Comparative Analysis of Intimal Hyperplasia After Sirolimus-Eluting Stent and Thin-Strut Bare-Metal Stent Implantation in Small Coronary Arteries

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OBJECTIVE
This study aimed at evaluating reduction in intimal hyperplasia volume following angioplasty using sirolimus-eluting stents (Cypher™) compared with thin-strut bare-metal stents (Pixel™) in patients with small vessels.

METHODS
Eighty patients with coronary artery disease were prospectively included in two consecutive series, the first using sirolimus-eluting stents (50) and the second using bare-metal stents (30).

RESULTS
The use of sirolimus-eluting stents reduced: in-stent net volume obstruction [5.0% (SE = 0.77) x 39.0% (SE = 4.72), p < 0.001], in-stent late loss [0.25 mm (SE = 0.03) x 1.11 mm (SE = 0.13), p < 0.001], in-segment late loss [0.30 mm (SE = 0.04) x 0.83 mm (SE = 0.11), p < 0.001], in-stent restenosis (0% x 33.3%, p < 0.001) and in-segment restenosis (4% x 36.7%, p < 0.001). The event-free survival rate was 96% in the sirolimus-eluting stent group versus 86.7% in the bare-metal stent group (BMS) (p = 0.190).

CONCLUSION
Sirolimus-eluting stents are superior to thin-strut bare-metal stents in reducing intimal hyperplasia (less in-stent obstruction and less late lumen loss) in patients with small vessels. The use of these stents significantly reduced angiographic restenosis at eight months.

KEY WORDS
Stent, restenosis, small vessels.
Treatment of patients with coronary artery disease (CAD) in small vessels currently accounts for up to 40% of all percutaneous revascularizations\textsuperscript{1,2}. Restenosis may be as high as 50% after bare-metal stenting in small vessels, depending on lesion length and on the presence of diabetes mellitus\textsuperscript{3-9}. Intimal hyperplasia is the primary mechanism of in-stent restenosis, and therapies focused on inhibiting neointimal growth should reduce restenosis\textsuperscript{10,11}.

In the FIM and RAVEL trials, the use of sirolimus-eluting stents in patients with vessels larger than 3.0 mm, compared with bare-metal stents, resulted in marked reduction in intimal hyperplasia\textsuperscript{12,14}. In the SIRIUS trial, angiographic restenosis was reduced from 36.3% after bare-metal stenting to 8.9% after sirolimus-eluting stenting ($p < 0.001$). However, in a subanalysis of this same trial, restenosis after sirolimus-eluting stenting in vessels with mean reference diameter of 2.29 mm was higher (18.4%) when compared to large vessels (1.9%), calling into question the role of these endoprostheses in patients with small-vessel disease\textsuperscript{15}.

At the same time, stents have been structurally modified to become thinner, and thin-strut stents were assessed in the ISAR-STEREO-2 trial, the results of which were decreased intimal hyperplasia\textsuperscript{16,17,18}. One study by Garcia et al evaluating these stents in patients with small vessels reported 19.3% of restenosis and only 4.1% of target-vessel revascularization. Since then, these thin-strut stents have been considered the best option among uncoated stents for the treatment of small vessels\textsuperscript{19,20}.

In this study, we compared intimal hyperplasia in small vessels (reference diameter < 2.75 mm) following either sirolimus-eluting or bare-metal stent implantation based on intimal hyperplasia volume measured by intravascular ultrasound.

**METHODS**

From December 2002 to December 2003, patients with established diagnosis of coronary artery disease and candidates for elective percutaneous coronary intervention (PCI) were prospectively included in this study according to the following criteria: age equal to or older than 18 years; diagnosis of stable angina defined by the Canadian Society Classification (CSC I, II, III or IV), silent ischemia, unstable angina (Braunwald classification IB, IC, IIB, IIC), or myocardial infarction > seven days; reference vessel diameter between 2.20 mm and 2.75 mm (quantitative coronary angiography); de novo native coronary artery lesion with target-lesion stenosis between 50% and 99% and ≤ 30 mm in length. Exclusion criteria were: presence of cardiogenic shock; serum creatinine > 2.0 mg/dL; peripheral vascular disease; known hypersensitivity or contraindication to heparin, acetylsalicylic acid (ASA), ticlopidine or clopidogrel; end-stage diseases associated with limited life expectancy (less than a year); left ventricular ejection fraction ≤ 30%; excessive target-vessel tortuosity, making intracoronary ultrasound difficult to perform; target-lesion ≥ 50% in unprotected left main coronary artery; ostial lesions; target-lesions located at a bifurcation involving side branches ≥ 2.0 mm in diameter, and the presence of thrombus at the target site. The study protocol was approved by the Institutional Research Ethics Committee of the Hospital.

Patients were nonrandomly assigned to the trial and divided into two sequential treatment groups, the first using the Cypher™ stent (coated with sirolimus) and the other using the Multilink Rx Pixel™ stent (uncoated). According to the standard technique, aspirin 200 mg/day was administered at least 24 hours prior to intervention and a thienopyridine (ticlopidine or clopidogrel), during two months. Ticlopidine dosage was 250 mg twice daily (started at least 48 hours prior to intervention). Clopidogrel was given in a loading dose of 300 mg followed by and 75 mg daily (at least 24 hours prior to intervention). Unfractionated heparin was administered by intravenous bolus of 100 IU/kg. The use of both glycoprotein IIb/IIa inhibitor and predilation was left to the operators’ discretion. Predilation balloons should be undersized at least 0.5 mm to the reference vessel diameter, in addition to being shorter than the chosen stent. Postdilation balloons (pressure > 12 atm) also should be shorter than the implanted stent. When multiple stents were required, they had to overlap by 3 or 4 mm to prevent gaps between the endoprostheses. At the end of the procedure, all patients underwent ultrasound evaluation. Outpatient visits following discharge were made one, three, six, and eight months after PCI, when other coronary angiography and ultrasound examinations were scheduled.

As for the endovascular prostheses used, the Cypher™ stent (with sirolimus) manufactured by Cordis, Johnson & Johnson, is made of 316L stainless steel coated with a 50/50 combination of two non-erodible polymers, polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA), mixed with sirolimus. A topcoat of PBMA polymer is applied to the stent surface. All stents contain 148 µg of sirolimus per cm\(^2\) of metal surface area and, in this formulation, the drug is released gradually over a prolonged period (95% is released up to 28 days after implantation). The Multilink Rx Pixel™, manufactured by Guidant™, is a stainless-steel, uncoated, balloon-expandable stent especially designed for small vessels. This thin-strut stent (0.05 mm) is composed of only five rings, allowing complete circumferential coverage with less metal.

Off-line quantitative angiographic analysis was performed using the CMS™ device (Medis, Netherlands) at end-diastolic frames. The frame displaying the most severe lesion, before and after stent implantation, would be chosen for analysis. Minimal lumen diameter (MLD) and late lumen loss (LLL) were measured at the in-stent...
RESULTS

Eighty patients were included in this study: the first fifty were sequentially treated with sirolimus-eluting stent (Cypher™) and the last thirty, with Multilink Rx Pixel™ (uncoated). Clinical characteristics of patients in both treatment groups are shown in Table 1, angiographic characteristics in Table 2, as well as the technical variables of procedure in Table 3. During follow-up, 94% of the patients underwent angiographic evaluation. Results of in-stent quantitative coronary angiography (QCA) are shown in Table 4. Mean reference vessel diameter [2.44 mm (SE = 0.02) x 2.37 mm (SE = 0.03), p = 0.075] and mean length of treated lesions [13.75 mm (SE = 0.92) x 12.87 mm (SE = 0.53), p = 0.498] were similar in both groups. Mean minimal lumen diameter did not differ between groups, either in the preprocedural (p = 0.926) or in the postprocedural findings (p = 0.952), but at eight months the vessels treated with sirolimus-eluting stents had increased MLD [2.14 mm (SE = 0.03) x 1.28 mm (SE = 0.13), p < 0.001]. This was due to the late lumen loss, which was significantly lower in the sirolimus group [0.25 mm (SE = 0.03) x 1.11 mm (SE = 0.13), p < 0.001].

No in-stent restenosis was found following sirolimus-eluting stenting, contrary to 33.3% of restenosis following bare-metal stenting (p < 0.001). Individual MLD variations, as well as in the stenosis rate over time, in both treatment arms are shown in Figure 1. These angiographic measurements obtained before and after the procedure are quite consistent in both treatment groups, but in late evolution, higher variability is observed with bare-metal stents. In-segment analysis showed less late...
lumen loss with sirolimus-eluting stents than with bare-metal stents [0.30 mm (SE = 0.04) x 0.83 mm (SE = 0.11), p < 0.001, respectively], in-segment restenosis being significantly lower in the sirolimus arm [4% x 36.7%, (p < 0.001)].

Eighty per cent of the patients underwent intravascular ultrasound examination. Intravascular ultrasound analysis showed that mean intimal hyperplasia volume was 5.0 mm³ (SE = 0.77) in the sirolimus-stent group versus 27.5 mm³ (SE = 3.60) in the BMS-group (p < 0.001). Mean intimal hyperplasia cross-sectional area was smaller in the sirolimus-stent group compared with the BMS-group [0.24 mm² (SE = 0.03) x 1.62 mm² (SE = 0.19), p < 0.001], as was mean in-stent volume obstruction [5% (SE = 0.77) x 39% (SE = 4.72), p < 0.001]. No stent malapposition was found in either group.

Stent implantation was successful in all the patients, without major in-hospital complications (death, myocardial infarction, or emergency revascularization surgery). No patient in this study was given glycoprotein IIb/IIIa inhibitor. Moreover, there were no in-stent thromboses, nonfatal myocardial infarctions nor deaths, either at 30 days or at eight months. All patients were clinically evaluated during this period, and two patients (4%) treated with sirolimus-eluting stents required repeat target-lesion revascularization. In these cases, additional...
angioplasty was performed with the implantation of another sirolimus-eluting stent. Six patients in the BMS-group experienced myocardial ischemia symptoms (20.0%), and four (13.3%) required repeat target-lesion revascularization (TLR): two balloon angioplasty and two coronary artery bypass surgery (CABG). Thus, although event-free survival and TLR-free survival were lower in the sirolimus-stent group when compared with the BMS-group, no statistically significant difference was found regarding these clinical outcomes in either group (96% x 86.7%; p = 0.190).

**DISCUSSION**

This study showed that sirolimus-eluting stenting in patients with small vessels is associated with a lesser degree of intimal hyperplasia compared with the reparative response following bare-metal stenting, and thus results in a lower rate of in-stent and in-segment restenosis. Clinical variables in this study characterized groups of patients with at least moderate complexity for percutaneous coronary intervention. Among all characteristics, it is worth noting the high prevalence
of diabetes mellitus: 40% in the sirolimus-eluting stent group and 30% in the BMS-group (p = 0.368). In most randomized trials comparing ballooning versus stenting in patients with small vessels, with the exception of the CHIVAS23 and RAP24 trials, the prevalence of diabetes was lower than 30%, ranging from 12% and 20%. Even in the era of sirolimus-eluting stents, the SVELT25 was the trial that included the highest number of diabetics (26.7%). In the RAVEL 14, SIRIUS, C-SIRIUS 26, E-SIRIUS 27 and SES-SMART28 trials, this subgroup accounted for 16%, 25%, 24%, 23%, and 19.4%, respectively.

The most relevant IVUS finding was the beneficial mechanism involved with sirolimus-eluting stent compared with bare-metal stent, that is, inhibition (in 87%) of excessive intimal hyperplasia evaluated by in-stent volume obstruction. This finding of marked decrease in in-stent intimal hyperplasia has been consistent in all sirolimus-eluting stent trials that used IVUS as the evaluation tool. Mean intimal hyperplasia cross-sectional area obtained in this investigation (0.24 mm²) was similar to that observed in the SVELT25 trial (0.08 mm²), as well as in trials of sirolimus-eluting stents in larger vessels, such as the RAVEL14 and the SIRIUS15 (0.11 mm² and 0.50 mm², respectively), meaning that intimal hyperplasia inhibition with these stents does not depend on vessel diameter. However, mean intimal hyperplasia associated with the thin-strut, bare-metal stents used in this study (Pixel™) was 1.62 mm², lower than that found in the DANTE29 trial (3.05 mm²) and in the respective arms of the RAVEL 14 and SIRIUS15 trials (2.05 mm² and 2.70 mm², respectively), which used a thicker strut model.

Moreover, no incomplete apposition of stent struts was found in either group. Unlike in large vessels, stent placement in small vessels is performed with a higher stent-to-vessel diameter ratio, favoring stent strut impaction in the atheromatous plaque. Therefore, incomplete stent apposition is usually less frequent in small vessels. In the RAVEL14 trial, for example, mean vessel diameter in ten patients with incomplete stent apposition was 3.16 mm (SD = 0.57), whereas that of 38 patients with well-apposed stents was 2.79 mm (SD = 0.43), (p < 0.05).

In the last decade, recommendations for bare-metal stenting emphasized the need to obtain as much lumen as possible to accommodate hyperplasia and, thus, reduce restenosis. However, in the investigation of drug-eluting stents showing significant decrease in-stent
intimal hyperplasia, as in the SIRIUS\textsuperscript{15} trial, the finding of border effects attracted special attention, because they accounted for the recurrences in this study. Based on this new perspective, additional technical observations were implemented to guide stent implantation.

One of these aspects is lesion coverage, because an incomplete metallic coverage in sirolimus-eluting stent implantation may affect late results. In this study, stent length–to–lesion length ratio was 1.4, and in the C-SIRIUS\textsuperscript{16} and E-SIRIUS\textsuperscript{17} trials was even higher (1.7 and 1.8, respectively), as well as in the RAVEL\textsuperscript{14} trial, in which no follow-up restenosis was found during the first year. Although lesions were more complex in the C-SIRIUS\textsuperscript{16} trial than those randomized in the RAVEL\textsuperscript{14} trial, requiring more than one stent per lesion in 48% of the cases (67% of which with overlapping stents), restenosis rate was very low (0% in-stent and 2.3% in-segment), demonstrating that longer stents are better, even when more than one stent is required. In this case, this should be done with a 2- or 3 mm overlap, to prevent target lesion ends from being exposed to balloon trauma and, thus, to intimal proliferation.

Among the limitations of this study, the lack of randomization should be noted. Logistics regarding limited availability of sirolimus-eluting stents prevented inclusion for a one-year period anticipated by the study design. Nevertheless, it must be emphasized that both treatment groups were quite homogeneous with respect to all variables related to lesion recurrence and thus minimized this aspect. In addition, the way patients were sequentially included and also the stents’ structural differences prevented a blind analysis of results. However, result analysis by quantitative angiography and intravascular ultrasound, with accurate and objective measurements, performed at a laboratory with large experience in this field, minimizes this aspect.

In view of these findings, we believe that treatment of vessels with reference diameter lower than 2.75 mm changed dramatically with the advent of sirolimus-eluting stents. Moreover, in the near future, as the costs of endoprostheses decrease, the use of sirolimus-eluting stents in patients with small vessels may be even more cost-effective compared with bare-metal stents, owing to a reduction in target-lesion revascularization, hospital admissions, and drug prescriptions.

Therefore, we can conclude that sirolimus-eluting stenting in patients with small vessels leads to reduced intimal hyperplasia, as evaluated by intravascular ultrasound, compared with thin-strut, bare-metal stenting. Angiographic measurements related to late results (degree of stenosis, late lumen loss, and restenosis) are significantly lower after sirolimus-eluting stent implantation. Late minimal lumen diameter is greater following sirolimus-eluting stenting compared with bare-metal stenting. Target-lesion revascularization is about 10% lower in patients treated with sirolimus-eluting stents, even though this difference was not statistically significant in the present study.

No potential conflict of interest relevant to this article was reported.

\textbf{References}


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COMPARATIVE ANALYSIS OF INTIMAL HYPERPLASIA AFTER SIROLIMUS-ELUTING STENT AND THIN-STRUT BARE-METAL STENT IMPLANTATION IN SMALL CORONARY ARTERIES


