

# Drug-Eluting Stents: Efficacy, Effectiveness, Efficiency, and Evidence

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## BACKGROUND

Public health systems aim to improve the health of a population at a cost whose limits are set, one way or another, by society. To ensure that the health of a population is improved, clinical procedures that are supported by scientific evidence of a more favorable outcome (risk/benefit ratio) compared to any other alternative should be used. To ensure that the outcomes are achieved at an acceptable social cost, the cost of obtaining an outcome with each of the technically possible alternatives should be known.

The outcome of a health intervention can be measured by efficacy (in ideal experimental conditions), effectiveness (in real everyday conditions), utility (survival time adjusted for quality of life) and benefit (outcomes expressed in monetary units). The best scientific evidence on the outcome of therapeutic interventions comes from randomized clinical trials with no methodological weaknesses. That is, clinical trials provide information on the efficacy of the interventions. Efficacy is necessary for effectiveness but it alone is not sufficient. Effectiveness depends not just on efficacy but also on local factors, which may differ from those of the clinical trial (technology, experience, organization, etc). Efficiency is the ratio of the outcomes to costs that have to be met to achieve the outcome, thus classic efficiency analyses evaluate cost/efficacy, cost/effectiveness, cost/utility, and cost/benefit.<sup>1</sup>

When a new technology appears in medicine, the key questions focus on the outcomes and the costs with respect to existing technologies, though the answers to these questions do not usually come quickly. Thus, some effective techniques spread slowly

whereas other ineffective techniques do so quickly. Health systems are increasingly emphasizing the use of procedures of proven efficacy. Nevertheless, evidence suggests that some procedures are overused (they should not be indicated for the patient in whom they are applied) whereas others are underused (they are indicated but not used). Sometimes, new technology permits implementation of devices that provide a novel approach to an unresolved health problem. The expectations surrounding each new technology range from rejection in favor of a known approach to enthusiasm for immediate incorporation of the innovation into regular clinical practice.

Interventional cardiology is an excellent example of a discipline whose birth, diffusion and growth are closely related to technological development. It has evolved alongside the capacity of health technology at a given time. In the case of ischemic heart disease, the clinical approach has been revolutionized by technological contributions right from the start of interventional cardiology. In fact, interventional cardiology started with the first balloon dilatation of the coronary artery. Then, the introduction of a mechanical device, the stent, to tackle the problem of restenosis led to a reconsideration of treatment. In a few years, stenting became the method of choice for coronary angioplasty procedures. Nevertheless, even though the rate of restenosis has decreased by 10% or more, the incidence of in-stent restenosis currently ranges from 10% to 40%. Stents that release antiproliferative drugs, the so-called drug-eluting stents (DES), are one strategy that has been tested recently to minimize the problem. Their novelty, along with promising early results, have aroused expectations.<sup>2</sup> Subsequent results, less optimistic though still positive, along with the high cost of the new stents, have sparked a controversy.

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## THE CONTROVERSY

The REVISTA ESPAÑOLA DE CARDIOLOGÍA recently published 2 studies on the use of DES in Spain.<sup>3,4</sup> To

initiate a debate about these 2 studies, 2 experts were asked to give their opinions on the generalized use of such devices. One argued in favor<sup>5</sup> and the other against.<sup>6</sup> Their contributions were presented in a section entitled "Controversies" and frame the current debate that is taking place in the medical community on the topic. The expert who argued "against" mentioned 4 points: the limited availability of type and size of DES, safety concerns due to late in-stent thrombosis, the overestimation of clinical benefit, and the high costs. The expert who argued "in favor" selected different and even opposing evidence, except with regard to the costs—he recognized that the cost of DES is the true limiting factor. In fact, the author who presented the arguments for such stents explained that "if the cost of the drug-eluting stent was the same as a traditional stent, this controversy would be pointless and implantation of drug-eluting stents would be universal."

Moreover, different interpretations of the clinical consequences of the finding of restenosis in the examination are cause for further discrepancy. This suggests that cardiologists differ in acceptance and interpretation of angiographic or ultrasound parameters to determine outcome. With regard to safety, there is a lack of agreement on the importance of late thrombosis as a complication. Finally, the analysis of how widespread the technology is and proposals for the future reflect different concepts of the way in which the health system should respond to the evaluation and implantation of technology, particularly new technology.

## THE TECHNOLOGY

There are currently only 2 types of DES available for clinical use, namely the Cypher stent (Cordis, Johnson & Johnson) coated with rapamycin (sirolimus) and the Taxus stent (Boston Scientific) coated with paclitaxel, although in the near future several more will become available. Drug-eluting stents are currently only available in a limited number of lengths and diameters and with limited flexibility, so they are only recommended for lesions in vessels between 3.5 mm and 2.0 mm in diameter, and their use is contraindicated in certain coronary vessels. Their effect on the lesion can be evaluated from clinical outcomes such as event-free survival, major cardiac events and decrease in revascularization of the treated lesion in comparison with a control group. The results published for DES for these outcomes are favorable for DES, and benefit is seen in both patients with simple lesions and in subgroups of patients with a higher rate of restenosis (for example, diabetics, long lesions, or lesions located in the left anterior descending coronary artery). Although outcomes of more than 2 years of follow up are not available, the safety of these devices with respect to incomplete apposition of these

stents in the vessel wall or to aneurysms is not in question as such events are of no clinical relevance. The most important potential long-term complication is late thrombosis. Finally, the average unit price of DES is around €2000, approximately twice the cost of a conventional stent. The cost, then, is the true limiting factor for their systematic use.

## EVIDENCE AVAILABLE ON OUTCOMES

In this edition of the JOURNAL, an extension and update of a report on DES by the Catalan Agency for Health Technology Assessment and Research is presented.<sup>7</sup> The article comprises three parts, namely, a systematic review, a metaanalysis and a costs evaluation.<sup>8</sup> The systematic review synthesizes the evidence with regard to the greater efficacy and effectiveness of these devices, and to their safety—the safety of these stents is considered comparable to conventional stents. This evidence is based on studies assessed for internal consistency, comparable to one another and classified according to quality criteria for evidence depending on the type of design.

The metaanalysis of clinical studies provides quantitative indicators that summarize the effectiveness of DES at reducing the rate of revascularization. The relative risk (RR) of revascularization (risk of revascularization with DES compared to the risk of revascularization with a conventional stent) ranged from 0% to 79% according to the studies in the metaanalysis. The RR according to the metaanalysis is 31% (95% confidence interval, 19%-51%). That is, the evidence suggests that DES reduce the risk of revascularization in comparison with conventional stents, though the large confidence interval—even in the conditions of a clinical study—suggests that the range of uncertainty is still great.

Another variable obtained in the metaanalysis from the outcomes of the clinical studies is the number needed to treat (NNT), which is calculated as the reciprocal of the absolute risk reduction (ARR). For example, in the E-SIRIUS study, the risk of revascularization in patients who received a conventional stent was 20.9% compared to a risk of 4% in those who received a DES. The ARR was therefore 16.9%. The reciprocal of 16.9%, NNT, is  $1/0.169=5.9$ . The NNT gives an idea of the number of patients who need to be treated to produce a desired result, thus, the lower the NNT, the greater the efficacy of the procedure. In our example, for every 6 (5.9) patients treated with a DES instead of a conventional stent, revascularization is avoided in one patient. The NNT ranges from 4.4 to 8.0 for sirolimus-eluting stents and from 9.4 to 32.3 for paclitaxel-eluting stents.

Clinical studies have shown no statistically significant differences in the probability of other major coronary events (death or acute myocardial infarction) be-

tween DES and conventional stents.

The metaanalysis presented in this edition of the journal clearly illustrates the gaps that remain in our knowledge. Some gaps refer to clinical knowledge, for example, the long-term outcomes, safety, outcomes with different antiproliferative agents, outcomes in lesions not dealt with in the clinical studies or outcomes by patient subgroup. Other gaps refer to pathophysiological knowledge, for example, whether the drug inhibits neointimal growth or merely delays it.

## EVIDENCE AVAILABLE ON COSTS

The cost evaluation made by the authors provides information for Spain such as, for example, the impact on the budget of application of the new technology (an additional €818 718 for every 1000 patients), the additional cost per patient (€819) or the neutral cost at which generalized use would not affect the health budget (€1448). This cost evaluation is made from the perspective of the provider (hospital) with a time window of 1 year. The sources of information used for assessment of costs are very limited. The authors have probably used the best available and there seems to be only one cost/effectiveness analysis sponsored by the manufacturer of the stent under evaluation. When no information was available, the authors resorted to experts. That is, even when the best scientific evidence available for costs is used, large gaps in our knowledge remain. This might explain why there are such discrepancies with the costs estimated by other groups. In fact, the additional cost per patient calculated for Spain is much greater than the cost of €166 calculated by Lemos et al from the RAVEL and BENESTENT II studies in the Netherlands.<sup>9</sup>

## THE HEALTH SYSTEM PERSPECTIVE

To improve the decisions made by health services, knowledge of costs should extend to the medium term at least. Social and not just hospital costs should be included because some of the costs and benefits occur in primary health care and at the patient's home and workplace (indirect costs and benefits). Finally, the cost analysis is of little help if it does not take into account outcomes. Efficiency studies, for example, of cost/effectiveness, cost/utility and cost/benefit, with a social perspective should eventually be undertaken. The decision makers would then be able to base their value judgments on whether the extra cost of avoiding revascularization or infarction is socially acceptable. In the macroenvironment, the decision makers are those responsible for health policy, in the mesoenvironment, they are the managers, and in the microenvironment, they are the physicians and occasionally the

patients.

Every 1000 patients revascularized with DES are estimated to cost an additional €818 718 compared to revascularization with conventional stents. This calculation has taken into account values for effectiveness of DES regarding the number of revascularizations prevented. In other words, in interventional cardiology, for every 1000 revascularizations performed without DES, it would be possible to revascularize 108 additional patients, that is, a total of 1108 with conventional stents if we include revascularizations that were not prevented. In relative terms, for a similar amount of money spent on revascularization of 1000 patients with DES, it would be possible to install and supply an electrophysiological laboratory (€629 176)<sup>10</sup> with staff to cover 1 shift for 1 year (1 medical section head, 1 associated physician, 1 laboratory technician, 1 technical assistant/nurse, and 2 ancillary nurses, giving a total of €146 868).<sup>11</sup> In absolute terms, using the figures provided in the review, systematic use of DES as an alternative to revascularization instead of the conventional approach during 1 year would be equivalent in cost to the installation and equipping of 10 more electrophysiological laboratories (€6 291 755), with staff necessary to cover 3 daily shifts (1 medical section head, 9 associated physicians, 5 laboratory technicians, 5 technical assistants/nurses, and 10 ancillary nurses, giving a total of €726 260 per laboratory), and 141 more revascularizations with conventional stents for each new room (1410 revascularizations=[total additional cost per revascularization with DES for 1 year–cost of 10 new electrophysiological laboratories]/unit cost of *de novo* intervention after 1 year with a conventional stent). For the calculations included in this paragraph, the costs have been adjusted to 2004 prices with an annual inflation of 3%.

Of course, the argument above is not a proposal for action but rather an example of the complexity of decision making when competitive strategies are available in which the key element is the opportunity cost—the extent to which a resource has to be foregone to obtain an additional unit of another. This implies that it is necessary for the health system to know the costs and outcomes of different strategies in the management of coronary revascularization, and to identify patients in whom the procedure is appropriate.

## APPROPRIATE USE OF MEDICAL PROCEDURES

The annual reports on coronary intervention by the Spanish Society of Cardiology illustrate the enormous variability in the rates of revascularization among regions of Spain. This might suggest that some regions overuse revascularization whereas others underuse such procedures. In Spain, few studies have investiga-

ted underuse but, as in other countries, overuse has been shown.<sup>12</sup> These findings suggest that resources are probably being dedicated to patients who do not benefit from treatment because revascularization procedures are only effective and cost-effective if they are applied to subjects indicated for such procedures. Cardiologists are already aware of this problem, and selective use of these stents has been proposed to remedy overuse. In fact, the Integrated Plan for Ischemic Heart Disease considers the availability of these devices in centers for use in patients who would most benefit from them.<sup>13</sup>

The underlying idea is that, given the high cost of DES, and because outcomes vary according to type of patient (for example, diabetic patients) and lesion (for example, lesions in small vessels, location, length of stenosis, etc), standards for use could be defined for DES. Each patient could be characterized by a combination of variables and then classified, thus determining whether implantation of the DES is appropriate, inappropriate or uncertain by application of these standards. The standards should reflect the best scientific evidence available on costs and outcomes to determine in which patients the technique is appropriate and in which patients it is more appropriate than in others. This would maximize the efficiency, given that the limited resources would be applied to patients in whom the best outcomes are obtained. It should also be possible to readily update these standards, given that costs can change (the cost of almost all new technologies decreases as they become more widely available), scientific evidence on outcomes is continually produced and new models of stents may become available or they may become available with different antiproliferative drugs. The standards developed with this methodology are not perfect—few things are in medicine—but their application would notably improve the quality of care and outcomes.<sup>14</sup> Coronary procedures are one of the areas where development of such standards has been greatest.<sup>15-17</sup> If this method were applied, the standards would have to be updated and adapted, particularly for DES. New information technologies could be applied to ensure that they are permanently updated and available in electronic format and real time in the cardiology department.

## CONCLUSIONS

Drug-eluting stents represent an important advance in coronary revascularization techniques, but their high cost compared to conventional stents limits more widespread use. They have been shown to be more effective than conventional stents in certain patient groups with certain lesions, but scientific evidence is lacking for medium and long-term outcomes and outcomes in other types of patient and lesion.

Our knowledge of costs, and above all, efficiency, is even more patchy. In this edition of the journal, the metaanalysis and cost analysis illustrate how, despite the methodological quality of systematic review and metaanalysis, areas still remain that need to be investigated.

For these reasons, clinical investigation of costs and outcomes of DES compared to alternative strategies should be encouraged. Such studies can be conducted in Spain where, in 2002, there were 1906 DES implanted—a figure similar to the number of patients included in the metaanalysis. More still will probably be implanted in 2004. Must we wait for clinical trials to be published or can we produce real evidence of costs and outcomes for DES implantation in several thousand patients each year in our country?

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