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ORIGINAL STUDIES

Mid-term clinical outcomes from use of Sirolimus coated balloon in coronary intervention; data from real world population

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Abstract

Background: Use of drug coated balloons (DCBs) in coronary intervention is escalating. There is a plethora of data on Paclitaxcel-DCB. However, when it comes of stents, Limus-drugs are preferred over Paclitaxel. There is very limited data on Sirolimus coated balloons (SCB). MagicTouch-SCB (Concept Medical, FL) elutes Sirolimus via nano-technology and have been used in our centers since March 2018. We report a mid-term follow-up with this relatively novel-technology.

Methods and results: We retrospectively analyzed all patients treated with MagicTouch-SCB between March-2018 and February-2019. Results are reported as cardiac-death, target-vessel myocardial-infarction (TVMI), target lesion revascularization (TLR) and Major Adverse Cardiac Events (MACE). During the study period, 288-patients (373-lesions) with a mean age of 65.8 were treated with MagicTouch-SCB. 84% (n = 241) were male, 155 (54%) were in the setting of acute coronary syndrome, 38% (n = 110) had diabetes and 62% (n = 233) were in de-novo lesions. Most lesions treated were in the LAD/diagonal-system (n = 170; 46%). Pre-dilatation was performed in 92% (n = 345) of cases. Bailout stenting was required in 9% lesions (n = 35). The mean diameter and length of SCBs were 2.64 ± 0.56 mm and 24 ± 8.9 mm respectively.

During a median follow-up of 363 days (IQR: 278–435), cardiac death and TVMI occurred in 5-patients (1.7%) and 10-patients (3.4%) respectively, TLR per-lesion was 12%. The MACE rate was 10%. There were no documented cases of acute vessel closure.

Abbreviations: DCB, drug coated balloons; DES, drug eluting stents; ISR, in-stent restenosis; MACE, major adverse cardiac events; PCB, Paclitaxel coated balloons; PCI, percutaneous coronary intervention; SCB, Sirolimus coated balloons; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction.

Relationship with Industry: None.

Conclusions: The results from mid-term follow-up with this relatively new technology SCB is encouraging with a low rates of hard endpoints and acceptable MACE rates despite complex group of patients and lesion subsets.

KEYWORDS
de novo lesions, in-stent restenosis, Paclitaxel coated balloon, Sirolimus coated balloon

1 | INTRODUCTION

The use of DCB in coronary intervention is escalating owing to a consistent trickle of data on their efficacy.[1-7] The data are relatively strong for ISR, which has compelled European Society of Cardiology to give class IA recommendations for DCB in treatment of ISR.[8] In contrast, data for de novo lesions are relatively scarce; however, the recently published Basket-Small 2 trial has demonstrated non-inferiority of DCB as compared to second generation DES in small vessel, de novo lesions.[7]

All the data that exists for DCB are from PCB,[1-7] a drug which is not used in stents anymore due to its cytotoxic properties and narrow therapeutic window.[9-12] On the other hand, there are limited data on SCB, a drug which is the default choice in all the currently available DES due to its cytostatic properties and wide therapeutic window. In addition, recent reports in peripheral interventions have raised the safety concerns of PCB with increased mortality signals.[13] Paclitaxel is highly lipophilic and hence diffuses easily into the vessel wall upon contact with the intima. In contrast, delivering Limus-drug to the vessel wall has been a challenge due to poorer lipophilicity, and this has been the main limitation for developing SCB technology. All these issues call for improvements in Sirolimus balloon technology for both coronary and peripheral intervention. Although, delivering Limus-drug into the vessel has been a major hurdle, this has now been achieved by encapsulating the drug inside a lipophilic carrier using nano-technology. The drug is then released into the vessel wall from the encapsulated nano-carrier, which exhibits its anti-proliferative effects. Concept Medical has been the pioneer in developing this technology on balloon (MagicTouch, Concept-Medical, FL).

We embarked on use of MagicTouch-SCB in March 2018 and in this study, we report our mid-term outcomes from 2 high-volume centers in the United Kingdom (UK).

2 | METHODS

We retrospectively evaluated all patients who underwent treatment with MagicTouch-SCB between March 2018 and February 2019 at 2 centres in the UK (Heartlands hospital, Birmingham and Harefield Hospital, London). The general indications for DCB in our setup are; ISR, small-vessel de novo disease, ostial stenosis of an important side-branch or in patients unable to take dual anti-platelet therapy beyond a month (e.g. awaiting cancer surgery or any issues with bleeding).

3 | PROCEDURE

Standard PCI procedures were employed. Patients were loaded with aspirin (300 mg) and clopidogrel (300–600 mg) or new P2Y12 inhibitors in acute coronary syndromes prior to the procedure. Heparin was administered at a dose of 70–100 units/kg. The lesions were generally predilated with the use of semi-compliant, non-compliant, scoring and/or cutting balloons before utilizing Magic Touch SCB. The Magic Touch SCB was generally inflated at a nominal pressure for a minimum of 60-seconds to aid drug delivery. Bailout stenting was defined as stent post-DCB use either due to dissection (flow-limiting or operator not comfortable accepting the dissection) or due to recoil of >50%. All bailout stenting was performed with second generation DES. Patients treated with only DCB received dual antiplatelet therapy for a minimum of 1-month post-procedure (unless if it was in the setting of acute coronary syndrome in which case it was extended to at-least 12 months). If patients received DES, dual antiplatelet therapy was prescribed for a minimum period of 6–12 months as per the current ESC guidelines. All patients were advised to continue lifelong Aspirin (75 mg).

4 | DEVICE (MAGICTOUCH SIROLIMUS COATED BALLOON) PROPERTIES

Magic Touch® Sirolimus Coated Balloon Catheter (SCB, Concept Medical, FL) is coated with encapsulated Sirolimus with 1.27 μg/mm^2 with drug to excipient ratio of 1:1. It is designed using Nanolute® technology wherby encapsulated Sirolimus is delivered in a protective lipophilic package, which accelerates drug diffusion and penetration into the arterial wall during balloon inflation (Figure 1).The sub-micron sizing of particles of Sirolimus (avg. 0.3 μm) helps in increasing the cellular uptake and reducing the in-transit drug loss. The smaller-sized "nano-particles" are effectively absorbed into the deep layers of the vessel wall by the process of diffusion.

Sirolimus distribution in tissue after balloon inflation was evaluated using DTF (5-[4,6-dichlorotriazinyl] aminofluorescein) labelling in an in vivo animal study.[14] The Sirolimus nano-particles were labeled with DTF and at 1 hour, they were observed on the luminal surface, involving approximately 60% to 70% of the circumferential area. After 3 days, the nano-particles were observed on the luminal surface and below the internal elastic lamina limits, with some positive signals deeper within the medial region. After 7 days, the DTF signal was

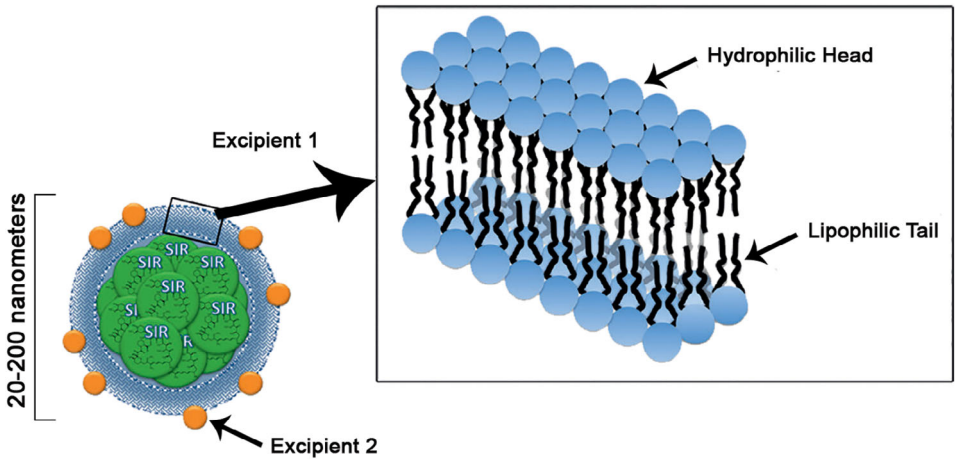

FIGURE 1 Schematic diagram of MagicTouch nano technology showing encapsulation of the drug in a nano particle [Color figure can be viewed at wileyonlinelibrary.com]

primarily observed in the medial layer, with the majority deep within the media and even into the adventitia (Figure 2).

5 | FOLLOW-UP

The follow-up was achieved through clinic visits, telephone calls and records from hospital admissions. The measured endpoints during this follow-up were: any death, cardiac-death, TVMI, TLR, MACE, acute vessel closure and stent thrombosis (definite and probable).

Death was considered cardiac in origin unless obvious non-cardiac causes could be identified. Target-vessel MI was defined when patients presented with elevation of troponin above the upper-range limit in combination with at least one of the following: symptoms of ischemia; ECG changes indicative of new ischemia; or the development of pathological Q waves on ECG. It was coded as TVMI unless coronary angiography demonstrated an acute occlusion within a vessel that was not treated by SCB during the same hospital admission. When angiography was not performed, or there was doubt on angiography as to the culprit vessel, the event was coded as a TVMI.[15] TLR was defined as any revascularization of the target lesion driven by: a positive functional ischemia study (on exercise testing, fractional flow reserve and/or nuclear imaging), ischemic symptoms, and a diameter stenosis ≥70% in anatomically important location of the vessel without ischemic symptoms or a positive functional study.[16] The MACE rate was defined as a combination of cardiac death, target vessel MI and TLR. Acute vessel closure was defined as symptomatic occlusion of the vessel closure within 24-hours of the procedure. Stent thrombosis was categorized according to the definitions proposed by the Academic Research Consortium.

6 | STATISTICS

The values are presented as mean ± standard deviation or median (interquartile range [IQR]) for continuous variables or as counts and percentages for categorical variables. The clinical endpoints are reported as percentages.

7 | RESULTS

During the study period, 373 lesions in 288-patients (mean age; 65.8 ± 11.6 years; range 36–90) years) were treated with MagicTouch-SCB. Patient's demographics are provided in Table 1. 38% (*n* = 110) of patients were diabetic and of which 12% (*n* = 35) were insulin dependent. 10% (*n* = 29) had chronic kidney disease, which was defined as estimated glomerular filtration rate (eGFR) of <60 ml/min. 54% (*n* = 155) of cases were in the setting acute coronary syndrome (ACS) and 55% (*n* = 157) had previous angioplasty.

Lesion and procedural characteristics are provided in Table 2. Thirty eight percent (*n* = 140) of the MagicTouch-SCB use was for inrestenotic lesions (ISR) and 62% (*n* = 233) in de novo lesions. 68% (*n* = 255) of cases were in small vessels (<3.0 mm). Pre-dilatation was performed in 92% of cases, of which 45% were with non-compliant balloons. Scoring and cutting balloons were used in 8% and 1.3% of cases respectively. Rotational atherectomy was used in 1% of cases. Most of the lesions were in the left anterior descending artery (LAD) and diagonal system (46%) followed by the left circumflex system (26%) and the right coronary artery (25%). The mean diameter of MagicTouch-SCB was 2.64 ± 0.56 mm and the mean length was 24 ± 8.9 mm. Bailout stenting (with DES) was required in 9% lesions (*n* = 359), of which 18 were due to dissections and 17 were due to >50% recoil following SCB use. All the bailout stenting was done with second generation limus eluting stents.

The median follow-up was 363-days (IQR: 278–435), ensuring all patients were followed-up for at-least 6-months (except when patients had died within 6-months of the procedure). The clinical outcomes are provided in Table 3. Total death occurred in 10 (3.4%) patients and of which, cardiac death occurred in 5 patients (1.7%). Of the 5 cardiac deaths, 2 were due to palliative heart failure, but had angioplasty with DES and DCB a few weeks before. TVMI occurred in 10 patients (3.4%). TLR per lesion was 12%. The overall MACE rate was 10%. The angiographic follow-up was achieved in 101 patients (35%). We had no documented case of acute vessel closure or stent thrombosis.

We analyzed the follow-up in the de novo and ISR lesion subgroups. There were 233-de novo lesions (in 186 patients). Small vessel

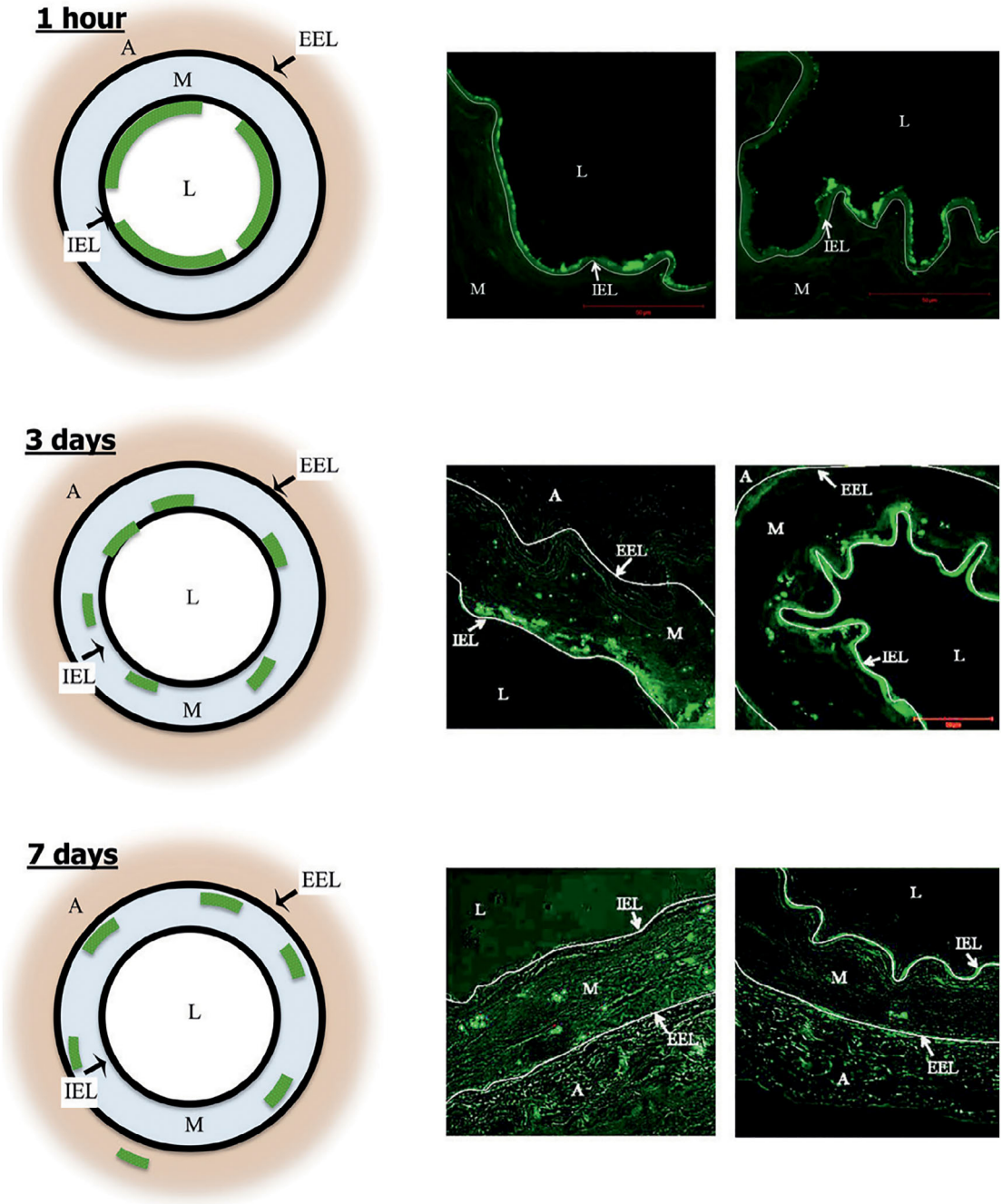

FIGURE 2 DTF labeled in vivo study in rabbits showing distribution of the drug in the intima (1 hour), media (3 days) and adventitia (7-days) [Color figure can be viewed at wileyonlinelibrary.com]

(<2.5 mm) and diffuse disease (≥25 mm) accounted for 60% (*n* = 140) of de novo lesions. The treatment of side-branches (either on their own in Medina 0, 0, 1 classification, or as a part of bifurcation treatment strategy) accounted for 21% (*n* = 48) of cases. Approximately 11% (*n* = 20) of patients received DCB as they were considered high bleeding risk (elderly, pre-existing anemia or previous gastro-intestinal bleeding) or unable to take DAPT for more than a month as they were awaiting urgent surgery. The mean diameter and length of the DCBs used in de novo were 2.4 and 23 mm, respectively. During the follow-up period, cardiac death and TVMI occurred in 2-patients (1.7%) and 4 patients (2%) respectively. TLR per lesions was 9% and the MACE rates were 6% (Table 3).

In the ISR group (140-lesions in 102-patients), the mean diameter and length of DCB used were; 3.0 mm and 25 mm respectively. During the follow-up period cardiac death and TVMI occurred in 2.5% and 6% respectively. TLR per lesions was 17%. The MACE rates were 17.6% (Table 3).

Since MagicTouch was embarked in March 2018, we looked at our initial experience (first 6 months; 187 lesions) and compared certain procedural characteristics and clinical outcomes with our later

TABLE 1 Demographics and Clinical Characteristics

Demographics	*N* = 288 patients
Age (mean ± *SD*)	65.8 ± 11.6
Male (%)	241 (84%)
Hypertension	216 (75%)
Diabetes mellitus (%)	110 (38%)
Insulin dependent mellitus (%)	35 (12%)
History of smoking (%)	101 (35%)
Stable angina (%)	133 (46%)
Acute coronary syndrome (%)	155 (54%)
CKD (%)	29 (10%)
Previous MI (%)	153 (53%)
Previous PCI (%)	157 (55%)
Previous CABG (%)	47 (16%)
Atrial fibrillation (%)	25 (9%)

TABLE 2 Procedural Characteristics

Procedural characteristics	*N* = 373, value (%)
In-stent restenosis	140 (38%)
De novo lesions	233 (62%)
Small vessel (<3.0 mm)	255 (68%)
Pre-dilatation	345 (92%)
Semi-compliant balloon	237 (64%)
Non-compliant balloon	168 (45%)
Scoring balloon	28 (8%)
Cutting balloon	5 (1%)
Rotational atherectomy	3 (1%)
Intravascular imaging	67 (18%)
Left main stem	6 (2%)
Left anterior descending artery/diagonal	170 (46%)
Left circumflex artery/marginal/intermediate	98 (26%)
Right coronary artery/PDA/ PLV	93 (25%)
Saphenous vein graft	11 (3%)
Mean diameter of DCB, mm	2.64 ± 0.56
Mean length of DCB, mm	24 ± 8.9
Bailout stenting	35 (9%)
Dissection	18 (51%)
Recoil of >50%	17 (49%)

experience (last 6 months; 186 lesions). Predilatation and use of non-compliant balloons were higher in the latter group (167; 89% vs. 178; 96%) and (71; 38% vs. 97; 52%), respectively. Repeat revascularization rates were higher in the earlier group (28;15% vs. 17;9%).

Case examples of the use of MagicTouch in ISR and de novo lesions with pre- and post-procedural and follow-up angiography images are illustrated in Figures 3–6.

TABLE 3 Clinical Outcomes

Clinical outcomes	Total 288 pts (373 lesions)	Denovo 186 pts (233 lesions)	ISR 102 pts (140 lesions)
Death	10 (3.4%)	5 (3%)	5 (4.3%)
Cardiac death	5 (1.7%)	2 (1.7%)	3 (2.5%)
Target-vessel MI	10 (3.4%)	4 (2%)	6 (6%)
TLR per lesion	45 (12%)	21 (9%)	24 (17%)
MACE	29 (10%)	11 (6%)	18 (17.6%)
Acute vessel closure and/or stent thrombosis	0	0	0

8 | DISCUSSION

The principle findings from this study of use of SCB in coronary lesions from a retrospective, real-world population are:

1 Low rates of hard endpoints (cardiac death and target vessel MI; 1.7% and 3.4% respectively) during the median follow-up of just under 1-year
2 Acceptable rates of repeat revascularization (TLR of 12%) and MACE (10%) in a complex group of patients and lesions

Drug coated balloons have become an excellent alternative to stents especially in those lesion and patient subsets where stents are not preferred (small vessel, diffuse disease, isolated ostial lesion of an important side-branch and issues with DAPT). Paclitaxel has been the principal drug on balloons given its lipophilic properties and cytotoxicity, although Limus-drugs have been proven to be the superior of the two in stents due to their cytostatic properties. Poor lipophilicity has been the Achilles heel for Limus-drugs to be used in balloon technology, but this has now been achieved with encapsulation of the drug in a lipophilic nano-carrier. A drug carrier is amphiphilic, i.e. having both lipophilic and hydrophilic properties. Lipophilic tail retains sirolimus for long term in encapsulation format and therefore it allows limus to enter in vessel wall for long term retention. Using nano-sized particles also provides a theoretical advantage such that in the event of distal embolization, nano-particles may be washed down the capillaries given their size in contrast to Paclitaxel macroparticles. Although there are data on animal models and some abstracts in scientific meetings, there is a scarcity of data on MagicTouch-SCB in real-world clinical practice. To our knowledge, this is the first reported clinical outcomes on SCB in treatment of coronary stenosis from a real-world population. Overall clinical outcomes appear encouraging with low rates of hard endpoints (cardiac death of 1.7% and TVMI of 3.4%). Acceptable rates of repeat revascularization and MACE are observed considering the complex group of patients (38% diabetics, 10% CKD and 54% of patients with ACS) and lesions subsets (38% ISR and 68% small vessels disease) treated. The MACE rate is comparable to various data on Paclitaxel balloons in the literature.[1,3,5-7,17-19]

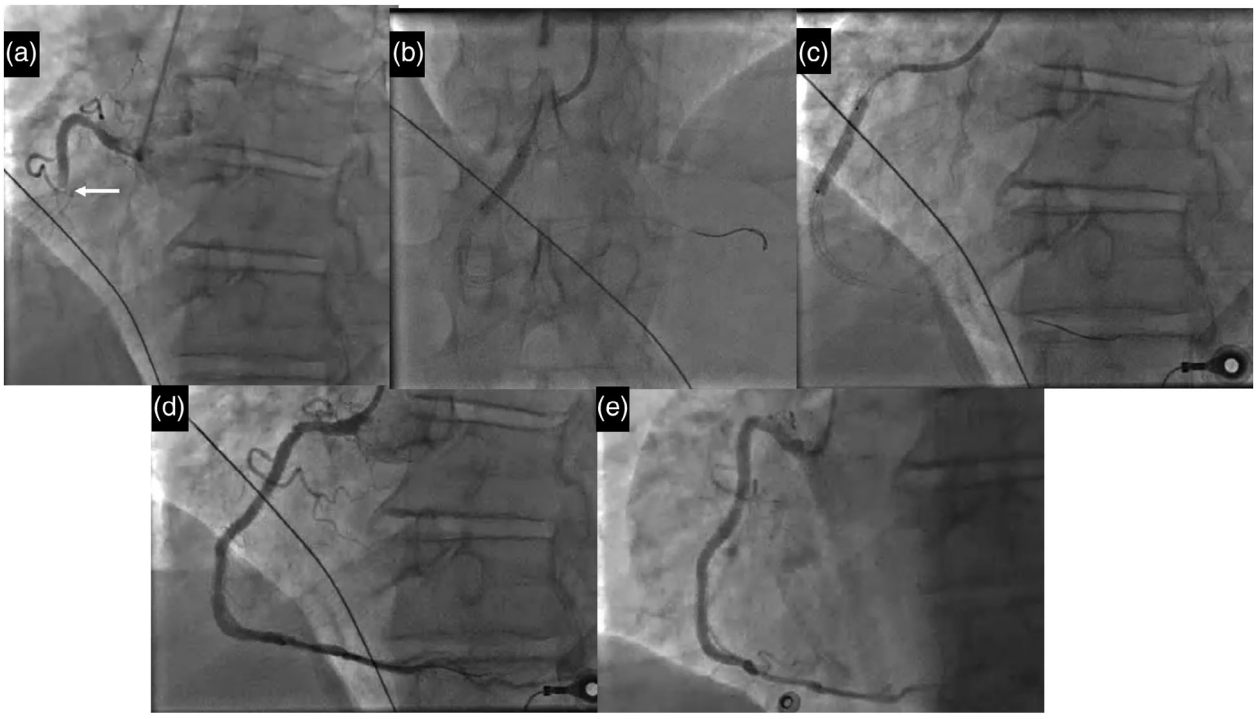

FIGURE 3 Intra-stent chronic total occlusion of a previously placed drug eluting stent treated in the rightcoronary artery treated with MagicTouch (a–c) to achieve good result (d) and continued good result during 6-month follow-up angiography (e)

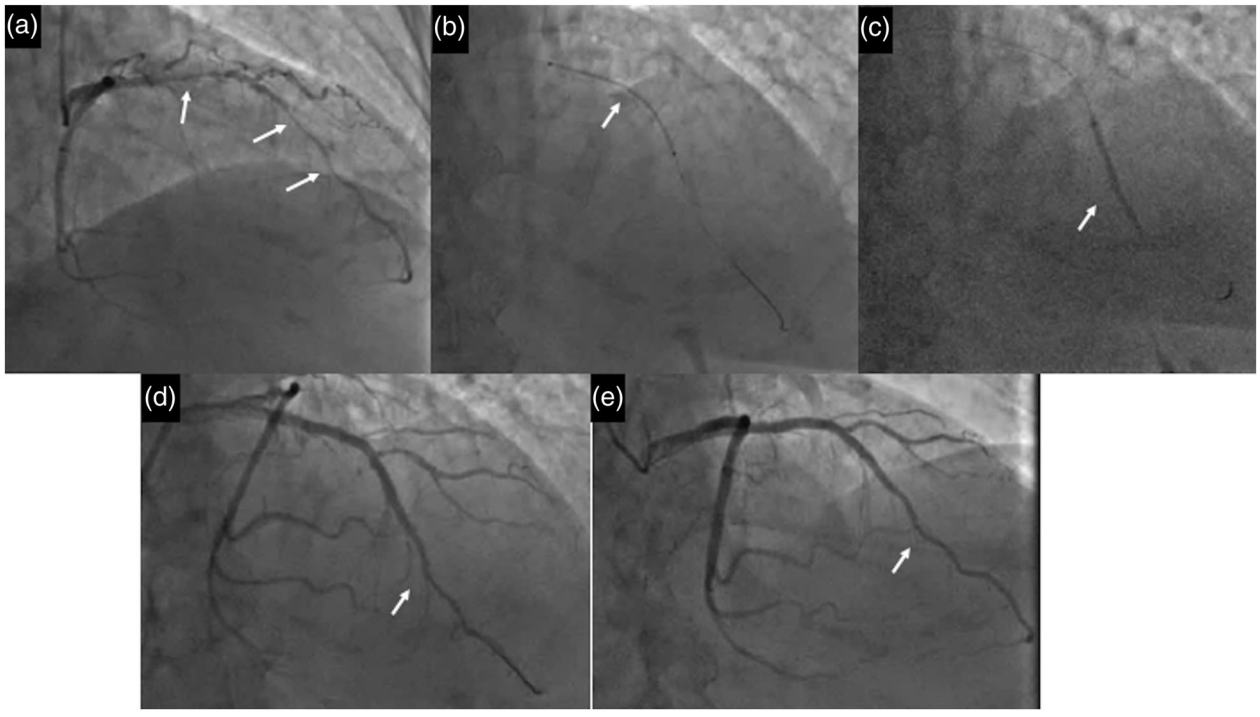

FIGURE 4 Diffuse lesion in left anterior descending artery (a) treated with DES proximal segment (b) and MagicTouch in the distal segment (c) to achieve good result (d) and continued good result during 6-month follow-up angiography showing positive remodeling in the distal vessel (E)

Use of DCB in de novo lesions is escalating, especially in small vessels and diffuse disease, as placing stents in such lesion subsets increases the risk of restenosis that is often difficult to treat. Our data on de novo lesions was mainly in small vessels (mean diameter of the DCB <3.0 mm) and diffuse lesions (mean length of the DCB was 26 mm). Despite this, the results are encouraging with low rates of repeat revascularization

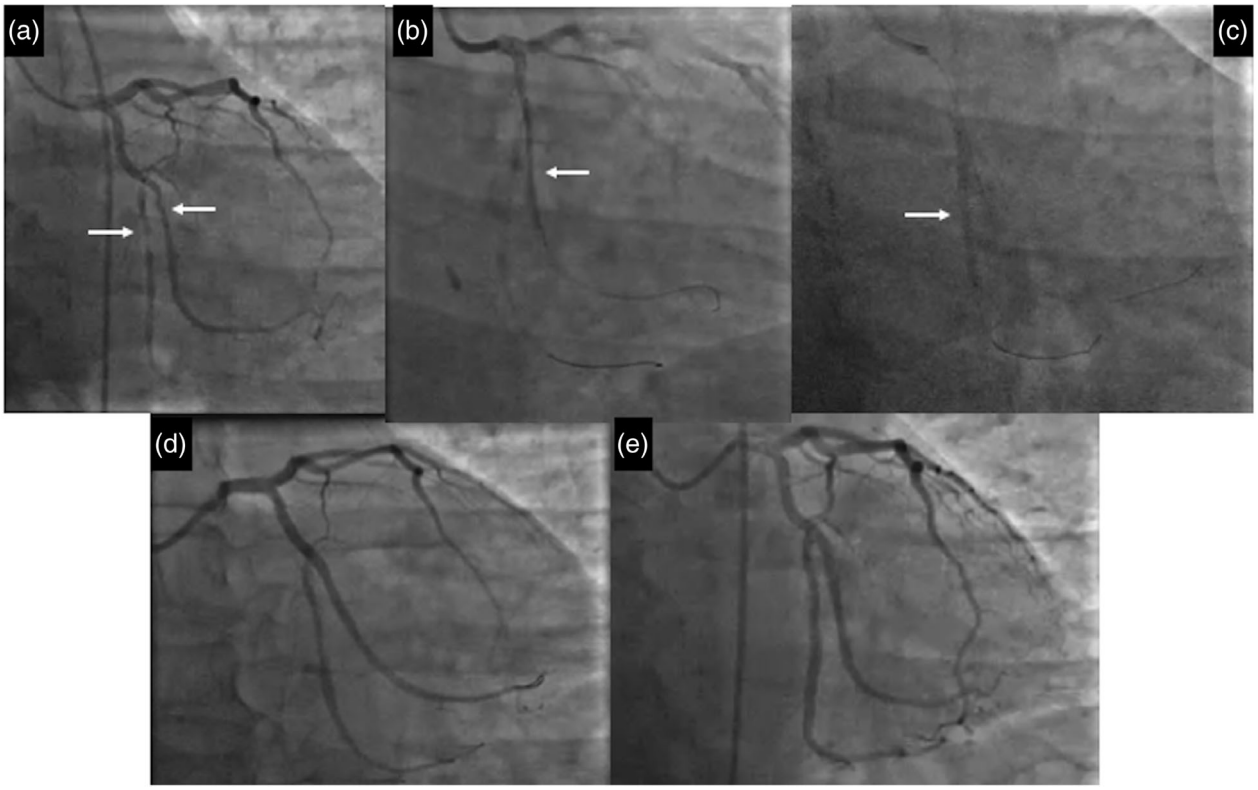

FIGURE 5 Bifurcation lesion in left circumflex and obtuse marginal system (a) treated with DES in main branch (b) and MagicTouch in the side-branch (c) to achieve good result (d) and continued good result during 3-month follow-up angiography showing positive remodeling in the side-branch (e)

(9%) and MACE rates (6%) supporting the use of MagicTouch DCB in such lesion subsets, although we need long-term data and head-to-head comparison with second generation DES and/or Paclitaxel coated balloons.

Restenotic lesions are extremely challenging, and irrespective of the mode of treatment (DES or DCB), the recurrence rates are high and this is also reflected in our data with relatively high rates of TLR, TVR, and MACE as compared with the de novo lesions.[1-5,17,18] In-fact, the overall high rates of TLR and MACE rates were driven by restenotic lesions. However, these results may have also been influenced by procedural issues such as under-utilization of scoring and cutting balloons in lesion preparation. In addition, a small proportion of lesions (8%) was directly treated with SCB without pre-dilatation. This may have influenced some of the repeat revascularization, which clearly signifies that lesion preparation by pre-dilatation is an important criterion for successful DCB results. Indeed, this is evidenced in our data comparing the initial and the last 6-months periods. In addition, we have also escalated use of scoring and cutting balloon especially in restenostic lesions. We now routinely predilate the restenotic lesions aggressively with non-compliant balloons, and prior to use of DCB, we also use cutting or scoring balloons to make some cracks in the ISR to aid better drug transfer.

It is also worth noting that bailout stenting was relatively low in our cohort (9%) as compared to previously published studies where it has ranged upto 21%[6,7,19] and this variation could be due to the different criteria used to consider bailout stenting (we used re-coil of ≤50% and bailout stenting was performed mostly in flow-limiting dissections). Our eyes are trained to expect stent-like result and anything less is considered sub-optimal and this could be one of the reasons for high incidence of bail-out stenting in previous studies. With our growing experience on DCB, we accepted non-stent-like results and non-flow limiting dissections (type A and B). Although acute gain post SCB is smaller as compared to stents, there seems to be positive remodeling of the vessel with time and this has been demonstrated in previous studies.[20,21] We have also demonstrated some of the examples in our practice where there was positive remodeling of the vessel in both restenotic and de novo lesions during follow-up angiography. Finally, we divided our experience on MagicTouch as early (first 6 months) and later (last 6-months) experience and noted that rates of pre-dilatation and use of non-compliant balloons were higher in the later on, indicating improvement in our practice. This was reflected in TLR rates, which were better in the latter group. Our current practice is to perform 100% pre-dilatation prior to use of DCB with liberal use of non-compliant, scoring and cutting balloons (especially for restenotic lesions) to aid better drug delivery.

9 | LIMITATIONS

The main limitations of this study relate to the retrospective analysis of use of SCB, and with no comparison with Paclitaxel coated balloons. The study provides only clinical follow-up with no angiographic analysis of binary stenosis and lumen gain or loss at follow-up.

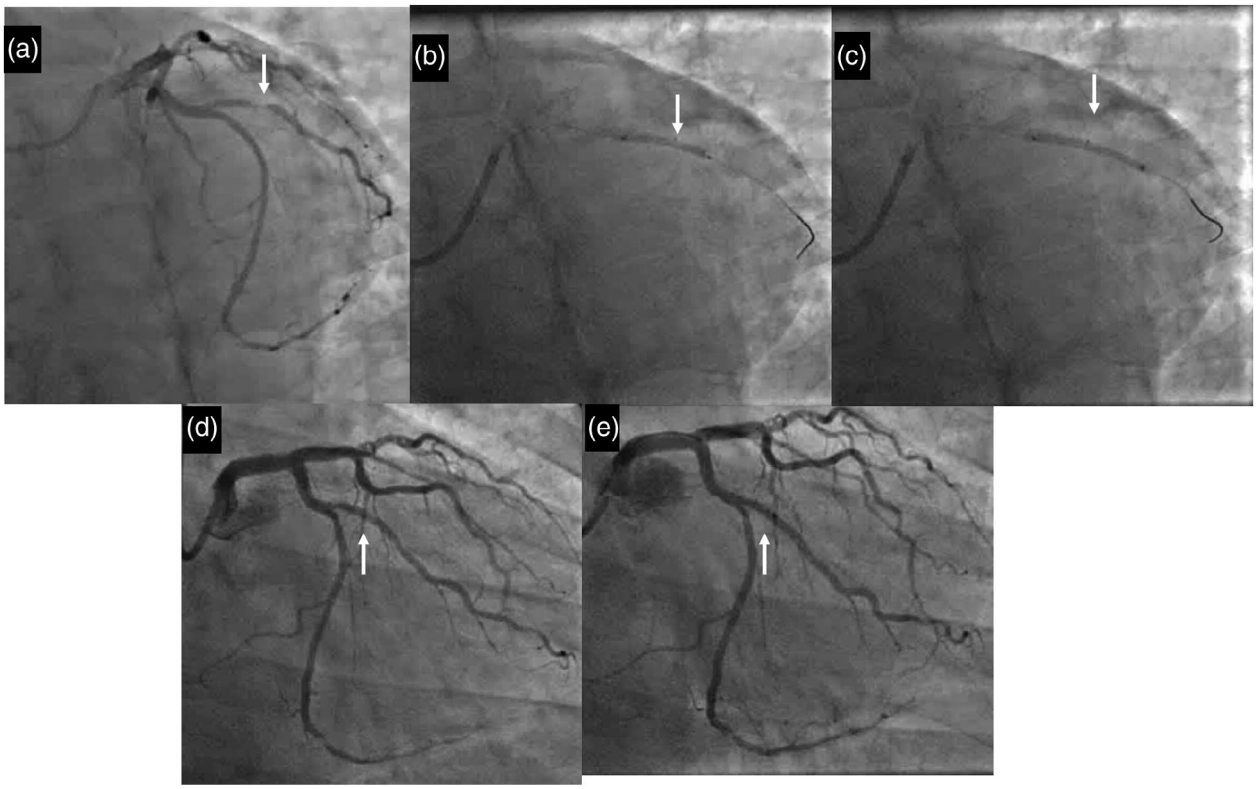

FIGURE 6 Significant disease in the proximal segment of first obtuse marginal branch (a) treated with MagicTouch following predilatation (b and c) to achieve good result (d) and continued good result during 6-month follow-up angiography showing positive remodeling of the vessel (e)

Nevertheless, this study provides important data on the widely used SCB especially in Europe and in US in the future as it has been recently approved by FDA for clinical trials in in both coronary and peripheral intervention.

10 | CONCLUSIONS

This mid-term retrospective analysis of SCB in all-comer patients from 2 high-volume centers has demonstrated that its use appears safe with low rates of hard endpoints, and with repeat revascularization rates comparable to Paclitaxel coated balloons. We need more long-term data and also comparison data with Paclitaxel coated balloons, but in the interim, these data provide some guidance and reassurance for DCB enthusiasts who want to trial or use SCB in their clinical practice.

11 | PERSPECTIVES

WHAT IS KNOWN? Use of DCB in coronary intervention is escalating and the European Society of Cardiology gives a class IA recommendation for DCB in in-stent restenotic lesions. Although, there is no recommendation for de novo lesions, their use is escalating. All the data that exists are from Paclitaxel DCB. Recent reports in peripheral intervention has raised long-term safety concerns with increased mortality signals.

WHAT IS NEW? Data from a real-world population on use of SCB for in-stent restenotic and de novo lesions show it to be safe at 1-year with low hard endpoints and acceptable MACE rates.

WHAT IS NEXT? We need data comparing Paclitaxel DCB and Sirolimus DCB from randomized trials and we are part of one such trial which is ongoing.

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