

Is Systematic Use of Drug-Eluting Stents Justified? Arguments Against

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Antiproliferative drug-eluting stents represent a miles tone in advances in interventional cardiology. The amount and quality of the scientific evidence now show these new stents to be highly effective in reducing neointimal proliferation, and hence the process of restenosis. Their clinical impact can be expected to become relevant in terms of both increased indications for angioplasty and the extent of stent usage. However, at this time the systematic use of drug-eluting stents for all patients is not considered justified, because of their limited availability, gaps in our knowledge of their safety, and because their unquestioned clinical benefits have been magnified by exaggerated reports of the clinical problem restenosis represents. Currently, the cost of these stents remains high, and the cost/benefit ratio for certain patients is unfavorable. For these reasons selective use of these new stents is considered more reasonable: they should be used only for those patients who will obtain, in absolute terms, the greatest clinical benefit.

Key words: *Stents. Drug-eluting stent. Sirolimus. Paclitaxel. Restenosis.*

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¿Está justificado el uso sistemático de *stents* con fármacos? Argumentos en contra

Los *stents* cubiertos de fármacos antiproliferativos (ST-F) están marcando un hito en el progreso de la cardiología intervencionista. Existe suficiente evidencia científica de calidad para poder asegurar que estos nuevos *stents* son muy efectivos para reducir la proliferación de la neoíntima y, por tanto, el proceso reestenótico. Su impacto clínico será relevante, tanto en la expansión de las indicaciones de angioplastia como en su grado de utilización. No obstante, en el momento actual, no consideramos que el uso sistemático de los *stents* cubiertos de fármacos esté justificado en todos los pacientes por su limitada disponibilidad, porque su seguridad todavía no se conoce bien y porque el beneficio clínico, que no se cuestiona, está magnificado, especialmente al sobredimensionar el problema clínico de la reestenosis. Por último, el coste económico actual de estos *stents* es muy elevado y la relación coste/beneficio en algunos pacientes no parece favorable. Por todo ello, y en el momento actual, creemos que es más razonable un uso selectivo de estos nuevos *stents*, implantándolos en los pacientes que en términos absolutos vayan a obtener un mayor beneficio clínico.

Palabras clave: *Stents. Stents liberadores de fármacos. Sirolimus. Paclitaxel. Reestenosis.*

THE MILESTONES

In the history of cardiology a number of events stand out that have had great impact and have marked the beginning of a new stage in the development of this field. These events are rightly called milestones. When Andreas Grüntzing first ventured, on September 16, 1977, to use a balloon device to dilate a stenosed

coronary artery in a young patient with angina, he could not foresee that his feat would lead to the development of interventional cardiology. Another important milestone in cardiology had taken place previously, when René Favaloro performed the first aortocoronary saphenous vein bypass graft.

CORONARY STENTING AND THE RESTENOSIS PROBLEM

The relatively brief history of interventional cardiology has also been marked by significant events. One such episode was the development and introduction of

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the coronary stent, particularly once the benefits of this device were reported in the BENESTENT and STRESS clinical trials.^{1,2}

Later, after more than 10 unsuccessful years during which different treatments were tried to curtail the restenosis problem, a mechanical strategy was found that reduced the restenosis rate by more than 10 percent. Within a few years this made stenting the standard treatment in coronary angioplasty procedures.³ Unfortunately, stents prevent only one element of restenosis: elastic recoil of the arterial wall after balloon dilation. Stents cannot prevent, and in some cases can actually exacerbate, neointimal proliferation, another important mechanism of restenosis. In fact, in some patients such as those with diabetes or unfavorable anatomical features such as long lesions located in the anterior descending artery, in small-caliber vessels or in a saphenous vein bypass graft, the rate of restenosis after stent implantation is as high as 30% or 40%—figures that make therapy with percutaneous intervention unattractive.

Two strategies have been tested to prevent or minimize restenosis problems: intracoronary brachytherapy and antiproliferative drug-eluting stents (DES). Although the two strategies differ widely, they share the same purpose: to inhibit neointimal proliferation after coronary angioplasty, which is the common pathophysiological substrate of in-stent restenosis. Intracoronary brachytherapy⁴ has been shown effective, but its complex regulatory and surgical processes impose severe limitations on its use.

DRUG-ELUTING STENTS: CLINICAL STUDIES

No such limitations have been imposed on the other strategy, DES. Currently available technology makes it possible to incorporate into conventional stents (made of stainless steel) a variety of substances such as polymers and drugs. After the stent is in place, the vascular wall becomes impregnated with the drug, whose pharmacokinetics—release rate and concentration—are modulated by the polymer. Once favorable results had been obtained in studies with experimental animals with regard to bioavailability and antiproliferative effect, clinical trials were begun. Initially observational in nature (first-in-man studies), these trials yielded favorable results when rapamycin⁵ and paclitaxel were used. Subsequent randomized clinical trials carried out with these drugs have included the RAVEL, SIRIUS, ASPECT, and TAXUS studies.

The RAVEL study⁶ was the first randomized clinical trial with DES, and included 238 patients with uncomplicated de novo lesions. After 9 months of follow-up there were no cases of binary angiographic restenosis (stenosis >50%) in the group of 120 patients who received a rapamycin-eluting stent, whereas 32

(27%) patients in the control group developed restenosis. For a brief period it was believed that the last battle against restenosis had been won, and enthusiasm within the cardiology community, particularly among interventional cardiologists, ran high. A number of editorials were published, and one of them, which appeared in *REVISTA ESPAÑOLA DE CARDIOLOGÍA*,⁷ spoke of restenosis as a “nightmare from the past.” However, the actual situation soon became apparent: restenosis decreased considerably, but did not disappear. Somewhat later the results of the SIRIUS study in the USA were published.⁸ This trial tested rapamycin-eluting stents and enrolled more than 1000 patients, but their lesions were complicated. In the control group the incidence of restenosis was high at 36%, in comparison to 9% in the DES group. In the subgroup of patients with diabetes, the rate of restenosis despite rapamycin was relatively high, approaching 18%. The most recent of the randomized clinical trials with rapamycin was the European SIRIUS study,⁹ with 350 patients who had complicated lesions. Again there was a significant reduction in restenosis from 43% in the control group to 6% in the rapamycin group. Several randomized clinical trials have also been done with paclitaxel. The TAXUS II¹⁰ study involved 558 patients with uncomplicated *de novo* lesions, and the rates of restenosis were 20% in the control group and 7% in the paclitaxel group. The ASPECT¹¹ study, with 177 patients, reported 4% restenosis as compared to 27% in the control group. The results of the TAXUS IV study,¹² which was similar to the USA SIRIUS study in size, patient profile and type of lesions treated, were recently published, and the results were again favorable to paclitaxel-eluting stents, with a restenosis rate of 8% versus 27% in the control group.¹²

DRUG-ELUTING STENTS IN THE REAL WORLD: OBSERVATIONAL STUDIES AND REGISTRIES

Although DES have not obviated the restenosis problem, available scientific evidence affirms that these new devices are highly effective in reducing neointimal proliferation and thus the process of restenosis, at least in lesions with a low- or moderate-level risk of restenosis investigated to date. The new stents have thus received official approval for clinical use in most of the world, and a consequence of this approval has been the appearance of nonrandomized studies such as the two which appear in this issue of *REVISTA ESPAÑOLA DE CARDIOLOGÍA*,^{13,14} and the RESEARCH registry,¹⁵ also published in 2004 in the journal *Circulation*.

The 2 studies in this issue of the journal have the same aim: to fill the void regarding an issue that randomized multicenter trials have yet to address, i.e.,

the benefits of rapamycin-eluting stents in patients with complex lesions. The studies were done at a single center with observational designs and no control group, and both involved consecutive patients with lesions involving a very high risk of restenosis. Both studies report similar clinical results and conclusions; however, certain differences are worth noting.

The study by de la Torre et al¹³ included 100 patients over a period of 6 months, a sample that represented 28% of all patients treated. The follow-up measures were precarious, consisting of a telephone survey in a study that reported clinical results only. Mean follow-up time was 8.5 ± 2 months, and the authors report a very high rate (94%) of survival free from major clinical events (death, myocardial infarction or need for revascularization). The limitations of this study are all the more relevant if we consider the characteristics of the patients and the lesions that were treated.

The study by Ruiz-Nodar et al¹⁴ involved a smaller number of patients (57) but was more selective in that it included only patients at high risk. In fact, 47% of their patients had diabetes. This study is also superior in methodological terms as it included angiographic documentation of the lesions. The rates of angiographically confirmed restenosis for this special cohort of patients was low at 8%, and the rate of major clinical events after a mean follow-up period of 8.7 ± 3.1 months was 7%, as in the study by de la Torre et al.

The RESEARCH registry (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital)¹⁵ is a registry that includes all patients with de novo lesions who were treated in an unrestricted approach with a rapamycin-eluting stent for 6 months at the Thoraxcenter in Rotterdam, The Netherlands. The characteristics of the 508 patients, the lesions treated, and the clinical results after one year of follow-up were compared with a "historical" cohort of 450 patients treated with a conventional stent during the period immediately before the registry was begun. Among patients in the RESEARCH registry the incidence of multivessel disease was higher and lesions were more complex than in patients treated with a conventional stent. After one year of follow-up, the cumulative incidence of major clinical events was 9.7% in the rapamycin group, and 14.8% in the conventional stent group ($P=.008$). This benefit resulted exclusively from the lower need for repeat revascularization for restenosis (3.7% vs 10.9%, respectively; $P<.001$).

CLINICAL IMPLICATIONS OF THE NEW DRUG-ELUTING STENTS: ACTUAL USE

Fortunately, we now face a new milestone in interventional cardiology. The low rates of restenosis

attained with these stents have relevant clinical implications, the most important of which is perhaps the increasing number of indications for angioplasty in patients with more widespread and severe coronary artery disease. A further issue, which comprises the main topic of this set of Controversy articles, is whether these stents should be used for all patients in general. Note that the question has been framed in the affirmative: Is the systematic use of drug-eluting stents justified? However, in view of the interrogative manner in which the issue is framed, and because I have been asked to take sides against the spread of the use of these devices—at least for now—I will offer some arguments below.

The systematic use of DES is not justified, because of limitations in their availability and safety. Their benefits must be judged with caution, and their cost remains high. Indeed, for some patients the cost/benefit ratio seems to be unfavorable.

Availability

Coronary stents cannot be implanted in 100% of the lesions we dilate. This is generally because of anatomical features that impede access to the vessel and implantation of a metallic mesh, as is the case in calcified or tortuous vessels. Fortunately stent design has improved substantially, and despite the fact that they are made of metal, it is now possible to access nearly 90% of the lesions that have been dilated.

Only 2 DES stents are currently available for clinical use: the Cypher device (Johnson & Johnson, Cordis), which is coated with rapamycin and was developed from the "Velocity" stent platform, and the paclitaxel-coated Taxus device (Boston Scientific), developed from the "Express" stent platform. Design constraints are imposed by the use of metal for these stent platforms, as at the current time they are neither the thinnest nor the most flexible. Their use is therefore limited to coronary vessels that fulfill certain anatomical criteria. In some studies including one published in this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA,¹⁴ an attempt to implant a Cypher stent failed, whereas a stent that was not coated with a drug but was more flexible was placed successfully.

In addition, the available lengths and diameters of DES are limited. For example, diameters larger than 3.0 or 3.5 mm are not available, and the use of drug-eluting stents is therefore inadvisable for vessels larger than 3.5 mm in diameter. Diameters narrower than 2 mm are likewise unavailable for smaller vessels. The limited range of sizes means these stents cannot be used for up to 20% of all lesions treated. The RESEARCH registry notes that no rapamycin-coated stents were used in 28% of the patients, usually because of inappropriate anatomy for the use of a Cypher DES.

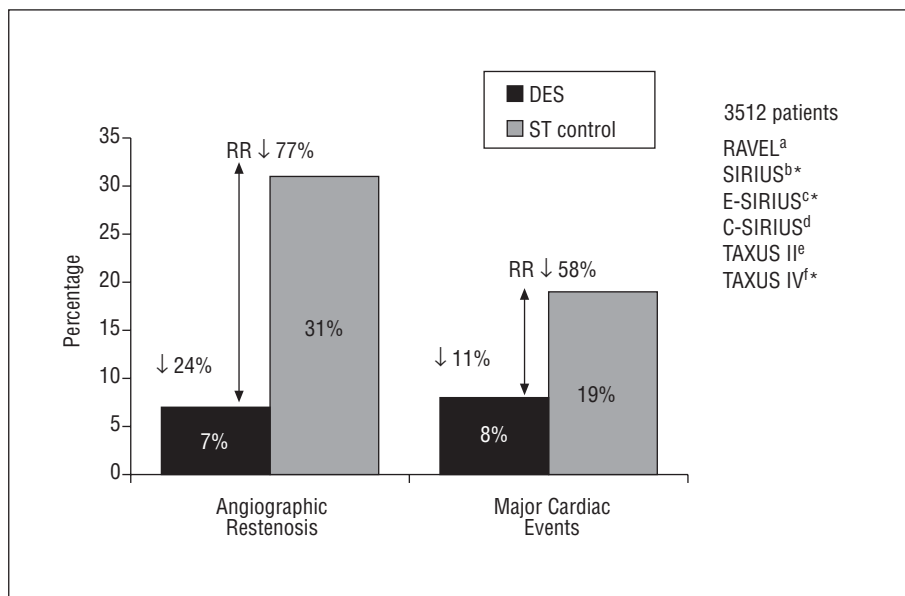


Fig. 1. Analysis of 3512 patients included in 6 randomized trials of drug-eluting stents. Rapamycin, RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS. Paclitaxel: TAXUS II and TAXUS IV. DES indicates drug-eluting stent group; ST-control, conventional stent group; RR, relative risk. *Main aim of the study was to report clinical results only. ^aNew England Journal of Medicine, 2002; ^bThe Lancet, 2003; ^cCirculation, 2003; ^dACC, 2003; ^eCirculation, 2003; ^fNew England Journal of Medicine, 2004.

Safety

The long-term outcomes with these new stents are unknown. The longest follow-up period reported to date is 2 years,⁵ and new clinical events ascribable to DES seem unlikely beyond this period. Although aneurysms and incomplete apposition between the stent and the vessel wall may be problems associated with these stents, they do not appear to be relevant from a clinical viewpoint. However, the potential problem of late occlusion of these new stents deserves mention.¹⁶ Patients treated with intracoronary brachytherapy are at high risk (up to 10%) for late thrombotic occlusion.⁴ This has been attributed to a delay in the process of postangioplasty neointimalization and incomplete apposition between the stent and the vessel wall. Both processes arise from the effective inhibition, induced by irradiation, of neointimal proliferation. Prolonged treatment (for at least one year) with clopidogrel has minimized this late complication of brachytherapy.⁴

The mechanism of action of DES bears certain similarities to that of brachytherapy. As a result, clinical studies with these new stents have always recommended extending clopidogrel treatment for longer than the one-month period habitually used for patients who receive a conventional stent. This treatment recommendation is based on empirical reasoning rather than scientific evidence, which is lacking. We do not know how long these patients should take clopidogrel; current regimens range from 3 months to indefinitely. In any case a problem does appear to exist: patients who receive an DES are exposed to a higher risk of late thrombotic occlusion. In the study by de la Torre et al¹³ two occlusions

occurred during the first month of follow-up, and in the study by Ruiz-Nodar et al¹⁴ two late occlusions were detected 3 and 7 months after the procedure. Other groups¹⁶ have also reported this problem.

Benefits

The benefits of these new stents should be evaluated within an appropriate context, i.e., with regard to their clinical benefits. In evaluating the effectiveness of a stent coated with an antiproliferative drug, the most suitable parameters of effectiveness should be used. For example, the degree of neointimal proliferation during follow-up should be measured with quantitative angiographic methods, or better still, with intravascular ultrasound. The clinical benefits, if the efficiency of these new stents is to be compared to that of conventional stents, should be evaluated with clinical events as the main outcome measure.

The randomized clinical trials analyzed here^{6,8-11} involved a total of 3512 patients (Figure 1). When the results are expressed as the binary restenosis rate, they illustrate a marked reduction in restenosis from 31% to 7% in patients who received an DES, with an absolute reduction of 24% and a relative reduction of 77%. However, when the anatomical problem of restenosis is considered within the clinical setting and the results are expressed as cardiac events, the benefit still appears but is much more discreet. The reduction falls from 19% to 8%, with an absolute reduction of 11% and a relative reduction of 58%. Moreover, in the control group the 31% rate of angiographically confirmed restenosis correlates poorly with the 19% rate of clinical events; the discrepancy, which is

unsurprising, is mainly a reflection of patients with asymptomatic restenosis. However, it is noteworthy that in the group treated with DES, angiographic restenosis correlated closely with clinical events. This suggests a process of restenosis that differs from the process that occurs with conventional stents. It should be recalled that all six studies were done in a double-blind fashion, which should rule out sources of bias that might account for these differences.

Randomized clinical trials are run according to a protocol for the selective inclusion of patients, and follow-up angiographic examination is usually done. It is well known that follow-up angiographic studies are accompanied by a higher rate of reintervention, and this may account for the relatively high rate of reintervention in the control group.

When the real world situation is considered, the percent rate of reintervention is much lower. The annual registries³ of the Hemodynamics and Interventional Cardiology Section of the Spanish Society of Cardiology place the rate of reintervention for restenosis at hemodynamics and interventional cardiology departments at less than 8% of the total number of angioplasties (Figure 2). It is true that this figure underestimates the extent of the problem, as it does not include patients with restenosis who are referred for surgery or patients for whom reintervention is not advised. Nevertheless, restenosis can be expected to have a clinical impact in 10% to 12% of the patients with a conventional stent. In the RESEARCH registry,¹⁵ which provides a close approximation of the real world situation, percutaneous and surgical reinterventions for restenosis were necessary in 10.9% of the patients in the conventional stent group, versus 3.7% in the rapamycin stent group. This means that for every 100 patients treated with a rapamycin stent, reintervention will be avoided in 7, while the other 93 will obtain no apparent benefits from the new stent.

Subgroup analysis of randomized clinical trial results and the RESEARCH registry data shows the benefits to be universal, especially in terms of relative reduction of restenosis. Clearly, the reduction in absolute terms is greater in subgroups with the highest rates of restenosis, such as patients with diabetes, longer lesions, or lesions located in the anterior descending artery. It is in fact these subgroups where the cost-effectiveness of DES are greatest. Although the new DES are likely to be effective in other clinical and anatomical contexts yet to be investigated, the information available to date regarding their use in patients with acute coronary syndrome, saphenous vein bypass graft, or a lesion in the main stem of the left coronary artery is limited.

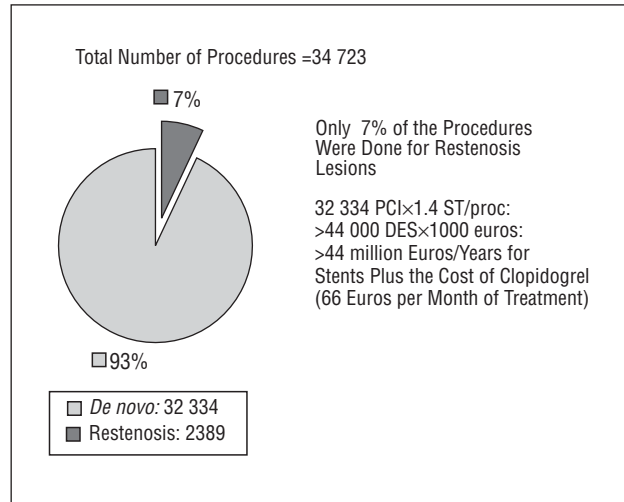


Fig. 2. Data from the Spanish Registry of Hemodynamics and Interventional Cardiology for the year 2002.³ Of the total number of percutaneous interventions performed during 2002, only 7% were for restenosed lesions. An approximate estimate of the additional cost incurred with the systematic use of drug-eluting stents in Spain is on the order of 44 million euros plus the cost of prolonged treatment with clopidogrel. PCI indicates percutaneous coronary interventions; DES, drug-eluting stents; ST/proc, stents per procedure.

Costs

Drug-eluting stents were approved for clinical use in Europe in May 2003, with a mean unit price slightly higher than 2000 euros. In Spain a conventional stent costs approximately 1000 euros, and the number of stents used per intervention ranges from 1.4 to 1.8.^{3,13-15} As a result, the cost of coronary angioplasty with an DES is considerably higher than with a conventional device (Figure 2).

In other countries such as France or Germany, where conventional stents tend to be cheaper than in Spain (500-600 euros vs 1000 euros), the increases in the cost of the procedure associated with the use of DES have been greater. If we add to this the additional cost of prolonging treatment with clopidogrel, a relatively expensive drug, the cost of percutaneous procedures rises even further. Obviously, purely economic reasons should not dissuade physicians or patients from using a particular technology or treatment, especially if its benefits are beyond question (even if they do require careful consideration). In this regard the Plan Integral de Cardiopatía Isquémica (PICI) (Integral Plan for Ischemic Heart Disease), recently developed by the Spanish Ministry of Health and Consumer Affairs¹⁷ and ratified by all autonomous communities in Spain, has made the use of these stents one of its goals, and aims to ensure the “availability at all centers that perform percutaneous interventions with DES for use in patients who benefit the most from them.”

However, health professionals should not take problems of health costs lightly, especially in European countries where most health care services are provided by the public health system. In Germany and France, where interventional cardiology is a highly regarded specialty, less than 10% of all stents used during 2003 were DES. In Spain, although the use of these stents varies between autonomous communities, they accounted for approximately 20% of all stents used in 2003.

Cost-benefit studies of different treatments or therapeutic strategies should be adapted to the social and health system they are intended for. This makes such studies difficult to perform, and their results difficult to apply. According to data from the RESEARCH registry,¹⁵ in order for 7 patients to benefit clinically from DES, i.e., to avoid reintervention (not irreversible events such as death or myocardial infarction), 100 patients need to be treated. Of these 100 patients, 97 will receive a rapamycin stent and then take clopidogrel for a prolonged period with no benefit. Obviously, the very considerable additional cost of these 100 interventions with a rapamycin stent+clopidogrel must be weighed against the benefits obtained by 7 patients. The expense saved by avoiding these 7 reinterventions would cover the cost of at least 100 percutaneous interventions with a conventional stent. Moreover, the cost/benefit ratio of percutaneous interventions for patients with multivessel disease who will require three or more drug-eluting stents may face tough competition from successful coronary surgery and grafting not requiring extracorporeal circulation.

These arguments suggest that more selective rather than more generalized use of DES is more reasonable. It is reassuring to see that the articles published by both groups of Spanish researchers agree that this is the most appropriate approach. Although the best scientific evidence available (from randomized clinical trials) supports the use of drug-eluting stents for lesions with a low to moderate risk of restenosis, these real world studies have been aimed at patients who in theory would benefit most, i.e., those at high risk of restenosis. Evidence-based medicine, a concept mentioned frequently these days, aims to apply the scientific method to medical practice based on the integration of individual clinical experience and the best evidence from scientific research.¹⁸ A number of technology evaluation agencies (in the autonomous regions of Catalonia, the Basque Country and Madrid) have analyzed the available scientific evidence on DES and prepared separate reports, some of which examine the issue of appropriate use. These reports attempt to identify which groups of patients will obtain the greatest clinical benefit, that is, which patients will show, in absolute terms, the greatest reduction in the event that treatment intends to

prevent: restenosis. Once again, there is consensus regarding the selective use of drug-eluting stents for patients at the greatest risk of restenosis. The groups that benefit most are patients with diabetes, severe disease in the main left coronary artery, long lesions (>20 mm), in-stent restenosis, and chronic complete occlusion.

CONCLUSIONS

Regardless of whether DES become the standard for percutaneous interventions in the future, their generalized use at the present time is not justified, for several reasons. The availability of different types and sizes of stents is limited, their safety is threatened by problems with late stent-related thrombosis; the clinical benefits have been magnified by exaggerated reports of the clinical problem of restenosis; and the cost of these stents and the additional pharmacological treatment they involve increases the cost of percutaneous intervention almost threefold.

For these reasons, and at a time when the physician's role in clinical decision-making is increasingly important, it seems more than reasonable to use these new stents selectively for patients who will obtain, in absolute terms, the greatest clinical benefit.

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