



## First-in-Man Study of Simvastatin-Eluting Stent in De Novo Coronary Lesions – The SIMVASTENT Study –

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**Background:** Statins have anti-inflammatory and antiproliferative properties irrespective of their cholesterol-lowering effects. The aim of the present study was to evaluate a simvastatin-eluting stent (SimvES) in the treatment of de novo coronary lesions.

**Methods and Results:** Forty-two patients with de novo coronary artery lesions were assigned to SimvES, bare-metal stent (BMS) or everolimus-eluting stent (EES) implantation followed by intravascular ultrasound (IVUS) for neointimal quantitative analysis. Six months later, quantitative coronary angiography (QCA) and IVUS were repeated. QCA showed no binary restenosis, a mean in-stent late loss of  $1.05 \pm 0.25$  mm (BMS,  $1.12 \pm 0.48$  mm; EES,  $0.20 \pm 0.16$  mm) and a diameter stenosis of  $33.5 \pm 7.1\%$  (BMS,  $35.5 \pm 15.30\%$ ; EES,  $7.2 \pm 3.12\%$ ). Control IVUS showed a mean in-stent obstruction of  $18.3 \pm 9.4\%$  (BMS,  $32.8 \pm 19.1\%$ ; EES,  $9.8 \pm 2.4\%$ ) and a neointimal volume index of  $1.58 \pm 0.75$  mm<sup>3</sup>/mm (BMS,  $2.93 \pm 1.76$  mm<sup>3</sup>/mm; EES,  $0.80 \pm 0.16$  mm<sup>3</sup>/mm). Thrombus, late incomplete apposition and major adverse cardiac events were not observed.

**Conclusions:** In this sample of patients with de novo coronary lesions, the use of a SimvES was not related to major adverse cardiac events, but it was associated with a higher level of neointimal proliferation than expected. (*Circ J* 2012; **76**: 1109–1114)

**Key Words:** Drug-eluting stent; Intravascular ultrasound; Simvastatin; Statins; Stent

Statins have anti-inflammatory and antiproliferative properties irrespective of their cholesterol-lowering effects. They reduce leukocyte adhesion, platelet aggregation, monocyte activation, and C-reactive protein levels,<sup>1</sup> which are components of the inflammatory process that drives all phases of atherosclerosis.<sup>2</sup> Experimental studies have shown that statins reduce both inflammatory response and neointimal hyperplasia after angioplasty and stent implantation.<sup>3–7</sup> Moreover, meta-analyses of human trials and porcine models have shown that oral statins reduce restenosis after stent deployment.<sup>8,9</sup> A pre-clinical study in swine with the simvastatin-eluting stent (SimvES) under evaluation in the present trial showed that it significantly reduced neointimal thickening compared to bare-metal stents (BMS).<sup>10</sup>

In light of its anti-inflammatory and antiproliferative properties, simvastatin seems to be a promising agent for prevention of in-stent restenosis. It may also have a more physiological mechanism of action than the antiproliferative drugs used

in current drug-eluting stents (DES), because its anti-restenosis properties do not significantly interfere with re-endothelialization.<sup>11</sup>

This first-in-man, prospective, controlled study evaluated a SimvES in the treatment of de novo coronary lesions using intravascular ultrasound (IVUS).

### Methods

#### Subjects

Forty-two patients with single de novo lesions  $\leq 14$  mm in length in coronary arteries of 3.0–3.8 mm in diameter were assigned to receive a SimvES (14 patients), BMS (14 patients), or an everolimus-eluting stent (EES; 14 patients). The BMS and EES groups were used as controls. Patients with left main coronary artery, ostial and/or bifurcation lesions were not included in order to avoid interference of technique issues in the results.<sup>12–14</sup> Atrial fibrillation was an exclusion criterion because, according

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| Characteristics        | BMS       | SimvES    | EES       | P value |
|------------------------|-----------|-----------|-----------|---------|
| Age (years)            | 59.8±8.7  | 62.6±9.9  | 63.9±7.8  | 0.46    |
| Male gender            | 10 (71.4) | 11 (78.5) | 10 (71.4) | 1.0     |
| Diabetes mellitus      | 4 (28.6)  | 5 (35.7)  | 5 (35.7)  | 1.0     |
| Hypertension           | 10 (71.4) | 11 (78.6) | 12 (85.7) | 0.89    |
| Smoking                | 11 (78.6) | 10 (71.4) | 10 (71.4) | 1.0     |
| Dyslipidemia           | 11 (78.6) | 9 (64.3)  | 10 (71.4) | 0.91    |
| Clinical presentation  |           |           |           | 1.0     |
| ACS (non-ST elevation) | 9 (64.3)  | 8 (57.2)  | 8 (57.1)  |         |
| Stable angina          | 5 (35.7)  | 6 (42.8)  | 6 (42.9)  |         |
| Target vessel          |           |           |           | 1.0     |
| LAD                    | 6 (42.9)  | 5 (35.7)  | 6 (42.9)  |         |
| LCX                    | 2 (14.3)  | 2 (14.3)  | 1 (7.1)   |         |
| RCA                    | 6 (42.9)  | 7 (50)    | 7 (50)    |         |
| ASA                    | 14 (100)  | 14 (100)  | 14 (100)  | 1.0     |
| Thienopyridine         |           |           |           | 1.0     |
| Clopidogrel            | 13 (92.9) | 13 (92.9) | 14 (100)  |         |
| Ticlopidine            | 1 (7.1)   | 1 (7.1)   | 0         |         |

Data given as mean ± SD and n (%).

BMS, bare-metal stent; SimvES, simvastatin-eluting stent; EES, everolimus-eluting stent; ACS, acute coronary syndrome; LAD, left descending anterior coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; ASA, acetylsalicylic acid.

to current guidelines, patients with a compelling indication for long-term anticoagulation should undergo BMS implantation or coronary artery bypass graft (CABG) over DES to restrict the duration of triple therapy to 1 month.<sup>15</sup> Also, patients with ST elevation acute coronary syndrome, visible thrombus on angiography, and excessive calcified culprit lesion, as well as patients who underwent thrombus aspiration or received glycoprotein IIb/IIIa inhibitors, were not included in order to avoid bias in the results arising from anatomical, technical, or pharmacological issues not related to the stent. The Ethics Committee of the institution where the study was conducted approved the protocol, and patients provided written informed consent prior to the procedure.

### SimvES

The stents implanted were 316L stainless steel balloon-expandable stents loaded with 0.4 µg/mm<sup>2</sup> simvastatin and coated with a biocompatible and non-absorbable polymer, delivering 30% of the total drug load in 14 days and approximately 40% in 30 days, according to the manufacturer.

### Procedure

Stent deployment was guided by IVUS performed before and at the end of the procedure to ensure stent apposition and to assess the final result. Pre-dilatation of the target lesion was performed at the operator's discretion. All patients received 100 mg aspirin daily indefinitely, started at least 24 h before the procedure at a loading dose of 300 mg, or 5 days before the procedure with no loading dose. They were also treated with 75 mg clopidogrel daily for 6 months, started ≥2 h before the procedure at a loading dose of 600 mg (or ≥12 h before the procedure at a loading dose of 300 mg, or >48 h before the procedure with no loading dose). Six months later, coronary angiography, IVUS and clinical follow-up were performed.

### Quantitative Measurements

Quantitative coronary angiography (QCA) and IVUS were performed immediately after the procedure and at 6-month follow-up in all patients after a bolus infusion of i.c. nitrate.

IVUS images were acquired using motorized pull-back at a constant speed of 0.5 mm/s. Mean stent volume, mean neointimal volume and mean in-stent obstruction were measured and calculated. The percentage of in-stent obstruction was then calculated as neointimal volume/stent volume×100, and the neointimal volume index was calculated as mean neointimal volume/stent length. The percentage of in-stent obstruction and the neointimal volume index were used to compare the results in the 3 stent groups in order to balance a small difference of 1 mm in stent length between the SimvES (stent length 14 mm) and the EES and BMS groups (stent length 15 mm).

### Statistical Analysis

A sample size of 10 patients per treatment group (total 30 patients) was calculated for a statistical power of 90% and an alpha error of 0.05; nevertheless, 14 patients per treatment group (total 42 patients) were enrolled in this study in order to minimize loss to follow-up.

Continuous variables are described as mean ± SD, and categorical data, as absolute and relative frequencies. Fisher's exact test was used for analysis of the categorical data, while 1-way analysis of variance (ANOVA) followed by the Tukey test for multiple comparisons was performed for comparison of continuous variables in the 3 different treatment groups. The P-values obtained from ANOVA refer to the general comparison of the 3 treatment groups. Different letters mean statistically significant differences between the means of the groups after multiple comparisons using the Tukey test. The level of significance was set at P<0.05.

### Results

The baseline clinical and procedural characteristics of the 42 patients enrolled in this first-in-man study indicated diabetes mellitus in 33.3% and acute coronary syndrome in 59.5% of the study participants, with no significant difference between the 3 groups (Table 1). All stents were implanted successfully, and all patients were discharged 24–48 h after the procedure

| Characteristics         | BMS                     | SimVES                 | EES                    | P value |
|-------------------------|-------------------------|------------------------|------------------------|---------|
| Before stenting         |                         |                        |                        |         |
| MLD (mm)                | 0.63±0.36               | 0.59±0.32              | 0.60±0.29              | 0.94    |
| DS (%)                  | 76.8±7.85               | 80.1±8.41              | 79.3±7.35              | 0.52    |
| After stenting          |                         |                        |                        |         |
| In-stent MLD (mm)       | 3.15±0.24               | 3.14±0.25              | 3.12±0.27              | 0.95    |
| In-stent DS (%)         | 7.7±4.5                 | 7.8±4.8                | 7.5±5.2                | 0.98    |
| Follow-up               |                         |                        |                        |         |
| In-stent MLD (mm)       | 2.03±0.40 <sup>a</sup>  | 2.08±0.23 <sup>a</sup> | 2.92±0.26 <sup>b</sup> | <0.001  |
| In-stent DS (%)         | 35.5±15.30 <sup>a</sup> | 33.5±7.13 <sup>a</sup> | 7.2±3.12 <sup>b</sup>  | <0.001  |
| In-stent late loss (mm) | 1.12±0.48 <sup>a</sup>  | 1.05±0.25 <sup>a</sup> | 0.20±0.16 <sup>b</sup> | <0.001  |
| Binary restenosis*      | 14.3 (2/14)             | 0                      | 0                      | 0.32    |

Data given as mean ± SD. \*Data given as % (n).

<sup>a-c</sup>Different letters, statistically significant differences between the means of the groups after multiple comparisons using Tukey test.

MLD, minimal lumen diameter; DS, diameter of stenosis. Other abbreviations see in Table 1.

| Characteristics                               | BMS                    | SimVES                 | EES                    | P value |
|---|------------------------|------------------------|------------------------|---------|
| Stent volume (mm <sup>3</sup> )               | 134.3±11.9             | 121.3±11.2             | 129.0±11.6             | –       |
| Lumen volume (mm <sup>3</sup> )               | 90.2±16.2              | 99.1±12.1              | 116.4±9.8              | –       |
| Neointimal volume (mm <sup>3</sup> /stent)    | 44.0±26.4              | 22.2±10.5              | 12.6±2.5               | –       |
| Neointimal volume index (mm <sup>3</sup> /mm) | 2.93±1.76 <sup>a</sup> | 1.58±0.75 <sup>b</sup> | 0.80±0.16 <sup>c</sup> | <0.001  |
| In-stent volume of obstruction (%)            | 32.8±19.1 <sup>a</sup> | 18.3±9.4 <sup>b</sup>  | 9.8±2.4 <sup>c</sup>   | <0.001  |

Data given as mean ± SD.

<sup>a-c</sup>Different letters, statistically significant differences between the means of the groups after multiple comparisons using Tukey test.

Abbreviations see in Table 1.

without any complications. No significant elevations in enzyme levels (creatinine kinase [CK] and CK-MB) were observed among these patients.

Angiographic follow-up at 6 months showed neither binary restenosis nor stent thrombosis according to the ARC definition<sup>16</sup> in the SimVES and EES groups, but there were 2 cases of restenosis in the BMS group (14.3%). Quantitative coronary analysis indicated an in-stent late loss of 1.05±0.25 mm, 12±0.48 mm and 0.20±0.16 mm and an in-stent diameter stenosis of 33.5±7.13%, 35.5±15.30% and 7.2±3.12% in the SimVES, BMS, and EES groups, respectively (Table 2).

On IVUS, in-stent volume of obstruction was 18.3±9.4%, 32.8±19.1% and 9.8±2.4%, and neointimal volume index was 1.58±0.75 mm<sup>3</sup>/mm, 2.93±1.76 mm<sup>3</sup>/mm and 0.80±0.16 mm<sup>3</sup>/mm in the SimVES, BMS, and EES groups, respectively (Table 3; Figure). There were no cases of acute or late incomplete apposition.

At 6-month clinical follow-up, all patients in the SimVES and EES groups were asymptomatic and there were no major adverse clinical events, such as cardiac or non-cardiac death, myocardial infarction, cerebrovascular accident or target vessel revascularization. One patient from the BMS group developed progressive chest pain on exertion and required early angiographic control at 4.5 months, which showed in-stent restenosis.

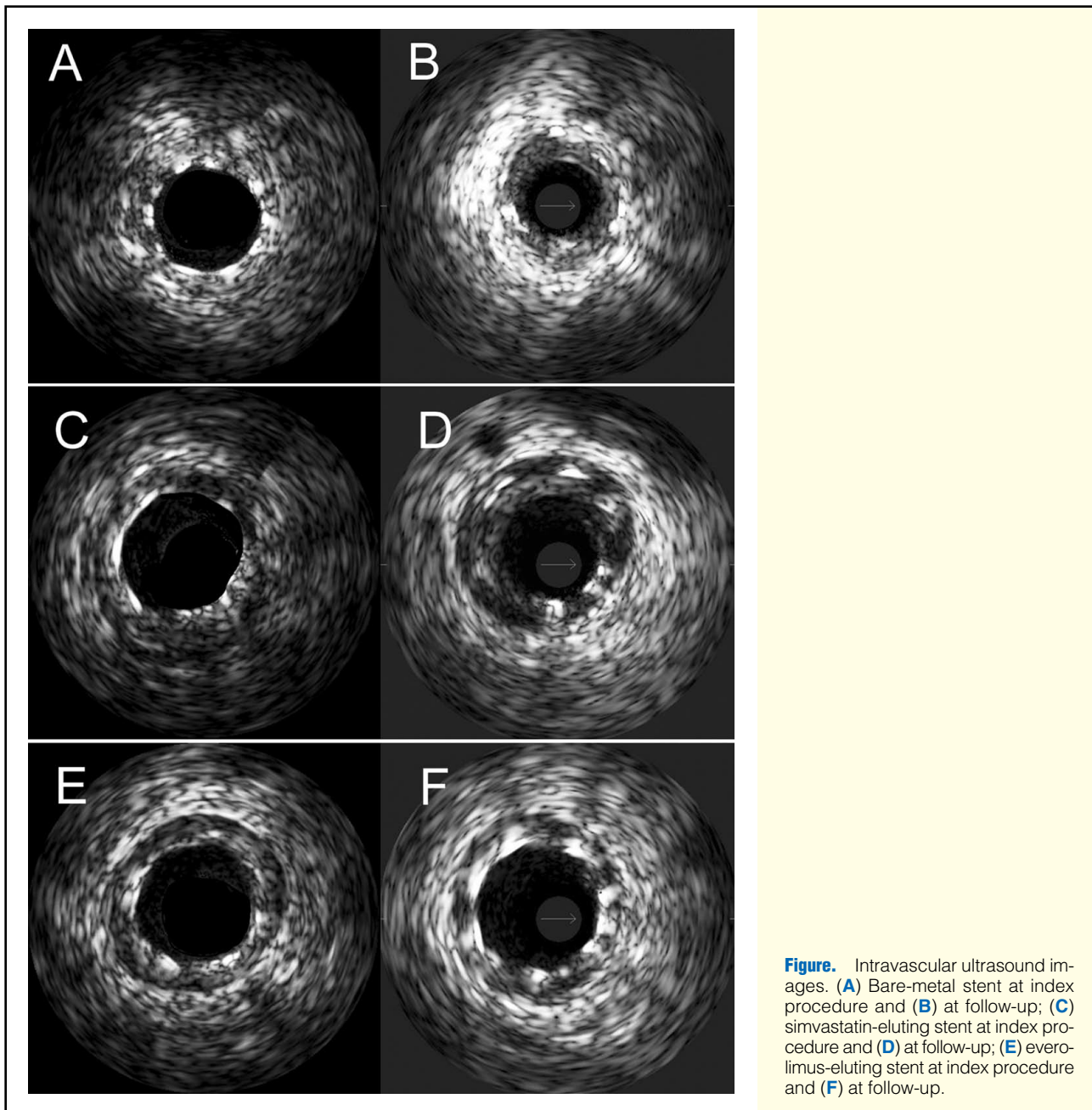
## Discussion

Simvastatin is readily available and well absorbed when taken orally. The local drug concentration achieved by local delivery through a DES, however, cannot be achieved by oral intake without a high risk of systemic toxic effects.<sup>17,18</sup>

In this first-in-man study, there was neither stent thrombosis nor restenosis with the use of the SimVES. There were also no cardiac deaths or deaths due to any cause, and no myocardial infarctions during hospital stay or within 6 months after stent implantation.

In the SimVES group, QCA indicated a late loss of 1.05 mm at 6 months; this was similar to findings in the BMS group as well as to the historical results of BMS studies (0.71–0.84 mm).<sup>19,20</sup> This late loss, however, was higher than that found in the EES group and with most first-generation DES, such as sirolimus-eluting (0.17 mm)<sup>21</sup> and paclitaxel-eluting stents (0.36–0.39 mm),<sup>19,22</sup> and second-generation DES, such as EES (0.10–0.12 mm),<sup>20,23</sup> and zotarolimus-eluting stents (0.61 mm).<sup>24</sup> In-stent diameter stenosis was 33.5%, again closer to the BMS group as well as to the historical results from BMS (37.2%)<sup>22</sup> but higher than the EES group as well as with most DES, such as sirolimus-eluting stents (10.4%),<sup>21</sup> paclitaxel-eluting stents (13.5–17.4%),<sup>19,22</sup> EES (5.9%)<sup>25</sup> and zotarolimus-eluting stents (22.4–27.9%).<sup>24,26,27</sup>

On IVUS, in-stent volume obstruction was found to be 18.3%, which was significantly lower than that found in the BMS group or that reported in historical BMS studies (28.1–33.4%).<sup>20,21,28</sup> The SimVES volume obstruction, however, was significantly higher than that found in the EES group and that reported for sirolimus-eluting stents (2.0–3.1%),<sup>21,29</sup> paclitaxel-eluting stents (8.0–13.0%),<sup>28</sup> EES (3.5–8.0%),<sup>20,30</sup> and zotarolimus-eluting stents (2.2–3.7%).<sup>31</sup> Volume obstruction was also lower with the new novolimus-eluting stent (6.0%).<sup>32</sup> The neointimal volume index of 1.58 mm<sup>3</sup>/mm was also significantly lower than that found in the BMS group, but significantly higher than that of the EES group, and again higher than the historical indices reported for EES (0.2–0.4 mm<sup>3</sup>/mm),<sup>30</sup> zotarolimus-eluting stents (0.2–



**Figure.** Intravascular ultrasound images. (A) Bare-metal stent at index procedure and (B) at follow-up; (C) simvastatin-eluting stent at index procedure and (D) at follow-up; (E) everolimus-eluting stent at index procedure and (F) at follow-up.

0.3 mm<sup>3</sup>/mm)<sup>31</sup> and novolimus-eluting stents (0.42 mm<sup>3</sup>/mm).<sup>32</sup> Therefore, the present study showed that the SimvES is associated with less neointimal proliferation than BMS, but more neointimal proliferation than all other DES.

The subjects did not significantly differ in terms of baseline clinical and procedural characteristics in the 3 treatment groups. Diabetes mellitus, which is a well-known predictor of restenosis, was present in approximately 30–35% of patients, as usually seems to occur in current practice. Non-ST elevation acute coronary syndrome was the most common clinical presentation (approximately 60% of patients) according to current practice, especially after the COURAGE trial;<sup>33</sup> moreover, previous first-in-man studies have also included patients with acute coronary syndrome.<sup>19,34</sup>

The SimvES has shown no focal advantage as compared with the BMS, because both exhibited similar rates of in-stent late

loss and diameter stenosis; the SimvES, however, provided better overall results due to the lower in-stent volume obstruction and neointimal volume index, which suggest an antiproliferative effect of simvastatin over smooth muscle cell proliferation that constitutes the basis of in-stent restenosis.<sup>35</sup> Nevertheless, the higher-than-expected rates of in-stent late loss, diameter stenosis, in-stent volume obstruction and neointimal volume index after implantation of the SimvES in comparison to the EES or to all other DES suggest that simvastatin is not as potent as antiproliferative drugs from the -limus family or paclitaxel. Therefore, the overall performance of the SimvES appears to be intermediate, being closer to that of BMS than to that of any other DES currently available in clinical practice.

Experimental studies with drugs other than the -limus family or paclitaxel have been performed due to their potential drawback of delaying vascular healing, leading to an increased

risk of late in-stent thrombosis and requiring prolonged dual antiplatelet therapy. One experimental in vitro and in vivo study with fludarabine, a nucleoside analog with anti-inflammatory and antiproliferative cellular effects, showed marked inhibition of smooth vascular cell proliferation in cell culture, as well as reduced neointimal formation after balloon angioplasty and reduced neointimal hyperplasia by 50% with the use of fludarabine-eluting stent compared to BMS in rabbits.<sup>36</sup>

Other experimental studies with angioplasty and/or stent deployment have shown that simvastatin reduces neointimal formation. An experimental study showed that simvastatin inhibits vascular smooth muscle cell proliferation in vitro and reduces neointimal formation in a dose-dependent manner in a rat model of vascular injury, either after balloon angioplasty or after stent deployment.<sup>6</sup> That study also demonstrated that the effects of simvastatin on cell proliferation was independent of the cholesterol concentration and dependent on the inhibition of the mevalonate pathway. Another experimental study in mice showed that simvastatin reduces neointimal thickening, cellular proliferation and leukocyte accumulation after angioplasty.<sup>3</sup> A cerivastatin-eluting stent was found to significantly reduce neointimal hyperplasia and to decrease early inflammatory response without inducing endothelial dysfunction in a porcine coronary model.<sup>7</sup> Moreover, the SimvES under evaluation in the present trial promoted a significant reduction of neointimal hyperplasia and inflammatory cell infiltrates compared to BMS.<sup>10</sup>

Despite these promising results of simvastatin in pre-clinical studies, this first-in-man study did not support the satisfactory results reported in previous experimental studies in humans. Two possible explanations for the lower-than-expected neointimal inhibition are: (1) lower efficacy of simvastatin in humans than in animals due to pathophysiological differences; or (2) a higher therapeutic threshold in humans as compared to animals. Thus, increasing the drug load of SimvES in an attempt to achieve better angiographic and ultrasonographic results could be an important change to be evaluated before drug failure is considered.

### Study Limitations

First, this first-in-man study enrolled a small number of patients, but the sample size was adequate to show statistically significant results. Second, the short-term results (6 months) may not predict subsequent findings, especially after discontinuation of dual antiplatelet therapy. Finally, the challenge of calculating the therapeutic drug load in humans on the basis of experimental studies alone, is noted.

### Conclusion

The SimvES evaluated herein was not related to major adverse cardiac events, but it was associated with a higher level of neointimal proliferation than expected. This can be attributed either to inadequate drug load or to the inefficacy of simvastatin in properly controlling neointimal proliferation in humans. Therefore, further evaluation of a SimvES with a higher drug load should be considered before simvastatin is ruled out as a potential agent for prevention of in-stent restenosis.

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