UPDATE

Myocardial Revascularization (VI)

Drug-Eluting Stents and Other Anti-Restenosis Devices

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Restenosis remains as the main limitation of percutaneous coronary intervention, even in the era of coronary stents. Recently, drug-eluting stents have been shown to reduce significantly both the rate of in-stent restenosis and the need for subsequent revascularization procedures compared with bare-metal stents. At present, these beneficial effects have been demonstrated mainly with Cypher (Cordis Corporation) and Taxus (Boston Scientific) stents. They persist for at least 3 years after implantation. Although the results of some complex clinical angiographic studies are still awaited, all the indications suggest that use of this type of stent will become standard in percutaneous coronary interventions in the future. With regard to other techniques, intracoronary brachytherapy is effective only for the treatment of in-stent restenosis. The recent withdrawal from the market of brachytherapy catheters means that the technique has effectively disappeared from the interventional cardiologist's armamentarium, at least in our setting. Other devices, especially rotational atherectomy catheters and cutting balloons, will survive in the era of drug-eluting stents as they facilitate stent implantation in particularly complex lesions.

Key words: Drug-eluting stent. Sirolimus. Paclitaxel. Restenosis. Intracoronary brachytherapy. Atherectomy.

Stents recubiertos y otros dispositivos antirreestenosis

La reestenosis ha continuado siendo el problema más importante del intervencionismo coronario incluso en la era del stent. Recientemente se ha demostrado que los stents liberadores de fármacos antiproliferativos reducen de forma clara la reestenosis y la necesidad de nuevos procedimientos de revascularización en comparación con los stents convencionales. Por el momento, este beneficio se ha obtenido fundamentalmente con los stents Cypher (Cordis Corp) y Taxus (Boston Sci) y se mantiene al menos hasta 3 años después de su implantación. Aunque aún están pendientes los resultados de algunos estudios en escenarios angiográficos complejos, todo parece apuntar a que estos stents se convertirán en el estándar de tratamiento de los procedimientos de intervencionismo coronario percutáneo. En cuanto al resto de los dispositivos, la braquiterapia intracoronaria sólo había sido útil en el tratamiento de la reestenosis intra-stent, y la reciente retirada del mercado de los catéteres de braquiterapia ha hecho que, desde el punto de vista práctico, hayan desaparecido del arsenal terapéutico del cardiólogo intervencionista, al menos en nuestro medio. Otros dispositivos, especialmente la aterectomía rotacional y el balón de corte, sobrevivirán en la era de los stents recubiertos al facilitar la implantación de éstos en lesiones con una especial complejidad.

Palabras clave: Stent recubierto. Sirolimus. Paclitaxel. Reestenosis. Braquiterapia intracoronaria. Aterectomía.

INTRODUCTION

Restenosis continues to be the main problem in percutaneous coronary intervention (PCI), usually defined via angiographic documentation during follow-up as stenosis >50% in the treated segment and/or in the adjacent 5 mm. It occurs in at least 30% of cases after balloon dilatation (G20% with standard stent), and new revascularization procedures are required in over half the cases.

The physiopathology of restenosis after balloon angioplasty includes 3 phenomena: *1)* early elastic recoil; *2)* negative remodeling, involving a decrease in the total area of the vessel due to shrinking during the weeks following angioplasty; and *3)* neointimal hyperplasia, primarily in the 3-5 months after PCI.

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Compared to balloon angioplasty, stenting decreases the risk of serious complications, and thus the need for emergency surgical revascularization,[1] as well as reducing restenosis.[2] A reduction in restenosis was initially demonstrated in patients with early elastic recoil[3] or suboptimal results[4] following balloon dilatation. Subsequently, the BENESTENT, STRESS, and START studies showed that elective stenting also reduces restenosis.[5-7] The lesions treated in these studies were favorable and occurred in patients with stable ischemic cardiopathy. However, later studies demonstrated that stenting also reduces restenosis in other contexts (Table 1). Studies on small vessels (<3 mm diameter) have not been conclusive, but a metaanalysis of 11 randomized studies found that there was significantly less restenosis with stenting (25.8% vs 34.2%).[8] Once these benefits were demonstrated, the use of high-pressure final balloon dilatations[9] and the administration of thienopyridines plus aspirin[10] made it possible to decrease the risk of thrombosis due to stenting to G1%, thus leading to their widespread use.

TABLE 1. **Studies Conducted to Evaluate the Effectiveness of Coronary Stenting in Several Unfavorable Clinical and Angiographic Contexts**

Study	Restenosis, %		Revascularization, %	
	Stent	Balloon	Stent	Balloon
Chronic occlusions				
GISSOC	32	68*	5	22*
TOSCA	55	70*	8	15*
MAJIC	57	55	29	46*
SARECCO	26	62a	24	55
SICCO	32	74*	22	42*
SPACTO	32	74*	28	45
STOP	42	71*	19	39*
Saphenous vein bypass graft				
SAVED	37	46*	17	26
VENESTENT	22	36	12	25*
Acute infarction				
PASTA	17	38*	19	38*
GRAMI FRESCO	17	43*	6	20*
Zoolle			4	17*
STENTIM-2	25	40a	17	26
STENT-PAMI	20	34*	6	16*
CADILLAC	22	41*	7	16*
Restenosis				
REST	18	36*	10	27*
Proximal DA				
Versaci	19	40*	7	23*
Long lesions				
ADVANCE	27	42*	18	15
Small vessels				
Park et al[28]	31	36	5	3
Isar-Smart	37	36	17	20
SISCA	19	10	23	10[a]*
Besmart	47	21*	27	15*
SISA	33	28	20	18
COAST	32	27	14	11
RAP	37	27*	22	12*
LASMAL-I	29	19	20	15
SVS	25	21	6	6
CHIVAS	44	31*	16	11
COMPASS	18	25		

*P<.05

Despite their advantages, the restenosis rate after implantation of standard stents exceeds 20%, and the need for new revascularization procedures, 10%.[11] In long and complex lesions, small vessels, and diabetic patients, the restenosis rate can be >50%. This is important given that most lesions currently treated with PCI are of this type.

The lower rate of stent restenosis is basically due to greater acute luminal gain, because late loss (reduction in minimum luminal diameter from implantation until 6 months later) is even higher than that obtained with balloon angioplasty. This is due to the fact that, although the stent virtually eliminates early elastic recoil and negative remodeling, neointimal hyperplasia is even more marked than with balloon angioplasty.[12] In addition, there are other factors related to a suboptimal initial procedures ("pseudorestenosis"), such as stent underexpansion, the early protrusion of material through the stent, and the implantation of stents with an incorrect diameter.[13]

Most drugs with systemic effects (antiplatelet agents, anticoagulants, antiinflammatory agents, hypolipidemic agents, ACE inhibitors, calcium antagonists, antioxidants, etc)[14,15] and a variety of mechanical devices have failed to reduce restenosis. Due to parallels between tumor growth and in-stent neointimal growth, it was decided to use antiproliferation agents to reduce in-stent restenosis (ISR). Initially, some drugs failed, probably due to limited effectiveness, insufficient doses, or inappropriate release methods. However, the strong belief that local administration of these drugs was more effective than their systemic use, because greater local concentrations could be obtained with virtually no systemic effects, gave way to the development of antiproliferative drug-eluting stents (DES).

ANTIPROLIFERATIVE DRUG-ELUTING STENTS

Antiproliferative DES consist of 3 components: the stent itself, the drug, and the drug-release mechanism.

1. The stent. This is the scaffold upon which the drug is placed making it possible to reach the vessel wall.

2. Antiproliferative drugs (Table 2). Rapamycin (sirolimus) and paclitaxel are the most-widely used drugs and yield the greatest benefits.

Rapamycin is a macrolide antibiotic, naturally pro-

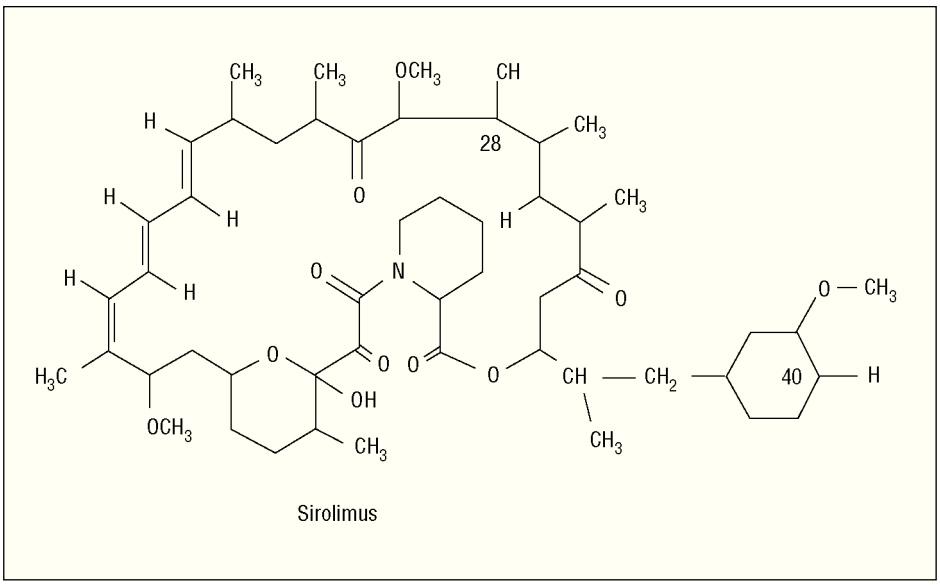

Figure 1. Chemical structure of rapamycin.

duced via fermentation by S*treptomyces hygroscopicus* (Figure 1). It was initially used as an antifungal agent, but when its immunosuppressive, antiinflammatory and antiproliferative properties were discovered, its use was suggested in other areas of medicine, such as the prevention of coronary artery bypass graft disease and restenosis in heart transplants as well as for managing rejection after kidney transplantation.[16] Rapamycin binds to the intracellular protein FKBP12, inactivates the TOR (Target Of Rapamycin) protein and, finally, inhibits transition from the G1 phase to the S phase (Figure 2). These mechanisms exert an antimigratory and antiproliferative effect on vascular smooth muscle cells.[17] When acting in such an early phase of the cell cycle, it blocks proliferation without inducing cell death, thus minimizing possible vascular sequelae.

Paclitaxel was initially extracted from the tree *Taxus brevifolia* (Figure 3). It inhibits proliferation and cell migration by suppressing microtubule dynamics.[18] In

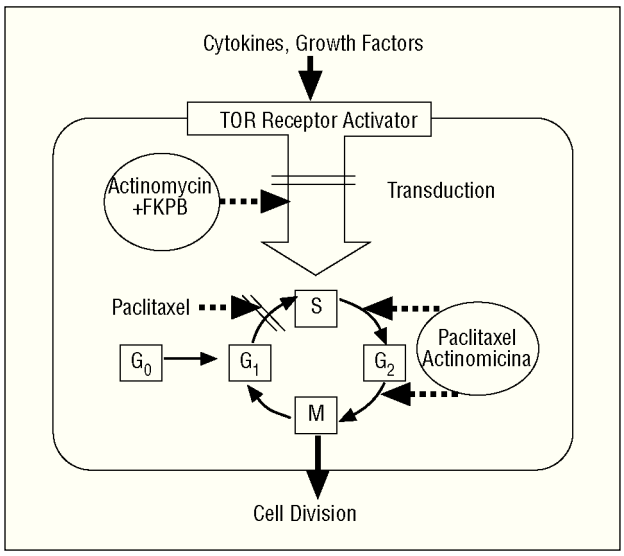

Figure 2. Mechanism of action of rapamycin.

TABLE 2. **Antiproliferative Drugs Studied or Under Evaluation for Use With Antiproliferative Drug-Eluting Stents***

Antineoplastic	Immunosuppressives	Migration Inhibitors	Healing Promotors
Paclitaxel	Sirolimus	Halofuginone	VEGF
Taxane QP-2	Tacrolimus	C-proteinase inhibitors	17-β-estradiol
Actinomycin D	Everolimus	Metalloproteinase inhibitors	BCP 671
Vincristine	ABT-578	Batimastat	HMG CoA reductase inhibitors
Methotrexate	Biolimus A9	Propyl hydroxylase inhibitors	
Angiopeptin	Tranilast		
Mitomycin	Dexamethasone		
BCP 678	Methylprednisolone		
C-myc Antisense	Interferon		
	Leflunomide		
	Cyclosporin		

*VEGF indicates vascular endothelial growth factor.

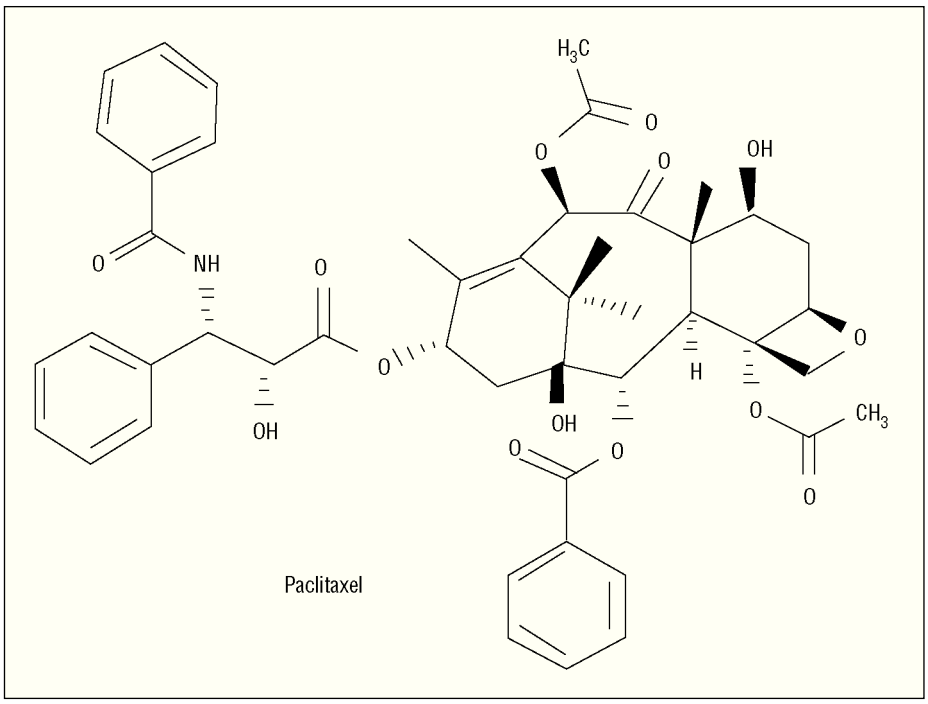

Figure 3. Chemical structure of paclitaxel.

low doses it acts in the transition between G0 and G1 and between G1 and S, producing cytostasis; however, in high doses it blocks the transition between G2 and M and between M and G1, leading to cell death. Thus, one of the most important aspects regarding paclitaxel has been to find the lowest dose capable of blocking cell response while avoiding vascular damage. Taxol is produced by dissolving 7.0 mmol/L paclitaxel in a lipoid vehicle.

3. Polymer. There are two ways to release the drug: by modifying the stent surface or by using a polymer from which the drug is released. Modifying the stent surface is simpler and cheaper, yet the drug release is less uniform and controlled; in addition, some of the drug can be lost during stent expansion. Using polymers is more expensive and can, in theory, be associated with inflammatory reactions and/or local hypersensitivity, but the dosage is more uniform and the drug is released in a more sustained and controlled manner.

Currently, several commercial antiproliferative DES are available or are about to be launched (Table 3). However, solid evidence regarding effectiveness is only available for the Cypher and Taxus stents; these are the BX Velocity (Cordis Corp.) and Express (Boston Scientific) polymer-based rapamycin- and taxol-eluting stents, respectively.

Antiproliferative Rapamycin-Eluting Stents

The Cypher stent is a polymer-coated stent that gradually and continuously releases rapamycin (140 μg/mm^2) (80% over 28 days) and has drastically reduced restenosis in de novo lesions compared to standard stents as confirmed in several randomized studies[19-22] (Figure 4): RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS.

In the RAVEL study, 238 patients with lesions =18 mm in vessels measuring 2.5-3.5 mm diameter were

TABLE 3. **Manufacturer and Components (Scaffold, Polymer, and Drug) of Antiproliferative Drug-Eluting Stents That Are or Will Be Available in 2005**

Antiproliferative DES	Manufacturer	Scaffold	Polymer	Drug
Cypher	Cordis Corp	BX Velocity	PEVA & PBMA	Sirolimus
Taxus	Boston Sci.	Express	Translute	Paclitaxel
Janus	Sorin	Tecnic	–	Tacrolimus
Xcience V	Guidant	Vision	Polylactic acid	Everolimus
Endeavor	Medtronic	Driver	Phosphorylcholine	ABT-578

*Antiproliferative DES indicates antiproliferative drug-eluting stents; PEVA, polyethylene-co-vinyl acetate; PBMA, poly n-butyl methacrylate; Translute, poly (styrene-b-isobutylene-b-styrene).

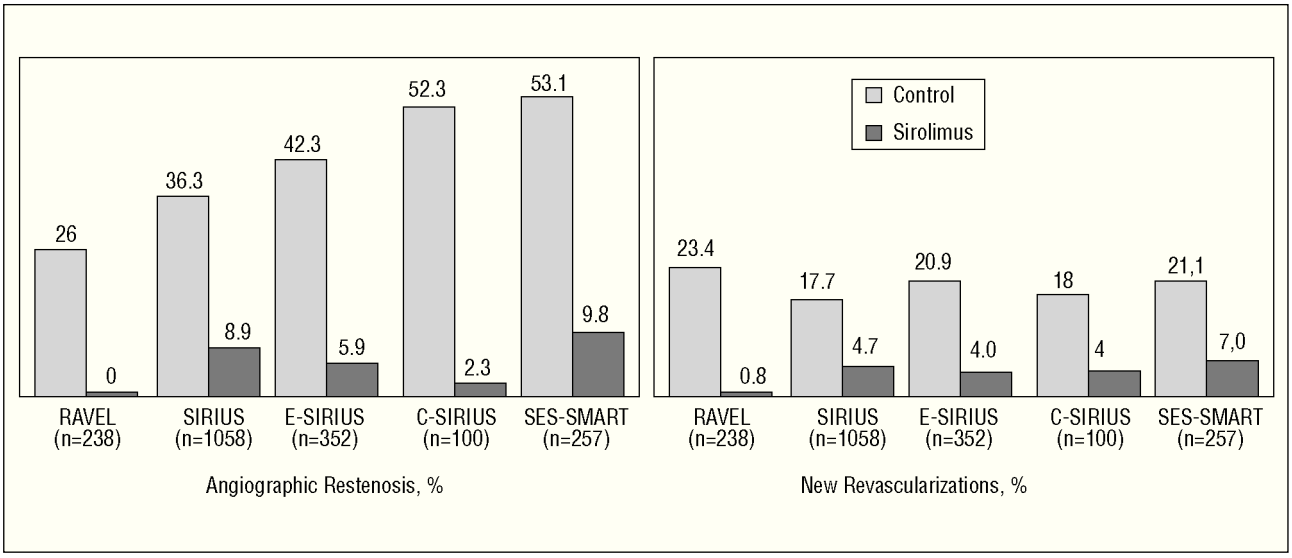

Figure 4. Benefit of the Cypher stent compared to standard stents in published randomized studies.

randomized to receive a Cypher or a standard bare metal stent,[19] obtaining a restenosis rate of 0% and 26.6%, respectively. This resulted in a reduction in the rate of events per year (15.8% vs 28.8%), especially regarding new revascularization procedures. The SIRIUS study included 1,058 patients with a less favorable outcome than those in the RAVEL study (vessels ranging from 2.5 mm to 3.5 mm diameter, lesions from 15 mm to 30 mm, and a higher proportion of diabetic patients).[20] The Cypher stent significantly reduced the restenosis rate (8.9% vs 36.3%) and new revascularization procedures (4.1% vs 16.6%). The E-SIRIUS study included 352 patients with lesions of 15-32 mm in small vessels (2.5-3.0 mm diameter). A significant reduction in the restenosis rate (5.9% vs 42.3%) and new procedures (4.0% vs 20.9%) was also found.[21] The C-SIRIUS study, with 100 patients similar to those of the E-SIRIUS study, also found a reduction in the restenosis rate (2.3% vs 52.3%) and need for new procedures (4% vs 18%).[22]

In total, 1748 patients were included in these four studies. The restenosis rate was 6.3% with the Cypher stent and 37.2% with the standard stent, representing an absolute and relative reduction of 30.9% and 83.1%, respectively (3-4 patients would have to be treated with the Cypher stent to avoid one restenosis). The need for new revascularization procedures was reduced from 18.5% to 3.6%, i.e., an absolute and relative reduction of 14.9% and 80.5%, respectively (6-7 patients would have to be treated with the Cypher stent to avoid a new procedure). A key fact is that these benefits have been consistent in all the subgroups of patients included, after stratifying them by vessel diameter, lesion length, presence of diabetes, etc.

Other studies exist, some of which are unpublished or are still under way. The Cypher stent has been evaluated in small vessels in the SVELTE and SES-SMART studies. In the SES-SMART study, 257 patients with vessels ≤2.75 mm diameter were randomized to receive a Cypher or standard stent, with a restenosis rate of 9.8% and 53.1%, respectively.[23] The results of the SCANDSTENT study have recently been reported, in which 322 patients with complex lesions were randomized to receive either a Cypher or standard stent. A significant reduction was found in the restenosis rate (2.0% vs 31.1%) and new revascularization procedures (2.4% vs 29.6%). The Cypher stent has been evaluated in patients with ISR in the TROPICAL registry and in the RIBS-II and ISAR-DESIRE randomized studies. This will be addressed later.[24,25]

The ARTS-II registry consisted of 607 patients with multivessel disease treated with the Cypher stent. Compared to the ARTS-I surgical group, the ARTS-II patients underwent more reinterventions (8.5% vs 4.1%; *P*=.003), presented less mortality (1.0% vs 2.7%; *P*=.03) and had a similar incidence of events (10.4% vs 11.6%). In the FREEDOM study, a population of diabetic patients with multivessel disease was randomized to receive the Cypher stent or coronary surgery. In the DIABETES study, which was coordinated in our center, the Cypher stent reduced restenosis and the need for new revascularization.[26]

Currently, several studies are under way with the Cypher stent—RESEARCH, e-CYPHER, RECIPE, SECURE, and others—where varied clinical situations and angiographic characteristics are being investigated. This means they will reflect the outcomes obtained with the Cypher stent in the "real world."

Antiproliferative Paclitaxel-Eluting Stents

Paclitaxel also reduces in-stent neointimal hyperplasia.[27] Antiproliferative paclitaxel DES have been developed with polymer-coating and without. However, only the Taxus antiproliferative paclitaxel-eluting polymer-coated stents have proved to be beneficial when compared to standard stents.

Antiproliferative Paclitaxel-Eluting Non-Polymer-Coated Stents

Antiproliferative paclitaxel-eluting non-polymer-coated stents reduce neointimal hyperplasia, but do not improve clinical evolution. The ASPECT, DELIVER, and ELUTES studies have been the most important in this context. The ASPECT study compared the Supra-G stent (Cook Inc.) without paclitaxel with the same stent but with two different doses of paclitaxel (1.3 μg/mm^2 and 3.1 μg/mm^2),[28] obtaining a restenosis rate of 27%, 12%, and 4%, respectively. However, there were no significant differences in the revascularization rate (8.6%, 6.9%, and 10%, respectively).

In the DELIVER-I study, 1043 patients were randomized to receive the Achieve stent (Cook Inc.) coated with 3 μg/mm^2 of paclitaxel or standard stent (Multi-Link Penta). A trend was found toward a smaller rate of restenosis with the Achieve stent (14.9% vs 20.6%; *P*=.076), but significant clinical benefits were not obtained (new revascularization procedures in 11.9% and 14.5% of patients, respectively; *P*=.12).[29]

Finally, in the ELUTES study, 190 patients were randomized to receive one of the five following treatments: standard stent (V-Flex Plus, Cook Inc.) or stent coated with 0.2 μg/mm^2, 0.7 μg/mm^2, 1.4 μg/mm^2, or 2.7 μg/mm^2 paclitaxel.[30] A dose-response relationship was found with restenosis rates of 21%, 20%, 12%, 14%, and 3%, while new procedure rates were 16%, 5%, 8%, 10%, and 5%, respectively (*P*=NS).

Antiproliferative Polymer-Coated Paclitaxel-Eluting Stents

The first antiproliferative polymer-coated paclitaxel-eluting stents not only failed to provide clinical benefits but also yielded a higher event rate, basically due to a very high incidence of stent thrombosis. The Quanam QuaDS-QP2 stent was used with very high doses of paclitaxel. It had a very particular design with polymer "sleeves." In the SCORE study, this stent reduced intimal hyperplasia and restenosis, but the thrombosis rate was >10% in the first year.[31]

The Taxus polymer-coated paclitaxel-eluting stents have demonstrated a reduced rate of restenosis and new revascularization events (Figure 5), which is not associated with increased risk of stent thrombosis, at least when combined with antiplatelet treatment with aspirin and thienopyridines for 6 months. The benefits of the Taxus stent have been demonstrated in the TAXUS-I, II, IV, and VI studies.[32-34]

In the TAXUS-I study, 61 patients with lesions ≤12 mm in vessels of 3.0-3.5 mm diameter were randomized to receive a Taxus stent (1.0 μg/mm^2, slow release) or standard stent (NIR, Boston Scientific Corp.), obtaining restenosis rates of 0% and 10%, respectively.[32]

This was a safety study and the primary end-point (death, infarction with Q wave, new revascularization or 30-day stent thrombosis) occurred in 3% and 10%, respectively (*P*=NS). An important fact is that

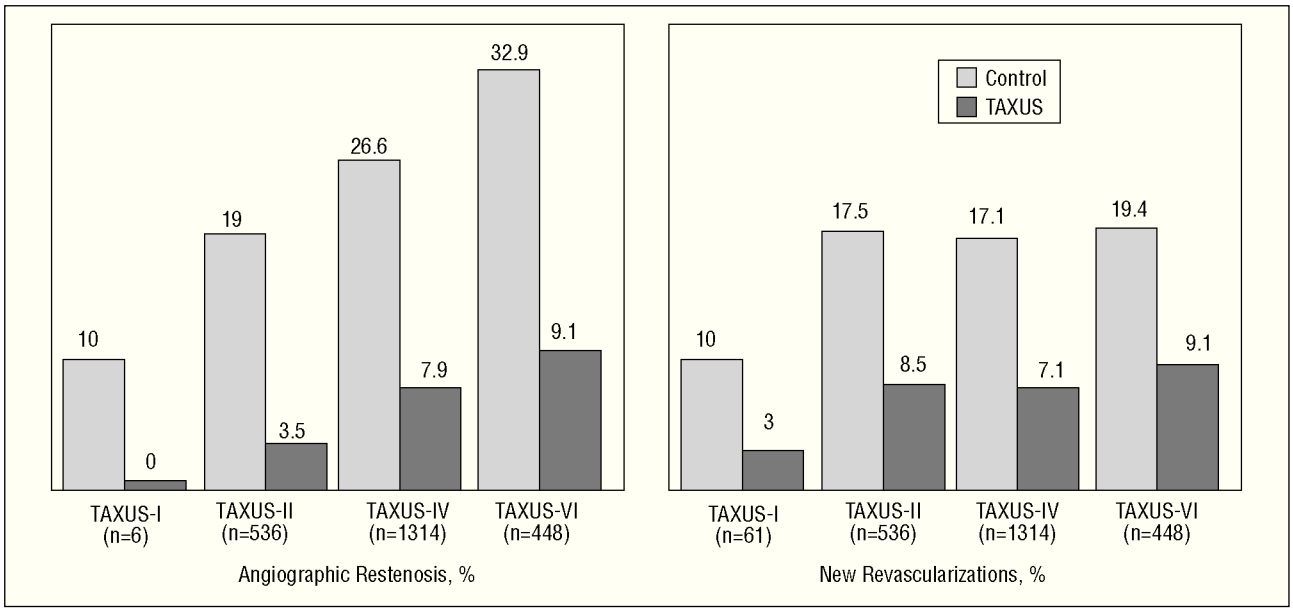

Figure 5. Benefit of the Taxus stent compared with standard stents.

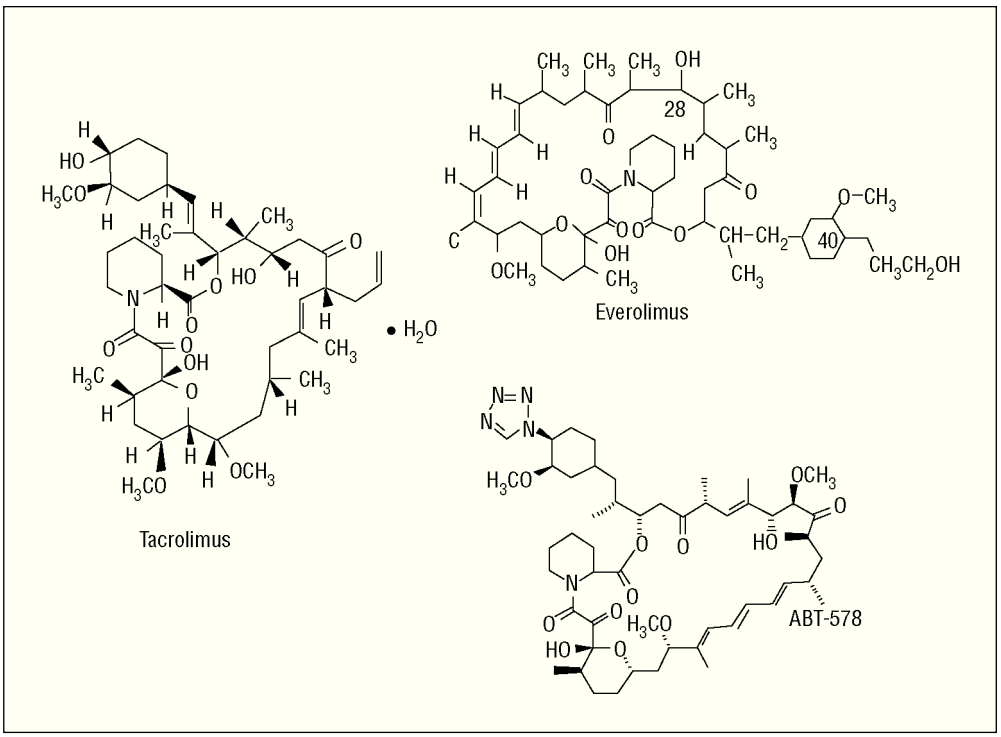

Figure 6. Chemical structure of some sirolimus analogues.

there was no stent thrombosis in either of the 2 groups over 12 months. The TAXUS II study randomized 536 patients with similar characteristics to those of the TAXUS-I study into 3 groups: standard NIR stent, slow-release Taxus stent, and moderate-release Taxus stent. The restenosis rates were 19%, 2.3%, and 4.7%, and new revascularization procedures 16%, 7.7%, and 6.2%, respectively.[33] The TAXUS-IV study randomized 1314 patients with lesions of 10-28 mm in vessels of 2.5-3.75 mm in diameter to receive a standard stent (Express, Boston Scientific Corp.) or a Taxus stent (1 μg/mm^2, slow release). The restenosis rate was reduced from 26.6% to 7.9%, and the revascularization rate from 11.3% to 3.0%.[34] Taking the TAXUS-I, II, and IV studies into account, the restenosis rate decreased from 23.5% to 6.9% (an absolute and relative reduction of 16.6% and 70.6%, respectively; 6 patients would have to be treated to avoid 1 restenosis).

Other studies using the Taxus stent are under way or still unpublished. In the TAXUS-VI study, 448 patients with long lesions (18-40 mm) were randomized to a moderate-release Taxus stent (an initial release of the drug eight times higher than the slow release) or standard stent. The Taxus obtained a significant reduction in the restenosis rate (35.7% vs 12.4%) and in new procedures (19.4% vs 9.1%). The results of the TAXUS-V study have been reported recently, where 1172 patients with long complex lesions were randomized to receive a Taxus or standard stent. Although in this study the outcomes were better with the Taxus stent than with the standard stent, there was a higher rate of restenosis (18.9% vs 33.9%), and new revascularization procedures (12.1% vs 17.3%). The TAXUS-V US Randomized Pivotal ISR Trial will compare the Taxus stent and intracoronary brachytherapy (ICB) in 488 patients with ISR. The SYRTAX study randomized a group of patients with multivessel disease to receive surgery or the Taxus stent. There also are registries on the use of the Taxus stent in the "real world", such as the WISDOM, T-RESEARCH, MILESTONE, TAXUS-Olympic, and others.

DES Using Other Antiproliferative Drugs

Currently, DES using other antiproliferative drugs, such as sirolimus analogues, are being evaluated (Figure 6). Some have already proven their safety and will be marketed in the coming months in Europe.

Everolimus is an immunosuppressive macrolide developed to prevent rejection in kidney, heart, and lung transplantation and it inhibits proliferation of smooth muscle cells. It is absorbed by local tissue more rapidly than sirolimus and remains in the cells longer. There are several studies where everolimus has been used (FUTURE-I, FUTURE-II, and SPIRIT). Its safety (no stent thrombosis was found) and effectiveness has been demonstrated with significantly reduced late loss, restenosis rates, and need for new revascularization. Nevertheless, these 3 studies included a small number of patients, in favorable angiographic and clinical contexts, and thus these benefits should be con-

firmed in other studies.

The antiproliferative tacrolimus-(FK-506) eluting stents were initially evaluated in the EVIDENT and PRESENT I and II studies, in saphenous vein bypass grafts and native vessels, respectively. No benefits were observed in the patients treated with tacrolimus. The Janus (Sorin) stent is specially designed with microreservoirs, ensuring a targeted local delivery of tacrolimus directly to the vessel wall. The JUPITER-I study evaluated this stent in a small population of patients. No stent thrombosis was reported, but there was elevated late loss especially in diabetic patients. Thus, the JUPITER-II randomized study (Janus stent vs Tecnic stent) was carried out with a higher dose of tacrolimus (2.3 μg/mm^2); its results will be released sometime in 2005.

Although several antiproliferative ABT-578 DES have been developed (Endeavor, TriMaxx, ZoMaxx), the Endeavor stent is the one that has been evaluated in the greatest number of patients up until now. This is a chromium-cobalt ABT-578 (10 μg/mm) polymer-coated stent (Driver, Medtronic Inc.) releasing 70%-80% of the drug in the first 48 h after implantation and the remainder during the following 30 days, approximately. It was evaluated in the non-randomized ENDEAVOR-I study with favorable clinical results (thrombosis 0%, restenosis 3%, clinical events 2%), but with a relatively high late loss (0.61 mm at 12 months). In the ENDEAVOR-II randomized study (n=1197), the patients treated with the Endeavor stent had lower restenosis rates (9.5% vs 32.7%) and fewer new procedures (5.7% vs 12.8%) than those treated with the Driver stent. The randomized ENDEAVOR-III and IV studies will compare the Endeavor stent with the Cypher and Taxus stents, respectively.

The STEALTH-I study, using biolimus A9, randomly compared (2:1) the BioMatrix stent (Biosensors) with a standard stent in 120 patients, obtaining a significant reduction in late loss (from 0.74 mm to 0.25 mm).

In addition to these sirolimus analogues, other antiproliferative drugs have been evaluated: dexamethasone, 17β-estradiol, batimastat, actinomycin-D, methotrexate, angiopeptin, temsirolimus (ICC-779), vincristine, cyclosporin, etc (Table 2). However, the results have been negative or are still in the early stages of research. On the other hand, "coated stents" are normally considered to be those which release antiproliferative agents, given that they have proven to reduce the restenosis rate and need for new revascularization procedures. Nevertheless, the concept of "coated stents" is broader and includes stents coated with other drugs. Heparin-coated stents were developed in attempt to reduce the thrombosis rate whose global incidence was <0.5%. However, the rate obtained was not significantly less than that achieved with standard stents. A reduction in the restenosis rate has not been demonstrated, and therefore the use of this type of stent has been very limited. Phosphorylcholine (Biodivysio stent) and silicone carbide (Tenas stent) are other coatings used in the attempt to reduce stent thrombogenicity. These stents do not reduce the risk of restenosis nor thrombosis.

Current Limitations of Antiproliferative Drug-Eluting Stents

Antiproliferative Drug-Eluting Stents in Non-Favorable Scenarios

Randomized studies have not been done in certain groups of patients, but the data obtained based on registries makes it possible to assume for the time being that antiproliferative DES are probably also more effective than standard stents.

Bifurcated lesions constitute an unfavorable context, not only due to the risk of loss of secondary vessels, but also because of the high rate of restenosis, especially in the secondary vessel. In the SIRIUS-Bifurcations study, 86 patients with bifurcated lesions were randomized to receive the Cypher stent in the main branch and balloon in the side branch versus the Cypher stent in both vessels.[35] The results can be summarized as follows: *1)* there was a high rate of Cypher-balloon to Cypher-Cypher crossover (51%); *2)* there was little restenosis in the main branch (G5% in both groups), a favorable outcome compared to classic series with standard stents; and *3)* treatment with the Cypher stent in both vessels did not provide advantages compared to the initial treatment with balloon in the side branch (new revascularization procedures in 11% and 10%, and restenosis in the side branch in 22% and 14%, respectively). Furthermore, all the thromboses occurred in patients treated with Cypher-Cypher stenting. Along with antiproliferative DES, a new technique has been developed for treating bifurcations (crushing technique). This basically consists of first implanting an antiproliferative DES in the side branch, but placed some 4 mm into the main branch. Subsequently, another antiproliferative DES is implanted in the main branch in front of the stent in the side branch. Ideally, this technique should end with simultaneous balloon expansion of both vessels (kissing balloon technique).

Given the concern regarding the possibility of an increase in thrombosis risk after implanting antiproliferative DES, until a short time ago the use of these stents in acute coronary syndromes was relatively limited, especially in ST-segment elevation myocardial infarction. However, in relation to restenosis and stent thrombosis, recent data have shown that the results of treatment with the CYPHER stent in these patients are comparable to those obtained in stable ischemic heart

disease.[36]

Data on the Cypher and Taxus stents in saphenous vein bypass grafts are based on studies with few patients, in which a new revascularization procedure rate of 2.5%-65% was obtained. In a recent study, a lower rate of restenosis (10.0% vs 26.7%; *P*=.03) and new revascularization procedures (4.9% vs 23.1%; *P*=.01) was obtained in a group of patients treated with antiproliferative DES (Cypher or Taxus) than in a control group with standard stents.[37] Similar results were obtained in another study (new revascularization in 6.4% vs 17.3%, respectively).[38] In a recent analysis of the SECURE registry, the need for new revascularization procedures in the patients who received the Cypher stent in saphenous vein bypass grafts was 17%. Although this is a high figure, it is similar to the one found in the patients with lesions in native vessels in the same registry (18%), since it included patients with a particularly unfavorable situation (mainly involving failed ICB).

Traditionally, left main coronary artery disease has been a surgical indication. However, stenting can be an alternative, especially in patients with high surgical risk. Given the great clinical importance of restenosis in the left main coronary artery, antiproliferative DES are especially attractive in this context. A series of patients have been described with left main coronary artery disease treated with Cypher or Taxus stents with a restenosis rate of G5%.[39,40] The two most important problems after treating left main coronary artery disease with antiproliferative DES are restenosis of the origin of the circumflex artery when the left main coronary artery lesion is distal, and stent thrombosis; this is the cause of some sudden death events that have taken place after treating the left main coronary artery via antiproliferative DES. Nevertheless, the risk of thrombosis with an antiproliferative DES implanted in the left main coronary artery is probably no higher than that with standard stents.

One problem in the treatment of chronic occlusions is that, although steering the guidewire, dilating the lesion, and implanting a stent may be successful, the restenosis rate is very high. In some series of chronic occlusions treated with antiproliferative DES,[41] a restenosis rate of 0%-11% was reported (reocclusion 0%-3%) with a need for new revascularization procedures in 0%-7.5% of cases. These data are favorable when compared to series with standard stents.

Systemic Side Effects of Antiproliferative Drug-Eluting Stents

In experimental studies, systemic high-dose rapamycin can have serious side effects, such as myocardial necrosis, retinal infarction, necrosis of the mucous membrane, and vasculitis. In therapeutic doses, the possible side effects of systemic rapamycin are: headache, polyarthralgia, nosebleed, diarrhea, myelosuppression, and others.[42] Furthermore, plasma concentrations of cholesterol and triglycerides can increase in humans.[43] Systemic side effects of rapamycin have not been reported when administered via antiproliferative DES, and their risk is virtually nil. In the SIROLIMUS PK study, after implantation of antiproliferative sirolimus-eluting stent, the maximum plasma concentration of rapamycin was 0.80±0.37 ng/mL, with a half-life of 213 h and the presence of detectable concentrations in the plasma for 1 week.

The following side effects have been reported when paclitaxel is administered systemically as an antineoplastic agent: myocardial infarction, heart failure, arrhythmias, hypotension, sudden death, repolarization changes, sinus bradycardia, and atrioventricular blocks.[44] However, in these situations, systemic concentrations are 100-1000 times higher than those used in antiproliferative DES. As with rapamycin, the implantation of antiproliferative paclitaxel-eluting stents has not been associated with systemic side effects, although this should be confirmed in a broad series of patients with long-term follow-up.

Side Effects of Antiproliferative Local-Delivery Drug-Eluting Stents

From the inception of DES there has been concern over a possible increase in the risk of stent thrombosis. This was justified by the following facts: *1)* parallels with ICB, since antiproliferative drugs can delay stent endothelialization; *2)* rapamycin can increase platelet aggregation in vitro[45]; *3)* in some studies, DES have been associated with a greater frequency of late stent malapposition. This fact was reported in 9% and 21% of the patients in the SIRIUS and RAVEL studies, respectively, after implantation of the Cypher stent. On the other hand, in the TAXUS-II study, the risk of late malapposition with the Taxus stent was similar to the standard stent; and *4)* in some initial studies with DES, the incidence of stent thrombosis was very high: >10% and 3% per year in the SCORE[31] and ASPECT studies, respectively.[28]

However, in the SCORE study, the high rate of thrombosis was probably due to the stent design and the extremely high doses of paclitaxel.[31] In the ASPECT study, all thromboses occurred in patients who received aspirin and cilostazol but not aspirin and thienopyridines.[28] No increase in the risk of thrombosis was found in the studies with Cypher or Taxus stents. In a recent metaanalysis of ten randomized studies, the stent thrombosis rate with DES and standard stents (0.58% vs 0.54%) was similar. In these studies, the length of treatment with thienopyridines was 1-6

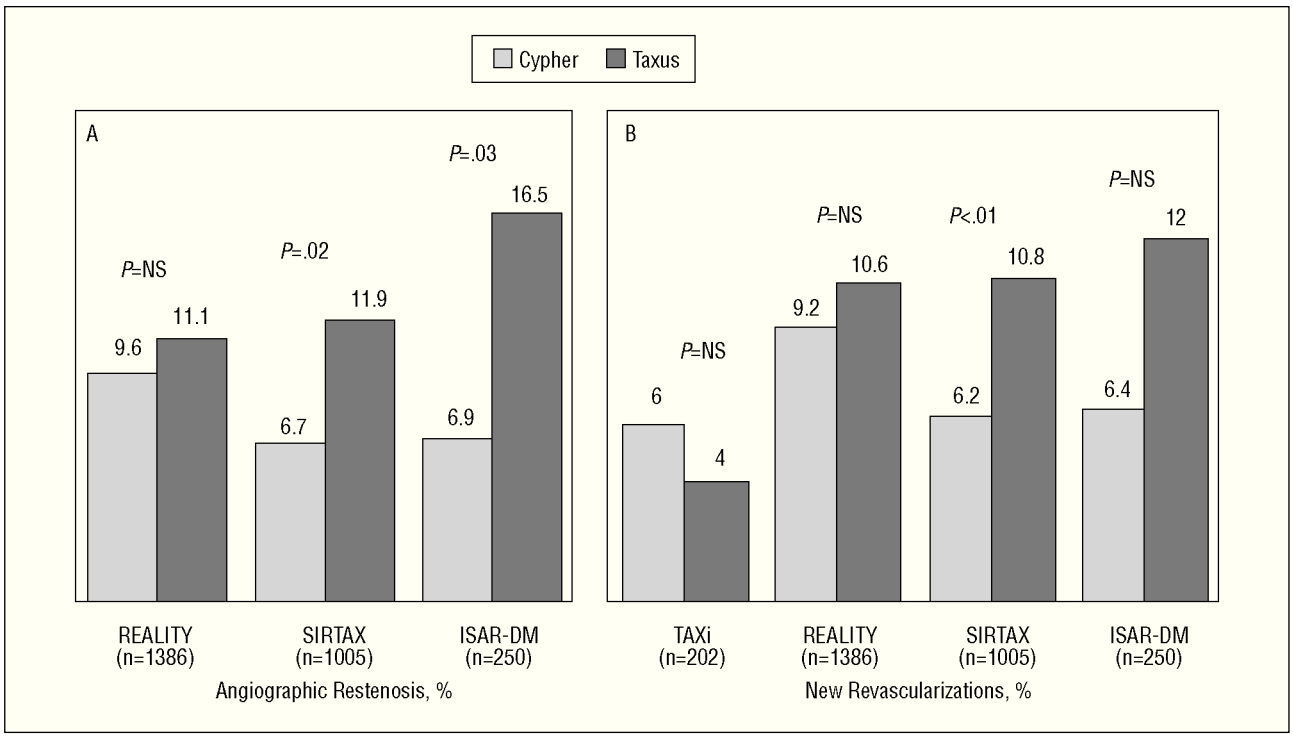

Figure 7. Restenosis rate (A) and new revascularization procedure rates (B) in randomized studies comparing the Cypher and Taxus stents.

months.[46]

Other possible side effects, with clinical implication still not well defined, may also occur, such as hypersensitivity and local inflammation, probably due to the polymer rather than to the antiproliferative drug. In contrast to what occurs in ICB, it has not been demonstrated that antiproliferative DES produce edge effects or more stent-edge restenosis than standard stents. The formation of coronary aneurisms in the long term, after the implantation of DES, has also been reported, but it appears to be infrequent and of little clinical relevance. In the TAXUS II study, for example, coronary aneurisms developed with the Taxus stent at a frequency similar to that of the standard bare metal stent (1.5%).

Finally, since the introduction of DES, the possibility that these would produce a delay rather than a reduction in intimal hyperplasia has been of some concern. However, the benefit of antiproliferative DES has been maintained for at least 2-3 years. In the TAXUS-II study, minimum lumen diameter did not decrease at 6 months and 2 years in patients treated with the Taxus stent, and the number of new revascularization procedures after 1-2 years was even higher with standard bare metal stent stent. Something similar to this occurred in the TAXUS-IV study, where new revascularization procedures were needed 1-2 years in 3.7% and 4.2% of the patients treated with the Taxus and standard stents, respectively. The 3-year results of the RAVEL study were published recently, where the Cypher stent was used.[47] Between 1 year and 3 years there was a greater frequency of target-vessel failure in the Cypher group, but the differences were not significant (5.9% vs 4.3%; *P*=.77) and the difference in the rate of events was preserved at 3 years (16.7% vs 34.5%; *P*=.002). The 3-year results of the SIRIUS study have also been published recently. In this study the differences in the incidence of new procedures between the Cypher and control groups at 9 months and 3 years were not only maintained, but even increased (18.9% vs 6.4% at 9 months [absolute reduction of 12.5%]; 27.2% vs 11.6% at years [absolute reduction of 15.6%]). The only aspect that remains unsolved is whether the long-term stent thrombosis rate is higher in patients treated with DES than with standard stents, once double antiplatelet aggregation treatment is suspended and more than 1 year has passed since implantation. In a combined analyses of the TAXUS I, II, III, and IV studies, the incidence of stent thrombosis between 6 months and 2 years with the Taxus stent was significantly higher than in the control groups (1.2% vs 0.7%). In contrast, in the SIRIUS study, the thrombosis rate at 3 years was 0.8% in both groups. Thus, the need for administering thienopyridines combined with aspirin over a longer period than in the randomized studies has still not been demonstrated.

Comparison Between the Cypher and Taxus Stents

We have already mentioned the ISAR-DESIRE study, in which the recurrence of ISR, after it was treated, was 14.3% and 21.7% with the Cypher and Taxus stents, respectively.[25] The Cypher and Taxus stents have been compared in several randomized studies in de novo lesions (Figure 7).[48-52] In the TAXi study, there were no significant differences between them regarding clinical evolution (there was no angiographic follow-up). In the REALITY, SIRTAX, and ISAR-DIABETES studies, late loss was significantly lower with the Cypher stent and in-lesion restenosis was significantly less frequent with the Cypher stent in the SIRTAX and ISAR-DIABETES studies. Nevertheless, these differences only translated into clinical differences in the SIRTAX study. The preliminary results of the CORPAL study group agree with these data, but it is limited by the fact that angiographic follow-up was done in a small number of patients.

Regarding safety, only the REALITY study reported a higher thrombosis rate with the Taxus stent (1.8% vs 0.4% in an analysis by treatment administered), but the differences were not statistically significant in an intention-to-treat analysis (1.6% vs 0.6%; *P*=.07). In other studies, the incidence of thrombosis was similar in both groups (in the SIRTAX it was 1.6% and 2.0% with the Taxus and Cypher stents, respectively). Although in the studies in which paclitaxel-eluting stents were used there was a trend toward greater duration of treatment with thienopyridines (4.4±2.3 vs 2.0±0.0 months, respectively; *P*=.08)—and thus we cannot rule out that this masked possible greater thrombogenicity with the paclitaxel-eluting stent—in our metaanalysis the thrombosis rate was not significantly different between rapamycin and paclitaxel DES (0.56% vs 0.66%) and neither were there significant differences in the late stent thrombosis rate (0.11% vs 0.33%).[46]

Cost of Antiproliferative Drug-Eluting Stents

In our context, the price of antiproliferative DES is 60%-80% higher than standard stents. Furthermore, it is necessary to add the indirect cost of administering thienopyridines over a longer period. The added clinical benefit derived from DES may possibly not be sufficient to justify such a difference in price (we should not forget that DES do not reduce mortality nor the infarction rate). Given current prices, we do not recommend the systematic use of DES, but do recommend them preferably in contexts in which the reduction of restenosis involves greater clinical benefit.

Despite previous considerations, economic analyses of the SIRIUS and TAXUS-IV studies shows that most of the extra cost of DES is compensated for by the savings derived from the reduction in the need for new revascularization procedures. The "cost neutral price" of a device (in this case, the DES) is that in which the initial extra cost is totally compensated for by the reduction in expenditures derived from its clinical benefit (in this case, reduction in expenditure due to fewer new revascularization procedures). An economic study has recently been carried out in Spain which estimated that the cost neutral price of a DES would be somewhat less than 1,500 Euros.[53]

Treatment of in-Stent Restenosis Via Antiproliferative Drug-Eluting Stents

Conceptually, the use of devices in *de novo* lesions is a restenosis "primary prevention" strategy, whereas their use in restenotic lesions (especially ISR) would correspond to "secondary prevention" strategies. In-stent restenosis has been classified into four angiographic types with prognostic implications (Table 4).[54] The risk of ISR is inversely related to the minimum lumen diameter after stent implantation, and is higher in diabetic patients, long lesions, small vessels, restenotic lesions, saphenous vein bypass grafts, and ostial lesions.[55] Some characteristics related to the type of stent could also have a relationship with restenosis.[56] Furthermore, some genetic factors can also be related to ISR, such as platelet glycoprotein IIIa PI^A polymorphism and a mutant form of methylenetetrahydrofolate reductase, while the allele 2 of interleukin 1 appears to be associated with a lower risk. On the other hand, positive reactions to nickel and molybdenum allergy tests (components of the coronary stents) have also been related to ISR.[57]

With the majority of devices, percutaneous treatment of ISR is associated with a very high initial success rate (G100% in most series) and a low rate of complications. This is due to the fact that, in ISR, the vessel wall is "protected" by the stent's metallic mesh, thus reducing lesion grade and risk of dissection. However, in contrast, ISR treatment is associated with a restenosis rate higher than that of *de novo* lesions. Although many devices have been evaluated in the treatment of ISR, only antiproliferative DES and ICB are

TABLE 4. **Angiographic Classification of in-Stent Restenosis**

Type I: focal (≤10 mm)
IA: in the stent articulation (especially with Palmaz-Schatz stents)
IB: at the edge of the stent
IC: focal, located in the body of the stent
ID: focal, in several in-stent locations (multifocal)
Type II: diffuse (>10 mm)
Type III: proliferative (>10 mm, exceeding the boundaries of the stent)
Type IV: occlusive (total in-stent occlusion)

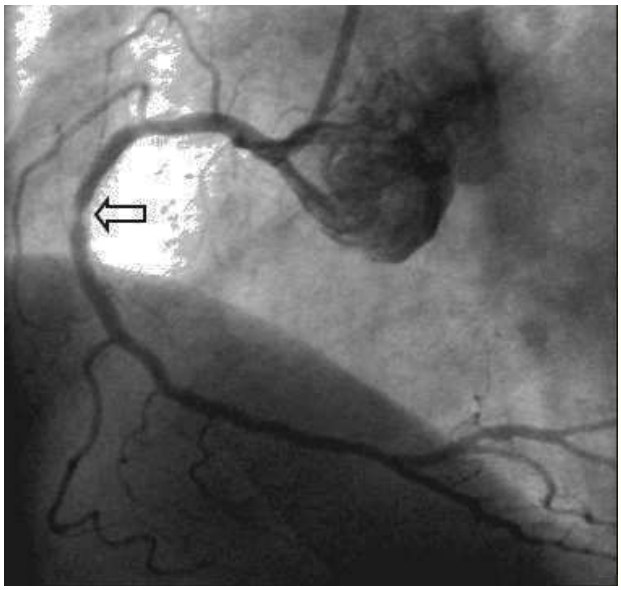

Figure 8. Focal restenosis located in the overlap area of two Cypher stents implanted in the right coronary artery.

more effective than balloon angioplasty.

Although the incidence of events was relatively high in some of the first registries of ISR treated with DES, angiographic results were consistently favorable, with low rates of late loss and restenosis.[24,25,58-60] In the São Paulo experiment, with 25 ISR patients treated with the Cypher stent, there was no stent thrombosis and there was only one recurrence of ISR.[85] In the TAXUS III study, with 28 ISR patients treated with the Taxus stent, the ISR recurrence rate was 16% (4/25). At 12 months, 6 patients (21%) underwent new revascularization (three due to restenosis and three due to intravascular ultrasound findings).[59] In another series of 16 patients with complex ISR, a higher restenosis rate has been reported (19% at 4 months).[58]

In the TROPICAL registry, 162 patients with ISR were treated with the Cypher stent and compared with the control groups from the GAMMA 1 and 2 studies, which had restenosis rates of 9.7% vs 40.3%, respectively. In the TROPICAL registry, the benefit of the Cypher was higher, since ISR length was significantly higher in the control group. In the RIBS-2 study 150 patients with ISR were randomized to receive treatment with the Cypher stent or balloon.[24] The provisional results showed an ISR recurrence rate of 11% and of 39% ($P<.01$), and the need for new revascularization procedures of 9% and 30% ($P<.01$), respectively. In the recently published ISAR-DESIRE study, 300 patients with ISR were randomized to 3 groups: balloon angioplasty, Cypher stent, and Taxus stent; there was ISR recurrence in 44.6%, 14.3%, and 21.7%, respectively.[25]

In the context of ISR treatment with DES, the patients in whom ICB has failed beforehand constitute a higher risk subgroup. In a recent update of the SECURE registry, with 193 patients with ISR treated with the Cypher stent (142 of them after failed ICB), the need for new procedures was 17%, but was higher after failed ICB (19%) than in the rest of the patients (12%).[61] The same occurred with thrombosis, which only occurred (1.4%) in the patients with previous failed ICB. In a study by Waksman et al,[62] treatment with DES in patients with ISR, in whom ICB had already failed, was associated with an even higher risk of events than that of patients treated with new ICB.

Restenosis After the Implantation of Antiproliferative Drug-Releasing Stents

The predictors of DES ISR are similar to those of standard stent ISR. In an evaluation of the RESEARCH study, the predictors of restenosis after implantation of the Cypher stent were treatment for ISR, ostial location, greater total stented length, small vessels, diabetes, and location in the left anterior descending artery.[63]

Although antiproliferative DES ISR is usually located within the stent, restenosis located at the edges is frequent (20%-30% of antiproliferative DES ISR), and also where 2 stents overlap (Figure 8). The incidence of restenosis in the stent edges can be reduced by attempting to cover the entire length dilated with the balloon with the stent. ISR of DES usually has a focal pattern and diffuse ISR is infrequent, either with rapamycin[64] or paclitaxel.[65] Possible explanations to this predominantly focal pattern of ISR after implantation of antiproliferative DES include underexpansion of the stent, non-homogeneous distribution of the drug, or incomplete coverage of the lesion with the stent.

There is very little data on the treatment of DES ISR. The best treatment is probably another DES. The RESEARCH study investigated 24 patients (27 lesions) undergoing percutaneous procedures with ISR related to the Cypher stent.[64] Approximately 85% were treated with another DES (Cypher or Taxus) and 15% with balloon or a conventional bare metal stent. There was ISR recurrence in 43% of the cases, but only in 18% of the patients treated with another DES. Intracoronary brachytherapy could also be a therapeutic alternative in these patients[66] but the devices used have been removed from the market quite recently.

OTHER DEVICES FOR THE PREVENTION AND TREATMENT OF RESTENOSIS

DES have revolutionized interventionist cardiology. Nevertheless, the beginning of the DES era is recent and other devices had already been evaluated in the

TABLE 5. **Randomized Studies Valuating Different Devices for the Treatment of de Novo Coronary Lesions**

	Stent	n	Restenosis, %		Revascularization, %	
			Control	Device	Control	Device
Directional atherectomy						
CAVEAT-I	No	1,012	57	50	37	36
CAVEAT-II	No	305	51	46	26	19
CCAT	No	274	43	46	26	28
BOAT	No	989	40	32*	25	28
START	No	122	33	16	32	18
Kim et al	Yes	86	28	37	11	12
AMIGO	Yes	753	27	22	23	20
DESIRE	Yes	500	16	15	12	13
Rotational atherectomy						
COBRA	No	502	51	49	24	21
DART	No	446	50	50	23	25
ERBAC	No	453	47	57	32	42
SPORT	Yes	735	28	30	12	14
Guerin et al	No	64	42	39		
Cutting balloon						
Umeda et al	No	178	51	33*	38	20*
GRT	No	1238	31	30	15	11*
Ergene et al	No	71	47	27*	46	25*
Molstad et al	No	64	26	17		
REDUCE-1	No	802	26	33	19	22
CAPAS	No	232	42	25*	36	25
CUBA	No	306	42	30*	24	20
REDUCE-3	Yes	521	19	12*	15	11
Laser						
ERBAC	No	454	47	59	32	46
LAVA	No	215			19	22†
AMRO	No	308	41	52	39	32
EXACTO	No	314			11	8
Intracoronary brachytherapy						
PREVENT	No	105	50	22*	24	6
Beta-Cath	Yes	1455	36	31	21	19†
BRIDGE	Yes	112	15	27	12	20*
Sabate et al[100]	Yes	92	26	24	24	22
Ultrasonography						
Euro-SPAH	Yes	403	25	23	23	14*

*$P<.05$.
†Events at 6-8 months.

prevention of restenosis (Table 5).

In the treatment of de novo lesions, no device other than the stent has proven to reduce restenosis. Regarding ISR, DES and ICB have only proven to reduce the recurrence of ISR as compared to conventional treatment. Balloon angioplasty is the conventional treatment for ISR and has been the most-used strategy in the pre-DES era, especially in centers without ICB. This treatment is technically simple and has few complications, but the recurrence of ISR is around 50% and the need for new revascularization procedures 14%-46%. These figures are especially high in type III-IV ISR, diabetics, saphenous vein bypass grafts, and when ISR is early (before 4 months after implantation of the stent).[67-69]

Initially, the implantation of a new stent for ISR was restricted to the patients with suboptimal outcomes or complications after the failure of other devices, but subsequently the possibility of electively implanting a new stent was evaluated. Most data on the treatment of ISR via stenting intra-stent have been obtained from the RIBS study, where 450 patients with ISR were randomized to receive intra-stent stenting or balloon angioplasty. There were no significant differences in restenosis rate and need for new procedures, but this study has demonstrated that elective implantation of an intra-stent stent is safe and is even associated with a smaller rate of periprocedural events than balloon dilatation.[70] This is important at present, when it is beginning to appear that DES can be the best treatment for ISR after the implantation of a standard stent.

Plaque Modification, Reduction, and Elimination Devices (Table 4)

Directional atherectomy (DA) yields some immediate favorable angiographic results, but in randomized studies a reduction in the rate of restenosis and new revascularization procedures has not been demonstrated. Furthermore, DA can increase periprocedural complications.[71] It has been demonstrated in the AMIGO and DESIRE studies that DA before the implantation of a stent neither reduces restenosis nor the need for new revascularization procedures. In most studies, DA was used with a relatively conservative strategy, but some later works have shown that a more aggressive strategy not only produces better immediate results, but also a lower rate of restenosis.[72] However, the use of DA is currently infrequent. Regarding ISR, DA is able to eliminate intra-stent neointimal tissue and obtain greater immediate luminal gain than balloon angioplasty. However, the relatively high rate of complications in *de novo* lesions and the possibility of stent strut deterioration have impeded the use of this device in the treatment of ISR.

In the treatment of *de novo* lesions, rotational atherectomy (RA) achieves better initial outcomes than balloon angioplasty in calcified lesions, and is especially useful in lesions which cannot be dilatated with balloon. In some studies, such as ERBAC and COBRA, RA obtained a higher initial angiographic success rate than balloon angioplasty in complex lesions, but did not reduce restenosis.[73,74] It is currently used in selected cases, especially when dilatation with balloon cannot be done and in severely calcified lesions where it can be predicted that a good outcome is unachievable. Currently, in the DES era, this technique still has its role, because it facilitates the implantation and correct expansion of DES in these types of lesions. In the treatment of ISR, RA acts by eliminating neointimal tissue and, if it is followed by expansion with balloon, an additional expansion of the stent is done and neointimal tissue is extruded outside the stent. Although ISR RA is associated with a high initial angiographic success rate and few complications,[75] contradictory results have been obtained in 2 randomized studies. In the ROSTER study (n=150), the IRS clinical recurrence rate was significantly lower with RA.[76] However, in the ARTIST study (n=298), the angiographic ISR recurrence rate was higher with RA.[77] Although it has been argued that the failure of RA in the ARTIST study could be due to an overly conservative strategy (low pressures used to expand the balloon after RA and absence of controls via intravascular ultrasound), the use of ISR RA is currently very limited.

In several randomized studies cutting balloon (CB) has been compared to standard balloon. In some studies, the results were favorable with CB, but in the majority there was no reduction in the rate of new revascularization procedures.[78-80] In the REDUCE-3 study, the benefit of CB was evaluated in comparison with standard balloon before the implantation of a stent; although the rate of angiographic restenosis was lower with CB, the incidence of new revascularization procedures was not significantly reduced.[81] The theoretical advantages of CB in the treatment of ISR are twofold. In the first place, the small incisions can facilitate the extrusion of neointimal tissue outside the stent lumen. Second, they can help prevent "watermelon seeding" (displacement of the balloon during inflation), a phenomenon that can cause damage to the segments of the vessel adjacent to the stent. This advantage means that CB is especially used when ICB is applied to avoid the phenomenon of geographic miss and thus the appearance of edge restenosis. In several observational studies favorable outcomes[82] have been obtained, but randomized studies have not demonstrated a significant reduction in the recurrence of ISR.[83-86]

In a randomized pilot study, the recurrence of ISR was less frequent with CB (4% vs 28%; *P*=.047).[83] In another randomized pilot study, a lower ISR recurrence rate was obtained in the group treated with CB, although without significant differences (12% vs 20%; *P*=NS).[84] However, in other studies with more patients, CB was not better than standard balloon. In the RESCUT study, there was a trend toward less need for implanting a new stent due to dissection in the group treated with CB, (4% vs 8%; *P*=.07), but the IRS recurrence rate (29% vs 31%) and the new procedure rate (17% vs 16%) was similar.[85] In the REDUCE II study, the recurrence of ISR was also similar with both treatments (24% vs 22%).

Exciser laser has been evaluated in several randomized studies,[73,87,88] but in addition to failing to reduce the incidence of new revascularization procedures it was associated with an increase in periprocedural infarction. When treating ISR, the laser produces an additional expansion of the stent, and ablation and extrusion of neointimal tissue. The preliminary studies showed the efficacy and safety of this device but the recurrence of ISR is high, with no difference in benefit when compared to balloon angioplasty.[89]

The application of ultrasound can reduce cell viability, and the production of cavitations through the use of high energy can inhibit the migration and adhesion of smooth muscle cells in vivo. Ultrasound can also directly inhibit the proliferation of smooth muscle cells in vivo. In some animal studies, the use of intravascular ultrasound reduced neointimal hyperplasia after the implantation of stents.[90] However, in humans, ultrasound has not been effective in de novo lesions. In the Euro-SPAH study, 403 stented patients were randomized to receive treatment or not with intraves-

sel ultrasonography, without there being any improvement in clinical outcomes or restenosis.[91]

Intracoronary Brachytherapy

Ionized radiation inhibits cell proliferation and has been applied to several pathological tumorous and non-tumorous processes. Given the parallels between neointimal hyperplasia in restenosis (especially in ISR) and tumor processes, the use of radioactive isotopes in the prevention of restenosis was relatively prompt. Local application of radiation therapy has an antiproliferative and antimigratory effect on the smooth muscle cells, and in this way reduces neointimal hyperplasia.[92] The positive effect of ICB on vessel remodelling also helps to reduce restenosis.[93]

There are 2 ways to apply ICB: via a catheter and via radioactive stents, with radiation therapy via catheter being the standard technique. Two different types are available for ICB: β and γ (Table 6). Basically, β is high energy/low tissue penetration and thus does not require additional radiation protection measures. In contrast, γ has low energy, but greater tissue penetration and a longer half-life, and exposes the operator to significantly higher radiation than β. Compared to γ, β could, in theory, be less effective due to lower penetration of the vessel wall and less homogeneous exposure, but in clinical studies with ICB β has obtained similar effectiveness to γ. In view of the fact that its application is less problematical, it is the type normally used in centers that offer ICB.

Although ICB has been used particularly in ISR, it was originally applied in de novo lesions.[94-100] It inhibits neointimal hyperplasia in such lesions, but is not effective (Table 4). This is basically due to the edge effect and late thrombosis which are more evident when a coronary stent has been implanted. In the BETA-CATH study, 1455 patients with de novo lesions were randomized to receive β ICB or placebo after standard treatment (a stent was implanted in ≈50% of the patients); the rate of events was not statistically significant (15.6% vs 17.4%, respectively). In the BRIDGE study, 112 patients were treated with stenting and randomized to receive ICB or not. Restenosis and the need for new revascularization procedures in the target segment were more frequent in the patients treated with ICB.[96] In a study conducted in our center with 92 diabetic patients, ICB after stent implantation was associated with a significant reduction in ISR, but the rate of new revascularization procedures was similar and the death or infarction rate was higher in the ICB group.[100]

Intracoronary brachytherapy was the first useful approach to the treatment of ISR, and until the development of DES it was the most effective[98,101-108] (Table 7).

γ radiation was used in the GAMMA-I and WRIST studies which randomized 252 and 130 patients with ISR, respectively, to receive treatment with ^{192}Ir or placebo.[101,103] In the SCRIPPS study, 55 patients were randomized to receive ^{192}Ir or placebo after the implantation of a stent for the treatment of restenotic lesions, 62% of which were ISR.[102] A significantly lower ISR recurrence rate was found in these three studies than that found with ICB. Subsequently, studies in subgroups of patients have been carried out (long lesions, saphenous vein bypass grafts, etc.) with similar results.[105]

Most of the studies with β radiation came after those with γ radiation. In the Beta-WRIST study, with 90-yttrium, a control group was used with the same characteristics as the original WRIST study,[92] with similar results.[106] In the START study,[107] the ISR recurrence rate was significantly lower in the patients treated with ^{90}Sr. In the INHIBIT study, with 332 patients, ICB also reduced the recurrence of ISR.[104] Finally, in the PREVENT study, although most of the patients had de novo lesions, 24% had ISR. There was a reduction in the recurrence of ISR with ICB.[98]

One of the limitations of ICB in the treatment of ISR is the partial loss of benefit over time. In the GAMMA-1 study, for example, the reduction in the rate of revascularization of the target lesion in the group of patients treated with balloon angioplasty only was 34%, 23%, 14%, and 11% at 1, 2, 3, and 4 years, respectively. At 5-year follow-up in the SCRIPPS study, the number of new procedures between 1 and 5 years was also greater in the ICB group.[106]

Some studies are under way which randomly compare DES and ICB for ISR. In 1 study, 97 diffuse ISR were randomized to receive treatment with the Cypher

TABLE 6. **Differences Between β and γ Radiation in Intracoronary Brachytherapy**

	β	γ
Isotopes	^{32}P, ^{90}Sr/AND, 1^{88}Re, ^{133}Xe, ^{166}Ho	^{192}Ir, ^{125}I, ^{145}Sm, ^{103}Pd
Degree of energy	High	Low
Tissue penetration	Low	High
Radiation protection	Simple	Complicated
Half-life	Short	Long
Edge effect	Yes	No

TABLE 7. **Randomized Studies Evaluating Intracoronary Brachytherapy and Other Techniques in the Treatment of in-Stent Restenosis***

Study	n	Restenosis, %		Revascularization, %	
		Balloon	BCB	Balloon	ICB
β ICB					
INHIBIT	332	52	26†	30	19†
START	476	45	29†	24	16†
γ ICB					
WRIST	130	60	22†	68	26†
Long-WRIST	120	75	45/38†	62	39/20†
SVG-WRIST	120	44	21†	57	17†
GAMMA-1	252	51	22†	42	24†
SCRIPPS	55	54	17	45	12
Rotational atherectomy					
ROSTER	150	42	56	45	32†
ARTIST	298	51	65†	31	39
Cutting balloon					
Chevalier et al	45			20	12
Mizobe et al	51	28	4†	28	4†
RESCUT	428	31	30	16	17
REDUCE-2	416	22	24	22	20
Montorsi	50	36	4†	40	13†
In-stent stenting					
RIBS	450	39	38	24	20

*ICB indicates intracoronary brachytherapy.
†$P<.05$

stent or ICB (^{188}Re). Both the recurrence of ISR (2% vs 27%; $P=.003$) and the rate of events (4% vs 13%; $P=.145$) favored the Cypher stent (Park SJ. Scientific sessions of the American Heart Association, 2004). The SISR study compared the Cypher stent and ICB (β or γ) in 400 patients with ISR. Its results will be published in 2005. In the TAXUS-V-ISR study, 488 patients with ISR were randomized to receive the Taxus stent or β ICB. Despite these studies, the emergence of DES as an effective strategy in the treatment of ISR, as well as the expected reduction in the incidence of ISR with the use of DES in de novo lesions, has meant that devices for the application of ICB which were available in this context have recently been withdrawn from the market.

The problems associated with ICB in the treatment of de novo lesions and ISR are now described in greater detail:

– Local side effects: *1)* ICB delays stent endothelialization, which can increase the risk of late thrombosis. In the first series, the risk was >5%, but was especially associated with early withdrawal (30 days) of thienopyridines and implantation of a new stent.[100] The establishment of prolonged treatment with aspirin and thienopyridines has succeeded in strongly reducing this complication; *2)* second, ICB can be associated with positive remodeling and late stent malapposition which can also favor late thrombosis[109]; *3)* third, ICB can be associated with restenosis in the edges or extremes of the irradiated area (edge or candy wrapper effect). Regarding the physiopathology of this phenomenon, there is the possibility of vascular damage caused at the ends of the irradiated segment and heterogeneity regarding the dose received, with a smaller dose being applied at the ends (geographic miss)[110]; and *4)* finally, due to multiple factors (tortuosity and modifications in vessel caliber, source movements during the cardiac cycle, etc), the radiation dose administered is not homogeneous over the entire segment treated, which can contribute to partially limiting the antirrestenotic effect of ICB.

– Logistic limitations: the use of ICB requires the collaboration and coordination of personnel not associated with catheterization laboratories (radiology service, etc). On the other hand, when γ radiation is applied the catheterization laboratory must be properly equipped. As a result of these obstacles, very few centers have carried out this technique.

– Elimination versus delay in restenosis. In view of the fact that radiation therapy depopulates smooth muscle cells, theoretically a greater number of cell divisions is all that is required (and, thus, more time) to finally produce the same degree of intimal proliferation. In fact, this is not the case, since the restenosis process may be finished before this occurs. What in fact occurs over the years is a partial loss of the benefit obtained with ICB. Some studies have

found a significant reduction in minimum lumen diameter and an increase in the number of new revascularization procedures between 6 months and 2-3 years.[102,103]

– Costs. Intracoronary brachytherapy involves a significant increase in PCI costs, not only due to the price of the material used, but also because of the costs involved in organizing the infrastructure needed to carry out this technique. Although part of this cost is compensated by the reduction in the need for new revascularization procedures in the target vessel, the final cost continues to be higher than that of standard techniques.

All these limitations have led to the use of ICB being minimal, even in the treatment of ISR. This meant that, together with the advent of antiproliferative DES, the ICB devices available have been withdrawn from the market by the manufacturers and, thus, from a practical standpoint, ICB has disappeared from the therapeutic armamentarium of the interventional cardiologist, at least in our setting.

The use of radioactive stents reduces instent neointimal hyperplasia compared to standard stents. However, the edge restenosis rate is very high (≥40%) since, by definition, the irradiated area (the stent) does not succeed in covering the entire area damaged by the balloon.[111] This has impeded them from being used in clinical practice.

CONCLUSIONS AND FUTURE PROSPECTS

The Cypher and Taxus stents have demonstrated significant reductions in restenosis and the need for new revascularization procedures. This benefit is maintained for at least 3 years. Nevertheless, their costs need to reduce in order to allow a more diffuse use in all types of lesions. On the other hand, if the results from the studies comparing DES and surgery in patients with multivessel disease show that DES are better, this fact will probably reduce the number of patients undergoing surgical revascularization procedures.

Other DES have been recently marketed or will be shortly, but their effectiveness has to be demonstrated in randomized equivalence studies in comparison with the Cypher or Taxus stents. In the near future, DES with polymers or even with biodegradable scaffolds will be evaluated regarding their capacity to minimize the risk of late stent thrombosis and eliminate the probability of allergic reactions or late hypersensitivity occurring. Some studies are under way investigating stents coated with monoclonal antibodies that attract endothelial precursor cells to accelerate stent endothelialization. Other approaches include stents with a combination of drugs (antiproliferative agents and drugs that improve endothelial function, etc). On the other hand, gene therapy is also under evaluation for preventing restenosis, although the evidence regarding its effectiveness and potential clinical application is probably still distant.

Although ICB has proven to be more effective than balloon angioplasty in ISR, its use is minimal. The recent launch of DES has led to fewer patients being treated with ICB in the last 2 years. Thus, the manufacturers have decided to withdraw ICB devices and, from a practical standpoint, ICB has disappeared from our setting.

Concerning the remaining devices, CB and RA can still have a role in the DES era since they facilitate the implantation of these stents in especially complex and/or calcified lesions.

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REFERENCES

1. Roubin GS, Douglas JS Jr, King SB 3rd, Lin SF, Hutchison N, Thomas RG, et al. Influence of balloon size on initial success, acute complications, and restenosis after percutaneous transluminal coronary angioplasty: a prospective randomized study. Circulation. 1988;78:557-65.
2. Kuntz RE, Baim DS. Defining coronary restenosis. Newer clinical and angiographic paradigms. Circulation. 1993;88:1310-23.
3. Rodríguez AE, Santaera O, Larribau M, Fernández M, Sarmiento R, Pérez Balino, et al. Coronary stenting decreases restenosis in lesions with early loss in luminal diameter 24 hours after successful PTCA. Circulation. 1995;91:1397-402.
4. Knight CJ, Curzen NP, Groves PH, Patel DJ, Goodall AH, Wright C, et al. Stent implantation reduces restenosis in patients with suboptimal results following coronary angioplasty. Eur Heart J. 1999;20:1783-90.
5. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med. 1994; 331:489-95.
6. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med. 1994;331:496-501.
7. Betriu A, Masotti M, Serra A, Alonso J, Fernández-Avilés F, Gimeno F, et al. Randomized comparison of coronary stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions (START): a four-year follow-up. J Am Coll Cardiol. 1999;34:1498-506.
8. Moreno R, Fernández C, Alfonso F, Hernández RA, Pérez MJ, Escaned J, et al. Coronary stenting in small vessels. A meta-analysis from eleven randomized trials. J Am Coll Cardiol. 2004;43:1964-72.
9. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance.

Circulation. 1995;91:1676-88.
10. Gregorini L, Marco J, Fajadet J, Bernies M, Cassagneau B, Brunel P, et al. Ticlopidine and aspirin pretreatment reduces coagulation and platelet activation during coronary dilation procedures. J Am Coll Cardiol. 1997;29:13-20.
11. Bauters C, Hubert E, Prat A, Bougrimi K, van Belle E, McFadden EP, et al. Predictors of restenosis after coronary stent implantation. J Am Coll Cardiol. 1998;31:1291-8.
12. Dussaillant GR, Mintz GS, Pichard AD, Kent KM, Satler LF, Popma JJ, et al. Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. J Am Coll Cardiol. 1995;26:720-4.
13. Castagna MT, Mintz GS, Leiboff BO, Ahmed JM, Mehran R, Satler LF, et al. The contribution of "mechanical" problems to in-stent restenosis: An intravascular ultrasonographic analysis of 1090 consecutive in-stent restenosis lesions. Am Heart J. 2001; 142:970-4.
14. Serruys PW, Foley DP, Jackson G, Bonnier H, Macaya C, Vrolix M, et al. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. Eur Heart J. 1999;20: 58-69.
15. Holmes DR Jr, Savage M, laBlanche JM, Grip L, Serruys PW, Fitzgerald P, et al. Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. Circulation. 2002; 106:1243-50.
16. Gregory CR, Huie P, Billingham ME, Morris RE. Rapamycin inhibits arterial intimal thickening caused by both alloimmune and mechanical injury. Its effect on cellular, growth factor, and cytokine response in injured vessels. Transplantation. 1993;55: 1409-18.
17. Poon M, Marx SO, Gallo R, Badimon JJ, Taubman MB, Markx AR. Rapamycin inhibits vascular smooth muscle cell migration. J Clin Invest. 1996;98:2277-83.
18. Herdeg C, Oberhoff M, Baumbach A, Blattner A, Axel DI, Schroder S, et al. Local paclitaxel delivery for the prevention of restenosis: biological effects and efficacy in vivo. J Am Coll Cardiol. 2000;35:1969-76.
19. Morice MC, Serruys PW, Sousa JE, Fajadet J, ban Hayashi E, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002;346:1773-80.
20. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315-23.
21. Schofer J, Schluter M, Gershlick AH, Wijns W, García E, Schampaert E, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet. 2003;362:1093-9.
22. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol. 2004;43:1110-5.
23. Ardissino D, Cavallini C, Bramucci E, Indolfi C, Marzocchi A, Manari A, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. JAMA. 2004;292:2727-34.
24. Alfonso F, Ángel J, Cequier A, Augé JM, López Mínguez JR, Bethencourt A, et al. Results of the restenosis intrastent: balloon angioplasty versus rapamycin-eluting stent implantation randomized study. J Am Coll Cardiol. 2005;45:A83.
25. Kastrati A, Mehilli J, Von Beckerath N, Dibra A, Hausleiter J, Pache J, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA. 2005;293:165-71.
26. Jiménez-Quevedo P, Sabaté M, Angiolillo DJ, Gómez-Hospital JA, Hernández-Antolín R, Goicolea J, et al. The diabetes and sirolimus-eluting stent diabetes trial: one-year clinical results. J Am Coll Cardiol. 2005;45:A70.
27. Heldman AW, Cheng L, Jenkins GM, Heller PF, Kim DW, Ware M Jr, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation. 2001;103:2289-95.
28. Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med. 2003;348:1537-45.
29. Lansky AJ, Costa RA, Mintz GS, Tsuchiya Y, Midei M, Cox DA, et al. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER clinical trial. Circulation. 2004;109:1948-54.
30. Gershlick A, De Scheerder I, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C, et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaLUation of pacliTaxel Eluting Stent (ELUTES) trial. Circulation. 2004;109:487-93.
31. Grube E, Lansky A, Hauptmann KE, Di Mario C, di Sciascio G, Colombo A, et al. High-dose 7-hexanoyltaxol-eluting stent with polymer sleeves for coronary revascularization: one-year results from the SCORE randomized trial. J Am Coll Cardiol. 2004;44:1368-72.
32. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, et al. TAXUS I: six- and twelve-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.
33. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation. 2003;108:788-94.
34. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004; 350:221-31.
35. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR. Jr, Spanos V, et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. Circulation. 2004;109:1244-9.
36. Lemos PA, Saia F, Hofma SH, Daemen J, Ong AT, Arampatzis CA, et al. Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. J Am Coll Cardiol. 2004;43: 704-8.
37. Hoye A, Lemos PA, Arampatzis CA, Saia F, Tanabe K, Degertekin M, et al. Effectiveness of the sirolimus-eluting stent in the treatment of saphenous vein graft disease. J Invasive Cardiol. 2004;16:230-3.
38. Ge L, Iakovou I, Sangiorgi GM, Chieffo A, Melzi G, Matteo M, et al. Treatment of saphenous vein grafts lesions with drug-eluting stents: immediate and mid-term outcome. J Am Coll Cardiol. 2005;45:A25.
39. de Lezo JS, Medina A, Pan M, Delgado A, Segura J, Pavlovic D, et al. Rapamycin-eluting stents for the treatment of unprotected left main coronary disease. Am Heart J. 2004;148: 481-5.
40. Arampatzis CA, Lemos PA, Tanabe K, Hoye A, Degertekin M, Saia F, et al. Effectiveness of sirolimus-eluting stent for treatment of left main coronary artery disease. Am J Cardiol. 2003; 92:327-9.
41. Hoye A, Tanabe K, Lemos PA, Aoki J, Saia F, Arampatzis C, et al. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. J Am Coll Cardiol. 2004;43:1954-8.
42. Kahan BD. Efficacy of sirolimus compared with azathioprine

for reduction of acute renal allograft rejection: a randomised multicentre study: the Rapamune US Study Group. Lancet. 2000;356:194-202.
43. Brattstrom C, Wilczek H, Tyden G, Bottiger Y, Sawe J, Groth CG. Hyperlipidemia in renal transplant recipients treated with sirolimus (rapamycin). Transplantation. 1998;65:1272-4.
44. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol. 1993;20:1-15.
45. Babinska A, Markell MS, Salifu MO, Akoad M, Ehrlich YH, Kornecki E. Enhancement of human platelet aggregation and secretion induced by rapamycin. Nephrol Dial Transplant. 1998; 13:3153-9.
46. Moreno R, Fernández C, Hernández R, Alfonso F, Angiolillo DJ, Sabate M, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol. 2005;45:954-9.
47. Fajadet J, Morice MC, Bode C, Barragan P, Serruys PW, Wijns W, et al. Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents: three-year results of the RAVEL trial. Circulation. 2005;111:1040-4.
48. A Goy JJ, Stauffer JC, Siegenthaler M, Benoit A, Seydoux C. Prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXi trial. J Am Coll Cardiol. 2005;45:308-11.
49. Morice MC. The REALITY trial. Sesiones científicas del ACC, 2005 [uted 28/04/2005]. Available from: http://www.tctmd.com/display/expert/pdf/132178/CRDUS_REALITY.pdf
50. Windecker S. The SIRTAX trial. Sesiones científicas del ACC, 2005 [uted 28/04/2005]. Available from: http://www.tctmd.com/display/expert/pdf/129315/Windecker_F1215.pdf
51. Kastrati A. The ISAR-DIABETES trial. Sesiones científicas del ACC, 2005 [uted 28/04/2005]. Available from: http://www.tctmd.com/display/expert/pdf/135010/Kastrati_slsides.pdf
52. Suárez de Lezo J, Medina A, Pan M, Romero M, Delgado A, Segura J, et al. Drug-eluting stent for complex lesions: latest angiographic data from the randomized rapamycin versus paclitaxel CORPAL study. J Am Coll Cardiol. 2005;45:A75.
53. Oliva G, Espallargues M, Pons JM. Stents recubiertos de fármacos antiproliferativos: revisión sistemática del beneficio y estimación del impacto presupuestario. Rev Esp Cardiol. 2004;57: 617-28.
54. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation. 1999; 100:1872-8.
55. Kastrati A, Schomig A, Elezi S, Schuhlen H, Dirschinger J, Hadamitzky M, et al. Predictive factors of restenosis after coronary stent placement. J Am Coll Cardiol. 1997;30:1428-36.
56. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schuhlen H, Neumann FJ, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation. 2001;103:2816-21.
57. Koster R, Vieluf D, Kiehn M, Sommerauer M, Kahler J, Baldus S, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. Lancet. 2000;356:1895-7.
58. Sousa JE, Costa MA, Abizaid A, Sousa AG, Feres F, Mattos LA, et al. Sirolimus-eluting stent for the treatment of in-stent restenosis: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation. 2003; 107:24-7.
59. Tanabe K, Serruys PW, Grube E, Smits PC, Selbach G, Van der Giessen WJ, et al. TAXUS III Trial: in-stent restenosis treated with stent-based delivery of paclitaxel incorporated in a slow-release polymer formulation. Circulation. 2003;107: 559-64.
60. Degertekin M, Regar E, Tanabe K, Smits PC, Van der Giessen WJ, Carlier SG, et al. Sirolimus-eluting stent for treatment of complex in-stent restenosis: the first clinical experience. J Am Coll Cardiol. 2003;41:184-9.
61. Teirstein PS, Kao J, Bass TA, Costa MA, Yakubov S, Carter AJ, et al. Use of the sirolimus eluting BX velocity stent for failed brachytherapy in recurrant in-stent restenosis: the results of the SECURE Registry. J Am Coll Cardiol. 2003;41: A48.
62. Waksman R, Torguson R, Ajan AE, Cheneau E, Chan RC, Bass B, et al. Drug eluting stents versus repeat vascular brachytherapy for patients with recurrent of in-stent restenosis who failed radiation therapy. J Am Coll Cardiol. 2005;45: A44.
63. Lemos PA, Hoye A, Goedhart D, Arampatzis CA, Saia F, van der Giessen WJ, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. Circulation. 2004;109:1366-70.
64. Colombo A, Orlic D, Stankovic G, Corvaja N, Spanos V, Montorfano M, et al. Preliminary observations regarding angiographic pattern of restenosis after rapamycin-eluting stent implantation. Circulation. 2003;107:2178-80.
65. Kapoor S. The angiographic pattern of restenosis after paclitaxel-eluting stents. Am J Cardiol. 2003;92:L56.
66. Angiolillo DJ, Sabate M, Jiménez-Quevedo P, Alfonso F, Galván C, Fernández JM, et al. Intracoronary brachytherapy following drug-eluting stent failure. It's still not time to hang up the spikes! Cardiovasc Radiat Med. 2003;4:171-5.
67. Eltchaninoff H, Koning R, Tron C, Gupta V, Cribier A. Balloon angioplasty for the treatment of coronary in-stent restenosis: immediate results and 6-month angiographic recurrent restenosis rate. J Am Coll Cardiol. 1998;32:980-4.
68. Alfonso F, Pérez-Vizcayno MJ, Hernández R, Goicolea J, Fernández-Ortiz A, Escaned J, et al. Long-term outcome and determinants of event-free survival in patients treated with balloon angioplasty for in-stent restenosis. Am J Cardiol. 1999;83:1268-70.
69. Bossi I, Klersy C, Black AJ, Cortina R, Choussat R, Cassagneau B, et al. In-stent restenosis: long-term outcome and predictors of subsequent target lesion revascularization after repeat balloon angioplasty. J Am Coll Cardiol. 2000;35: 1569-76.
70. Alfonso F, Zueco J, Cequier A, Mantilla R, Bethencourt A, López-Minguez JR, et al. A randomized comparison of repeat stenting with balloon angioplasty in patients with in-stent restenosis. J Am Coll Cardiol. 2003;42:796-805.
71. Topol EJ, Leya F, Pinkerton CA, Whitlow PL, Hofling B, Simonton CA, et al. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. The CAVEAT Study Group. N Engl J Med. 1993;329: 221-7.
72. Simonton CA, Leon MB, Baim DS, Hinohara T, Kent KM, Bersin RM, et al. "Optimal" directional coronary atherectomy: final results of the Optimal Atherectomy Restenosis Study (OARS). Circulation. 1998;97:332-9.
73. Dill T, Dietz U, Hamm CW, Kuchler R, Rupprecht HJ, Haude M, et al. A randomized comparison of balloon angioplasty versus rotational atherectomy in complex coronary lesions (COBRA study). Eur Heart J. 2000;21:1759-66.
74. Reifart N, Vandormael M, Krajcar M, Gohring S, Preusler W, Schwarz F, et al. Randomized comparison of angioplasty of complex coronary lesions at a single center. Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison (ERBAC) Study. Circulation. 1997;96:91-8.
75. Moreno R, García E, Soriano J, Acosta J, Abeytua M. Long-term outcome of patients with proximal left anterior descending coronary artery in-stent restenosis treated with rotational atherectomy. Catheter Cardiovasc Interv. 2001;52:435-42.
76. Sharma SK, Kini A, Mehran R, Lansky A, Kobayashi Y,

Marmur JD. Randomized trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-stent Restenosis (ROSTER). Am Heart J. 2004;147:16-22.
77. Vom Dahl J, Dietz U, Haager PK, Silber S, Niccoli L, Buettner HJ, et al. Rotational atherectomy does not reduce recurrent in-stent restenosis: results of the angioplasty versus rotational atherectomy for treatment of diffuse in-stent restenosis trial (ARTIST). Circulation. 2002;105:583-8.
78. Mauri L, Bonan R, Weiner BH, Legrand V, Bassand JP, Popma JJ, et al. Cutting balloon angioplasty for the prevention of restenosis: results of the Cutting Balloon Global Randomized Trial. Am J Cardiol. 2002;90:1079-83.
79. Izumi M, Tsuchikane E, Funamoto M, Kobayashi T, Sumitsuji S, Otsuji S, et al. Final results of the CAPAS trial. Am Heart J. 2001;142:782-9.
80. Moris C, Bethencourt A, Gómez-Recio M, Bordes P, Augé J, Melgares R, et al. Angiographic follow-up of cutting balloon vs conventional balloon angioplasty: results of the CUBA study. J Am Coll Cardiol. 1998;31:A223.
81. Ozaki Y, Suzuki T, Yamaguchi T, Nakamura M, Kitayama M, Nishikawa H, et al. Can intravascular ultrasound guided cutting balloon angioplasty before stenting be a substitute for drug-eluting stents? Final results of the prospective randomized multicenter trial comparing cutting balloon with balloon angioplasty before stenting [Reduce-III]. J Am Coll Cardiol. 2004;43:A82.
82. Iijima R, Ikari Y, Anzai H, Nishida T, Tsunoda T, Nakamura M, et al. The impact of cutting balloon angioplasty for the treatment of diffuse in-stent restenosis. J Invasive Cardiol. 2003;15:427-31.
83. Chevalier B, Royer T, Guyon P, Glatt B. Treatment of in-stent restenosis: short and midterm results of a pilot randomized study between balloon and cutting balloon. J Am Coll Cardiol. 1999; 33:A62.
84. Mizobe M, Oohata K, Osada T. The efficacy of cutting balloon for in-stent restenosis compared with conventional balloon angioplasty. Circulation. 1999;100:I308.
85. Albiero R, Silber S, di Mario C, Cernigliaro C, Battaglia S, Reimers B, et al. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the restenosis cutting balloon evaluation trial (RESCUT). J Am Coll Cardiol. 2004;43:943-9.
86. Montorsi P, Galli S, Fabbiocchi F, Trabattoni D, Ravagnani PM, Bartorelli AL. Randomized trial of conventional balloon angioplasty versus cutting balloon for in-stent restenosis. Acute and 24-hour angiographic and intravascular ultrasound changes and long-term follow-up. Ital Heart J. 2004;5:271-9.
87. Stone GW, de Marchena E, Dageforde D, Foschi A, Muhlestein JB, McIvor M, et al. Prospective, randomized, multicenter comparison of laser-facilitated balloon angioplasty versus stand-alone balloon angioplasty in patients with obstructive coronary artery disease. The Laser Angioplasty Versus Angioplasty (LAVA) Trial Investigators. J Am Coll Cardiol. 1997;30:1714-21.
88. Appelman YE, Piek JJ, Strikwerda S, Tijssen JG, de Feyter PJ, David GK, et al. Randomised trial of excimer laser angioplasty versus balloon angioplasty for treatment of obstructive coronary artery disease. Lancet. 1996;347:79-84.
89. Koster R, Hamm CW, Seabra-Gomes R, Herrmann G, Sievert H, Macaya C, et al. Laser angioplasty of restenosed coronary stents: results of a multicenter surveillance trial. The Laser Angioplasty of Restenosed Stents (LARS) Investigators. J Am Coll Cardiol. 1999;34:25-32.
90. Fitzgerald PJ, Takagi A, Moore MP, Hayase M, Kolodgie FD, Corl D, et al. Intravascular sonotherapy decreases neointimal hyperplasia after stent implantation in swine. Circulation. 2001; 103:1828-31.
91. Serruys PW, Hoye A, Grollier G, Colombo A, Symons J, Mudra H. A european multi-center trial investigating the anti-restenotic effect of intravascular sonotherapy after stenting of de novo lesions (EUROSPAH: EUROpean Sonotherapy Prevention of Arterial Hyperplasia). Int J Cardiovasc Intervent. 2004;6:53-60.
92. Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J. Intracoronary irradiation markedly reduces restenosis after balloon angioplasty in a porcine model. J Am Coll Cardiol. 1994; 23:1491-8.
93. Cottin Y, Kollum M, Chan RC, Kim H, Bhargava B, Vodovotz Y, et al. Differential remodeling after balloon overstretch injury and either beta- or gamma-intracoronary radiation of porcine coronary arteries. Cardiovasc Radiat Med. 2001;2:75-82.
94. Condado JA, Waksman R, Gurdiel O, Espinosa R, González J, Burger B, et al. Long-term angiographic and clinical outcome after percutaneous transluminal coronary angioplasty and intracoronary radiation therapy in humans. Circulation. 1997;96:727-32.
95. Verin V, Urban P, Popowski Y, Schwager M, Nouet P, Dorsaz PA, et al. Feasibility of intracoronary beta-irradiation to reduce restenosis after balloon angioplasty. A clinical pilot study. Circulation. 1997;95:1138-44.
96. Serruys PW, Wijns W, Sianos G, de Scheerder I, van den Heuvel PA, Rutsch W, et al. Direct stenting versus direct stenting followed by centered beta-radiation with intravascular ultrasound-guided dosimetry and long-term anti-platelet treatment: results of a randomized trial: Beta-Radiation Investigation with Direct Stenting and Galileo in Europe (BRIDGE). J Am Coll Cardiol. 2004;44:528-37.
97. King SB 3rd, Williams DO, Chougule P, Klein JL, Waksman R, Hilstead R, et al. Endovascular beta-radiation to reduce restenosis after coronary balloon angioplasty: results of the beta energy restenosis trial (BERT). Circulation. 1998; 97:2025-30.
98. Raizner AE, Oesterle SN, Waksman R, Serruys PW, Colombo A, Lim YL, et al. Inhibition of restenosis with beta-emitting radiotherapy: report of the Proliferation Reduction with Vascular Energy Trial (PREVENT). Circulation. 2000;102:951-8.
99. Verin V, Popowski Y, De Bruyne B, Baumgart D, Sauerwein W, Lins M, et al. Endoluminal beta radiation therapy for the prevention of coronary restenosis after balloon angioplasty. The Dose-Finding study group. N Engl J Med. 2001;344:243-9.
100. Sabaté M, Pimentel G, Prieto C, Corral JM, Banuelos C, Angiolillo DJ, et al. Intracoronary brachytherapy after stenting de novo lesions in diabetic patients: results of a randomized intravascular ultrasound study. J Am Coll Cardiol. 2004; 44:520-7.
101. Leon MB, Teirstein PS, Moses JW, Tripuraneni P, Lansky AJ, Jani S, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med. 2001;344:250-6.
102. Teirstein PS, Massullo V, Jani S, Popma JJ, Mintz GS, Russo RJ, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. N Engl J Med. 1997;336:1697-703.
103. Waksman R, White RL, Chan RC, Bass BG, Geirlach L, Mintz GS, et al. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. Circulation. 2000;101:2165-71.
104. Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L. Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. Lancet. 2002;359:551-7.
105. Waksman R, Cheneau E, Ajani AE, White RL, Pinnow E, Torguson R, et al. Intracoronary radiation therapy improves the clinical and angiographic outcomes of diffuse in-stent restenotic lesions: results of the Washington Radiation for In-Stent Restenosis Trial for Long Lesions (Long WRIST) Studies. Circulation. 2003;107:1744-9.
106. Grise MA, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, et al. Five-year clinical follow-up after intracoronary radiation:

results of a randomized clinical trial. Circulation. 2002;105:2737-40.
107. Waksman R, Bhargava B, White L, Chan RC, Mehran R, Lansky AJ, et al. Intracoronary beta-radiation therapy inhibits recurrence of in-stent restenosis. Circulation. 2000;101:1895-8.
108. Popma JJ, Suntharalingam M, Lansky AJ, Heuser RR, Speiser B, Teirstein PS, et al. Randomized trial of $^{90}Sr/^{90}Y$ beta-radiation versus placebo control for treatment of in-stent restenosis. Circulation. 2002;106:1090-6.
109. Okura H, Lee DP, Lo S, Yeung AC, Honda Y, Waksman R, et al. Late incomplete apposition with excessive remodeling of the stented coronary artery following intravascular brachytherapy. Am J Cardiol. 2003;92:587-90.
110. Sabate M, Costa MA, Kozuma K, Kay IP, van der Giessen WJ, Coen VL, et al. Geographic miss: a cause of treatment failure in radio-oncology applied to intracoronary radiation therapy. Circulation. 2000;101:2467-71.
111. Albiero R, Nishida T, Adamian M, Amato A, Vaghetti M, Corvaja N, et al. Edge restenosis after implantation of high activity (32)P radioactive beta-emitting stents. Circulation. 2000;101:2454-7.