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DRUG ELUTING STENT

RAPSTROM™ First-in-Man Study Long-Term Results of a Biodegradable Polymer Sustained-Release Sirolimus-Eluting Stent in De Novo Coronary Stenoses

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***Background**: Durable polymers used for first-generation drug-eluting stents (DES) potentially contribute to persistent inflammation and late DES thrombosis. We report the first real-life human experience with the rapamycin-eluting biodegradable polymer-coated Rapstrom stent.*
***Methods**: All consecutive patients with single de novo native coronary stenosis (<30 mm and between 2.5 and 4.0 mm) were enrolled. Major adverse cardiac events (MACE) at 1 year (cardiac death, myocardial infarction [Q and non-Q], or ischemia-driven target lesion revascularization) were the primary end-point.*
***Results**: A total of 123 patients were enrolled. The stent was implanted without complications in all patients, and no MACE were recorded at 30 days. At 12-month follow-up 9 patients (7.3%) experienced a MACE and 4 (3.2%) required a target lesion revascularization, while 1 (1%) stent thrombosis was recorded. A planned angiographic follow-up (FU) was performed in 73 patients (59%) at 9.4 ± 2.6 months following the index procedure. In-stent late loss was 0.16 ± 0.09 mm, and in-segment late loss was 0.18 ± 0.8 mm.*
***Conclusion**: The Rapstrom biodegradable polymer rapamycin-eluting stent appeared safe and efficacious in this first real-life human experience, due to a low late lumen loss. Larger randomized studies are required to confirm these preliminary results.* (J Interven Cardiol 2014;27:373–380)

Introduction

Drug-eluting stents (DES) have markedly reduced the rate of in-stent restenosis compared with bare metal stents (BMS), resulting in a significant reduction in repeat revascularizations,[1–3] also for patients with severe coronary artery disease and with technological advances.[4–7] Their efficacy relies on the ideal combination of key components including metallic scaffold, drug carrier, and antiproliferative agent, which are critical to achieving adequate drug delivery and release at the target site.[8] Moreover, strut thickness and cell design might also contribute to DES efficacy, since strut thickness in BMS has previously been reported to significantly reduce neointimal hyperplasia (NIH) as compared to platforms with thicker struts.[3,4,9] However, the implications of strut thickness and cell design on DES have still to be determined. Importantly, despite the overall efficacy demonstrated by older-generation DES,[5,6] persistent concerns regarding deliverability, effectiveness, and especially long-term safety[7,10–12] have led to the development of new DES systems including low-profile platforms, drug carriers (durable or nondurable) with optimized biocompatibility, and potent antiproliferative drugs.[13–18]

Meantime, enthusiasm for this technology has been dampened by concerns about late stent thrombosis, an

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event often associated with severe complications.[19,20] Pathological autopsy studies suggested that delayed endothelialization is one of the causes leading to DES thrombosis. Localized hypersensitivity reactions to the durable polymer coating and/or to the drug itself may also add to stent thrombosis.[21–24] A biodegradable polylactic acid (PLA) polymer with sustained drug release was employed in the Rapstrom stent (VasMed Technologies Ltd., Fujairah, UAE) to maintain high tissue concentration of rapamycin. This polymer coating is fully absorbable and may minimize adverse effect, such as possible hypersensitivity reactions, caused by the permanent presence of a durable polymer. Although this new Rapstrom stent had shown good reendothelialization and reduction of neointimal thickening in a porcine model, it has yet to be confirmed in humans. The objective of this registry study was to test the safety and feasibility of the Rapstrom stent to treat de novo coronary lesions.

Methods

Study Design. This study was a prospective, nonrandomized, single-arm, first-in-man (FIM) clinical evaluation of the performance of the novel Rapstrom™ rapamycin-eluting stent (VasMed Technologies Ltd.) in the treatment of noncomplex coronary lesions, to provide preliminary safety, feasibility, and efficacy evaluations. The study complied with the Declaration of Helsinki regarding investigation in humans, and was approved by the local ethics committee at the participating institution. All patients provided written informed consent prior to enrollment.

Inclusion Criteria. All consecutive patients undergoing percutaneous coronary intervention (PCI) from March 2011 through March 2012 were enrolled. Inclusion criteria were: (a) over 18 years of age; (b) presenting with stable or unstable angina, or acute coronary syndrome (including NSTEMI and STEMI without angiographic evidence of thrombus with TIMI flow type II-III in the culprit lesion); (c) a single de novo native coronary artery stenosis in 1 or 2 coronary vessels; (d) target lesions with a reference diameter of 2.5 and 4.0 mm and lesion length less than 30 mm were included (all of them have to be met for inclusion).

Exclusion criteria were: (a) chronic total occlusion with TIMI 0 flow; (b) previous target site stent implantation within 1 year; (c) renal insufficiency with baseline serum creatinine >2.0 mg/dL; (d) previous PCI <30 days to index procedure; (e) left ventricular ejection fraction $<30\%$; (f) left main coronary artery disease; (g) moderate or severe calcium; (h) severe tortuosity or angulation; (i) large burden thrombus; (j) bifurcation with a side branch ≥ 2.0 mm; (k) aorto-ostial location; (l) any clinical or nonclinical condition leading to noncompliance with dual antiplatelet therapy (DAPT) during study duration; (m) known illness or any serious clinical condition with life expectancy <2 years (one of these was enough for exclusion).

Study Device. All enrolled patients were treated with the Rapstrom stent, manufactured by VasMed Technologies Ltd., which is a sirolimus-eluting stent and biodegradable polymer premounted on the Vas Track balloon catheter. The stent is a thin 70 μm cobalt/chromium alloy. This copolymer formulation provides uniformly thin coating (<0.5 μm), which degrades completely in approximately 180 days after implantation (data on file at VasMed Technologies Ltd.). The average rapamycin dosage of the Rapstrom stent is 1.4 μg/mm^2, representing approximately the same dosage of Cypher stent. The properties and mechanisms of action of sirolimus, the pharmacological agent used in Rapstrom BioMime, have previously been detailed elsewhere.[25] Briefly, sirolimus exhibits potent immunosuppressive and anti-inflammatory properties, as well as potent suppression of vascular smooth muscle cell proliferation due to cell cycle arrest at the G_1-S interface. The following sizes of Rapstrom stent were used in the study: 8–30 mm length and 2.5–4.0 mm diameter; stents were deployed at least to 14 atm.

Preclinical Studies

The histopathology and histomorphometric evaluations comparing the Rapstrom SES versus a control polymer-coated only stent in a porcine model were performed using a previously described methodology. Overall, there were 41 stents implanted (Rapstrom, 20; control polymeric, 21) in 16 animals. At 7 days mean endothelialization scores with Rapstrom and polymeric stent were 2.97 and 2.94, respectively, and at 28 days they were 3.02 and 3.0, respectively, suggesting near complete strut coverage at early follow-up (Fig. 1, all P not significant). Furthermore, at 28 days Rapstrom performed superior to control for mean % diameter stenosis (DS) and neointimal thickness (18% vs. 28%; $P = 0.05$, and 0.14 mm vs. 0.28 mm; $P = 0.001$),

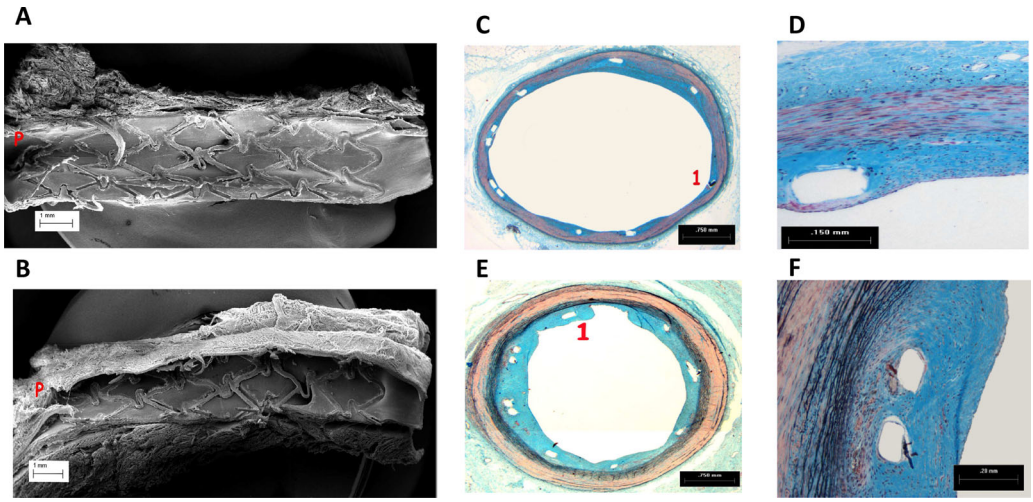

Figure 1. Histomorphometric analysis in preclinical study. SEM analysis in half Rapstrom (A) and polymeric stent (B), overall view at 28 days showing complete endothelialization of stents struts. Histologic section at low magnification shows the pattern of neointimal growth (marker on picture) at 90 days in Rapstrom stent (C) and polymeric stent (D), and at high magnification (E—Rapstrom, F—polymeric stent) showing tissue response to single struts.

respectively, as at 90 days (21% vs. 34%; $P < 0.05$, and 0.19 mm vs. 0.41 mm; $P = 0.001$). Regarding inflammation and injury scores, both Rapstrom and control polymeric devices showed positive and comparable results at 28 days (0.9 vs.1.08, and 1.1 vs. 1.02) and at 90 days (1.04 vs. 1.03, and 1 vs. 1.2, all P not significant), respectively. Finally, the pharmacokinetics of the Rapstrom SES was assessed. In this analysis, 8 stents were implanted in coronary arteries in 4 animals, and the results demonstrated that around 52% of the drug was released in the first 3 days, with an additional 34% of drug released by 14 days; at 28 days, nearly all the drug was released. (Study performed at the Division of Animal Pathology, Life & Science, University of Turin, Turin, Italy; data on file at VasMed Technologies. Ltd.)

Quantitative Angiography. Quantitative coronary angiography (QCA) analyses were performed by an independent angiographic core laboratory at Torino University (Italy) using the Angio XA analysis software (Medis Medical Imaging System, Inc. Leiden, the Netherlands). Standard QCA methodology was used including analysis of the stent and the peri-stent segments defined by 5 mm proximal and distal to the stent edge. Binary restenosis was defined in every segment (proximal, distal, and stent) as a >50% DS at follow-up. Late lumen loss was defined as the difference between the postprocedure and follow-up minimal lumen diameter.

End-points and Clinical Follow-Up. The primary safety end-point was the rate of major adverse cardiac events (MACE) at 12 months after procedure. The primary efficacy end-point was in-stent late lumen loss (LLL) at angiographic FU at 8 months. Secondary end-point included single components of MACE at 30 days both at follow-up. MACE was defined as the composite end-point of cardiac death, myocardial infarction (MI), and ischemia-driven TLR. Target vessel revascularization (TVR) included any new revascularization to the target vessel including TLR. By protocol, all deaths were considered cardiac unless a noncardiac cause could be clearly established by either clinical assessment or pathological study. MI was classified according to its type (Q-wave or non-Q-wave) and occurrence (periprocedural, spontaneous, or post-CABG), following standard definitions as previously reported. ST was classified according to the definitions of the Academic Research Consortium.[26] Angiographic success was defined as residual stenosis <20% plus final TIMI flow 3 after PCI with the study device. Procedural success was defined as angiographic success plus absence of MACE during index hospitalization. Data management and analysis were performed by an independent clinical research unit (University of Turin).

Statistical Analysis. Continuous variables are presented as mean standard deviation, and categorical variables are presented as counts and percentages.

Paired comparisons between postprocedure and 6- and 12-month follow-up were done by a Wilcoxon's signed rank test. All statistical tests were 2-tailed, and a P-value of 0.05 was considered as statistically significant. The current study is an FIM single-arm study, and was designed to provide preliminary hypothesis-generating observations for further studies. The sample size was not defined on the basis of an end-point hypothesis but rather to provide some information about efficacy and safety of the device. Statistical analysis was performed with SAS 8.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient Characteristics. One hundred twenty-three patients were included between March 31, 2011 and March 31, 2012. The baseline clinical characteristics are presented in Table 1. The average age of the patients was 57.9 ± 9.7 years, whereas 32% were diabetic and 79% were male. Clinical indication for PCI was unstable angina in 48 patients (39%), and 42 patients (34%) underwent coronary angiography and PCI for NSTEMI/STEMI.

Quantitative Coronary Angiography Analysis. Baseline angiographic characteristics as well as procedural data are represented in Table 2. Seventy-two patients (58%) had single-vessel disease and received a single stent (3 patients in this group received a second stent at the same target lesion), while 39 patients (31%) had 2-vessel and 12 patients (11%) had 3-vessel disease. Twenty-one in these later groups received at least 2 stents/patient (single stent/vessel). All other patients with 2/3-vessel disease received only single stent at "culprit lesion." Thus, a total of 144 lesions were treated in 142 vessels (mean 1, 2 vessels/patient). A total of 148 Rapstrom stents were used (1.2 stents/patient and 1.03 stents/vessel). Treated lesions were mainly type B1 a B2 lesions according to AHA/ACC lesion classification.

Table 1. Baseline Clinical Characteristics

Patients (n)	123
Male, n (%)	97 (79%)
Age (years ± SD)	57.9 ± 9.7
BMI (kg/m^2 ± SD)	25.3 ± 2.1
Cardiovascular risk	
Diabetes mellitus, n (%)	40 (32%)
Current smoker, n (%)	38 (31%)
Hypercholesterolemia, n (%)	77 (63%)
Family history of CAD, n (%)	64 (52%)
Hypertensive, n (%)	66 (54%)
Previous MI, n (%)	24 (20%)
Previous CABG, n (%)	5 (4%)
Prior PCI, n (%)	5 (4%)
Clinical presentation, n (%)	
STEMI-NSTEMI	42 (34%)
Unstable angina	48 (39%)
Stable angina	23 (19%)
Silent ischemia	10 (8%)

SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Table 2. Baseline Angiographic and Procedural Characteristics

Patients (n)	123
Patients with single-vessel disease, n (%)	72 (58%)
Patients with 2-vessel disease, n (%)	39 (31%)
Patients with 3-vessel disease, n (%)	12 (11%)
Total treated vessels (n)	142 vessels
Total treated lesions (n)	144 lesions
Target lesion	
Left main (shaft)	1 (0.7 %)
Left anterior descending artery, n (%)	81 (56%)
Left circumflex artery—OM, n (%)	24 (16,6%)
Right coronary artery, n (%)	37 (26%)
Intermediate ramus, n (%)	1 (0.7%)
Total no. of treated lesions/vessels	144/142
Total number of stents used	148
Stent/vessel ratio	1.03
Stent/patient ratio	1.2
AHA/ACC lesion classification, n (%)	
A	17 (12%)
B1	45 (31%)
B2	69 (48%)
C	13 (9%)
Reference vessel diameter (mm ± SD)	2.84 ± 0.41
Lesion length (mm ± SD)	17.8 ± 9.6
Minimal lumen diameter (mm ± SD)	1.02 ± 0.39
Stent/artery ratio (mean ± SD)	1.03 ± 0.13
Maximal inflation pressure (atm ± SD)	15.2 ± 5.7

SD, standard deviation; OM, obtuse marginal.

Angiographic and QCA Follow-Up. The angiographic follow-up was performed in all patients enrolled consecutively in the first 6 months (73 patients). Quantitative angiographic analysis (QCA) at baseline, postprocedural, and follow-up angiography is presented in Tables 3 and 4, which demonstrate the cumulative frequency of in-stent MLD immediately after the index procedure and after 9 months. There was no significant difference in reference vessel diameter and minimal lumen diameter at baseline and 9-month angiography. In-stent LLL at angiographic FU was 0.16 ± 0.12 mm, and in-segment LLL was 0.18 ± 0.10 mm. Binary in-segment restenosis was 6.8% occurring in 5 patients:

Table 3. Baseline and Final QCA Analysis (Angiographic Follow-Up in 73 Patients at 9.4 ± 2.6 Months)

Variable	N = 73
Baseline (preprocedure)	
Lesion length (mm)	17.8 (10–23)
<10 mm	12.3 (9/73)
10–20 mm	64.4 (47/73)
>20 mm	23.3 (17/73)
Reference diameter (mm)	2.96 (2.62–3.84)
MLD	0.38 (0.28–1.02)
%DS	84 (73–94)
Final (postprocedure)	
Reference diameter (mm)	3.04 (2.94–3.92)
In-stent	
MLD (mm)	3.02 (2.78–3.69)
%DS	4.2 (2.5–6.8)
Acute gain (mm)	2.64 (1.85–2.92)
In-segment	
MLD (mm)	2.63 (2.32–3.19)
%DS	7.6 (4.1–17.6)
Acute gain (mm)	2.15 (1.73–2.49)
Proximal edge	
MLD (mm)	2.96 (2.72–3.54)
% DS	6.3 (3.7–14.8)
Distal edge	
MLD	2.87 (2.75–3.48)
%DS	7.2 (5.4–16.7)

MLD, minimum lumen diameter; DS, diameter stenosis.

Table 4. QCA Results at Angiographic Follow-Up (Angiographic Follow-Up in 73 Patients at 9.4 ± 2.6 Months)

Variable	N = 73
Reference diameter (mm)	3.02 (2.76–3.45)
In-stent	
MLD (mm)	2.86 (2.47–2.94)
% DS	7.8 (6.9–17.4)
Late lumen loss (mm)	0.16 (0.08–0.28)
Binary restenosis (%)	5.5 (4/73)
In-segment	
MLD (mm)	2.76 (2.31–2.98)
% DS	19.8 (15.7–26.3)
Late lumen loss (mm)	0.18 (0.08–0.32)
Binary restenosis (%)	6.8 (5/73)
Proximal edge	
MLD (mm)	2.85 (2.42–3.24)
% DS	22.8 (7.6–32.6)
Late lumen loss (mm)	0.20 (0.11–0.35)
Binary restenosis (%)	1.3 (1/73)
Distal edge	
MLD (mm)	2.74 (2.21–2.98)
% DS	14.2 (9.7–21.5)
Late lumen loss (mm)	0.19 (0.07–0.26)
Binary restenosis (%)	0.0 (0/73)

MLD, minimum lumen diameter; DS, diameter stenosis.

in-stent in 4 patients and at the proximal edge in 1 patient (Table 4).

Clinical Follow-Up. Twelve-month follow-up was completed in all 123 patients and 24-month FU in 83 patients (68%). Total MACE at 12-month follow-up was 7.3%, with 1 (0.8%) cardiac death caused by severe heart failure occurring in an 80-year-old man with depressed left ventricular function. A noncardiac death (0.8%) occurred also in 72-year-old man who died following severe gastric bleeding. Myocardial infarction occurred in 2 patients (1.6%); both were NSTEMI and both had multiverse disease. Clinical event was due to progression of disease on a remote vessel in 1 patient, while in the other 1 NSTEMI was caused by proximal edge restenosis and was interpreted also in this patient as "possible" stent thrombosis. TLR/TVR occurred in 6 patients (4.8%): 3 patients had focal and 1 diffuse in-stent restenosis and the other 2 had proximal edge restenosis. All were successfully treated by a new procedure. Twenty-four-month follow-up was completed in 83 patients. One cardiac death occurred in a 78-year-old man with previous myocardial infarction and multivessel disease. TLR/TVR occurred in 3 patients (3.6%). No stent thrombosis was reported (Table 5).

Discussion

In the present study, the novel Rapstrom SES demonstrated favorable outcomes in de novo coronary lesions including (a) high angiographic and procedural success (100%) in lesions with moderate complexity (mainly type B); (b) low in-stent LLL (0.15 mm) at mid-term angiographic FU; and (c) low MACE rate or ST up to 24 months. Particularly, at 12 months only 1 "possible" stent thrombosis occurred (Table 5). Interestingly, a relatively young population (57 years) with a relatively high prevalence of diabetes (32%) was present, representing the high prevalence of coronary artery disease found in adults in India. Furthermore, most treated lesions were type B and 73% of patients were treated for acute coronary syndromes (including NSTEMI/STEMI), thus representing a real-life patient population. The Rapstrom FIM Clinical Registry was a multicenter registry including 123 patients with standard-risk lesions, representing the registry feasibility and effectiveness assessment of this novel device.

Table 5. Clinical Follow-Up

Variables	1 Month (123 pts)	6 Months (123 pts)	12 Months (123 pts)	24 Months (83 pts)
Cardiac death	0	0	1 (0.8%)	1 (1.2%)
Noncardiac death	0	0	1 (0.8%)	0
Myocardial infarction	0	1 (0.8%)	2 (1.6%)	0
iTLR	0	1 (0.8%)	2 (1.6%)	1(1.2%)
TLR/TVR	0	2 (1.6%)	4 (3.2%)	2 (2.4%)
Any ARC stent thrombosis				
Possible	0	1 (0.8%)	1 (0.8%)	0
Probable	0	0	0	0
Definite	0	0	0	0
MACCE	0	4 (3.6%)	9 (7.3%)	4 (4.8%)

iTLR, ischemia-driven target lesion revascularization; MACCE, major adverse cardiac and cerebrovascular events; TLR, target lesion revascularization; TVR, target vessel revascularization; ARC, Academic Research Consortium.

However, it should be underlined that 32% of enrolled patients were diabetics and 34% were treated at index procedure for STEMI/NSTEMI. As planned angiographic follow-up was completed in the first 70 enrolled patients. Late lumen loss is a well-validated and accepted surrogate of target lesion revascularization (efficacy) and the results obtained in this study are encouraging since LLL is low at follow-up (Table 3). These data provide initial evidence for the proof of concept (safety and efficacy) of this new DES platform and serves as the rationale for a larger multicenter randomized approval study in more complex lesions and long-term follow-up. The impact of stent design on outcomes has been already reported. Thin strut stents are associated with a more favorable outcome (significantly lower LLL, ISR, and TLR) as compared to thick struts stents.[26–32] In general, thicker struts appear to induce more NIH with uncoated stents [5–8]; hence, a similar behavior would be intuitively anticipated with coated devices. Therefore, most newer-generation DES systems developed to date have incorporated low-profile cobalt–chromium platforms with open cell designs in order to reduce strut thickness, enhance flexibility and deliverability, and improve outcomes.[1–11,33]

Furthermore, biocompatible polymers appear to be vital constituents of DES since their absence has been related to DES failure due to poor drug delivery and uncontrolled release kinetics.[34] Durable polymers have been used in first- and second-generation DES systems[4–6,10,35]; however, their presence (mainly first-generation DES) has been associated with marked local inflammatory response over time that could lead to intense tissue proliferation or delayed healing and extensive vessel enlargement.[14] Even though the genesis of ST has been well recognized as multifactorial,[36–41] we may speculate that the drug carrier's everlasting presence may play a role. In a porcine overstretched stent restenosis model, the rapamycin-eluting biodegradable polymer-coated RAPSTROM stent significantly inhibited smooth muscle cell proliferation without obvious delayed vessel wall healing and demonstrated equivalent efficacy compared with the permanent polymer rapamycin stent (data on file at VasMed Technologies Ltd.). To minimize rapamycin drug concentrations in the vessel, a proprietary fully absorbable composite coating of rapamycin and PLA polymer matrix were applied to the stent surface. This enables controlled rapamycin drug concentration by targeting the vessel wall with the goal of minimizing long-term inflammation and decreasing stent thrombosis rate, while maintaining anti-restenosis effect. The Rapstrom Clinical Registry study demonstrates the feasibility and clinical safety and efficacy of this design 12 months following implant. The LEADERS trial showed improved strut coverage of the biolimus-eluting stent (BES) using a biodegradable polymer compared with the durable polymer-based SES Cypher Select stent, and a recent sub-group analysis showed a reduced cardiac mortality in patients with high Syntax scores compared with the SES Cypher Select group.[34]

Limitations

In the current study, there were no safety concerns up to 12 months, but the relatively low number of patients precludes any definite conclusions regarding safety

beyond the perspective of this preliminary feasibility study. Angiographic results at 8-month FU (70 planned consecutive patients) suggested high efficacy of the Rapstrom SES in inhibiting NIH, but serial IVUS analysis was not available.

Conclusion

The novel Rapstrom SES demonstrated good performance in single coronary lesions including high procedural success and efficacy, as demonstrated by the relatively low LLL (a surrogate of Neointimal hyperplasia) at 8-month angiographic FU. Overall, there were no safety concerns in this preliminary evaluation including MACE or ST up to 12 months. These preliminary safety and efficacy data provided by the present study represent a requisite to the ongoing pivotal randomized trial (Helios Trial) comparing the Rapstrom to the Xience stent and to bare metal stent (Angostrom II stent) in 12 cardiac centers in India and the Middle East.

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