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1-Year Results of the Hydroxyapatite Polymer-Free Sirolimus-Eluting Stent for the Treatment of Single De Novo Coronary Lesions

The VESTASYNC I Trial

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Objectives We sought to assess the safety and efficacy of the novel VESTAsync-eluting stent (MIV Therapeutics, Atlanta, Georgia) combining a stainless steel platform with a nanothin-microporous hydroxyapatite surface coating impregnated with a polymer-free low-dose of sirolimus (55 μg).

Background Durable polymers in first-generation drug-eluting stents (DES) have been linked to local inflammatory reaction leading to a positive vessel remodeling, late incomplete stent apposition, and in some cases, stent thrombosis. The removal of the polymer from the DES system could increase the safety profile of this novel technology.

Methods A total of 15 patients with single de novo lesions in native coronary arteries with 3.0- to 3.5-mm diameter and ≤14-mm length were enrolled in this first-in-man study. Primary end point was in-stent late lumen loss (LL) at 4 and 9 months.

Results Baseline characteristics included mean age of 63 years and 33% of diabetics. Reference vessel diameter and lesion length were 2.7 ± 0.3 mm and 10 ± 2.0 mm, respectively. Procedure success was obtained in all cases. Lifelong aspirin and 5-month clopidogrel treatment were prescribed to all patients. At 4 months, in-stent LL and percentage of neointimal hyperplasia were 0.3 ± 0.25 mm and 2.6 ± 2.2%, respectively, with a nonsignificant increase at 9 months (0.36 ± 0.23 mm and 4.0 ± 2.2%, respectively). Serial intravascular ultrasound did not show late incomplete stent apposition. There were no major adverse cardiac events within 1 year of follow-up.

Conclusions The novel VESTAsync-eluting stent was effective in reducing LL and neointimal hyperplasia at 4 and 9 months, with no evidence of late catch-up by quantitative coronary angiography or intravascular ultrasound. (J Am Coll Cardiol Intv 2009;2:422–7) © 2009 by the American College of Cardiology Foundation

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Due to its marked efficacy in reducing the need for repeat lesion revascularization, first-generation drug-eluting stents (DES) (Cypher, Cordis, Miami Lakes, Florida; and Taxus, Boston Scientific, Natick, Massachusetts) rapidly became the first option for percutaneous coronary artery revascularization (1–4) . However, mid- to long-term safety of these novel devices are still in question mostly because of the late and very late stent thrombosis, partially attributed to the presence of a durable polymer (5–9).

Lower but still effective drug doses combined with nonpolymeric coatings may be beneficial in reducing these adverse events. Recently developed, the VESTAsync-eluting stent (MIV Therapeutics, Atlanta, Georgia) combines a stainless steel platform with a nanothin-microporous hydroxyapatite surface coating impregnated with a polymer-free low-dose lipid-sirolimus mixture (55 μg). In vitro testing on crimped and expanded stents at 37°C in 7.4 pH buffered saline demonstrates a drug release rate (in micrograms per time point, not percentage of loaded drug) that is almost the same as Cypher for the first hour. Thereafter the release rate slows down to less than half the rate of Cypher. One hundred percent of the sirolimus is expected to be released within the first 3 months of the procedure and the hydroxyapatite is stable over 4 months in an in vitro testing environment. The in vivo lifetime of hydroxyapatite coating ranges from 9 to 12 months. After that period, it is expected to completely dissolve (100% according to pre-clinical data).

The VESTASYNC I clinical trial represents the first evaluation of this third-generation DES for the treatment of human coronary lesions. Four-month angiographic and ultrasonographic results as well as 6-month clinical outcomes of this study have been previously reported (10). In the present paper, we present the 9-month angiographic and intravascular assessment along with the 1-year clinical results of this novel nonpolymeric DES.

Methods

The VESTASYNC I trial was a prospective, nonrandomized, single-center evaluation of the hydroxyapatite polymer-free sirolimus-eluting stent in patients with de novo coronary lesions. Patient eligibility criteria, device description, and study procedure have been previously detailed (10).

Briefly, the study population included consecutive patients with single, de novo coronary obstructions >50% and <100% in arteries of 3.0 to 3.5 mm in diameter (visual assessment). Lesions should not exceed 14 mm in length and had to be pre-dilated before the DES implantation. Patients treated within 72 h of an acute myocardial infarction and/or requiring more than 1 stent to treat the target lesion were excluded from this study. We also excluded patients with heavily calcified lesions, those with lesions at bifurcations or involving the ostium of the coronary vessel, patients with severe left ventricular dysfunction (left ventricular function <30%), those with visible thrombus and also with contraindication to any of the protocol medications. Dual antiplatelet therapy (aspirin + clopidogrel) was given for 5 months and then patients were kept on aspirin only.

The protocol was approved by the local ethics committee and written informed consent was obtained from all patients before inclusion in the study.

Follow-up and study end points. After discharge, patients were clinically followed by medical appointment at 1, 3, 6, 9, and 12 months. Up to 2-year clinical follow-up is expected by protocol.

Angiography and intravascular ultrasound (IVUS) follow-up were scheduled for 4 and 9 months after the baseline procedure.

The primary end points of this analysis were in-stent luminal late loss as measured by quantitative coronary angiography (QCA) and in-stent percentage volume obstruction by IVUS, measured at 4 months.

Secondary end points included acute success (angiographic and procedure success), cumulative rate of major adverse cardiac events (MACE) up to 2 years, rates of target-lesion and target-vessel revascularization up to 2 years, and in-stent luminal late loss and in-stent percentage volume obstruction at 9 months. Here we report the 9-month in-stent luminal late loss and in-stent percentage volume obstruction as well as 1-year cumulative MACE and target lesion revascularization rate.

Abbreviations and Acronyms

DES = drug-eluting stent(s)
IVUS = intravascular ultrasound
MACE = major adverse cardiac events
MLD = minimum lumen diameter
QCA = quantitative coronary angiography

Device success was defined by the presence of residual stenosis <20% in the treated segment, in the presence of TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 flow following implantation of the VESTAsync stent. Procedure success was defined by device success associated with no in-hospital major adverse events. We defined MACE as death, nonfatal myocardial infarction (Q- and non–Q-wave), and need for repeat lesion revascularization (by new percutaneous intervention or coronary artery bypass graft). All deaths were considered cardiac unless a clear noncardiac reason was identified. Myocardial infarction was defined by an increase in the creatine kinase-myocardial band twice upper the normal limit with or without new Q waves on the electrocardiogram.

QCA analysis. Angiographic studies were performed at baseline, post-procedurally, and at follow-up, in 2 orthogonal views, after the intracoronary administration of 100 to 200 μg of nitroglycerin. The same angiographic angles performed at baseline were reproduced at the subsequent studies. Digital angiograms were analyzed offline with the use

of an automated edge-detection system (QCA-CMS, Medis Medical Imaging Systems, Nuenen, the Netherlands).

Lesion morphology was assessed by using standard criteria, and lesion complexity defined according to the modified American College of Cardiology/American Heart Association classification system. A contrast-filled catheter tip was used for calibration.

Quantitative angiographic parameters included: 1) reference vessel diameter; 2) minimum lumen diameter (MLD); 3) lesion length; 4) percent diameter stenosis (difference between the reference diameter and MLD divided by the reference diameter and multiplied by 100); and 5) late luminal loss (difference between MLD at the end of the procedure and MLD at follow-up). Quantitative analysis was performed in the "in-stent" area (inside the stented segment) and in the "in-lesion" segment, including the stented area as well as both 5 mm proximal and distal to the stent. In-stent and -lesion restenosis were defined as ≥50% diameter stenosis at follow-up located within the stent and the target lesion, respectively.

IVUS analysis. Intravascular ultrasound studies were performed immediately after the procedure and at follow-up, after an intracoronary administration of 100 to 200 μg of nitroglycerin.

All IVUS studies were performed with a motorized automatic transducer pullback system (0.5 mm/s) and commercially available scanners (i-Lab, Boston Scientific) consisting of a rotating 40-MHz transducer catheter (Atlantis SR Pro, Boston Scientific) with a 2.6-F imaging sheath. The images were digitalized for offline quantitative analysis according to the American College of Cardiology's Clinical Expert Consensus Document on IVUS. Quantitative IVUS analysis was made using a commercially available computerized planimetry program (EchoPlaque, INDEC Systems, Mountain View, California).

Quantitative parameters of lumen, stent, and vessel (external elastic membrane) cross-sectional areas were determined. Neointimal area was calculated as the stent area minus the lumen area at the follow-up. Late lumen area loss was calculated as the minimum lumen area following initial stent deployment minus the minimum lumen area within the stented segment at follow-up. Lumen, stent, vessel and neointimal volumes were calculated using the Simpson rule. Percent of neointimal volume obstruction was determined by the neointimal volume at follow-up divided by the follow-up stent volume and multiplied by 100.

Incomplete stent apposition was defined as ≥1 stent strut clearly separated from the vessel wall with evidence of blood speckles behind the struts and was classified as: 1) persistent (when present both in the post stent implantation and follow-up studies); 2) late-acquired (when not present after stent implantation, but detectable at the follow-up study); and 3) resolved (when present after stent implantation, but not detectable at the follow-up study).

The QCA and IVUS analyses were performed by independent core laboratories at Cardiovascular Research Center, São Paulo, Brazil.

Statistical analysis. Continuous variables are expressed as mean ± SD. Comparisons between post-intervention and follow-up measurements were performed with 1-way repeated-measures analysis of variance and post-hoc tests as appropriate. A p value <0.05 was considered statistically significant.

Results

During May 2007, a total of 15 consecutive patients who matched the inclusion/exclusion criteria were treated with the VESTAsync-eluting stent and included in this analysis. Most patients were male (60%) with low to moderate profile of clinical and angiographic complexity (Table 1). Procedural as well as in-hospital outcomes have been previously presented (10).

Table 1. Baseline Patient, Lesion, and Procedure Characteristics

Characteristics	Patients (n = 15)
Mean age, yrs	63.8 ± 11.4
Female	6 (40%)
Hypertension	9 (60%)
Dyslipidemia	7 (47%)
Diabetes	5 (33%)
Smoking	7 (47%)
Family history of CAD	6 (40%)
Previous MI	7 (47%)
Previous CABG	2 (13%)
Treated coronary artery	
LAD	7 (47%)
LCX	4 (25%)
RCA	4 (25%)
Lesion complexity*	
Type A	1 (7%)
Type B1	3 (20%)
Type B2	11 (73%)
Pre-dilation	15 (100%)
Post-dilation	7 (47%)
Number of stents per lesion	1.0
Mean final deployment pressure, atm	12.4 ± 2.1
Pre-procedure QCA	
Mean reference vessel diameter, mm	2.67 ± 0.32
Mean lesion length, mm	9.98 ± 1.98
Minimum lumen diameter, mm	0.98 ± 0.29
Diameter of stenosis, %	63.5 ± 9.90
Angiographic success	15 (100%)
Procedure success	15 (100%)

Values are mean ± SD or n (%). *According to American College of Cardiology/American Heart Association classification.

CABG = coronary artery bypass graft; CAD = coronary artery disease; LAD = left anterior descending artery; LCX = left circumflex coronary artery; MI = myocardial infarction; QCA = quantitative coronary angiograph; RCA = right coronary artery.

Table 2. 9-Month QCA and IVUS Results (n = 15)

QCA	
In-stent MLD, mm	2.28 ± 0.38
In-stent DS, %	15.9 ± 8.20
In-stent late lumen loss, mm	0.36 ± 0.23
Binary restenosis, %	0
IVUS	
In-stent neointimal volume, mm^3	6.1 ± 4.2
In-stent volume of obstruction, %	4.0 ± 2.2

DS = diameter stenosis; IVUS = intravascular ultrasound; MLD = minimum lumen diameter; other abbreviations as in Table 1.

9-month QCA analysis. All patients returned at 9 months for an invasive evaluation (Table 2). Therefore, serial QCA evaluation (baseline, post-procedure, 4-, and 9-month) was available to the entire cohort.

At 9 months, in-stent MLD, percentage of diameter stenosis, and lumen loss were 2.28 ± 0.38 mm, 15.9 ± 8.20%, and 0.36 ± 0.23 mm, respectively. As compared with the post-procedure and 4-month evaluations, the results were sustained (Fig. 1A).

Figure 2A shows the distribution of in-stent late loss among the 15 patients at 9 months. Of note, the vast majority of patients had a late loss ≤0.5 mm. Only 2 outliers had a more pronounced, focal neointimal formation. None of the patients presented binary restenosis.

9-month IVUS analysis. Adequate IVUS images were obtained in all patients at 9-month follow-up (Table 2). VESTAsync eluting stent elicited minimum neointimal proliferation as demonstrated by the very low in-stent neointimal volume and in-stent volume of obstruction (6.1 ± 4.2 mm^3 and 4.0 ± 2.2%, respectively).

Serial IVUS examination (baseline, 4-, and 9-month) was obtained in 14 cases. In 1 case, IVUS image at 4-month follow-up was deemed inappropriate for analysis and, therefore, this patient was excluded from serial evaluation. Compared with 4-month results, there was a slight, nonsignificant increase in the amount of in-stent neointima hyperplasia (2.8 ± 2.2 mm^3 vs. 4.0 ± 2.2 mm^3, p = 0.4). Importantly, vessel, stent, and lumen volumes did not significant vary from post-procedure to 4- and 9-month evaluations (Fig. 1B). Notably, in all patients, the percentage of stent obstruction was <10% at 9 months (Fig. 2B).

The 2 cases of acute incomplete stent apposition observed in the baseline IVUS analysis persisted at 9 months, with a nonsignificant decrease in the volume of malapposition (0.25 ± 0.75 mm^3 at baseline vs. 0.11 ± 0.13 mm^3 at 4 months and 0.09 ± 0.3 mm^3 at 9 months, p = 0.3). No case of late acquired incomplete stent apposition was observed in this series.

1-year major adverse events and clinical outcomes. At the 12-month clinical follow-up, all patients were asymptomatic with negative noninvasive ischemia test. There were no major adverse clinical events, including cardiac/noncardiac death, cerebrovascular accident, nonfatal myocardial infarction, and stent thrombosis.

Discussion

The 1-year results of the VESTASYNC I trial confirm the sustained efficacy of this nonpolymeric elution of low-dose sirolimus for the treatment of noncomplex de novo coronary lesions, with no late adverse events.

Sirolimus potent antiproliferative properties have been extensively demonstrated following its local coronary delivery using a durable polymer (Cypher) (3,4). However, Mehilli et al. (11) in a recent comparison among 3 sirolimus-eluting stents with different coating strategies (durable and biodegradable polymers vs. polymer-free formulation) showed the inferiority of the nonpolymeric DES in suppressing the neointimal tissue proliferation when compared with the 2 other formulations (11). At invasive

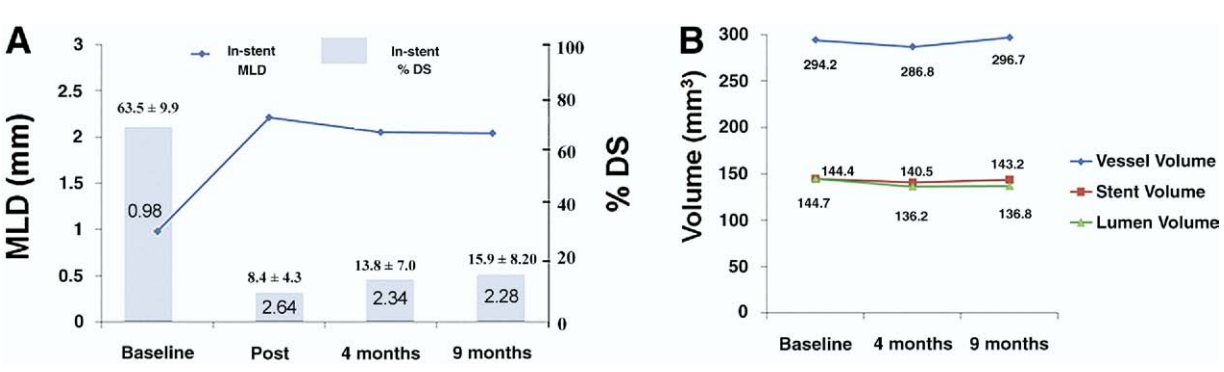

Figure 1. Quantitative Coronary Angiography and Intravascular Ultrasound Main Parameters

(A) In-lesion percentage of diameter of stenosis (DS) and minimum lumen diameter (MLD) over a period of 9 months. **(B)** Vessel, lumen, and stent volume variation among post-procedure, 4-, and 9-month follow-ups.

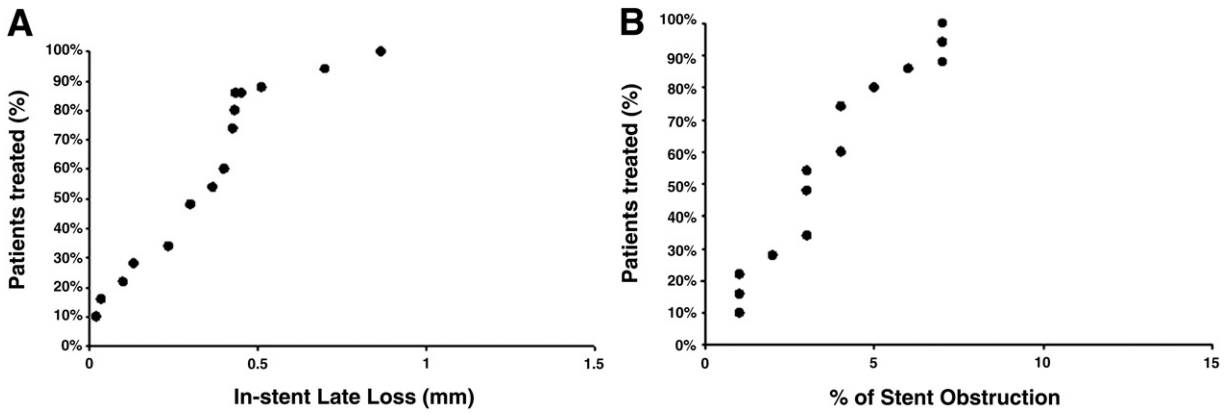

Figure 2. In-Stent Late Luminal Loss and Percentage of Stent Obstruction

Cumulative distribution curves of in-stent late lumen loss **(A)** and percentage of stent obstruction **(B)** at 9 months.

follow-up (6 to 8 months), late lumen loss following the use of the polymer-free sirolimus formulation was 0.47 ± 0.56 mm vs. 0.17 ± 0.45 mm and 0.23 ± 0.46 mm with the durable polymer and biodegradable polymers, respectively ($p < 0.001$). As a result, patients treated with the polymer-free DES had significantly higher angiographic and clinical restenoses. Despite the differences in the populations of the 2 studies, in the present analysis, the hydroxyapatite non-polymeric sirolimus-eluting stent was shown to elicit, at a similar time point assessment, less neointimal tissue formation than the polymer-free system used in the ISAR-TEST-3 (Intracoronary Stenting and Angiographic Restenosis Investigators–Test Efficacy of Rapamycin-Eluting Stents with Different Polymer Coating Strategies) trial.

Of note, the efficacy of the VESTAsync DES was achieved with a very low dose of sirolimus (2.9 μg/mm vs. 7.8 μg/mm in Cypher). Pre-clinical analysis and studies with ex vivo human models have pointed to more inflammatory reaction and delayed local healing following higher doses of antiproliferative agents (e.g., in DES overlapping segments) (12,13).

Finally, recent serial invasive studies with second-generation DES (Endeavor, Medtronic, Minneapolis, Minnesota) showed a marked increase in late loss and percentage of stent neointimal obstruction following the implant of those devices (14). Although the increase did not translate to higher rates of ischemia-driven restenosis in those trials, the results raised concern about long-term maintenance of the good initial results obtained with the second-generation DES. It is important to stress the lack of late catch-up response following the use of the VESTAsync stent in this analysis. Although the sample size might be underpowered to assess its impact on clinical restenosis, the sustained suppression of late loss (QCA) and percentage of stent obstruction (IVUS) observed between the 4- and 9-month follow-ups may indirectly support this premise.

Study limitations. The small sample size included in this study precludes definite conclusions about the safety of this novel DES. Additionally, long-term follow-up (>24 months) in more complex scenarios is necessary to confirm these enthusiastic preliminary results.

Conclusions

The novel VESTAsync sirolimus-eluting stent was effective in reducing lumen loss (0.30 mm) and neointimal hyperplasia formation (2.8%) at 4-month angiographic follow-up. These initial results were sustained at 9-month follow-up (0.36 mm and 4.0%, respectively), with no evidence of late catch-up by QCA and IVUS evaluation (p = NS). In confirming the present findings by large, randomized trials, this novel technology is likely to represent a major advance in the percutaneous treatment of coronary artery disease.

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Key Words: polymer-free sirolimus eluting stent ■ intravascular ultrasound ■ quantitative coronary angiography.