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ORIGINAL STUDIES

Long-term follow-up after sirolimus-coated balloon use for coronary artery disease. Final results of the Nanolutè study

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Abstract

Objectives: To test the long-term efficacy of a sirolimus-coated balloon (SCB).

Background: Nanoluté was a prospective registry to evaluate the clinical performance of a novel SCB (Concept Medical Research Private Limited, India) for the treatment of de novo coronary lesions and in-stent restenosis (ISR). We here present the 24 months clinical data.

Methods: All patients treated with SCB for any type of coronary indication between July 2012 and September 2015 were enrolled at Indian centers and clinically followed up to 24 months. Primary endpoints were major adverse cardiovascular events (MACE) defined as a composite of cardiac death, target lesion revascularization (TLR), and target vessel-myocardial infarction (MI).

Results: A total of 484 SCBs were used in 408 patients to treat 435 lesions. In detail, the SCB was used for 183 patients with ISR, 185 with de novo small vessel disease, and 40 with de novo large vessel disease. Mean balloon length and diameter (average ± *SD*) were 22.3 ± 7.1 mm and 2.7 ± 0.40 mm, respectively. All patients with 24 months follow-up were included. Overall MACE rate was 4.2% (n = 17) with three cardiac deaths (0.7%), 13 TLR (3.2%), and one MI (0.2%).

Conclusion: The Nanoluté prospective registry is the first long-term clinical evidence of the safety and feasibility of this type of SCB, both in patients with ISR or de novo lesions.

KEYWORDS

DCB, long-term follow-up, prospective registry, sirolimus-coated balloon

1 | INTRODUCTION

The first drug-coated balloon (DCB) was marketed in Europe in 2007, and for almost a decade all this type of devices eluted paclitaxel. DCB was used for the treatment of coronary in-stent restenosis (ISR) and native vessel disease, depicting a variable efficacy depending on the device used, but no signals of impaired safety were described. Especially with the latest-generation devices paclitaxel, a lipophilic drug, when added to a carrier was shown to be able to persist into the vessel wall in order to pursue its antirestenotic effects. However, the narrow therapeutic window of paclitaxel was the main reason for developing alternative drugs.

After 9 years, the first sirolimus DCB (sirolimus coated balloon [SCB]) entered the European market. Magic Touch (Concept Medical Research Private Limited, India) elutes sirolimus by means of a nanocarrier technology (Nanolutè™), which allows effective drug delivery upon balloon inflation, and long-lasting drug encapsulation. After contact of the balloon with the blood, the hydrophilic surface of the nanocarrier becomes wet and during balloon expansion, the maximum drug delivery is achieved.[1] Sirolimus is less lipophilic than paclitaxel, but exerts only cytostatic and not cytotoxic effects. In order to consent adequate drug delivery and persistence, a dedicated technology had to be developed. Animal studies showed how Magic Touch is able to effectively deliver sirolimus, which reaches the tunica

TABLE 1 Baseline characteristics

No. of patients, *N* = 408	*N* (%)
Age, years ± *SD*	59.9 ± 10.0
Male, *N* (%)	332 (81.4)
Female, *N* (%)	76 (18.6)
Diabetes mellitus	183 (44.9)
Hypertension	192 (47.1)
Family history of CAD	14 (3.4)
MI	125 (30.6)
PCI	222 (54.4)
CABG	27 (6.6)
Peripheral vascular disease	2 (0.5)
Renal insufficiency	14 (7.3)
Left ventricular dysfunction	20 (4.9)
Multivessel CAD	26 (6.4)
Inducible ischemia	18 (4.4)
Stable angina	196 (48.0)
ACS	194 (47.5)
Unstable angina	125 (64.4)
Non-ST elevation MI	23 (11.9)
ST-elevation MI	46 (23.7)

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

TABLE 2 Lesion and procedural characteristics

Total number of lesions, N_L = 435	N_L (%)
Culprit vessel	
Left anterior descending	205 (47.1)
Left circumflex	106 (24.4)
Right coronary artery	105 (24.1)
Ramus	15 (3.4)
Graft	3 (0.7)
Left main	1 (0.23)
Type of lesions, N_L (%)	
ISR	195 (44.8)
De-novo	240 (55.2)
Procedural details, *N* (%)	
SCB + additional stenting	30 (7.4)
Device length, mm	22.3 ± 7.1
Device diameter, mm	2.7 ± 0.4
Inflation pressure, bar	12.6 ± 2.6
Inflation time, s	59.4 ± 9.4
Device used per patient	1.2
Procedural success	430 (98.9)

Abbreviations: ISR, in-stent restenosis; SCB, sirolimus-coated balloon.

adventitia within 4–6 days after deployment; small amount of drug is still detectable after 4 weeks at the treated segment, but no drug is present in other cardiac segments or other organs.

The first study aiming to assess the safety and efficacy profile of this device in the coronary setting was the Nanolutè registry, whose characteristics and 12 months clinical outcome have already been published.[2] We here report the final 2-year outcome of this registry.

2 | METHODS

Nanolutè registry was a prospective, spontaneous, multicenter all-comer clinical registry performed at Indian centers.

The design, enrollment criteria, and methods of the Nanolutè study have been previously reported.[2] All patients included aged more than 18 years old, with any clinical presentation at admission and with at least one lesion treated with SCB, were included into the study. Both de novo and ISR lesions were treated, including small vessel disease (≤2.75 mm). Only exclusion criteria were hypersensitivity or contraindication to aspirin, clopidogrel, sirolimus, or contrast media, presence of visible thrombus which could not be treated using the aspiration device, patients involved in other clinical trials, unsuccessful predilatation, torturous vessels, or heavy calcification and patients who did not complete their follow-up at 24 and 36 months.

2.1 | Procedure

All percutaneous coronary interventions (PCI) procedures were 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). A loading dose of clopidogrel 300 mg was administered prior to procedure (600 mg in case the procedure was scheduled within 2 hr). Aspirin 100–325 mg was given prior to procedure. All patients were given aspirin (100 mg) daily indefinitely after the procedure; clopidogrel 75 mg was prescribed for 3–12 months depending on the clinical indication for PCI. Lesion predilatation with either a semi-compliant or noncompliant balloon (following operators' preferences) was mandatory. SCB was inflated for at least 45 s if clinically tolerated.

2.2 | Study endpoints and follow-up

The primary study endpoints were procedural success and major adverse cardiovascular events (MACE) at 24 months. Procedural success was defined as angiographic success without the occurrence of adverse events during hospitalization; MACE 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 MACE at 24 months. MI was defined as the presence of pathological and new Q-waves on the ECG, or an increase in creatinine kinase-MB level to more than five times the upper limit of the normal range.

All patients had a clinical follow-up at 24 months, by visit or phone call. Angiographic follow-up was not mandatory, unless clinically indicated. All events were adjudicated by a Clinical Event Committee, consisting of cardiologists not participating in the registry.

2.3 | Device description

Magic Touch–SCB is the first device eluting sirolimus, which has been marketed in Europe upon receiving the CE approval. Peculiar of the device is the nanocarrier technology, which allows for long-lasting sirolimus encapsulation. Nanocarriers are coated on the hydrophilic surface of the balloon, in a circumferential configuration. After contact of the balloon with the blood in the arterial lumen, the hydrophilic surface of the nanocarrier becomes wet and during balloon expansion, the maximum drug delivery is achieved. Drug nominal dose on a 3.0/15 mm balloon is 180 mcg (~1.27 μg/mm^2). The delivery system is a semicompliant 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 microchannels by a wetting mechanism, which upon inflation of balloon deliver drug faster.

TABLE 3 Cumulative clinical outcomes at 2 years

Clinical outcomes, *N* (%)	
MACE	17 (4.2)
TLR	13 (3.2)
TV-MI	1 (0.2)
Cardiac death	3 (0.7)
Noncardiac death	4 (1.0)
All cause death	7 (1.7)
Clinical outcomes-ISR cohort, *N* (%)	
MACE	10 (5.5)
TLR	8 (4.4)
TV-MI	1 (0.5)
Cardiac death	1 (0.5)
Noncardiac death	2 (1.1)
All cause death	3 (1.6)

Abbreviations: ISR, in-stent restenosis; MACE, major adverse cardiovascular events; MI, myocardial infarction; TLR, target lesion revascularization; TV-MI, target vessel myocardial infarction; TVR, target vessel revascularization.

2.4 | Statistical analysis

Continuous variables were expressed as mean values ± *SD*, values were reported as numbers with relative percentages of standard deviation. *p* values less than .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).

3 | RESULTS

Between July 2012 and September 2015, a total of 408 patients (435 lesions) were enrolled and treated. The baseline demographics of the patients (Table 1) showed 45% of diabetics and 48% of acute coronary syndromes. ISR and native vessel disease were respectively

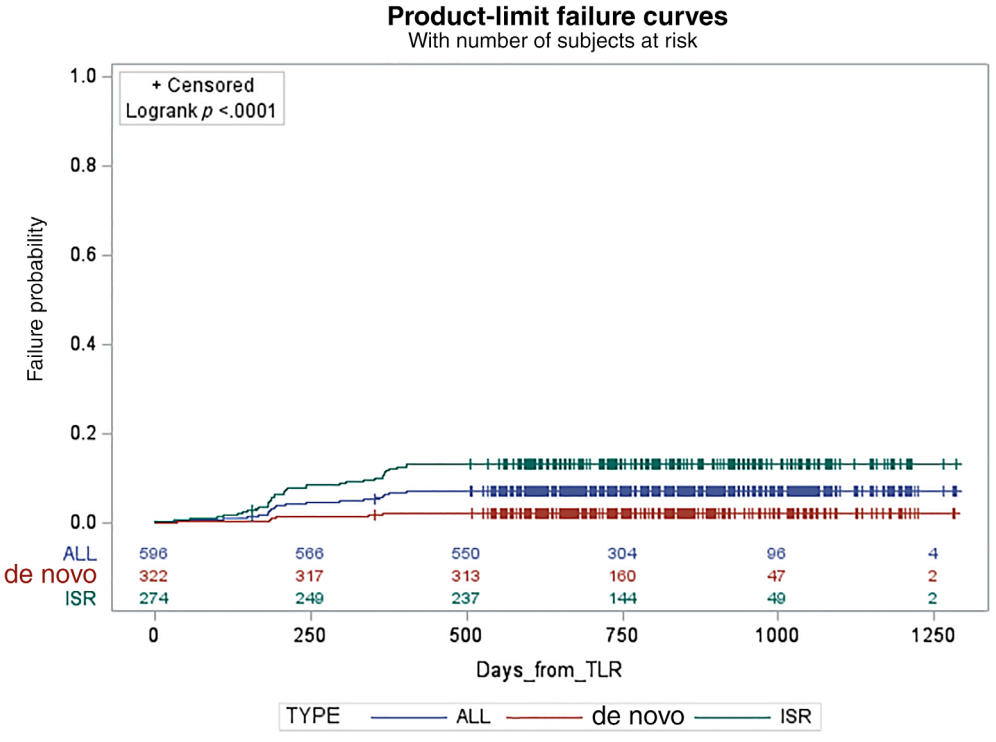

FIGURE 1 Kaplan–Meier cumulative survival curves at 2 years for the overall population and for de novo and in-stent restenotic lesions [Color figure can be viewed at wileyonlinelibrary.com]

45 and 55% of lesion types. Table 2 describes the procedural characteristics. Lesion length was 22.3 ± 7.1 mm, and average diameter 2.7 ± 0.4 mm. There were used 1.2 devices per patient. Lesion predilatation, required by the protocol, was performed for 97% of the lesions. Notably, in only 7.4% of the cases bailout stenting was required, because of flow-limiting dissections of impaired final thrombolysis in myocardial infarction flow. Procedural success, primary study endpoint, was achieved in 98.9% of the lesions. Data on 1-year outcomes have already been published.

Final follow-up after 2 years was available for 97% of the patients enrolled (Table 3). The coprimary study endpoint MACE after 24 months occurred in 17 patients (4.2%), 10 in patients with ISR (5.5%), and seven in patients with de novo lesions (3.1%). MACE were driven almost entirely by TLR, which occurred in 13 patients (3.2%: 4.4% in the ISR cohort, and 2.7% in the de novo lesion setting). ISR was focal in 10 cases and was managed with paclitaxel DCB use; in one case it was caused by underexpansion of a previously implanted stent and was managed with high pressure predilatation and paclitaxel DCB use. In the remaining three cases (two total occlusions), it was treated with drug-eluting stents (DES) implantation. No cases of abrupt vessel/thrombotic closure at lesion site were recorded. There were four cases of noncardiac death (1%), three cases of cardiac death (0.7%), and one case of target vessel MI (0.2%).

4 | DISCUSSION

The long-term follow-up of the Nanolutè registry confirms the safety and efficacy of this device in a broad population of patients with coronary artery disease. Important to mention, the adjudicated events were all related to TLR and no thrombotic complications occurred during the follow-up. Despite the assessment that a "class effect" for DCB does not make sense, these findings are comparable to the best-in-class paclitaxel-DCB.

In 2016 the Magic Touch SCB, was the first DCB to obtain the CE mark and became available in Europe. Since, its introduction several small studies have confirmed the safety and efficacy of this device, in different settings. The FASICO study,[3] first showed the short-term efficacy and safety in an all comer small populations of 32 patients; the primary endpoint of procedural success was obtained in 100% of patients, while the rate of MACE, coprimary endpoint, was very low, with just three cases of TLR.

The FASICO natives[4,5] study enrolled 27 patients with de novo lesions and a 6 months angiographic follow-up (Core-lab: Cardialysis, NL); at follow-up late lumen loss was 0.09 ± 0.34 mm with only two cases of binary restenosis, confirming the efficacy of the device at short-term follow-up, in a de novo lesion setting.

To date, Nanolutè is the largest available study on an all-comer population treated with SCB. In this registry the rate of MACE and TLR at 24 months are comparable to the ones reported in the BASKET-SMALL II trial,[6,7] which enrolled 758 patients with de novo lesions after careful and successful lesion preparation, randomly allocated to Sequent Please (BBraun, Germany), or DES after successful predilatation. After 12 months, MACE rate was 7.5% and target vessel revascularization 3.4% in the DCB arm, and noninferiority with the DES arm was demonstrated. The results of the Nanolutè registry also confirm the efficacy and safety of the drug itself, since most of data available in the literature were obtained with paclitaxel-coated balloons.

To note, there are several differences among the pharmacokinetic properties of the drugs. Thanks to its lipophilia, paclitaxel has a higher tissue retention, however the drawback is its narrower therapeutic window.[8] Sirolimus has a broader therapeutic window, but balloon coating and local delivery to the vessel wall were more challenging, in fact this drug requires encapsulation in a protective pack in order to persist for 3–4 weeks in the vessel, aiming to exert its antiproliferative effect. The results of the Nanolutè and the studies available on the Magic Touch device, suggest how a correct encapsulation of the sirolimus drug is of paramount importance for its efficacy on the mid and long-term.[1]

Interesting finding of the current analysis, this is the first DCB which shows comparable outcome in terms of TLR for de novo or ISR lesions (TLR occurred respectively in 2.7 and 4.4%, $p = .38$) (Figure 1). The long-term data on this novel SCB depicted in the Nanolutè registry confirms the safety and feasibility of this technology, either in patients with ISR and in those with de novo lesions.

One final remark should be done regarding the recently reported safety signal of increased mortality after paclitaxel application for femoro-popliteal interventions on the long-term.[9] The authors of the current article do not quote this finding, however the image of paclitaxel drastically changed over the past 12 months, and many physicians worldwide are awaiting new data and different drugs for local arterial applications.[10,11] Regarding the coronary segment, there have been performed some rigorous analyses on paclitaxel DCB, and none showed any signal of increased mortality on the long-term. More specifically, in the meta-analysis by Scheller et al. signals of trend toward reduced mortality was shown by paclitaxel as compared to other treatments including first and second-generation DES and balloon angioplasty (J Am Coll Cardiol 2020, in press). The effect of SCB on hard clinical endpoints will be assessed in the ongoing investigator-driven EASTBOURNE registry, which will finish the enrollment in Q2 2020 (B. Cortese, oral presentation, TCT 2019 Conference, SF).

All the inherent limitations of a registry apply here. First of all 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, prespecified, and per-protocol definition of all the events.

5 | CONCLUSIONS

Data from the Nanolutè registry after a follow-up of 24 months, evidence the safety and efficacy of this type of SCB, both in patients with ISR and de novo lesions.

CONFLICT OF INTEREST

Dr. Bernardo Cortese is consultant for Concept Medical. All the other authors have no conflicts of interest to declare.

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