Through the drug-eluting stent labyrinth

Giulio Guagliumi, Giuseppe Musumeci, Angelina Vassileva, Maurizio Tespili, Orazio Valsecchi

Cardiovascular Department, Ospedali Riuniti, Bergamo

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For interventional cardiologists restenosis has represented the main limit for the successful long-term treatment of coronary artery disease. The past 2 years witnessed the extraordinary results of drug-eluting stents (DES), putting this technique at the center stage. The safety and efficacy of sirolimus and paclitaxel-eluting stents have been proved in large prospective, multicenter, randomized trials (RAVEL, SIRIUS, TAXUS II). It is possible that the introduction of DES will lead to substantial changes in the therapeutic and/or the economic strategies of the treatment of ischemic coronary artery disease (increase in the complexity of patients treated, reduction in surgical indications, growing costs). Realizing the potential value of this technology will require the successful management of more complex coronary situations (for lesions and patients characteristics). Many extreme situations are still unexplored, although for some of them studies are currently in progress or already being planned.

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Address:

Dr. Giulio Guagliumi

Dipartimento Cardiovascolare Ospedali Riuniti Largo Barozzi, 1 24128 Bergamo
E-mail: guagliumig@interfree.it

For interventional cardiologists restenosis has represented the main limit to the successful long-term treatment of coronary artery disease[1]. The past 2 years witnessed the extraordinary results of drug-eluting stents (DES), placing this technique at center stage. A string of recent works suggests that DES might represent the first substantial documented therapy for the prevention of restenosis in *de novo* lesions[2]. While the results are extremely encouraging, many aspects remain to be explored: is it a safe therapy and is it really successful for all lesions? How important are respectively the drug chosen, the dosage and the release kinetics? What does it change in the daily practice of percutaneous interventions? Some of these questions are still unfulfilled, others already have figures and answers, even though in many cases not yet published. We decided to report them to the best of our current knowledge and as far as new forms of communication allow to render unpublished data available (abstracts and presentations at international congresses, dedicated medical web sites and submitted papers). Whilst we are aware that such an approach is not fully scientific, we believe that it might help to gain a more up to date picture of what is going on and what remains to be done.

The advantage of coronary stents in reducing the occurrence of restenosis after percutaneous coronary interventions is essentially due to their ability to eliminate the elastic recoil and negative vessel remodeling which occur after balloon dilation. Therefore in-stent restenosis is a more simple reaction to the coronary intervention, resulting from an excessive proliferative neointimal response[3]. It is a common event, with an expected rate in the real world (one fourth of diabetic patients, long lesions, small vessels) ranging between 20 and 40%. While the risk of developing in-stent restenosis is linked to a variety of clinical and procedural factors[4,5], all bare metal stents, regardless of the thickness of the struts, provoke a considerable proliferative response (late lumen loss ranging between 0.8 and 1 mm), losing, on average, more than 50% of the initial gain in the lumen area in 3 mm vessels and up to 75% in vessels with a 2 mm reference diameter. Stents coated with materials with a better level of biocompatibility have not shown a significant impact on neointimal growth[6] (Fig. 1).

Systemic drug delivery to prevent restenosis has been the subject of extensive research, with very disappointing results. Over 80 randomized studies using antiplatelet agents, anti-inflammatory drugs, steroids, growth factor inhibitors and antiproliferative drugs have been performed; all were substantially negative despite promising experimental studies[7-9]. The hypothesis of being able to inhibit restenosis with new stents that contain drugs, released in a con-

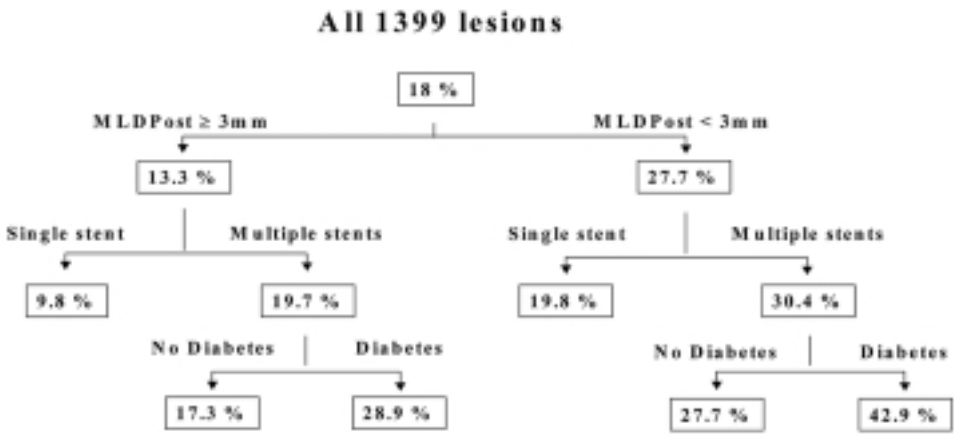

Figure 1. *Predictive factors of restenosis after coronary stent placement: the variables that most strongly influence the likelihood of target lesion revascularization during follow-up. MLD = minimal lumen diameter. Reprinted from Kastrati et al.[4], with permission of the American College of Cardiology Foundation.*

trolled fashion, potentially offers three advantages: a high local concentration, the absence of systemic toxic effects, and the use of an identical device to that used up to now. The astonishing results of the studies performed with rapamycin- and paclitaxel-eluting stents back up the idea that a high local concentration is essential in order to control the excessive proliferative response[10].

While stents with antimitotic agents appear to be a conventional stent with the same mechanical features, in actual fact they are not just "another stent". Remarkably, the stent is converted into a system capable of releasing antiproliferative drugs locally. The coating of the stent, which influences the way in which the drug is released, is an ultra-thin, biologically inert polymer (5-10 μ)[11,12], free from all undesired reactions (cracking, flaking, peeling) both during the sterilization process and during high pressure implantation; by increasing the thickness of the polymer the release of the drug is slowed down, whilst by varying the coating thickness/drug ratio, the total dose released is altered. The drug has to be a powerful, non-cytotoxic antiproliferative agent (that stops the cells at a safe point in the cellular cycle), capable of spreading from the stent in high concentrations into the surrounding tissues, without rapid washout (lipophylic). As at high concentrations most antiproliferative drugs have toxic effects on the vessel (not due to the conventional mechanism of action), the choice of the correct dose (neither too much nor too little) is of critical importance. It must therefore be clear that these stents are unique, being simultaneously a device and a drug. However, they are burdened by some potentially stunning setbacks: for example, the direct implantation of the stent, without pre-dilation, could damage the surface coating and alter the drug release kinetics.

A moving story

Among the antimitotic agents tested so far, two, sirolimus and paclitaxel, have proved capable of inhibiting or substantially reducing intimal hyperplasia both in animals and in humans.

Sirolimus (rapamycin) is a sophisticated natural antibiotic, developed for its powerful immunosuppressive activity. Approved for the prophylaxis of rejection in kidney transplant patients, it has been found to be characterized by a high level of tolerability and safety for systemic human use. In healthy subjects a blood peak of 100 ng/ml is considered to be safe. The dose of sirolimus applied to a DES produces a transient blood peak after 1 hour of 1-2 ng/ml. Sirolimus inhibits the cellular cycle in the phase (G1-S) in which the stimulated cell decides whether or not to complete the cycle; therefore it stops only the activated cells. Within the cell, sirolimus binds to a specific receptor (FKBP-12), blocking a key enzyme in the transmission of the signal for cellular proliferation and growth (TOR, G1-Checkpoint)[13].

Remarkably, atherectomy tissue specimens retrieved from patients with in-stent restenosis showed a significant upregulation of FKBP binding protein 12, providing a potential explanation for the extreme effectiveness of sirolimus in controlling in-stent neointimal hyperplasia[14].

The sirolimus-eluting Cypher™ stent (Cordis, Johnson & Johnson, Warren, NJ, USA) has recently obtained the unanimous consent of the expert's Food and Drug Administration panel for the approval of new devices for the circulatory system[15]. The decision was based, in addition to the data of animal studies, upon the analysis of the results of two prospective, multicenter, randomized triple-blind clinical trials (RAVEL, SIRIUS) and of the FIM observational register.

FIM was the first phase 1 open label study conducted in man with antimitotic DES. Forty-five consecutive patients with relatively low-risk *de novo* lesions (lesion length 13 mm, reference diameter 2.95 mm, less than 20% diabetics) were treated with a single sirolimus-eluting stent. Two different dose release formulations were tested: fast release (drug release in < 15 days, 15 patients) or slow release (drug release in > 28 days, 30

patients). At 3 years of follow-up, the survival without major adverse cardiac events (MACE) is over 90% (1 non-cardiac death, 1 myocardial infarction 15 months after implant, 1 target vessel revascularization – due to progression of the pathology in the treated vessel, and 1 target lesion revascularization), without any new MACE from 2 to 3 years[16]. Serial quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) assessments have shown a marked and protracted inhibitory effect on in-stent neointimal formation: the percent in-stent volumetric obstruction at 1 year was 2.3 ± 5.5%[17], the late lumen loss at 2 years was -0.09 ± 0.24 with no binary restenosis.

RAVEL was the first prospective, multicenter, randomized study on the safety and performance of sirolimus-eluting stents conducted in man. Carried out in 19 European and South American centers, the RAVEL trial was sensational. It could not be otherwise considering the "historical" result achieved: 0% of binary restenosis after 6 months in the group (120 patients) treated with slow-release sirolimus stents compared with 26.6% of restenosis for the 118 patients treated with bare metal stents. Presented at the European Congress of Cardiology in Stockholm in August 2001, it was only published in the *New England Journal of Medicine* in June 2002[2], in order to add the clinical follow-up figures at 1 year (not a primary endpoint but a critical issue for the patients' safety at follow-up).

After 6 months the sirolimus-eluting stent enabled the complete abolition of neointimal hyperplasia (late lumen loss -0.01 mm, 95% confidence interval -0.08-0.04) without evidence of any edge effect. In diabetic patients and in vessels with a diameter < 2.5 mm there was an equally effective reduction. The extraordinary angiographic efficacy was confirmed in a subgroup of 88 patients assessed at 6 months with IVUS (neointimal hyperplasia 2 ± 5 mm^3 compared with 37 ± 28 mm^3, $p < 0.001$)[18] (Fig. 2, Table I).

Although the reduction in the mean proliferative values is impressive, the most stunning revelation obtained with sirolimus-eluting stents emerged from the narrow range of the 95% confidence intervals and standard deviations, as they were completely different from the figures observed in the control group and in any other previous trial conducted for the prevention of restenosis. While in patients treated with non-coated stents there was a spectrum of the neointimal response (from trivial to marked hyperplasia) almost all patients treated with sirolimus seemed to respond in the same way (no or irrelevant in-stent proliferation). After 1 year, the abolition of neointimal growth translated clinically into the absence of repeat interventions and in an event-free survival of 94%, significantly better ($p < 0.0001$) than the 1 year event-free survival (70.7%) in the control group.

At multivariate analysis, the only independent predictors of late lumen loss were the stent type used (DES vs bare metal stents, $p = 0.001$) and the post-procedure minimal lumen diameter ("the bigger is better", $p = 0.004$).

Even though the RAVEL results were obtained for relatively simple lesions (single *de novo*, lesion length < 10 mm), nevertheless, there are also hints of some unfavorable characteristics in the study patients' cohort: the treated vessels were substantially smaller in size compared to the reference diameter of the stented vessel in the main trials dealing with coronary restenosis (reference diameter 2.60 ± 0.5 vs 2.9 ± 3.1 mm)[6,7,19-22]; about 50% of the patients enrolled had stent placement in the left anterior descending coronary artery, and

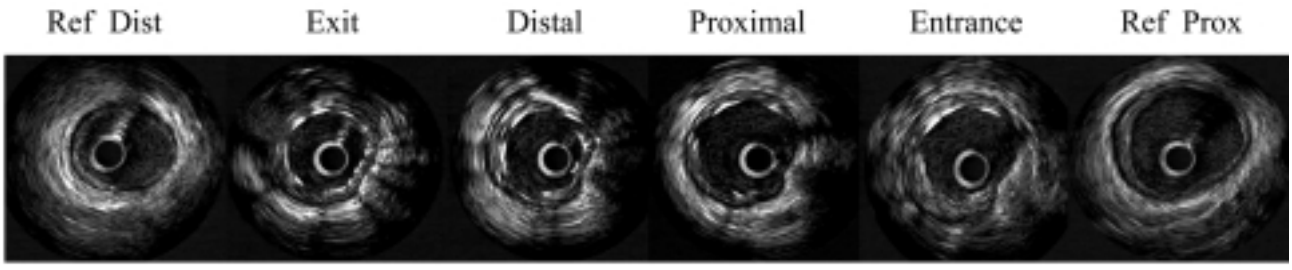

Figure 2. *Six-month intravascular ultrasound multiple cross-sections of the sirolimus-eluting stent in the RAVEL trial, showing uniform absence of neointima proliferation.*

Table I. RAVEL: intravascular ultrasound analysis at 6-month follow-up. Core lab analysis.

	Sirolimus™ (n=45)	Bx Velocity™ (n=43)	Difference (95% CI)
Neointimal area (mm^2)	0.09 ± 0.26	2.08 ± 1.59	-1.99 (-2.44, -1.54)
Volume obstruction (%)	1.4 ± 2.8	28.6 ± 19.8	-27.1 (-33.2, -21)

CI = confidence interval.

more than 90% were type B lesions. A lot of criticisms were raised to the high rate of restenosis in the control group (26.6%), interpreted as an excess of neointimal growth due to thicker stent struts (0.0055"). However, the mean value of the late lumen loss observed in the Bx-Velocity bare metal stent group of this trial is essentially equal to the late lumen loss obtained with thinner stainless steel or new cobalt chromium alloy stent struts (Table II)[2,19,20,23].

Finally, RAVEL does not represent the real world, inasmuch as it does not express the complexity of the lesions treated today in interventional cardiology. Whether this result could be extended to all complex lesions and high risk patients is still unknown.

SIRIUS US (and the E-SIRIUS and C-SIRIUS studies respectively conducted in Europe and Canada) has assessed the safety and efficacy of the sirolimus stent in more complex lesions and patients (approximately 1500) compared with RAVEL. This study included a higher percentage of diabetics (24.6% compared with 15.8%, $p < 0.04$), of longer lesions (14.4 vs 9.6%, $p < 0.001$) and of overlapping stents (28 vs 0%, $p < 0.001$). At the moment, only the results (unpublished) of the SIRIUS trial were reported. Among the 1058 randomized patients, 533 were treated with sirolimus-eluting stents while 525 were treated with bare metal stents. Clinical and angiographic follow-up (QCA) at 9 months (later compared with the RAVEL study to highlight any potential late neointimal growth) and each year up to 5 years of follow-up have been planned.

What does SIRIUS add to RAVEL? First of all, SIRIUS confirms that the safety profile of this antimitotic-eluting stent is identical to that of conventional stents, even in case of more complex lesions and patients (identical intra-hospital MACE rate and equal mortality and reinfarction rates at follow-up) with a considerable gain in terms of repeat interventions (free from repeat revascularization after 9 months: 91.1% compared with 78.6%, $p < 0.001$)[24]. The efficacy of the inhibition of the proliferative response inside the stent was similar to that observed in RAVEL: an 83% reduction in late lumen loss and a > 90% reduction in intimal hyperplasia (4.1 vs 56.8 mm^3, $p < 0.0001$) in the 145 patients assessed with IVUS[25]. However, some patients without proliferation inside the stent showed restenosis at the proximal margin. The restenosis rate in the whole stented segment (stent +5 mm proximally and distally to the stent) was reduced by 75% compared with controls (8.9% compared with 36.3%, $p < 0.001$)[26]. The abnormal neointimal growth at the proximal margin was more evident in small vessels (reference diamter 2.32 mm).

There has been extensive discussion with regard to the reasons for this untoward effect which was not observed in previous studies with DES (RAVEL, TAXUS I); the various hypotheses include that of a more aggressive implantation technique in SIRIUS (RAVEL had used a "gentle" pre-dilation technique, undersizing the balloon by 0.5 mm and anchoring the stent in angiographically normal segments of the vessel), or of a longitudinal downward shift of the drug. None appear to be really plausible. Considering that the drug spreads for very short distances from the stent and that the flow turbulence is more evident at the stent entrance, it is possible that, at this level, an inadequate concentration of drug penetrates into the vessel wall in some patients. E-SIRIUS, with a different implantation technique (direct stenting, less frequent post-dilation) might shortly supply a lot of information which may be of significant help in the interpretation of some DES failures.

Nevertheless all the clinical subgroups showed a minor incidence of restenosis with the sirolimus-eluting stent, with only a modest increase in the confidence limits for diabetics (Fig. 3).

Paclitaxel (Taxol) may be considered as an unique antiproliferative agent for many reasons: its mechanism of inhibition of cellular proliferation (it renders the microtubules completely rigid, preventing the changes in conformation that are necessary for replication), its very high level of lipophylicity (it can be linked to the stent without any polymer), its dose-dependent efficacy and toxicity (the higher the dose, the greater the inhibition of proliferation, the higher the level of toxicity)[27], and finally its uniqueness in relation to the juridical conflict that it has triggered.

The drug is cytostatic in low doses (interruption in phase G1) and cytotoxic in high concentrations (mitotic interruption in phase M)[28]. The most delicate aspect of paclitaxel-eluting stents is therefore the selection of the lowest dose capable of blocking the immediate response to stent injury, then to provide continuous low level release of the drug to maintain the blunted response, avoiding doses that may induce local vascular

Table II. Impact of different thicknesses of bare metal stent (BMS) struts on restenosis and late lumen loss.

	RAVEL BMS[2] (n=118)	TAXUS II BMS* (n=270)	Multi-Link[19] (n=309)	ML Penta[20] (n=200)	ML Vision[23] (n=297)
Strut thickness (inch)	0.0055	0.0043	0.0022	0.0036	0.0032
Restenosis (%)	26.6	22	15	17.5	16.7
Late loss (mm)	0.80	0.78	0.93	0.90	0.83
Reference diameter (mm)	2.64	2.75	2.92	2.91	3.0-4.0

* Colombo, unpublished data.

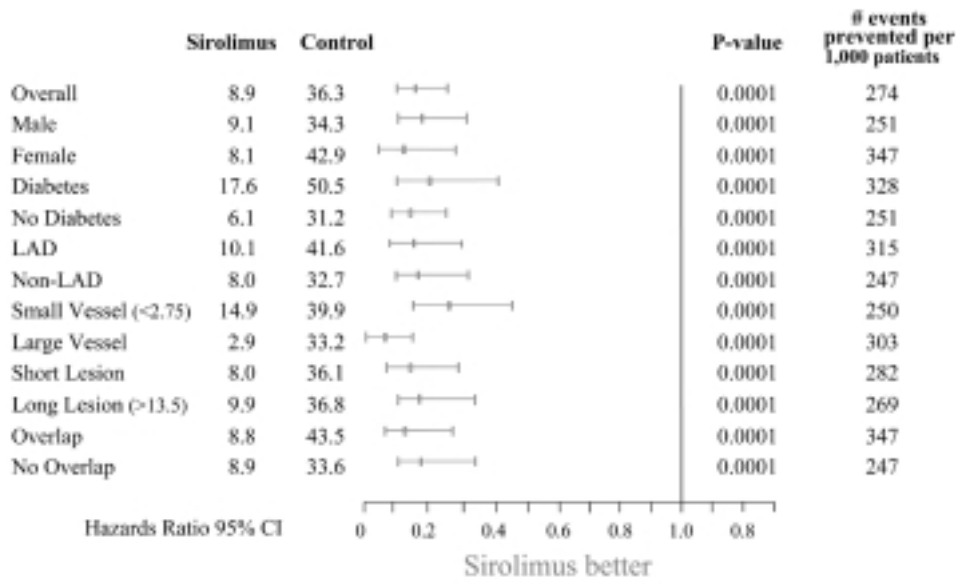

Figure 3. *SIRIUS: in-stent restenosis. CI = confidence interval; LAD = left anterior descending coronary artery.*

damage. Unlike water-soluble drugs (i.e. heparin), paclitaxel persists in the tissues for some time. After 1 hour from the intravascular release, the concentration in tissues is 20 times higher than that of heparin. Exploiting these properties, the drug was loaded directly onto the surface of the stent without any polymeric coating (Cook Angiotech™). The lack of filtered information on the technology used to directly bind the drug to the stent created a sort of magical halo around the procedure. In actual fact, the surface of the stent facing the vessel wall is texturized with the high-pressure nebulosity of the micro-particles of $NaHCO_3^-$. The paclitaxel, dissolved in 100% ethanol, is then applied to the treated surface, allowing the alcohol to evaporate. In this way the drug sticks to the surface. Some aspects of this method are still not very convincing: what happens to the residual solvent? How is the release of the drug controlled? In man, paclitaxel stents without polymer have been initially assessed in two randomized controlled studies (ELUTES and ASPECT)[29,30], using progressively increasing dose-densities. Altogether 272/369 patients with lesions with a low risk of restenosis (17% diabetics, lesion length 10.9 mm, vessel reference diameter 2.95 mm), have been treated. There were two main conclusions: a) there is an almost linear relationship between the dose of paclitaxel and the percentage of restenosis (the higher the dose the clearer the reduction in the rate of restenosis; b) the identification of the minimum effective dose of 3 $\mu g/mm^2$ (in the absence of polymer). Only the highest doses tested (2.9 and 3.1 $\mu g/mm^2$) proved to be effective in significantly reducing restenosis (3% compared with 20.6%, $p < 0.05$ in ELUTES, 4% compared with 27%, $p < 0.001$ in ASPECT). However, the doses which proved to be effective at 6 months were not equally effective at 1 year of follow-up, due to the development of some late restenosis (5.9% compared with 13%, p = NS) (Gershlick, unpublished data). Similar negative results have been recently reported in the DELIVER trial, evaluating the non-polymer paclitaxel-coated ACHIEVE™ stent against the corresponding bare metal stent in 1042 randomized patients (9-month angiographic restenosis rate 17 vs 22%)[31].

A completely different choice (biocompatible polymer, minimum dose of 1 $\mu g/cm^2$, release in two phases – burst in the first 48 hours and subsequent slow release for about 30 days) is at the basis of the TAXUS program (Boston Scientific, Natick, MA, USA).

The proof of the principle that low doses of paclitaxel may interrupt the cascade of restenosis without toxicity (no detectable plasmatic levels of paclitaxel, no stent thrombosis, excellent clinical outcome, 0% binary restenosis after 6 months) has been obtained by the study entitled TAXUS I (pilot, double-blind, randomized, single stent measuring 16 mm, vessels with a diameter approximating 3 mm). The clinical advantage of the paclitaxel-eluting stent persisted at 18 months after implantation (MACE 3% compared with 18%)[32].

In the TAXUS II study, the safety and performance of two different paclitaxel-eluting formulations were assessed (slow release and moderate release) in order to choose the better. The same dose of drug (1 $\mu g/mm^2$) was charged on the stent, but with different kinetics: during the first 48 hours following implantation the amount of drug released by the moderate release formulation was 8-10 times higher than that of the slow release formulation. TAXUS II is a randomized, multicenter, triple-blind study, conducted on 536 patients with *de novo* lesions and with a standard risk of restenosis (14% diabetics, average lesion length 10.3 mm, average reference diameter of the vessel 2.75 mm). It collected a set of extremely solid data (> 95%

QCA and > 87% IVUS in follow-up), with angiographic and clinical endpoints, but also with IVUS, so as to assess, in the maximum detail, every possible local effect of the drug on the vessel wall. The results were comparable for both formulations (moderate and slow release) and for this reason they were described all together (Colombo et al., unpublished data). The stent was found to be safe (1 periprocedure thrombosis out of 266 implants, 0% subacute or late thrombosis) with a sustained, combined, antiplatelet regimen (6 months of clopidogrel and acetylsalicylic acid). At 6 months the vessel volumes were unchanged in all the groups (no positive remodeling), with a significant reduction in neointimal hyperplasia and in the percentage obstruction for the paclitaxel-eluting stent (7.8 ± 9% compared with 21.9 ± 17%, $p < 0.0001$). The QCA figures confirm the IVUS results, with a substantial reduction of binary restenosis (5.5% slow release, 8.6% moderate release compared with 22%, $p < 0.0005$) and of late lumen loss (0.30 ± 0.38 compared with 0.78 ± 0.47 mm, $p < 0.0001$) in the treated segment. Clinically, there was a significant reduction in adverse effects at 6 months of follow-up (8% compared with 19.8%, $p < 0.005$).

Other prospective, randomized, triple-blind studies are about to answer the same questions for high risk lesions and patients. TAXUS IV (single stent with a slow release formulation) has already enrolled 1326 patients with longer lesions (10 to 28 mm) and balanced randomization for co-varied diabetes mellitus. The results at 9 months of follow-up have been presented at the Scientific Session of the American College of Cardiology (Chicago, IL, USA, March 2003) (Fig. 4).

A few words of caution

The first 2 years of clinical experience have been characterized by important successes but, unfortunately, also by incredible defeats. Antiproliferative stents are not a neutral: either they are vessel compatible or they cause disasters. Two mechanisms are responsible for this: the non-dose-dependent drug toxicity and the negative effects of too high concentrations and prolonged release. Both can jeopardize the performance of DES and the health of patients. The ACTION (actinomycin) and SCORE trials (QP2, a taxan derivative used in very high doses) are unpleasant evidence of this concept.

Actinomycin D, already included in the list of the hazard substances for health, works through a very solid (low reversible) and unselective (cytotoxic for cells in every phase) link with DNA. Despite some encouraging reported figures in animals, in humans stents which release low doses of actinomycin (2.5 and 10 $\mu g/cm^2$) have caused unacceptable toxic vascular effects (edge effects, as observed in radioactive stents, and aneurysms), with a dramatic increase in early MACE compared with the controls (+230%, mainly target vessel revascularization) (Serruys, unpublished data). In addition to the agent toxicity, there is also the toxicity linked with an excessive dose of the antiproliferative drug. Knowing the dose-dependent reduction in neointimal thickness for taxol derivatives, Quanam Medical, a small Californian company with considerable expertise in polymers, developed a stent capable of releasing the highest possible dose of drug (4000 μg of QP2 for a stent with a length of 17 mm), with the aim of abolishing any proliferative response. The stent coated with non-biodegradable sleeves worked like a sort of reservoir, with constant release of the drug for about 6 months. In the SCORE study, 400 medium-high risk patients should have been randomized to a bare metal stent or to the Quanam QP2-eluting stent. The study was interrupted after 267 patients had been enrolled, due to an excess of MACE (5 deaths, 9 periprocedure myocardial infarction and a percentage

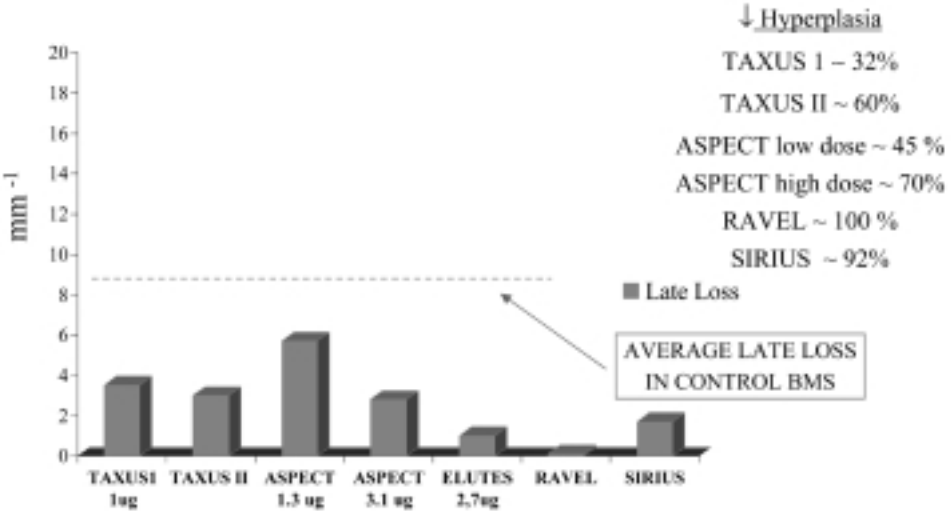

Figure 4. *Drug-eluting stent trials: reduction of the late lumen loss and intimal hyperplasia. BMS = bare metal stents.*

of stent thrombosis of 13%, 5.1% of which after 6 months, $p < 0.001$)[33]. Another crucial step recently emerged: due to the protracted release of high doses of drug, the QP2 stent, apparently effective at 6 months (-83% binary restenosis, $p < 0.001$)[34] was associated with a higher rate of late restenosis at 1 year (62%), with evidence of persistent deposits of fibrin and varying degrees of neointimal inflammation[35,36].

Which are the points? Many DES can fail the validation process. Coatings with non-erodible thick polymer sleeves, very high concentrations of the active drug and prolonged release kinetics, may compromise the vascular compatibility of DES. Moreover, there is another word of caution which must be made. Antimitotic-eluting stents delay the conventional healing process following a stent placement. They require more time for endothelialization and have more fibrin deposits around the stent struts[37,38]. This creates a need for a prolonged regimen of antiplatelet therapy (from 2 to 6 months depending on the agent and the complexity of the lesion) (Fig. 5).

Short and long-term safety: is this still uncertain?

The DES mechanism (inhibition of the cellular cycle) and some aspects in common with brachytherapy highlighted during preclinical studies (late endothelialization, thinning of the media with an increased vessel size) justified the achievement of an acceptable safety profile as the top priority among the clinical aims of DES programs.

Safety assessments are provided at different time intervals for each clinical study:
• 30 days, incidence of subacute thrombosis;
• 1-9 months, incidence of late occlusion, local cytotoxicity: aneurysms, incomplete late apposition;
• 1-3 years, long-term biocompatibility, maintenance of the long-term antiproliferative effects.

The first two items seem to have been satisfied, at least in non-extreme clinical conditions, strengthening the concept that the right drug at the right dose does not seem to be associated with a higher thrombotic risk or with a higher incidence of coronary aneurysms. In over 1500 patients involved in the RAVEL, SIRIUS, E-SIRIUS, TAXUS II and TAXUS IV randomized studies and treated with DES, the rate of thrombosis at 30 days was between 0 and 0.5%, less than or equal to that of the control groups, while late occlusion (31-270 days) remained unlikely (0% in 120 RAVEL patients, 0% in 266 TAXUS II patients, 0.2% in 533 SIRIUS patients). In the same studies, the incidence of vessel aneurysms was identical to that of the control groups (TAXUS II 1.5% compared with 1.6%; SIRIUS 0.6% compared with 1.1%). None of the patients with aneurysms had major clinical events during follow-up. It is still necessary to clarify the meaning of a higher incidence of late incomplete apposition of the stent[39]. About 10% of patients treated with DES (TAXUS II 8.5-9.6%; SIRIUS 9.7%) compared with 5% of the control patients had at least one stent strut which was not adequately adherent to the vessel surface. This inadequate apposition was not identifiable at the time of the implant but became evident during follow-up (by means of IVUS assessment). This is prob-

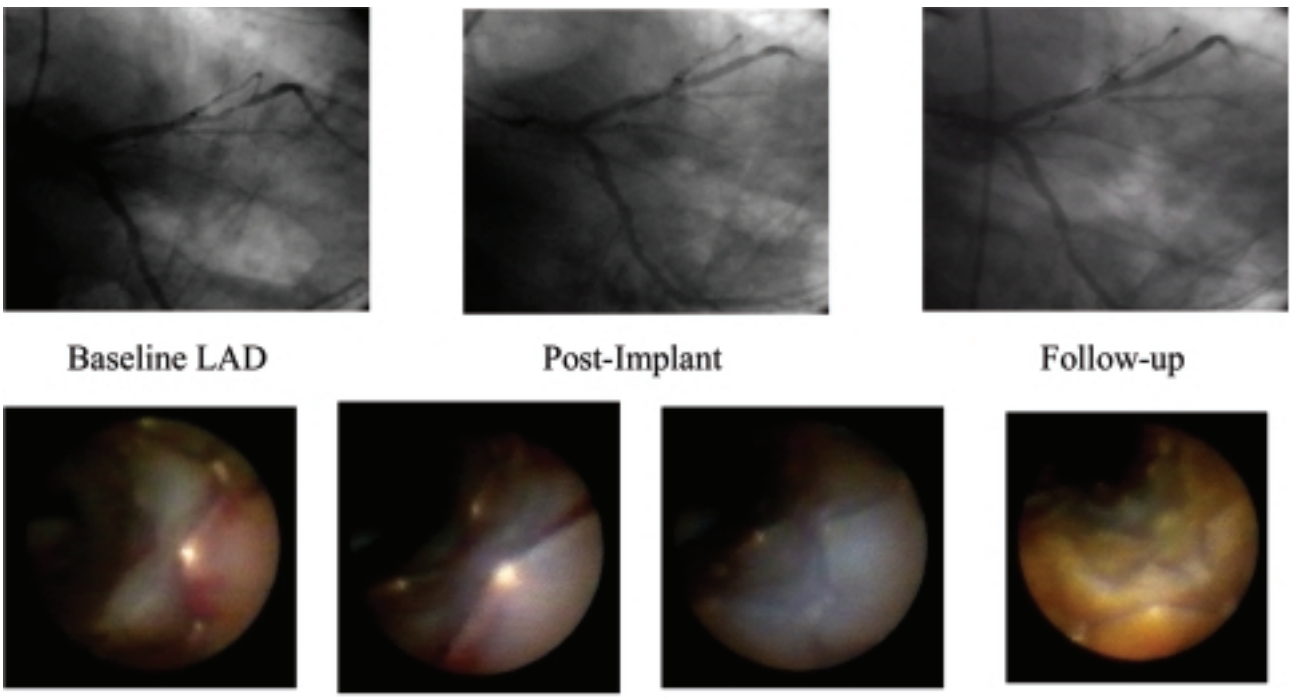

Figure 5. *Two Chypher™ stents (8 + 18 mm) in overlap: 8-month coronary angioscopy. LAD = left anterior descending coronary artery.*

ably a biological effect (high local concentration of drug in the absence of neointimal growth), which does not seem to induce MACE (0% in SIRIUS). Finally, we must continue with a close observation of the long-term compatibility. While so little is known about the long-term local effects of DES in humans, recent histological and electron microscopy data seem to confirm, at least for the sirolimus-eluting stent, the absence of any chronic inflammatory response, the persistence of fibrin deposits around the struts and the presence of properly connected endothelial cells with rare non-confluent areas[40] (Fig. 6).

Is this therapy suitable for all patients?

Whether similar results would be obtained with broadened indications is impossible to know. As previously mentioned, this is a rapidly evolving story in which the complexity of clinical trials is on the increase; many extreme situations are still unexplored, although for some of them studies are currently in progress or already being planned:
- multivessels: ARTS II (sirolimus),
- multivessels, diabetics: DECODE (sirolimus),
- long lesions: TAXUS VI (paclitaxel),
- small vessels: SVELTE (sirolimus),
- left main stem: LM (sirolimus),
- in-stent restenosis: TAXUS V (paclitaxel), TROPICAL (sirolimus).

Overlapping stents represent another major challenge. What toxic effects and clinical sequelae will result from an increased local dose of drug at the site of stent overlap? In the SIRIUS trial 344/1058 randomized patients received multiple stents in partial overlap (mean overlap 4 mm). At 9 months of follow-up the MACE rate for the sirolimus multiple stent group was still significantly lower compared with the control group (8.5 vs 22.6%, $p < 0.001$), while the rate of stent thrombosis was identical (0.6 vs 0.6%), with no late angiographic aneurysm within the overlapping segment for both groups.

Will it take a long time to have adequate answers for extreme circumstances? Probably no. Considering how quick the patient enrollment was for most recent trials (1170 patients randomized in TAXUS IV within 8 weeks), all we probably have to do is to wait a little bit more. Finally, as DES are already on the market (Cypher™, Cordis, sirolimus) or will be released soon (BSCI, paclitaxel), real time monitoring registers have been created and activated for all the implants performed (on and off label) with web based data collection. This innovative form of post-marketing surveillance has the advantage of large data generation and safety monitoring on the indications which have not yet been scientifically proven.

Costs and possibilities of use

It is possible that the introduction of DES will lead to substantial changes in the therapeutic and/or the economic strategies for ischemic coronary artery disease (increase in the complexity of patients treated, reduction in surgical indications, growing costs).

The first DES approved in Europe in April 2002, costs between 2100 and 2300 , about 4 times the cost of a bare metal stent. The strict control of the financial resources at the European hospitals has meant that use has been limited to about 10% of patients treated with percutaneous coronary interventions. While it is cost-effective due to a substantial reduction in the percentage of repeat interventions, the DES risk tantalization.

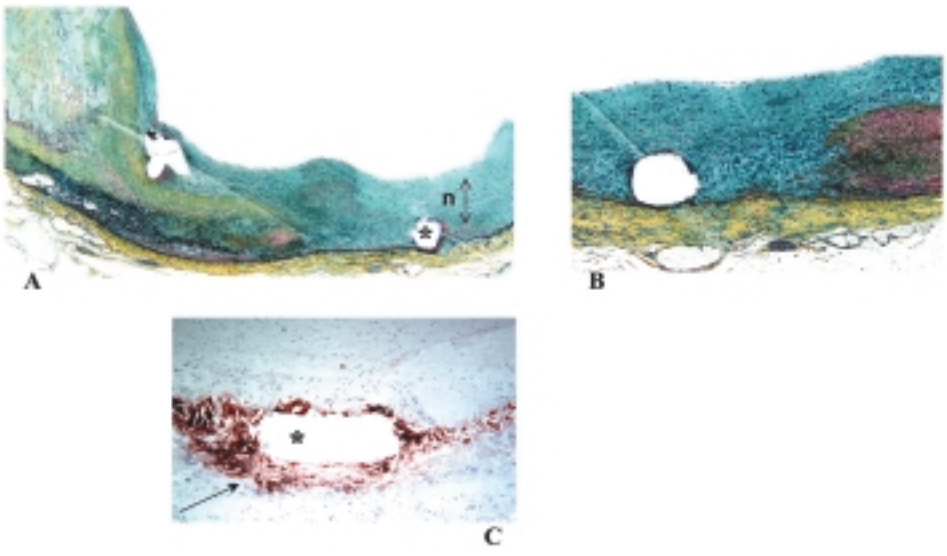

Figure 6. *Sirolimus-eluting Bx Velocity stent in the left anterior descending coronary artery: 16 months post-deployment.* A *and* B: *a thicker neointima (n) overlies a strut associated with a healed ruptured media* (arrow). C: *persistent fibrin deposition (brown staining) associated with strut (* in* A*). From Guagliumi et al.[40], with permission.*

The alternative to a careful stratification of the risk of restenosis and to a selective use of DES in some cohorts of patients is difficult for the physician as well as for the patient. At the moment, the indications tested in terms of a reduced target lesion revascularization are not those at the highest risk of restenosis (diabetes, small vessels, long lesions), and there is a lot of confusion regarding the choices to be made. In-hospital economic negotiation (fewer procedures repeated at follow-up), the availability of other DES (competition) and an adequate reimbursement policy (for the stent and for the protracted antiplatelet therapy) are unforgettable prerequisites for an extensive use of this innovative therapy. In August 2002, anticipating approval by the Food and Drug Administration, the American Medicare and Medicaid service centers created a new DRG for the reimbursement of the use of DES.

Conclusions

Uncontrolled hyperplasia inside a stent is not a natural phenomenon and has a greater impact in more complex lesions and patients (diabetes, multivessel disease) where it is harder to compete with coronary surgery. Avoiding restenosis has represented an impossible challenge for almost a quarter of a century; today it has become a primary need if we wish to keep increasing the percutaneous minimal-invasive approach. DES are a real innovation, both in concept (bioactive therapy) and in practice (unique results). Assessing recent innovations in biotechnology (new generation polymers that enable the release of multiple drugs with different kinetics, nanoporous ceramic structures for drug storage inside the stent struts) it is hard to think that this path will be rejected. Making the most of the potential value of this technology will require the successful management of more complex coronary situations (for lesions and patient characteristics). The gap between scientific discovery and proven clinical benefit must be filled with other studies and more complete data.

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