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.

Palabras clave: Stents *liberadores de fármacos. Sirolimus. Paclitaxel. Eficacia. Efectos secundarios.*

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 trials[1,2] 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.

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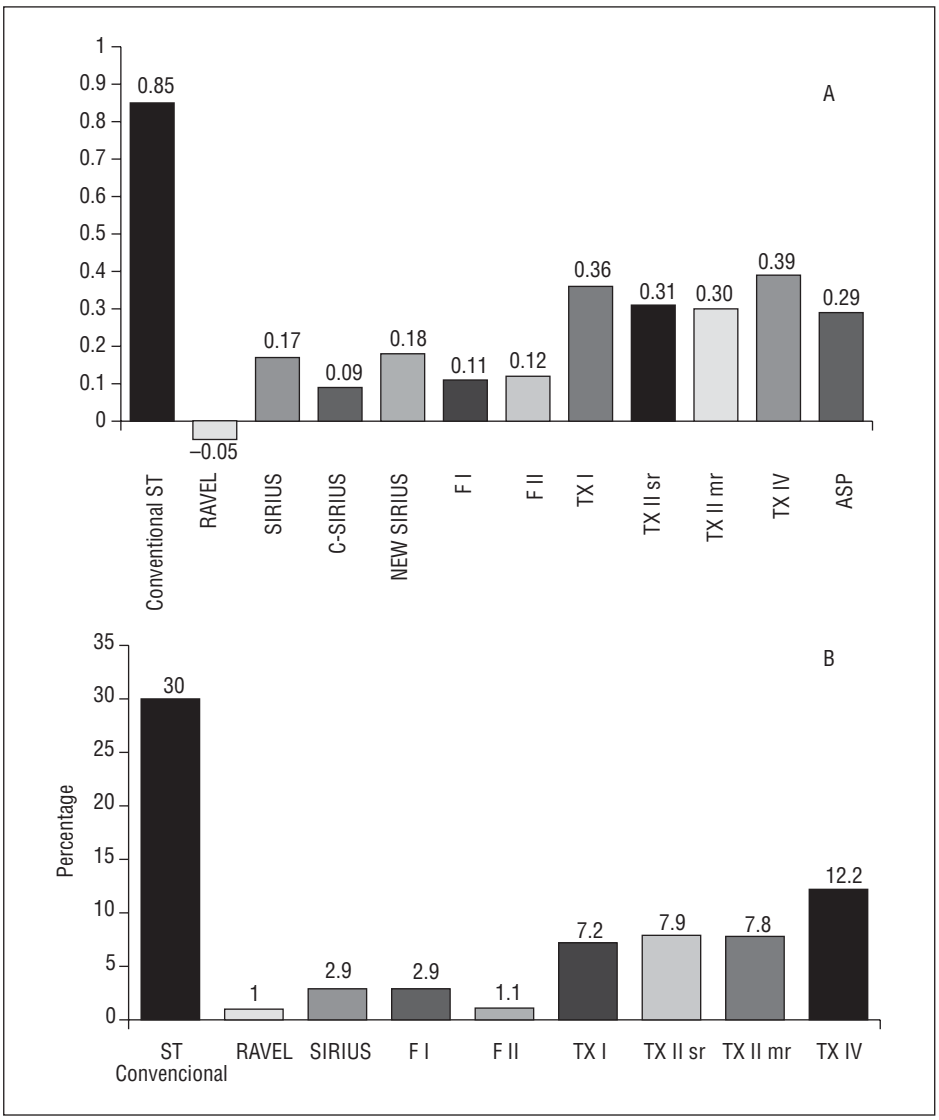

Fig. 1. Comparison of the effectiveness of conventional (ST) and drug-eluting stents (DES) in randomized trials. Ultrasonographic parameters. A: late lumen loss. B: percentage neointimal volume.
FI indicates FUTURE I; F II, FUTURE II; TX I, TAXUS I; TX II sr, TAXUS II slow release; TX II mr, TAXUS II moderate release; TX IV, TAXUS IV; ASP, ASPECT.

Examples are the RAVEL,[11-13] SIRIUS,[14] and E-SIRIUS[15] studies, registries such as the RESEARCH compendium,[16,17] and the studies of in-stent restenosis carried out in São Paulo[18] and Rotterdam.[19] Studies with paclitaxel incorporated in a polymer formulation include the TAXUS I,[20] II[21], and IV[22] trials, and the ASPECT trial, which investigated non-polymer-encapsulated paclitaxel-coated stents.[23-25] Further randomized trials have been reported at a number of congresses, e.g., C-SIRIUS[26] (sirolimus-eluting stents), FUTURE (everolimus-eluting stents),[26-28] and TAXUS IV (polymer-based paclitaxel-eluting stents).[29,30] Subgroup analyses and follow-up studies of earlier trials include the SIRIUS,[31,33] E-SIRIUS[34,35], and RAVEL[36] studies. In addition, several registries have been described, e.g., the E-CHYPHER,[37] Wisdom[38], and RESEARCH[39] compilations, the Swiss Registry,[40] and the German Cypher registry.[41] Further publications have reported the findings at different centers for different lesions, i.e., in the left main coronary artery[42,43] bifurcated lesions,[44,45] saphenous vein bypass graft disease,[46,47] in-stent restenosis,[48-51] total occlusion,[52,53] multivessel stenting,[54] small vessel lesions,[55,56] long lesions (>36 mm),[57] and acute myocardial infarction (AMI).[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

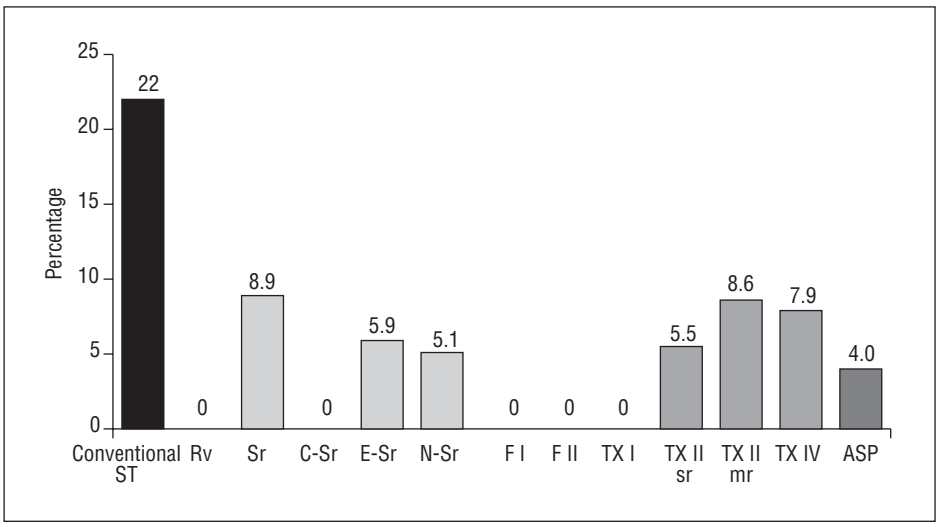

Fig. 2. Comparison of the effectiveness of conventional (ST) and drug-eluting stents (DES) in randomized trials. Angiographically confirmed restenosis.
ASP indicates ASPECT ; C-Sr, C-SIRIUS; E-Sr, E-SIRIUS; F I, FUTURE 1; F II, FUTURE II; N-Sr, NEW SIRIUS; Rv, RAVEL; Sr, SIRIUS; TX I, TAXUS I; TX II sr, TAXUS II slow release; TX II mr, TAXUS II moderate release; TX IV, TAXUS IV.

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.[60] 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,"[61] 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

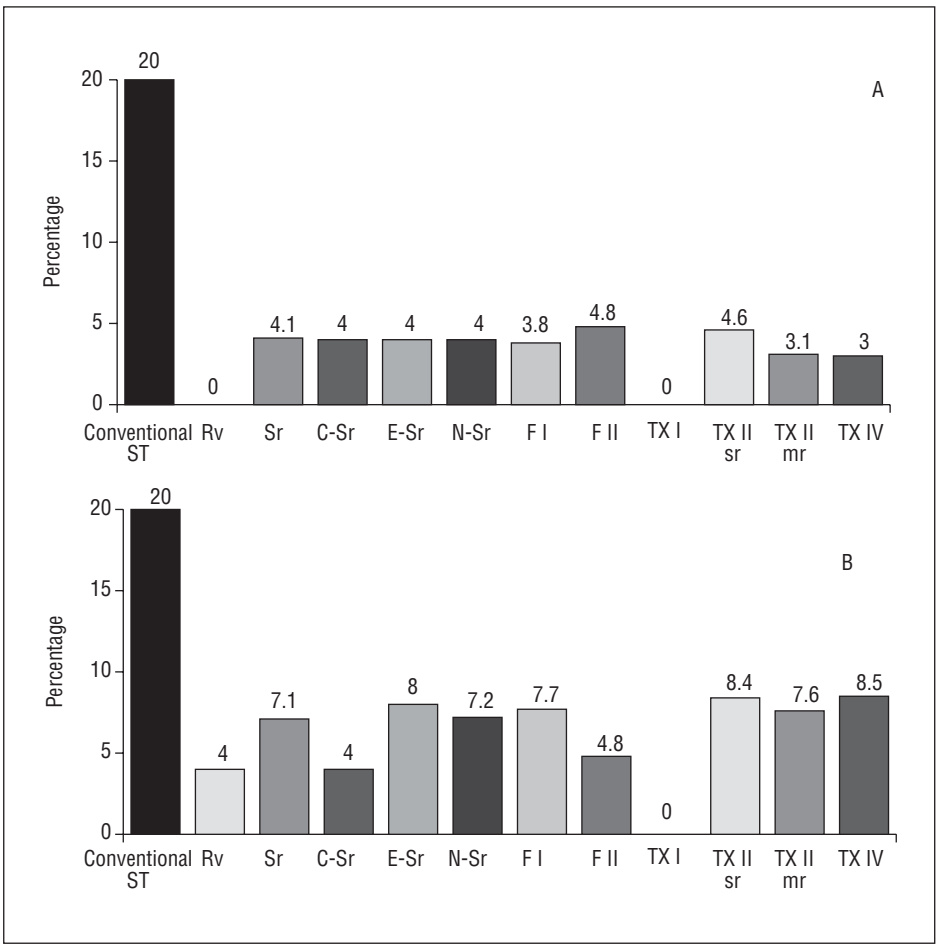

Fig. 3. Comparison of the effectiveness of conventional (ST) and drug-eluting stents (DES) in randomized trials. Clinical findings. A: revascularization of the treated lesion (RTL). B: major cardiac events. C-Sc indicates C-SIRIUS; E-Sr, E-SIRIUS; F I, FUTURE 1; F II, FUTURE II; N-Sr, NEW SIRIUS; Rv, RAVEL; Sr, SIRIUS; TX I, TAXUS I; TX II sr, TAXUS II slow release; TX II mr, TAXUS II moderate release; TX IV, TAXUS IV.

considerably more benign than with uncoated stents, regardless of whether the DES were coated with sirolimus or paclitaxel.[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

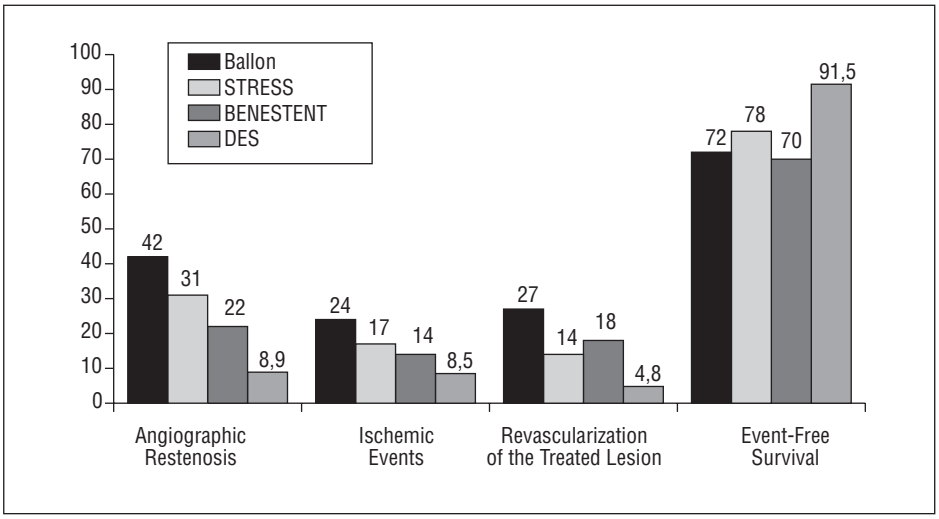

Fig. 4. Comparison of clinical and angiographic results with balloon angioplasty and conventional stents in the Benestent and STRESS studies and results with drug-eluting stents (DES) in randomized trials.

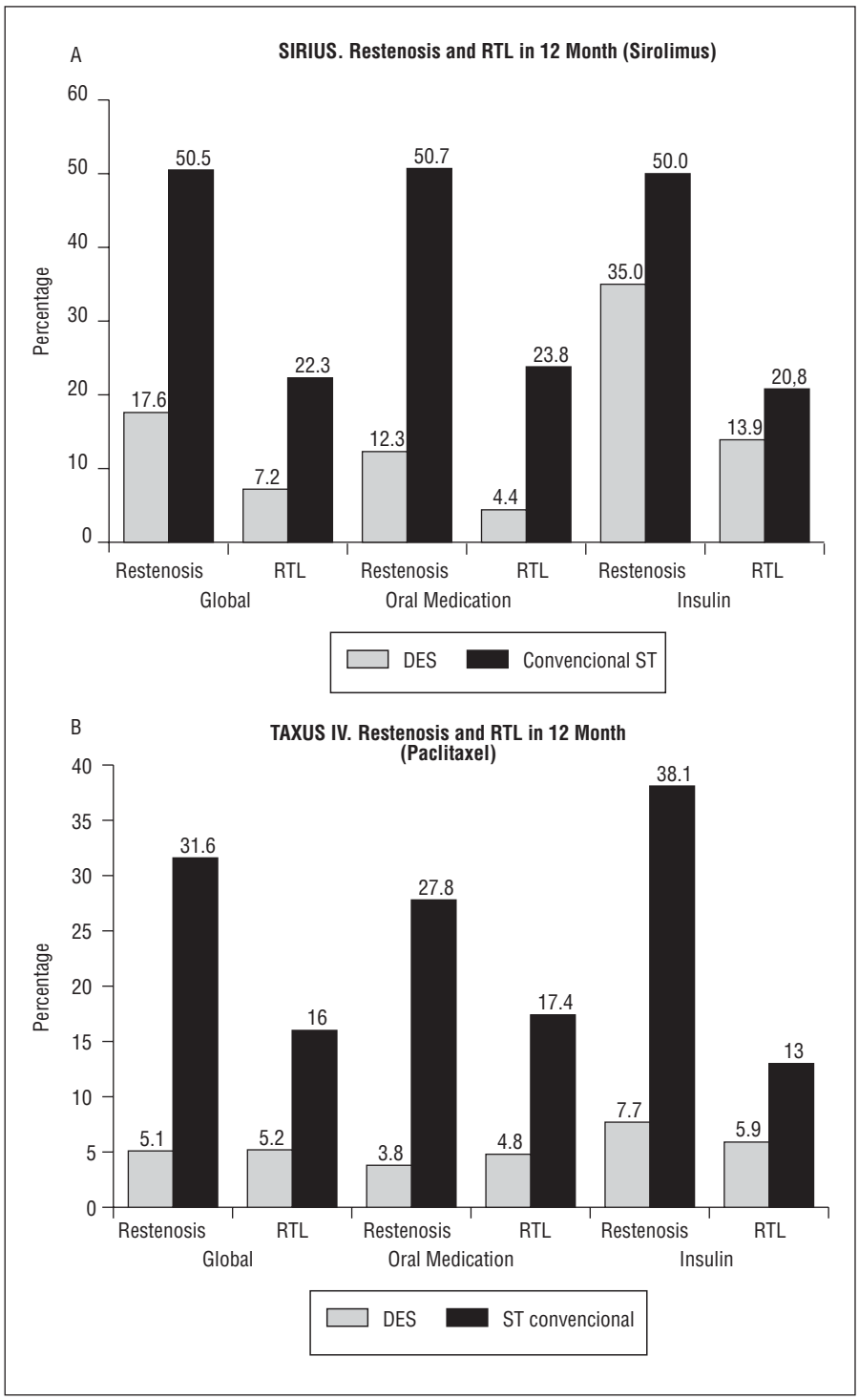

Fig. 5. 12-month incidence of restenosis and revascularization of the treated lesion (RTL) in patients with diabetes in the SIRIUS and TAXUS IV studies.
DES indicates drug-eluting stent; ST, conventional stent.

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

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[35] 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[37] 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,[38] 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[67] 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[68,69] 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 USA[71] 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 al[72] 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.

REFERENCES

1. Serruys PW, De Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al, for the Benestent Study Group. A comparison of balloon-expandable-stent implantion with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489-95.
2. Fischman DL, Leon MB, Baim DS, Schatz R, Savage MP, Penn I, et al, for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496-501.
3. de la Torre JM, Burgos V, González-Enríquez S, Cobo M, Zueco J, Figueroa A, et al. *Stent* liberador de rapamicina en el tratamiento de lesiones coronarias con alto riesgo de reestenosis. Seguimiento clínico a 6 meses de los primeros 100 pacientes. Rev Esp Cardiol 2004;57:116-22.
4. Ruiz-Nodar JM, Frutos A, Carrillo P, Morillas P, Valero R, Rodríguez JA, et al. Utilización del *stent* recubierto de rapamicina en la revascularización de lesiones complejas: estudio con seguimiento clínico y angiográfico. Rev Esp Cardiol 2004;57:123-9.
5. Babapulle MN, Eisenberg MJ. Coated stents for the prevention of restenosis: Part I. Circulation 2002;106:2734-40.
6. Babapulle MN, Eisenberg MJ. Coated stents for the prevention of restenosis: Part II. Circulation 2002;106:2859-66.
7. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology. Drug-eluting stents: Part I. Circulation 2003;107:2274-9.
8. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology. Drug-eluting stents: Part II. Circulation 2003;107:2383-9.
9. Sousa EJ, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IMF, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries. A quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2001;103:192-5.
10. Degertekin M, Serruys PW, Foley D, Tanabe K, Regar E, Vos J, et al. Persistent inhibition of neointimal hyperplasia after sirolimus-eluting stent implantion. Long-term (up to 2 years) clinical, angiographic, and intravascular ultrasound follow-up. Circulation 2002;106:1610-3.
11. Morice MC, Serruys PW, Sousa JE, Fajadet J, Hazashi EB, Perin M, et al, for the RAVEL Study Group. A randomized comparaison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.
12. Serruys PW, Degertekin M, Tanabe K, Abizaid A, Sousa E, Colombo A, et al, for the RAVEL Study Group. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (Randomized study with the sirolimus-eluting Velocity ballon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. Circulation 2002;106:798-803.
13. Regar E, Serruys PW, Bode C, Holubarsh C, Guermonprey JL, Wijns W, et al, on behalf of the RAVEL Study Group. Angiographic findings of the multicentre randomized study with the sirolimus-eluting bx velocity balloon-expandable stent (RAVEL). Circulation 2002;106:1949-56.
14. Moses JW, Leon MB, Popma JJ, Fitzgerald P, Holmes DR, O'Shaughnessy, et al, for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315-23.
15. Schofer J, Schlüter M, Gershlick AH, Wijns W, García E, Schampaert E, et al, for the E-SIRIUS Investigators. 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.
16. Lemos PA, Lee C-H, Degertekin M, Saia F, Tanabe K, Arampatzis CA, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes. J Am Coll Cardiol 2003;41:2093-9.
17. Saia F, Lemos PA, Lee CH, Arampatzis CA, Hoye A, Degertekin M, et al. Sirolimus-eluting stent implantation in ST-elevation acute myocardial infarction. A clinical and angiographic study. Circulation 2003;108:1927-9.
18. Sousa JE, Costa MA, Abizaid A, Sousa AGMR, 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.
19. Degertekin M, Regar E, Tanabe K, Smits PC, van der Giesen 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.
20. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L,

Gerkens 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.
21. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, et al, for the TAXUS II Study Group. Randomized study to asess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108:788-94.
22. Tanabe K, Serruys PW, Grube E, Smits PC, Selbach G, van der Giesen 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.
23. Park SJ, Shim WH, Ho DS, Raizer AE, Park S-W, Hong M-K, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med 2003;348:1537-45.
24. Hong MK, Mintz GS, Lee CW, Song J-M, Han K-H, Kang D-H, et al. Paclitaxel coating reduces in-stent intimal hyperplasia in human coronary arteries. A serial volumetric ultrasound analysis from the asian paclitaxel-eluting stent clinical trial (ASPECT). Circulation 2003;107:517-20.
25. Mintz GS, Tinana A, Hong MK, Lee CW, Kim J-J, Feranot NE, et al. Impact of preinterventional arterial remodeling on neointimal hyperplasia after implantation of (non-polymer-encapsulated)paclitaxel-coated stents. A serial volumetric ultrasound analysis from the asian paclitaxel-eluting stent clinical trial (ASPECT). Circulation 2003;108:1295-8.
26. Schampaert E. The canadian multicenter, randomized, double-blind trial of the sirolimus-eluting stent in the treatment of patients with de novo coronary artery disease [abstract]. Circulation 2003;108:3193.
27. Costa RA, Lansky A, Mehran R, Tsuchiya Y, Cristea E, Negoita M, et al. Everolimus-eluting stent for the treatment of de novo coronary lesions-angiographic follow-up of the FUTURE trial [abstract]. Circulation 2003;108:3191.
28. Grube E, Buellesfeld L, Mueller R, Staberock M, Selbach G, Schmidt T, et al. First human experience using a new everolimus stent coating: procedural and six-month follow-up results of the FUTURE trial. J Am Coll Cardiol 2003;41(Suppl A): 1006-183.
29. Stone G, Ellis S, Cox D, Hermiller J, O'Shaughnessey C, Mann JT, et al. The pivotal US study of the slow-rate release polymer-based paclitaxel-eluting TAXUS stent in patients with de novo coronary lesions [abstract]. Circulation 2003;108:IV533.
30. Ellis S, Stone G, Popma J, Weissman N, Hermiller J, Cox DA, et al. The TAXUS IV study: final angiographic results [abstract]. Circulation 2003;108:IV532.
31. Kereiakes D, Moses JW, Leon MB, O'Shaughnessey C, Caputo R, Brown C, et al. Durable clinical benefits following CYPHER coronary stent deployment: SIRIUS study 2-year results [abstract]. Circulation 2003;108:IV532.
32. Ako J, Morino Y, Honda Y, Sonoda S, Terashima M, Hassan A, et al. Effects of sirolimus-eluting stents in diabetics patients: volumetric intravascular ultrasound analysis from the SIRIUS trial. J Am Coll Cardiol 2003;41(Suppl A):1198-80.
33. Moses JW, Kereiakes D, Williams DO, Douglas J, Lambert C, Simonton C, et al. Should sirolimus-eluting stents be the new standard for left anterior descending artery? A SIRIUS substudy. J Am Coll Cardiol 2003;41(Suppl A):1198-279.
34. Guagliumi G, Hoffman R, Schofer J, Musumeci G, Petronio AS, Reimers B, et al. Intravascular ultrasound findings in the multicenter, randomized, double blind e-SIRIUS trial [abstract]. Circulation 2003;108:3185.
35. Schofer J, Breithardt G, Gerslick A, Wijns W, García E, Kuntz R, et al. Nine-month subgroup analysis of the E-SIRIUS trial: direct stenting vs predilatation [abstract]. Circulation 2003;108: 2431.
36. Morice MC, Serruys P, Costantini C, Wuelfert E, Wijns W, Fajadet J, et al, on behalf of the RAVEL trial investigators. Two-year follow-up of the RAVEL study: a randomized study with the sirolimus-eluting bx velocity(tm) stent in the treatment of patients with de-novo native coronary artery lesions. J Am Coll Cardiol 2003;41(Suppl A):805-1.
37. Guagliumi G, Sousa E, Urban P, Gershlick A, Schofer J, Lotan C, et al. Sirolimus-eluting stent in routine clinical practice: a 6-month follow-up report from the international E-CHYPHER registry [abstract]. Circulation 2003;108:2437.
38. Abizaid A, Chan CH, Kaul U, Patel T, Tan HC, Sutandar Dr, et al. Real world evaluation of slow-release, polymer-based, paclitaxel-eluting TAXUS stents in native coronary arteries: the Wisdom International [abstract]. Circulation 2003;108:2436.
39. Lemos PA, Saia F, Arampatzis CA, Hoye A, Tanabe K, Degertekin M, et al. Unrestricted utilization of sirolimus-eluting stent implantation in the real world reduces events compared with previous strategies using conventional bare stents. A study of 1200 consecutive patients from the RESEARCH registry [abstract]. Circulation 2003;108:2430.
40. Igual M, Vettiger B, Amann P, Rickli H, Syed R, Vuilliomenet A, et al. The Swiss registry for sirolimus eluting stents in complex coronary lesions [abstract]. Eur Heart J 2003;24(Suppl): 3658.
41. Hamm CW, Schneider S, Senges J, for the German CYPHER stent registry. Initial results of the german drug-eluting stent registry [abstract]. Circulation 2003;108:2434.
42. Suárez de Lezo J, Medina J, Pan M, Romero M, Segura J, Delgado A, et al. Sirolimus-eluting stents for the treatment of unprotected left-main coronary lesions [abstract]. Circulation 2003;108:1885.
43. Chieffo A, Michev I, Stankoviv G, Airoldi F, Montorfano M, Orlic D, et al. Sirolimus-eluting stents in unprotected left main [abstract]. Eur Heart J 2003;24(Suppl):2255.
44. Airoldi F, Spanos V, Stankovic G, Di Mario C, Chieffo A, Briguori C, et al. Bifurcational coronary artery lesion treatment with rapamicine-eluting stents: results from a single center experience. J Am Coll Cardiol 2003;41(Suppl A):839-43.
45. Tanabe K, Lemos PA, Lee C-H, Degertekin M, Regar E, Arampatzis AC, et al. The impact of sirolimus-eluting stents on the outcome of patients with bifurcation lesions. J Am Coll Cardiol 2003;41(Suppl A):1030-180.
46. Costa MA, Moses JW, Leon MB, Teirstein PS, Yakubov S, Carter AJ, et al. Sirolimus-eluting stent for the treatment of bypass graft disease: the initial US experience. J Am Coll Cardiol 2003;41(Suppl A):1030-183.
47. Costa M, Gilmore P, Carter A, Teirstein P, Yakubov S, Sasseen B, et al. Sirolimus-eluting stents for the treatment of bypass graft disease: long-term results of the initial US experience [abstract]. Circulation 2003;108:1806.
48. Medina A, Suárez de Lezo J, Pan M, Hernández E, Romero M, Delgado A, et al. Inmediate and late results of drug-eluting stents for the treatment of in-stent restenosis [abstract]. Circulation 2003;108:1884.
49. Emig U, Wermer GS, Scwarz G, Figulla HR. Sirolimus-eluting stents for the treatment of recurrent instent-restenosis: a worst case scenario to prove the effectiveness of drug-eluting stents [abstract]. Circulation 2003;108:2692.
50. Terstein P, Moses JW, Leon MB, Kao J, Bass T, Costa MA, et al. Use of the sirolimus-eluting bx VELOCITYtm stent for failed brachytherapy in recurrent in-stent restenosis: results from the SECURE registry [abstract]. Circulation 2003;108:1889.
51. Commeau P, Barragan PT, Roquebert PO, Bouvier JL, Comet B, Macaluso G. Treatment of in-stent restenosis using sirolimus-eluting stents: ISR II registry. J Am Coll Cardiol 2003;41(Suppl A):839-45.
52. Nakamura S, Muthusumay T, Bae J-H, Cahyadi YH, Pachirat O. Impact of sirolimus-eluting stents on the outcome of patients with chronic total occlusions: multicenter registry in Asia [abstract]. Circulation 2003;108:1888.
53. Tavano D, Airoldi F, Montorfano M, Carlino M, Chieffo A, Michev Y, et al. Immediate-term and midterm clinical results of sirolimus-eluting stents in coronary chronic total occlusions. Am J Cardiol 2003;92(Suppl):449.
54. Orlic D, DiMario C, Bonizzoni E, Satnkovic G, Corvaja N,

Sangiorgi G, et al. Multivessel coronary artery stenting with sirolimus-eluting stent implantation: inmediate and midterm results. Am J Cardiol 2003;92(Suppl):211.
55. Lemos PA, Arampatzis AC, Hoye A, Tanabe K, van der Giessen WJ, de Feyter P, et al. Sirolimus-eluting stent implantation in very small coronary-vessels treated in RESEARCH Registry [abstract]. Eur Heart J 2003;24(Suppl):521.
56. Meier B. SVELTE trial: a multicenter, historically controlled study in patients with de novo native coronary artery lesions in small vessels treated with the CYPHER stent. Am J Cardiol 2003;92(Suppl):207.
57. Degertekin M, Saia F, Lemos PA, Lee CH, De Feyter P, Sianos G, et al. Efficay of sirolimus-eluting stent implantation in long (> 36 mm) stented segments. A RESEARCH substudy [abstract]. Eur Heart J 2003;24(Suppl):3654.
58. Saia F, Lemos PA, Lee C-H, Arampatzis CA, Hoye A, Tanabe K, et al. Comparison between sirolimus-eluting stents and conventional interventional strategies for patients with acute myocardial infarction. Results of the RESEARCH registry [abstract]. Circulation 2003;108:1890.
59. Weber F, Schneider H, Laubenthal F, Nienaber CA, Sabin GV, on behalf of German CHYPHER (TM) registry. Sirolimus-eluting stent Cypher in patients with acute myocardial infarction [abstract]. Eur Heart J 2003;24 (Suppl):528.
60. Safian RD, Zidar J, Hermiller J, Greenbaum J, Goldberg S. Coronary stents. In: The Manual of Interventional Cardiology. 3th ed. Michigan: Physicians' Press, 2001; p. 511-615.
61. Regar E, Serruys PW. El estudio RAVEL. Reestenosis del cero por ciento: ¡un sueño del cardiólogo hecho realidad! Rev Esp Cardiol 2002;55:459-62.
62. 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.
63. Kapoor S. The angiographic pattern of restenosis after paclitaxel-eluting stents. Am J Cardiol 2003;92(Suppl):124.
64. Regar E, Lemos PA, Lee C-H, Tanabe K, Saia F, Degertekin M, et al. Subacute stent trombosis after sirolimus-eluting stent implantation in daily practice: results from the rapamycin eluting-stent evaluated at Rotterdam hospital (research) registry. J Am Coll Cardiol 2003;41(Suppl A):1053-202.
65. Degertekin M, Serruys PW, Tanabe K, Lee CH, Sousa JE, Colombo A, et al. Long-term follow-up of incomplete stent apposition in patients who received sirolimus-eluting stent for de novo coronary lesions. An intravascular ultrasound analysis. Circulation 2003;108:2747-50.
66. Leon MB, Moses JW, Weisz G, Teirstein PS, Fitzgerald P, Holmes DR, et al. The frequency and consequences of angiographic aneurysms after sirolimus-eluting stents: results from SIRIUS. J Am Coll Cardiol 2003;41(Suppl A):1030-181.
67. Degertekin M, Lemos PA, Lee CH, Tanabe K, Sousa JE, Abizaid A, et al. Intravascular ultrasound evaluation after sirolimus eluting stent implantion for de novo and in-stent restenosis lesions. Eur Heart J 2004;25:32-8.
68. Sousa JE, Costa MA, Abizaid A, Rensing BJ, Abizaid AS, Tanjura LF, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents. One-year angiographic and intravascular ultrasound follow-up. Circulation 2001;104:2007-11.
69. Sousa JE, Costa MA, Sousa AGMR, Abizaid AC, Seixas AC, Abizaid AS, et al. Two-year angiographic and intravascular ultrasound follow-up after implantation of sirolimus-eluting stents in human coronary arteries. Circulation 2003;107:381-3.
70. O'Neill WW, Leon MB. Drug-eluting stents. Costs versus clinical benefit. Circulation 2003;107:3008-11.
71. Cohen DJ, Bakhai A, Shi C, Githiora L, Berezin RH, Caputo RP, et al. Cost-effectiveness of sirolimus drug-eluting stents for the treatment of complex coronary stenoses: results from the randomized SIRIUS trial. J Am Coll Cardiol 2003;41(Suppl A):805-2.
72. Lemos PA, Serruys PW, Sousa JE. Drug-eluting stents. Cost versus clinical benefit. Circulation 2003;107:3003-7.