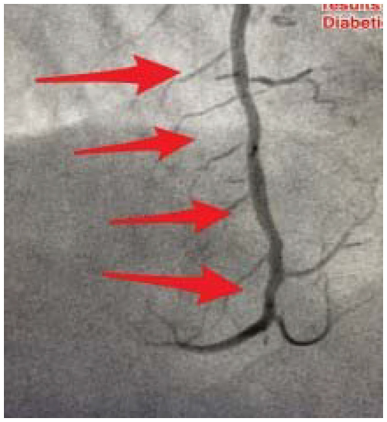

Fig. 7. One year angiographic follow-up.

Table 1
Baseline demographics.

n = 332	
Age, years (mean ± SD)	59.80 ± 9.85
Male, n (%)	272 (81.93)
Diabetes mellitus, n (%)	154 (46.39)
Hypertension, n (%)	156 (46.99)
Previous MI, n (%)	114 (34.14)
Previous CABG, n (%)	21 (6.33)
Stable angina, n (%)	104 (52.11)
Unstable angina, n (%)	104 (31.33)
STEMI, n (%)	36 (10.84)
NSTEMI, n (%)	19 (5.72)

CABG - coronary artery bypass graft, MI – myocardial infraction, N-STEMI - non ST segment elevation myocardial infarction, SD – standard Deviation, STEMI - ST segment elevation myocardial infarction.

3.1. Clinical outcome

All patients had complete clinical follow up at 1 year. The co-primary endpoint, DOCE at 12 months, occurred in 14 patients (4.2%). Among the total of 14 DOCE (1 year), 9 events were reported in patients with ISR lesions and 5 events reported in patients with de-novo lesions. We registered 1 (0.3%) case of non-cardiac death, 1 (0.3%) MI and 12 (3.6%) TLR. These results are shown in Table 4.

4. Discussion

This is the first study which evaluates the feasibility and safety of PCI with a novel SCB. The main findings of the Nanoluté registry are the good immediate performance of this device, and an overall low DOCE rate at mid-term follow-up; the DOCE rate was mainly driven by TLR, whose rates were acceptable considering that about half of the patients were admitted for ISR during index procedure. Of note 10.8% of patients presented a ST-elevation myocardial infarction (STEMI); these patients which presented a STEMI during index procedure had 51 lesions treated with 54 SCB. The causes for the STEMI were ISR in 67% of the cases, and small coronary vessel disease in the remaining patients.

Until 2016, all DCB available in Europe eluted paclitaxel delivered with various drug carriers. Paclitaxel is a drug with limited therapeutic window with possible toxicity at high dosages, whereas the -limus group of antiproliferative agents is considered safer due to the lone cytostatic properties. On the other hand, the higher lipophilia of paclitaxel, assisted by a drug-carrier with drug to excipient ratio 1:1, has made it the drug of choice for coronary and peripheral applications until now [7] [6,10].

The device clinically tested in this registry was developed with a new technology that allows sirolimus, a much less lipophilic drug, to be delivered to the vessel wall and to be absorbed in the *tunica media* and *adventitia*. Encapsulation of sirolimus with the unique phospholipid drug carrier gives improved drug retention profile and bioavailability in

Table 2
Baseline procedural characteristics.

n = 356	
Target vessel location: left anterior descending, n (%)	131 (36.80)
Right coronary artery, n (%)	72 (20.22)
Left circumflex artery, n (%)	52 (14.61)
Obtuse marginal branch	33 (9.27)
Multivessel PCI, n (%)	23 (6.33)
Average number of lesions treated per patient	1.19
SCB length, mm (mean ± SD)	21.83 ± 6.70
SCB diameter, mm (mean ± SD)	2.69 ± 0.45
Inflation pressure, bar (mean ± SD)	11.81 ± 5.37
Inflation time, seconds (mean ± SD)	59.63 ± 10.47
SCB-alone therapy, n (%)	310 (93.37%)

SCB – sirolimus-coated balloon.

Table 3
Type of stent with in-stent restenosis.

Type of stent with in-stent restenosis, N_L (%), no. of ISR lesions = 153	
DES	122 (80%)
BMS	16 (10.4%)
BVS	1 (0.9%)
CABG	3 (1.6%)
Unknown	11 (7.1%)

atherosclerotic or restenotic lesions thanks to a dedicated nanotechnology. Preclinical studies were conducted on various animal models, which showed adequate pharmacokinetic level of sirolimus at lower dosages. Drug was quantified by pharmacokinetic up to 14 days [9]. A drug travelling study established travel of sirolimus from *tunica intima* to *media* and later *adventitia* over a time domain when sirolimus was conjugated using DTAF fluorescent molecule [11].

In the current registry the rate of TLR was 3.6%, which is comparable to the TLR rate of 2.9% at 7.5 months of the Valentines II trial [12] and the 5.2% of the Sequent Please World Wide Registry [13], two registries with paclitaxel-eluting balloons.

Of note, most of the SCB in this study were used without stenting, also following DCB consensus document recommendations [6]. In all patients DAPT duration was prescribed for up to 6 months and no vessel thrombosis was recorded on follow-up. Usually, in case of DCB-only PCI DAPT is prescribed for 1 month. Additional research is needed to determine the optimal duration of DAPT after SCB use.

In Europe, at our center, Ospedale Fatebenefratelli in Milan, we first had the chance to extensively try this new device, and described our experience in the FASICO (FAtebenefratelli SIrolimus COated-balloon) registry [14]. This was a prospective single-center study of the first consecutive patients, with at least one lesion treated with the Magic Touch SCB between April and July 2016.

Our aim was to demonstrate the acute performance and the 6-month efficacy and safety of this device in a real world, complex population, including acute coronary syndromes, ISR (around half of the population), long lesions and calcified vessels.

Despite the small population enrolled (32 patients with 34 lesions) we found the results were encouraging; the primary study endpoint, procedural success, was obtained in 100% of the cases, with no in-hospital complications, while the co-primary endpoint, rate of major adverse cardiac events (MACE), a sum of cardiac death, myocardial infarction-MI, TLR at 6-months, occurred in 3 patients during the follow up (6.9 ± 1.7 months). No cases of death or MI were observed, while the 3 cases of TLR occurred in patients where a second-generation DES (2 cases) or PCB (1 case) had already failed.

The inherent limitations of a registry apply here. This was a single-arm treatment group analysis without a comparative reference technique. The adjudication of the events was performed by single cardiologists of each center that were not participating at the study, but there was a common, pre-specified and per-protocol definition of all the events. The study included only patients which completed 1-year follow-up or of which the survival state was known: therefore the outcome of patients which left the study (12) for any reason and did not inform the investigator is unknown. The low total TLR rate can be partially justified by the fact that almost half of the patients had small vessel disease, a less symptomatic clinical condition.

A larger prospective study with longer follow-up is needed to further investigate the long-term safety of this novel therapeutic option in patients with coronary artery disease.

For this reason, we designed, and is currently undergoing, the EASTBOURNE registry a prospective, spontaneous, multicenter, single arm, interventional study, which is enrolling all patients with coronary artery disease and clinical indication for coronary angioplasty, and treated with SCB.

The aim of this study is to evaluate the performance of the Magic Touch SCB in terms of efficacy and safety when used in a real world population, for a broad spectrum of coronary lesions, including native vessel disease and ISR.

Similarly to other registries on DCB, the primary endpoint of the study is TLR at a 12 months clinical follow-up, while secondary endpoints are angiographic success (residual stenosis < 50% and final TIMI flow 3), procedural success (angiographic success in absence of cardiovascular adverse events during hospitalization), MACE at 6, 12 and 24 months, every single component of MACE.

So far, nearly half of the planned patients have been enrolled and an interim analysis performed in December 2017 showed the Magic Touch to be highly effective in this all-comer population with an angiographic success of 98%; the 1-month clinical follow up, available for 280 patients, showed a good safety and efficacy profile.

Table 4
Primary and secondary study endpoint.

Endpoints	Primary endpoints DOCE at 6 months procedural success N = 332	Secondary endpoints DOCE at 12 months N = 332
DOCE	11 (3.3%)	14 (4.2%)
-TLR/TVR	10 (3%)	12 (3.6%)
-TV-MI	1 (0.3%)	1 (0.3%)
-Cardiac death	1 (0.3%)	1 (0.3%)
Procedural success	331 (99.7%)	-

5. Conclusions

The Nanoluté prospective registry, along with the depicted limitations, constitutes the first clinical evidence of the safety and feasibility of this type of SCB, both in patients with in-stent restenosis or de novo lesions. Further studies are required before suggesting a SCB broader adoption.

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