Is Systematic Use of Drug-Eluting Stents Justified? Arguments in Favour
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The efficacy of drug-eluting stents measured as the late loss, percentage neointimal volume, restenosis, target lesion revascularization and major cardiac events is significantly better than that of bare metal stents. The incidence of thrombosis and aneurysms is similar. Although there is a slight increase in late malapposition, this is not followed by an increase in cardiac events. Despite the arguments against the routine use of drug-eluting stents, their cost is the only limiting factor for their unidespread use.

Key words: Drug-eluting stents. Sirolimus. Paclitaxel. Efficacy. Side effects.

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¿Está justificado el uso sistemático de stents con fármacos? Argumentos a favor

La eficacia de los stents liberadores de fármacos medida por la pérdida tardía de luz, el porcentaje de volumen neointimal, la reestenosis, la revascularización de la lesión tratada y los eventos cardíacos mayores es significativamente mejor que la de los stents convencionales. La incidencia de la trombosis y aneurismas coronarios es similar. Aunque hay un ligero aumento no significativo de las aposiciones incompletas tardías, éstas no conducen a un aumento de los eventos clínicos. A pesar de diferentes argumentaciones contra su uso sistemático, en la actualidad sólo los costes limitan su uso generalizado.


INTRODUCTION
At the present time the fundamental role of stents in the development of modern interventional cardiology is undeniable. In 1994 two large studies—the BENESTENT and STRESS trials1,2 were published. These trials involved lesions at least 3 mm in diameter and with a maximum length of 15 mm, i.e., simple lesions representative of no more than 20% of all those seen in daily practice. Nevertheless, they led to “stentmania,” which spread inexorably to the point where the maxim “Just stent it” became commonplace, and stents were used in practice for as many lesions as possible. However, the differences with respect to balloon angioplasty, although spectacular at the time, left in their wake a 6-month rate of restenosis of 22% to 31%, rates of revascularization of the treated lesion (RTL) and event-free survival that left considerable room for improvement, and no significant gains in terms of a reduction in ischemic events.

It is therefore unsurprising that constant improvements in recent decades have led to a number of options intended to eliminate or at least substantially reduce the high rate of restenosis, which in more problematic lesions can be as high as 60%-70%. Two examples are the studies by 2 Spanish groups and published in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA.3,4
The aim of this commentary is not to review the many options available to treat restenosis or those options that specifically involve stents.5-8 Nor will this article review the various types of drug-eluting stent (DES) or the positive and negative results obtained thus far. Instead, I will discuss whether the currently available Cypher (Johnson & Johnson) and Taxus devices (Boston Scientific) are safe and effective enough to be used systematically in place of conventional stents.

EFFECTIVENESS AND SAFETY OF DRUG-ELUTING STENTS
Since publication of the first reports of implantation in humans by Sousa and Serruys,9,10 randomized studies have appeared with sirolimus-eluting stents.
Examples are the RAVEL\textsuperscript{11-13}, SIRIUS\textsuperscript{14} and E-SIRIUS\textsuperscript{15} studies, registries such as the RESEARCH compendium\textsuperscript{16,17} and the studies of in-stent restenosis carried out in São Paulo\textsuperscript{18} and Rotterdam\textsuperscript{19}. Studies with paclitaxel incorporated in a polymer formulation include the TAXUS I\textsuperscript{20}, II\textsuperscript{21}, and IV\textsuperscript{22} trials, and the ASPECT trial, which investigated non-polymer-encapsulated paclitaxel-coated stents.\textsuperscript{23-25} Further randomized trials have been reported at a number of congresses, e.g., C-SIRIUS\textsuperscript{26} (sirolimus-eluting stents), FUTURE (everolimus-eluting stents)\textsuperscript{26-28}, and TAXUS IV (polymer-based paclitaxel-eluting stents).\textsuperscript{29,30} Subgroup analyses and follow-up studies of earlier trials include the SIRIUS\textsuperscript{31,33}, E-SIRIUS\textsuperscript{34,35} and RAVEL\textsuperscript{36} studies. In addition, several registries have been described, e.g., the E-CHYPHER\textsuperscript{37}, Wisdom\textsuperscript{38}, and RESEARCH\textsuperscript{39} compilations, the Swiss Registry\textsuperscript{40} and the German Cypher registry.\textsuperscript{41} Further publications have reported the findings at different centers for different lesions, i.e., in the left main coronary artery\textsuperscript{42,43} bifurcated lesions, \textsuperscript{44,45} saphenous vein bypass graft disease,\textsuperscript{46,47} in-stent restenosis,\textsuperscript{38-51} total occlusion,\textsuperscript{52,53} multivessel stenting,\textsuperscript{54} small vessel lesions,\textsuperscript{55,56} long lesions (>36 mm),\textsuperscript{57} and acute myocardial infarction (AMI).\textsuperscript{58,59}

According to data from the initial phase of study, the BENESTENT and STRESS studies included a total of 923 patients. To date, the number of participants in randomized trials is 1598 for sirolimus-eluting stents, 625 for polymer-based paclitaxel stents, and 177 for polymer-encapsulated paclitaxel-eluting stents, for a total of 2400 patients. If we add the figures from randomized trials reported at congresses—100 patients in the C-SIRIUS trial and 1326 in the TAXUS IV trial—the figure for DES rises to 3826, versus 923 patients in trials with conventional stents. Combining patients from different trials increases not only the number of participants, but also the number of baseline

![Comparison of the effectiveness of conventional (ST) and drug-eluting stents (DES) in randomized trials. Ultrasonographic parameters. A: late lumen loss. B: percentage neointimal volume. FI indicates FUTURE I; F II, FUTURE II; TX I, TAXUS I; TX II sr, TAXUS II slow release; TX II mr, TAXUS II moderate release; TX IV, TAXUS IV; ASP, ASPECT.](image-url)

\textsuperscript{100} Rev Esp Cardiol 2004;57(2):99-108
characteristics to consider. As noted earlier, the lesions studied in the BENESTENT and STRESS trials were 3 mm in diameter or more, and up to 15 mm long. These dimensions are similar to the ones in the TAXUS I and II studies (3-3.5 mm by 12 mm), and denote lesions somewhat easier to manage than those in the RAVEL study (2.5-3.5 mm in diameter, treated with an 18-mm-long stent), but not comparable to the lesions treated in the E-SIRIUS trial (2.5-3.5 mm by 15-30 mm), the C-SIRIUS trial (up to 32 mm long) or the TAXUS IV trial (2.5-3.5 mm by up to 28 mm long).

Although the data available for conventional stents cannot be compared in overall terms with those for DES, it is worth recalling that the number of randomized clinical trials that support the use of conventional stents over balloon angioplasty is not very large. Stents were favored for total occlusions in 10 studies, for saphenous vein bypass graft disease in 2, for small vessel stenosis in 6, for long vessel stenosis in 2, for lesions in the left main coronary artery 2, for restenosis in 1, and for acute myocardial infarction (AMI) in 11. The total number of patients with each type of lesion is less than 1500 in all cases except for AMI, for which data are available for more than 4500 patients. For four types of lesion the total number of patients falls short of 500: saphenous vein graft disease, long lesions, lesions in the left main coronary artery, and restenosis. With the exception of the BENESTENT and STRESS studies, published in 1994, the remaining studies were published in 1998, 1999 and 2000, by which time conventional stents were already being used systematically in daily practice. Randomized clinical trials eventually confirmed the observations from daily practice, and the lack of large trials did not impede their use.

Two main types of criteria—angiographic and clinical—have been used to evaluate the effectiveness of different types of stent. Angiographic or ultrasonographic criteria have been used to determine late lumen loss, percentage neointimal volume, and the occurrence of restenosis. Clinical criteria have been based on revascularization of the treated lesion (RTL) and major cardiac events (MCE). As can be seen, late lumen loss ranges from 0.85 to 1 mm with conventional stents, but is less than 0.20 mm the limus-coated stents and less than 0.40 mm with paclitaxel-coated devices. The findings for percentage neointimal volume are similar, with values of 30% for conventional stents but less than 3% for limus-coated stents and less than 13% for paclitaxel-coated devices (Figure 1). However, when the results are compared for restenosis (defined as >50% restenosis), the figures are similar for both types of drug at about 22% for conventional stents and below 9% for DES (Figure 2). In more favorable lesions similar to those investigated in the BENESTENT and STRESS studies, even lower rates of restenosis were reported, e.g., 0% in the RAVEL, FUTURE I, FUTURE II, and TAXUS I studies. These results were what led initially to “the dream of zero restenosis,” but in lesions that more closely approximated those encountered in daily practice the percentages were as high as 8%. The difference between the values for neointimal proliferation and final restenosis rates is worth noting. All evidence seems to suggest that as long as intimal proliferation remains below a certain threshold value, angiographic restenosis does not occur. Thus, although the capacity of sirolimus and everolimus to inhibit proliferation is greater, angiographically documented restenosis is similar in patients treated with these and conventional stents.

Subgroup analysis of restenosis in patients with DES yields information worth considering. Firstly, in lesions treated with conventional stents, restenosis is predominantly diffuse, proliferative or complete. In contrast, restenosis is focal in 87% of the lesions treated with DES. In other words, in-stent restenosis is...
considerably more benign than with uncoated stents, regardless of whether the DES were coated with sirolimus or paclitaxel.\textsuperscript{62,63} Secondly, post-implant restenosis is directly related to length of the stent when a conventional device is used, increasing from 29.7\% with 8-mm stents to 52.4\% with 40-mm devices. This relationship is not seen with DES: restenosis occurred in 1.7\% of the patients with 8-mm stents, and increased to only 6.5\% with 40-mm devices. Thirdly, in women, persons with diabetes, multiple stents and lesions in
small vessels, conventional stents clearly increase the percentage rate of restenosis. In contrast, the rates of angiographic restenosis with DES, are similar across all types of lesion.

With regard to clinical findings (Figure 3), the rate of RTL is 20% with conventional stents and less than 5% with DES, with no differences between the 2 groups of drugs or between lesions of different characteristics, as found for angiographic restenosis. The rates of MCE are again higher than 20% with conventional stents but lower than 9% for DES, and are similar for both groups of drugs.

It has therefore clearly been shown that DES coated with sirolimus or polymer-based paclitaxel produce significantly less neointimal proliferation, angiographic restenosis, RTL and major ischemic events, and

**Fig. 5.** 12-month incidence of restenosis and revascularization of the treated lesion (RTL) in patients with diabetes in the SIRIUS and TAXUS IV studies. DES indicates drug-eluting stent; ST, conventional stent.
are associated with greater event-free survival, than conventional stents (Figure 4). Despite the smaller number of patients studied to date, stents that release everolimus or non-polymer-encapsulated paclitaxel yield results similar to those obtained with the Cypher and Taxus devices, both of which are widely sold and used in Spain.

Although effectiveness is important, safety is no less so. The 3 issues that need to be mentioned in this regard are thrombi, incomplete apposition, and aneurysms.

Thrombosis is perhaps the most dreaded complication, and the one which has created the most unease as a result of information that has appeared in the lay press. However, in randomized clinical trials and registries, the incidence of acute, subacute or delayed thrombosis is no higher than with conventional stents at approximately 1%-2%.64

Incomplete apposition is not infrequent initially if the wrong size stent is used or if it is improperly expanded. Because DES release antiproliferative and immunosuppressive substances, and because intracoronary ultrasonography has disclosed late incomplete apposition that was not initially detected, it was thought that positive remodeling as a result of a weakened adventitia might be the cause, and late thrombosis the consequence. Reports to this effect have appeared sporadically in the literature. The incidence of late incomplete apposition is higher with DES, although it now appears to be decreasing (1.1% in the TAXUS IV trial as compared to 8.5% in the TAXUS II and 8.7% in the SIRIUS trials), probably because of improvements in deployment technique. Nevertheless, incomplete apposition has not been related to delayed stent thrombosis or MCE.65

With regard to aneurysms—localized dilation at the site of the stent with risk of rupture—the data show that initially, the incidence is the same with DES as with conventional stents, at 0.50% to 0.7%. During follow-up the incidence is higher with conventional stents (1% vs 0.4%), although the difference is not significant. As with incomplete apposition, the presence of an aneurysm does not correlate with the appearance of stent thrombosis or MCE.66

It therefore seems to be well documented that the safety of DES is similar to that of conventional stents, with no increase in the incidence of thrombosis or aneurysms, and a slightly higher incidence of late incomplete apposition with no clinical repercussions.

**WHY AREN’T THEY USED IF THERE IS SCIENTIFIC EVIDENCE OF THEIR EFFECTIVENESS AND SAFETY?**

Despite the data published to date, their validity from a scientific standpoint is still being questioned. It has been said that randomized clinical trials are not representative of usual daily practice, as the former have centered on less severe lesions with more favorable success rates. Moreover, data for many types of lesion are still missing, follow-up findings are limited to periods that are too short to rule out the appearance of catch-up phenomena, expert guidelines do not universally recommend these stents, nobody uses them for 100% of their patients, and given the cost of DES, they would bankrupt the system. For these reasons DES should be implanted only in patients with high-risk lesions.

With regard to the representativeness of clinical trials, several registries have been designed for the express purpose of obtaining real-world data. The ESIRIUS registry of patients with sirolimus-coated DES includes 8215 cases of stents used for vessels between 2.25 and 3.5 mm in diameter and 8 to 33 mm long. In addition to 6330 de novo lesions, this registry also includes 1027 restenoses, 172 saphenous vein bypass graft disease, 145 left main coronary artery lesions, 698 complete occlusions, and 702 bifurcated lesions. Despite the greater complexity of these lesions, the results are similar to those of randomized clinical trials, with an RTL rate of 7% and a 6-month event-free survival rate of 92%. The RESEARCH registry compiled at the Thoraxcenter in Rotterdam includes 1072 patients and 2346 stents, with 338 multivessel lesions, 205 lesions smaller than 2.25 mm in diameter, 214 bifurcated lesions, 312 stenoses longer than 48 mm, 71 total occlusions, 51 left main coronary artery lesions, 462 patients with unstable angina and 241 with AMI. Nevertheless, the RTL rate remains low, with a global figure of 2.7%, and lesion-specific figures of 0% for AMI and 9.8% for bifurcated lesions. The results are similar in the WISDOM registry of polymer-based paclitaxel-coated stents, a compilation of 778 patients and 968 stents. In this series of patients, 33% had diabetes, 18% had AMI, 34% had unstable angina, 12% had a lesion smaller than 2.5 mm in diameter, 14% had a lesion longer than 30 mm, and 15% had a lesion in the left main coronary artery. After 6 months the RTL rate was 3% and the MCE rate was 4.3%, and after 12 months 94% of the patients had not required reintervention. These results confirm that in daily practice, the findings are similar to those in clinical trials in terms of both effectiveness and safety.

The second problem—lack of data for certain types of lesion—pertains to problems such as long stenoses, narrow vessels, lesions that bridge the ostium, saphenous vein bypass graft disease, left main coronary artery lesions, bifurcated lesions, total occlusions and AMI. Clinical trials have not been done for DES use in all types of lesion, just as such studies have not been done for conventional stents. However, the information published to date includes observational studies for all lesions, all of which reported positive re-
sults. While we await further clinical trials, many of which are recruiting patients as of this writing, we may anticipate that the results will be more or less similar in all lesions. Two situations in particular in which neointimal proliferation features strongly, i.e., diabetes and in-stent restenosis, may provide data confirming that concerns about differences in neointimal proliferation between different types of lesion are unwarranted.

Although no studies have been done exclusively in patients with diabetes, an analysis of the SIRIUS and TAXUS IV trials, in which 25% of the patients had diabetes, shows that although restenosis and RTL rates were clearly higher than in patients without diabetes, the differences in comparison to control participants remained overwhelmingly in favor of DES in patients treated with both oral medication or insulin (Figure 5). Surprisingly, the results for patients with diabetes treated with insulin were better with paclitaxel-coated stents than with sirolimus, and restenosis rates were also better in patients on oral medication. This may have been due to the limited number of patients treated with insulin, or to as yet undocumented effects of paclitaxel.

Another lesion associated with a high proliferative capacity is in-stent restenosis. However, although no clinical trials have yet been completed, a comparative study of four registries is available\(^6\) in addition to many observational studies. In all reports the results have been positive, with clear differences in favor of DES in comparison to conventional stents. The São Paulo series reported an RTL rate of 0\%, whereas other studies reported rates that ranged from 10\% to 20\%. The restenosis rates were 4\% in the São Paulo study and ranged from 12.5\% to 16\% in other reports. These figures are much lower than the rates obtained with conventional stents, which ranged from 40\% to 60\%.

With regard to the possibility that follow-up periods may be too short for late delayed restenosis (catch-up) to appear, the available data do not support this likelihood. The first-in-man study published by Sousa et al.\(^{64,69}\) used a follow-up period of 1 or 2 years, and after this time the in-stent lumen had remained practically unchanged with no late restenosis. After the 24-month follow-up period in the TAXUS I study, the rate of MCE was the same as after 9 months at 3.3\% with DES, as compared to 10\% with conventional stents. The rate of RTL was 0\% and volume of neointimal hyperplasia was unchanged at 8.3 after 6 months and 9.7 after 12 months). These results are similar to those of the TAXUS II and TAXUS IV trials after 1 year of follow-up: event-free survival was similar with both types of stent. The differences in comparison to conventional stents became greater with time: in the TAXUS II study event-free survival was 8.8\% after 6 months and 10.5\% after 12 months, and in the TAXUS IV study the figures were 9.3\% after 6 months and 10.7\% after 12 months. In the SIRIUS study the reduction in RTL was 12.5\% at 9 months and increased to 15.1\% after 12 months, and in the RAVEL study RTL-free survival in patients with DES was 97.5\% after 2 years, versus 86.4\% in patients with a conventional stent. Thus none of the reports appears to indicate that the beneficial effect is lost with time, but rather, that the benefits are maintained and may in fact increase.

With regard to the cost versus clinical benefit analysis, it should be recalled that this document was prepared by only 2 authors, O’Neill and Leon,\(^{70}\) and thus does not constitute a set of guidelines developed by consensus among contributors representing a cardiological society. Moreover, this analysis was communicated more than 6 months ago, and was therefore written nearly 8 months ago. The authors note, just before their conclusions, that “because many studies have been completed although not yet published, these criteria may change markedly within the next year.” During 2003 the results of the C-SIRIUS, E-SIRIUS, and TAXUS IV trials and the RESEARCH registry have been announced, and this information, in addition to more than 100 recent congress presentations has changed the nature of the evidence that was available one year ago.

Arguments based on “usual practices” in Europe, Spain, or the USA seem of limited value. Although the scientific basis of the evidence may be solid, actual practice in any particular setting may be influenced, in many cases, by circumstances unrelated to the evidence. The evidence in favor of DES is clear and consistent, and is not affected by the fact that setting-specific situations, usually economic and transient in nature, make it difficult to use DES stents as often as is desired.

Before concluding, a brief mention of economic issues and cost/benefit analyses is in order. We should recognize that at present, in Spain as in the rest of the world, cost is the actual limiting factor regarding the use of stents. If a coated stent cost the same as an uncoated stent, the controversy would be meaningless and drug-eluting stents only would be used in all cases. If we recall the cost 10 years ago of materials we now use on a daily basis, it becomes clear that the price of balloon devices and stents has fallen by about 50\% to 60\%. There is nothing to suggest that DES will be an exception. The decrease in costs will depend mainly on the spread of DES and competing products, which will force industry, as before, to consider pricing policies carefully when new stents are placed on the market. In addition, the Spanish public health system may need to consider other sources of financing compatible with its aim to guarantee an appropriate level of medical care.

Progress in medicine is so rapid that a decade during our time represents many centuries of earlier times, and within the process of change, DES are just
one more phase which, within a few years, will have given way to newer measures that are no less costly to society. Although cost/benefit studies by Cohen et al. in the USA71 and by Serruys et al at the Thoraxcenter in Rotterdam are not entirely applicable to Spain, an initial analysis of the RAVEL findings by Lemos et al72 found that the cost of treatment with DES, which achieved a low rate of restenosis, increased by only 166 euros. This suggests that in other lesions for which the incidence of restenosis is higher, the cost/benefit ratio may be favorable to DES. Despite these initial studies, the need for cost/benefit analyses within the Spanish health system setting is clear, not only for DES but for other diagnostic and therapeutic procedures. To maintain that the cost factor should limit the use of DES to lesions that involve the greatest risks makes little sense, as zero rates of restenosis have been achieved in lesions that are easier to manage. Moreover, no reliable method is available to calculate the incidence of restenosis for individual patients and different types of lesion.

CONCLUSIONS

In conclusion, the data now available in the literature evidently support the use of DES for any patient who requires a stent. The safety of DES is at least comparable to that of conventional stents. The wider use of DES would lead inevitably to an increase in the number of indications. Lesions previously not amenable to percutaneous procedures may well become treatable with this approach within the next few years. Introduction of the first metallic stents triggered the first revolution just as changes ensued when surgical revascularization with saphenous vein bypass grafting was perfected. It could also be said that the appearance of DES has led to a second revolution, comparable only to that which took place with surgical arterial revascularization. Close collaboration between policymakers, health professionals and industry should make it possible to use DES for all patients with coronary arteriosclerosis amenable to percutaneous revascularization.

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