Editorial
The "0%" restenosis study

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The RAVEL (RAndomized study with the sirolimus-coated bx VElocity balloon-expandable stent in the treatment of patients with *de novo* native coronary artery Lesions) will probably enter the history books on interventional cardiology as the first and probably the only study achieving no restenosis in patients assigned to the treatment group[1]. The recently completed PRESTO study (The Prevention of REStenosis with Tranilast and its Outcomes trial), which failed to demonstrate any advantage of oral tranilast in 11 500 patients randomized to one of four treatment arms or placebo, is the hallmark of a time period of years with consecutive disappointing studies in numerous attempts to achieve even a slight statistical gain in reducing restenosis[2]. Paradoxically, we now see "a home run".

This study, conducted in 15 European centers, in 3 centers in Brazil and in one center in Mexico, randomized 120 patients with significant coronary artery disease and ischemia to angioplasty and implantation of a stainless steel stent coated with a slow release formulation (30 days) of sirolimus (rapamycin) and 118 patients to a standard stainless steel stent alone (Bx Velocity, Cordis J&J, Warren, NJ, USA). Sirolimus, also named rapamycin, after Rapa Nui (Easter Island), is a macrolide antibiotic discovered in 1975 and is a product of a fungus present in the soil of this island. This drug is currently approved as an oral formulation for immunosuppression following renal transplantation. Sirolimus has multiple actions the most important one of which is the blockade of essential cytokines necessary for the cell cycle progression through proliferation[3,4]. A unique property has been found to be the suppression of vascular smooth muscle cell proliferation by blockade of a specific enzyme TOR (target of rapamycin) essential for smooth muscle cell progression into the proliferative cycle following stimulation caused by trauma and thrombus formation[5,6]. In addition to decreasing intimal hyperplasia, this drug has been able to reduce strut-associated inflammation with more than a 50% reduction in the inflammatory score[6]. A dosage of 180 μg of sirolimus is blended with a 5 μm layer of nonerodable polymer matrix and applied to the surface of an 18 mm long stainless steel stent. A second layer of polymer is then applied to allow slow diffusion (30 days) of the drug. This formulation allows the achievement of a tissue concentration of 3.9 ng/mg of sirolimus in the wall of the artery with a peak blood concentration < 0.5 ng/ml following implantation of one stent. The corresponding dose necessary to induce significant systemic immunosuppression is > 8 ng/ml. Sirolimus has been tested in animal models of vessel angioplasty and has been found to reduce neointimal proliferation both as systemic and local formulations[5,7,8]. It is worth mentioning that compared to controls in these models the effect of the drug was a reduction in neointimal thickness not superior to 50%.

The concept of local drug delivery via coated stents couples the biological and mechanical solutions necessary to maximize the angiographic result and facilitate the recovery of the vessel from the injury caused by the stent implantation itself. At the same time local drug delivery using a drug-eluting stent offers the advantage of allowing high local concentrations of drug at the treatment site while minimizing systemic toxic effects.

As in most of the prior stent randomized studies[9-11], the RAVEL study included only

patients with one single treated lesion and excluded patients with lesions located in a saphenous vein graft, ostial lesions, bifurcational lesions, total occlusions, and patients presenting with acute myocardial infarction. One important exception compared to other studies was that the lower minimal reference vessel size acceptable for inclusion was 2.5 mm instead of the usual 3.0 mm. This aspect is quite important when considering the rather high restenosis rate encountered in the patients randomized in the control group with the standard stainless steel stent. The primary endpoint of this study was the angiographic late lumen loss as determined at the control angiogram performed 6 months following stenting. All patients were also scheduled for clinical follow-up at 12 months following the index procedure and in some centers angiographic follow-up included an intravascular ultrasound examination.

Following randomization, the two groups (sirolimus and standard stent) were found to be well matched except for the presence of a significantly higher percentage of male patients in the standard stent group (81 vs 70%). Overall there were 36% of patients with a prior myocardial infarction, 19% with diabetes mellitus, and 20% with unstable angina.

The vessel most frequently treated was the left anterior descending coronary artery (50% sirolimus group vs 49% standard stent). Over 50% of the lesions in each group were complex in their morphological characteristics. Of importance was the fact that the average reference vessel diameter was only 2.62 mm, a value lower than the one reported in most of the prior stent studies[9,10,12]. Stent placement was successful in 96.6% of the patients in the sirolimus group and in 93.1% of the patients in the standard stent group and yielded a similar angiographic result in both groups (11.9 vs 14% average stenosis). Follow-up angiography was available for 88.7% of patients. According to the definition of restenosis as a $\geq$ 50% diameter reduction in the treated segment, no patient (0%) in the sirolimus group had restenosis while 26.6% of the patients in the standard stent group presented a significant lesion renarrowing ($p < 0.001$). A remarkable finding at follow-up was that the mean in-stent late loss (the amount of tissue growth or hyperplasia) was -0.01 mm in the sirolimus group (a negative value due to variability in the measurements) compared to 0.80 mm in the standard stent group. Even in the small group of patients with diabetes mellitus (16 and 21 respectively) the late luminal loss was 0.07 mm in the sirolimus group compared to 0.82 mm in the standard stent group ($p < 0.001$). Intravascular ultrasound evaluation performed at the time of angiographic follow-up in 48 patients in the sirolimus group and in 47 patients in the standard stent group confirmed the minimal hyperplasia in the sirolimus group (2 ± 5 vs 37 ± 28 mm^3 in the standard stent group, $p < 0.001$). While a late (more than 1 year) intravascular ultrasound follow-up is in progress, some concerns have been raised by the detection of late incomplete strut apposition in the sirolimus group. Of reassurance is the lack of late adverse clinical events and the fact that there is no documentation of late aneurysm formation or of persistent dissections. The absence of late luminal deterioration at more than 1 year of follow-up[13] and at over 2 years[14] for the initial group of patients treated in Brazil[15] are reassuring data. These findings testify that the drug-eluting stent eliminated any hyperplasia present in the stainless steel stent. It is important to consider that this goal was obtained without an apparent increase in the risk of stent thrombosis despite the continuation of double antiplatelet therapy (aspirin and ticlopidine/clopidogrel) for only 2 months (one sudden death in the sirolimus group). We cannot be absolutely firm on this statement because the small sample size does not permit us to draw a statistically meaningful conclusion regarding an adverse event such as stent thrombosis which will manifest in less than 1% of patients[16].

Due to the absence of restenosis only one patient in the sirolimus group required revascularization within 1 year of follow-up, due to disease progression in the left main coronary artery. On the other hand, a new revascularization procedure of the target vessel was necessary in 23% of the patients randomized to a standard stent.

Following the positive results obtained with brachytherapy[17-20], this report is the only one showing a meaningful impact on the occurrence of restenosis after coronary stenting. Important differences compared to brachytherapy are that the first technique has mainly been applied to treat an already developed in-stent restenosis with a limited role in preventing restenosis following *de novo* stenting. This limitation is a consequence of the profound interference of brachytherapy in the endothelialization of the stent struts, exposing the patient to a considerable risk of stent thrombosis[21] and to the need of prolonged antiplatelet therapy[22].

The same type of drug-eluting stent has been tested in a recently completed trial: the "Sirolimus-coated bx velocity balloon-expandable stent in the treatment of patients with *de novo* artery lesions" (the SIRIUS trial)[23]. The SIRIUS trial, conducted in the United States, randomized 1100 patients with longer and more complex lesions. An *interim* analysis of the first 190 patients treated with the sirolimus-eluting stent has been disclosed, showing a 9.2% restenosis rate which increases to 17.9% in diabetics, and an almost 3 times higher late loss in small vessels compared to large vessels (0.31 vs 0.11 mm respectively, $p < 0.001$). These results place the whole field in a more realistic perspective especially when more complex lesions, closer to "real world" patients, are being treated.

Studies with other drug-eluting stents (paclitaxel, estrogen, dexametasone) are in progress and even these preliminary results appear encouraging[24-28].

It is finally very rewarding to see that progress is being made in preventing stent restenosis, a field notorious for repeated failures. To rephrase what recently

written by Paul Teirstein[29] it is pleasant to feel like a surgeon who does not expect that the gallbladder will grow again following its removal.

We can say that a new chapter in interventional cardiology has just been initiated; the hopes are high and very much justified, but the work to be conducted is still a lot before stating that in-stent restenosis has finally been fully conquered.

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