Introduction
The technique of coronary stenting introduced in the early 1990s contributed widely to the enhancement of percutaneous intervention outcomes in patients with coronary artery disease. However, the phenomenon of in-stent restenosis has long been the stumbling block of interventional cardiology and the target of many research projects in this field including the use of various devices or radiation therapy, and systemic or local delivery of biochemical substances and drugs. Indeed, angiographic restenosis, defined as a stenosis or narrowing of the vessel diameter by 50% at follow-up evaluation (binary restenosis), is still reported in 17-30% of patients following cardiac stenting with uncoated or bare stents.\(^1\)\(^2\) Restenosis following stenting is largely due to neointimal hyperplasia, which is the healing response to the vascular injury induced by stent implantation and mechanical dilatation and translates into proliferation of smooth muscle cells\(^3\)\(^-\)\(^6\). It is in this context that the technology of site specific, stent-based drug delivery to inhibit the restenosis process has emerged.

The ability of a wide variety of pharmaceuticals to inhibit restenosis following coronary interventions has been assessed. Evaluation of some of these agents, (actinomycin D, Batismastat and QP2) was discontinued in view of the poor results obtained in the preliminary phases of clinical trials. Among the various drugs investigated, Sirolimus and Paclitaxel stood out as yielding very promising results. The largest body of data has been collected through studies conducted with the sirolimus molecule\(^7\)\(^-\)\(^9\). The two-year follow-up period of patients who received a sirolimus-eluting stent is now available\(^10\).

Clinical Trials Conducted with Sirolimus-eluting Stents
Sirolimus (rapamycin) has been approved for use in the prevention of graft rejection following renal transplant. It is a cytostatic, antibiotic and anti-inflammatory agent which has been shown to reduce neo-intimal hyperplasia and smooth cell muscle proliferation by inhibiting G1 phase of the cell cycle.\(^11\)\(^-\)\(^13\)

The First-in Man Pilot Study
The safety and efficacy of stent-based delivery of sirolimus was first evaluated in a pilot study conducted in Brazil and Holland in 45 patients in whom follow-up analysis was performed at 4, 6, 12 and 18
Table 1 : RAVEL Subsegmental QCA analysis

<table>
<thead>
<tr>
<th>Treatment assignment</th>
<th>Proximal edge</th>
<th>Stented segment</th>
<th>Distal edge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sirolimus</td>
<td>Control</td>
<td>p</td>
</tr>
<tr>
<td>Mean diameter (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure</td>
<td>2.66 ± 0.59</td>
<td>2.62 ± 0.58</td>
<td>ns</td>
</tr>
<tr>
<td>Post procedure</td>
<td>2.78 ± 0.55</td>
<td>2.78 ± 0.53</td>
<td>ns</td>
</tr>
<tr>
<td>Follow up</td>
<td>2.73 ± 0.59</td>
<td>2.55 ± 0.60</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure</td>
<td>2.27 ± 0.60</td>
<td>2.23 ± 0.66</td>
<td>ns</td>
</tr>
<tr>
<td>After procedure</td>
<td>2.47 ± 0.53</td>
<td>2.46 ± 0.54</td>
<td>ns</td>
</tr>
<tr>
<td>6 months</td>
<td>2.41 ± 0.58</td>
<td>2.19 ± 0.64</td>
<td>0.005</td>
</tr>
<tr>
<td>Percent diameter stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure</td>
<td>15.2 ± 9.1</td>
<td>16.2 ± 12.2</td>
<td>ns</td>
</tr>
<tr>
<td>After procedure</td>
<td>11.4 ± 5.0</td>
<td>12.1 ± 5.2</td>
<td>ns</td>
</tr>
<tr>
<td>6 months</td>
<td>12.2 ± 4.7</td>
<td>15.4 ± 8.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>0.05 ± 0.39</td>
<td>0.29 ± 0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Restenosis rate (%)</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are mean±SD. p values refer to differences between sirolimus and uncoated metal stents treatment groups.
MLD=minimum luminal diameter

Table 2 : RAVEL: Small vessel sub study

<table>
<thead>
<tr>
<th>RAVEL</th>
<th>stratum I &lt;2.36mm</th>
<th>stratum II, RD 2.36 mm to 2.84mm</th>
<th>stratum III, RD&gt;2.84mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restenosis rate-sirolimus stent group</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Restenosis rate-bare stent group</td>
<td>35%</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>In-stent late loss-sirolimus stent group</td>
<td>0.01 +/-0.25mm</td>
<td>0.01 +/-0.38mm</td>
<td>-0.06+0.35mm</td>
</tr>
<tr>
<td>In-stent late loss-bare stent group</td>
<td>0.80 +/-0.43mm</td>
<td>0.88/-0.57mm</td>
<td>0.74 +/-0.57mm</td>
</tr>
</tbody>
</table>

Table 3 : SIRIUS Small vessel sub study

<table>
<thead>
<tr>
<th>SIRIUS</th>
<th>sirolimus stent group</th>
<th>control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-segment restenosis (overall)</td>
<td>8.9%</td>
<td>36.3%</td>
</tr>
<tr>
<td>In-segment restenosis rate (2.3mm reference diameter)</td>
<td>18.6%</td>
<td>42.9%</td>
</tr>
</tbody>
</table>
months and at 2 years. The recently presented two-year outcome confirmed the absence of neo-intimal proliferation and, consequently, the stability of the shorter-term results in most patients.

The Ravel Study

The performance of the Sirolimus-eluting stents compared with that of standard uncoated stents was assessed in a randomized, double-blind trial conducted from August 2000 to August 2001 in 19 centers worldwide. This study included patients with documented stable or unstable angina or silent ischemia, presenting with a single de novo lesion in a native coronary artery 2.5 mm to 3.5 mm in diameter. Double blind randomization of the study patients to implantation of an uncoated stent or a Sirolimus-eluting stent was carried out following successful pre-dilatation. A total of 238 patients were included in the study of whom 120 received a sirolimus stent and 118 an uncoated stent. The baseline characteristics of the study patients were comparable in both groups. Mean patient age was 60.7 and 76% were male. Stent deployment was successfully performed in 96% of patients in the sirolimus group and in 93.1% in the uncoated group (p=NS). Angiographic follow-up was obtained in 88.7% of the patients included in the study. Quantitative angiographic measurements are shown in Table 1.
Mean in-stent late loss, percent diameter stenosis and binary restenosis rates were 0.01 mm, 14.7 % and 0 % respectively in the sirolimus group versus 0.80mm, 36.5% and 26.2% respectively in the uncoated stent group. The cumulative frequency distribution of diameter stenosis in each treatment group immediately after the procedure and at 6 months is shown in Figure 1 and the results of sub-segmental quantitative angiographic analyses are presented in Table 1. The loss in luminal diameter at the proximal and distal edges of the stent was markedly lower (p<0.001) in the recipients of the sirolimus stent compared with the patients included in the control group.

The intravascular ultrasound examination carried out at 6 months revealed neointimal hyperplasia (2±5 versus 37±28 mm³) and percent volume obstruction 1 ±3% versus 29±20%) were significantly
smaller in the sirolimus group compared with the uncoated stent group. Furthermore, no edge effect, aneurysm formation, in-stent thrombosis or persistent dissection was evidenced. Overall, the rate of major adverse cardiac event was 5.8% in the sirolimus group versus 28.8% in the uncoated stent group. The sirolimus coating of the active stent was not associated with any untoward effect. The follow-up analysis carried out at two years showed practically no neointimal in-stent proliferation and very little target lesion and target vessel revascularization in recipients of the sirolimus-eluting stent with a 90% event-free survival rate.

The Sirius Study

The purpose of this randomized, double blind, controlled clinical trial\textsuperscript{14} conducted in 53 US centers and involving 1,101 patients was to further assess the sirolimus stent in more complex lesions and in patients at higher risk (lesion length between 15 and 30 mm: diabetes in 25% of patients, and overlapping stents in 28% of cases).

Though less dramatic than the RAVEL findings, the 8-month results of the SIRIUS study confirmed the efficacy of the sirolimus stent. Indeed, in-stent and in-segment restenosis as well as target lesion revascularization were markedly reduced in patients treated with sirolimus-eluting stents and no instances of acute, sub-acute or late thrombosis were reported in this study group. The restenosis rate of the stented segment was 8.9% in sirolimus stent group as opposed to 36.3% in the control group and event-free survival rates were 92.5% and 80.7% respectively. These results were consistently observed in male and female patients, diabetic or non-diabetic, in the left anterior descending artery as well as in the other vessels, in small and large arteries, in long or short lesions, and in the presence of overlapping stents.

Clinical Trials with Paclitaxel Eluting Stents

Paclitaxel (Taxol) is a taxane, a class of cytotoxic anti-cancer agent that has been used in ovarian and breast cancer. Paclitaxel has an inhibitory effect on the microtubules and reduces cellular proliferation and migration\textsuperscript{15}. Implantation of paclitaxel-coated stents has shown to reduce neo-intimal hyperplasia in an animal model of coronary restenosis\textsuperscript{16}. Subsequently several clinical programs (TAXUS, ASPECT, ELUTES, DELIVER) were set up to assess the effectiveness of paclitaxel according to the delivery system and the formulation used. The results of these trials have shown minimal 6-month angiographic binary restenosis rates in recipients of paclitaxel-releasing stents\textsuperscript{17}. In the TAXUS II\textsuperscript{18}, 563 patients with de novo, short lesions in vessels between 3.0 and 3.5 mm in diameter were randomized to receive a stent delivering either a moderate-release or a slow-release formulation of paclitaxel, or a bare stent. Binary in-stent restenosis was 19% in the control group versus 4.7% in the moderate-release group and 2.3% in the slow-release group (p= 0.001). The 6-month follow-up results showed an 8.5% event rate in the slow-release group, 7.8% in the moderate release group and 19.8% in the bare stent control group (p=0.001).

It is also important to underline that, though unable to replicate the 0% restenosis rate reported in RAVEL, results from other trials (TAXUS, ELUTES, ASPECT) using taxol-derived agents have shown favourable 6-month angiographic binary restenosis rates compared to uncoated stents.

Treatment of In-stent Restenosis

A feasibility study from Sao Paulo and Rotterdam with sirolimus eluting stents in the treatment of in-stent restenosis (ISR) in a group of 41 patients, 4-month follow-up data had shown minimally low in-stent late lumen loss, zero restenosis, no TLR, stent thrombus or death in Sao Paulo. However, more events were reported in the Rotterdam cohort involving very complex patients (transplanted patients already treated by radiation therapy and multiple stenting). Further several studies\textsuperscript{19,20} have shown the safety and the utility of sirolimus-eluting stents for the treatment of in-stent restenosis.
Thus, sirolimus eluting stent implantation is an effective treatment for patients with complex ISR, even when they are at an intrinsically high risk for complications. As the use of drug-eluting stents increases, their complexity and the range of indications will expand towards higher risk patient populations. In this setting, stenting the whole area injured by the balloon, overlapping SESs properly, and good stent deployment with low residual stenosis, as well as an appropriate anti-platelet regimen will be the key to successful treatment. When more than one eluting stent is used to treat long in-stent restenotic lesions, IVUS guidance may be advisable to optimize complete coverage of previously implanted bare metal stents and to ensure that the edges of implanted stents are overlapped.”

Safety and Effectiveness
In the case of the Sirolimus-eluting stent, available pre-clinical and clinical trial data confirm that it is safe (at least upto 2 years), effective in de novo lesions and suitable for use in a wide range of patients. Data from the SIRIUS trial appear to support its use in overlapping stents. There has been some recent concern that the use of drug-eluting stents increases the incidence of incomplete stent apposition, a phenomenon detected by intravascular ultrasound that occurs when 1 or more of the stent struts fails to expand fully against the vessel wall. Apparently, late stent incomplete apposition or aneurysm formation does not occur more frequently in drug-eluting stents than in bare stents.

There are a few issues that have not been completely addressed, such as thrombosis, edge effect, late in ammannation due to choice of polymer used to bind the drug, the release of toxins, and potential interaction with brachytherapy.

Lesion Subsets
The application and testing of the Sirolimus-eluting stents in different lesion subsets is a natural evolution of this process of going from straightforward to more demanding patient groups and lesion types.

Diabetic Patients
Diabetic patients represent a seriously high-risk group, especially in the occlusive form of the disease, which is a powerful predictor of long-term (10-year) mortality in diabetic patients after coronary balloon angioplasty and face even greater risk of complications and events following intervention. Findings from the Bypass Angioplasty Revascularization Investigation (BARI) also support the concept that maintaining coronary artery patency is critical to longer-term outcomes in patients with diabetes. Now, however, drug-eluting stents may even be able to effectively treat this high-risk population.

A subgroup analysis from drug-eluting stent trials that indicates the new therapy has the same astounding efficacy in diabetic patients. For instance, in the SIRIUS trial, the minimal lumen diameter at 8-month angiography follow-up was 2.28 mm in diabetic patients (late loss 0.29 mm) treated with sirolimus-eluting stents, compared with 1.46 mm in the control group (late loss 1.20 mm; delta 0.91, P < .001). Similar results were obtained in subgroup analysis from the TAXUS SR and MR studies (unpublished) (Figure 2).

Small Vessels
Small-vessel lesions have also shown clinical benefit from the use of a drug-eluting stent. A subgroup analysis of RAVEL trial showed that the classic inverse relationship between vessel diameter and restenosis rate was seen in the bare stent group but not in the sirolimus-eluting stent group (Table 2). In the SIRIUS trial, the reduction achieved in in-stent late loss and restenosis rates were similar regardless of the size of the stented vessel. A post hoc analysis addressing patients with small vessels (2.3mm reference diameter) showed a restenosis rate of 18.6% of patients in the sirolimus stent group compared to 42.9% in the control group. The less effective suppression of neointimal hyperplasia at
the stent margins was disproportionately greater in small vessels (table 3). The frequency of TLR in small versus large vessels (7.3% versus 1.8%), was usually associated with proximal margin peri-stent restenosis.

In the Taxus II\textsuperscript{18}, the restenosis rates in the analysed segment including the stent margins were 13.5% (2.5 mm vessel) versus 0% (vessels more than 3 mm) and restenosis rates within stent were 2.7% (2.5 mm vessel) versus 0% (vessels more than 3 mm)\textsuperscript{19}. Thus, the restenosis rate was higher at the stent margins and was disproportionately greater as the reference vessel diameter decreased.

In small vessels, the sirolimus eluting stent has only attenuated, and not completely eliminated the restenosis. The reason for this high persistence of restenosis in small versus large vessels is the higher frequency of edge restenosis. An argument has been made that the higher frequency of edge restenosis in smaller vessels may be secondary to inappropriate lesion coverage, but it remains to be seen whether longer stents will attenuate the frequency of this phenomenon. A overall analysis accounting for small vessels (2.3 mm) showed that the rates of restenosis in this patient population mirrored those reported for patients with large vessels (3.3 mm) (Figure 3).

Bifurcation Lesions

In the Bifurcation feasibility study\textsuperscript{21}, using sirolimus eluting stents, though the sub acute thrombosis rates were higher, restenosis rates were clearly improved. Based upon vessel size, restenosis rates of perhaps 50% could have been predicted compared to the actual rate of 21.9%. An essential point of interpretation of this data set is that technique matters — restenosis that occurred in the side branch was related to full lack of coverage at the ostium. If the drug-eluting stent does not fully cover a lesion, it may not work to prevent restenosis. The optimal technique still remains to be determined. It is essential to treat the dominant vessel with a drug-eluting stent. The side branch remains an issue - does it always need to be stented? What technique should be used? The basic principles still apply - we need to work towards an optimal result, if stents are used they must be fully deployed and completely cover the stenosis.

Should we Use Drug-eluting Stents in all Patients and for all Lesions?

The use of drug-eluting stents is unlikely to reduce the already low rates of in-hospital death and myocardial infarction in the general patient population already treated by Percutaneous Coronary Intervention (PCI). The major impact of drug-eluting stents is likely to be among high-risk sub-groups and patients with lesions currently not considered amenable to PCI such as left main lesions or triple vessel disease.

However, only when the 18 on-going or planned investigational studies evaluating the Sirolimus eluting stent across a range of challenging lesion types (bifurcation, left main, chronic total occlusion and acute MI) and patient groups (diabetics and CABG) as well as the numerous series of trials with other drugs report their findings, will the interventional cardiology community know which patients are most likely to benefit from this promising and innovative technology. Moreover, it seems likely that the use of drug eluting stents will be extended to patients currently not eligible for PTCA due to unfavourable anatomic presentations; this could lead to a dramatic reduction in the rate of CABG surgery which might become a last resort treatment strategy.

In Stanford, patient-oriented guidelines emphasize using drug eluting stent in higher risk patients. All de novo lesions considered for drug eluting stent should be ischemia producing (Stress test or FFR) and preferably covered by one stent. The scoring system developed was proximal lesions with reference less than 3.5 mm (1 point), proximal LAD (2 points), diabetes (1 point) and positive remodeling with IVUS (1 point). Drug eluting stent is used when there are 2 or more points\textsuperscript{23}.

To date, more than 1011 patients worldwide have been treated with the sirolimus drug-eluting stent.
with excellent results (Figure 4), including a binary restenosis rate in all completed trials ranging from as low as 0% to 9%, accompanied by an event-free survival rate greater than 90%. Even in simple lesions for which the restenosis rates were anticipated to be low regardless of intervention (such as in short lesions with a large final cross-sectional area), drug-eluting stents had an even lower binary restenosis rate.

Conclusion
Interventional cardiology has been plagued by the phenomenon of restenosis since the description of the initial patient series. This has proven recalcitrant to a whole host of therapies both mechanical and pharmaceutical. The introduction of drug-eluting stents promises to meet the expectation of a revolutionary breakthrough technology. Drug eluting stents have proven their efficacy in eliminating the occurrence of in-stent restenosis. In the initial randomized trials, the results were incredibly positive both from the standpoint of safety but also that intermediate and now longer-term efficacy. As each trial was developed, patient and lesion characteristics became more challenging. This trend continues with now a new generation of registry and randomized trials being directed at the utilization of drug eluting stents in more complex subsets such as multivessel disease, small coronaries (less than 2.5 mm), diabetic patients, bifurcation lesions and left main stenting. If similar results could be reproduced in these subgroups who are at high risk for restenosis, it could herald a new era in the current interventional cardiology practices.

References
8. J E Sousa. Late (Two-Year) Follow-Up From the First-in-Man (FIM) Experience After Implantation of Sirolimus-Eluting Stents. 51st Scientific Sessions, American College of Cardiology (Oral Presentation)
month results from a randomized double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107:38-42
18. Antonio Columbo, TAXUS II Slow-release and moderate-release stents improve clinical, angiographic and IUS outcomes at 6 months, Transcatheter Cardiovascular Therapeutics meeting-2002, Washington