

Drug Eluting Stent Thrombosis: Light in the Darkness and a Defense of the Obvious

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When the first stents started to be implanted in the 1990s (initially the Gianturco-Roubin and the Palmaz-Schatz), which we nowadays call “conventional,” the indications for their use were of the so-called “Benestent Type.” These were mainly anatomical: lesions in vessels of more than 2.75 mm and <15 mm long in patients with stable angina. The extraordinary contribution of these coronary endoprostheses to increasing the safety of interventional procedures, evident from the fact that the rates of acute occlusion were reduced by 1%-2% with its use, which added up to 12% of cases, was associated with the systematic administration of dual antiplatelet regimens. This fact made the restrictive phase of clinical indication in which stents were only implanted in cases of “occlusion or threat of occlusion of the artery treated” be overcome and its use became widespread in clinical and anatomical contexts different from those which justified the initial concession of the EC mark that had permitted them to be marketed. The reason was simple. The results were better than those obtained by treating these same lesions (off-label lesions, as they are nowadays defined) with conventional balloon catheters without a stent placement.

We are now experiencing a similar situation, although this time we are comparing the most up-to-date drug-eluting stents with the conventional ones. The current situation is as follows: *a*) with the exclusion of certain clinical situations or cases of specific patients, percutaneous revascularisation has not modified mortality rates more than surgery; *b*) in contrast, it has contributed to making percutaneous coronary revascularisation procedures very safe; *c*) the technological improvements introduced (balloon, conventional stent, drug-eluting

stent) have drastically reduced the need to perform further revascularization procedures (restenosis in more than 35% in the era of the exclusive use of balloon catheters; 20% with conventional stents, and between 5%-10% with drug-eluting stents); and *d*) each new technology introduced has shown new problems (occlusive coronary dissection and restenosis with the balloon catheters, or thrombosis with conventional and drug-eluting stents). Similarly, after becoming widespread in cardiac surgery, cases of occlusion of venous grafts (20% in the first year and 4% for each additional year) and of arterial grafts or thrombosis of the mechanical valve prostheses (at annual rates of 1%-2%) were detected over time.

The question, at least from my point of view, is not to show up these new problems (which occur as a result of having introduced new techniques that contribute great benefits), but to understand their causes and find solutions to abolish, or at least minimize, their negative effects, without dramatizing neither their consequences nor their incidence or using the information in a skewed manner to defend media interests.

The article published in this edition of *Revista Española de Cardiología*¹ is an example of how far the conjunction of the authors' good will can go when they try to analyze the results of their actions for watching over their patients' safety, and a retrospective data analysis, in the absence of comparison groups. In this article, it is pointed out that the use of the paclitaxel-eluting stent in a population of 604 patients treated between 2003 and 2006 showed an overall late-stent thrombosis rate of 3.8% (5% in the 464 patients in the off-label use group) in a 3-year follow-up period. My first comment is to thank the authors for the effort and intellectual honesty in shedding light on this debate. In my opinion, it is disproportionately excessive in its negative aspects, but I don't want to stop seeing the woods because of the trees. Consequently, I would like to highlight what is most relevant, so I will not focus my comments on the limitations of the study—of which there are many as the authors themselves point out: disparity in the definition of “off-label,” both that used in the article and in the references; characteristics of poor prognosis of the population treated; single-centre retrospective observational study design; losses in follow up; skewed gathering of information; failure to assess relevant variables such as the degree of compliance with antiplatelet treatment; or the decision to use a drug-eluting

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stent and the implantation technique being dependent on different operators, among others, so as not to unjustly extrapolate the conclusions to the generality of the procedures to place drug-eluting stents that are currently performed.

I am more interested in discussing and demonstrating the concept of effectiveness and safety of drug-eluting stents, particularly the one applicable to its use in populations with an off-label indication.

Clearing up the Confusion

1. The studies showing higher rates of combined major ischemic events when using drug-eluting stents rather than with conventional stents, including that published in this edition, analyze populations that are not comparable, or which are at high risk. Their clinical-angiographic characteristics justify the differences in the ischemic events seen during the follow-up.² Differences that, on the other hand, and fundamentally, refer to the different frequencies of need for further revascularizations, not to mortality rates (the authors of the article published in this edition, in fact, fail to find differences in the isolated event of death).

2. The use of drug-eluting stents with an off-label indication (in the same way as occurred with conventional stents when compared with the results of dilatation only with balloon in off-label groups), in at least 2 years follow-up, is associated with death/non-fatal myocardial infarction rates lower than those that would be obtained if these patients were treated with conventional stents.³

3. Not only are there no adverse differences for drug-eluting stents in the rate of major ischemic events (death or non-fatal infarction) between comparable groups (called in statistical terms "matched by propensity score"), but the results ostensibly favour them (rate of major events, 23.6% vs 16.7%; $P < .004$), as previously mentioned, mainly at the expense of a reduction in the need for further target lesion revascularization (16.4% vs 7.8%; $P < .001$) and target vessel revascularization (20.2% vs 13.1%; $P = .0003$).⁴ Other groups that have also analysed comparable patients have shown the same: absence of differences in rates of procedural complication or in acute stent thrombosis (on-label, 0; off-label, 0.3%; $P = .55$), in those for sub-acute thrombosis (0 vs 0.6%; $P = .3$) or in late-stent thrombosis (1.4% vs 1.2%; $P = .78$). Neither were there any differences observed in the death rates during the follow-up (4.9% vs 4.1%; $P = .53$) or in those for acute myocardial infarction (1.9% vs 2.4%; $P = .83$). Only the off-label use has been associated with higher rates of new revascularizations (13.2% vs 24.1%; $P = .0001$), as corresponds to more complex populations. These higher rates of further revascularizations are those that increase the frequency of the combined event rate (17.6% vs 28.2%; $P = .0001$).⁵ This supports the criteria that the use of drug-eluting stents in off-label

contexts or patients with complex characteristics is adequate and safe.⁶

4. In daily practice, the off-label definition is extraordinarily ambiguous, and is considered to include anatomical contexts such as lesions with restenosis in saphenous vein grafts, left main coronary artery lesions, ostial lesions, and chronic total occlusions. It also includes angiographic features, such as arteries < 2.5 mm or > 3.75 mm in diameter, or lesions lengths < 30 mm,⁶ and finally clinical contexts such as acute myocardial infarction or severe left ventricular dysfunction. According to the NHLBI registry, among the 6551 patients analyzed, the off-label indications presented in 48.7% the patients treated with drug-eluting stents, against 54.7% of those treated with conventional stents, and in the Applegate et al³ series, in 25% of both types of stent (drug-eluting and conventional). Does this mean that there are other reasons for choosing one type of stent or the other? Probably it does. Indeed, in my opinion there are 2 reasons explaining the above: firstly, the need to look for the greatest theoretical benefit for the patient, based on an individualized decision-making process according to their characteristics of risk. Thus, more drug-eluting stents are chosen when there is a greater theoretical likelihood of clinical restenosis, due to diabetes, long lesion or location in a small vessel or unfavourable clinical conditions, such as prior percutaneous coronary intervention or surgery, renal failure, or multivessel disease. The second reason is of economic nature. The limitation of the widespread use of drug-eluting stents has only one reason at the moment: the resources available for their purchase or, if you prefer, the type of health care system you have: a capitation payment system, as is the case in Spain, or a fee-for-service system, as is the case in France, Germany, or the United States. Thus, the first case usually limits its use, and the second promotes it when health insurance systems include its payment.⁷

5. The differences in the incidence of late-stent and very-stent onset thrombosis are also probably related (and there is increasingly more evidence that not all drug-eluting stents behave in the same way) to the characteristics of the stent itself: depending on the metallic platform (which show great differences between some models and others), the type of antiproliferative agent and its cell-inhibiting power and the selectivity of its effect (some affect the endothelial cells more than others and, therefore, these influence reendothelization and vascular function in an inconsistent way), or with the polymer that maintains and controls the release of the drug (in fact late-stent thrombosis has been described from reactions to the polymer). Here, we interventional cardiologists in particular must make a genuine effort to be unaffected by commercial pressures and be objective when using one type of stent or another, based on proven scientific information and for the exclusive benefit of the patient.

Defending the Obvious

In recent years, attempts have been made to demonize drug-eluting stents, for which the problem of the phenomenon of late stent thrombosis has been used.

In this respect, it is worth highlighting several facts. Firstly, more than 2 years have needed to pass for things to start returning to normal and contradict those who even published adverse data (such as the Swedish Registry and the Basket-late study, among others), when actually they were not only not adverse, but entirely the opposite.⁸⁻¹⁰ Secondly, conventional stents in general are excellent technology, but they also have problems and limitations. Indeed, they are not always as innocuous as they try to make us see them in comparison to the drug-eluting stents. In large series such as that of Doyle et al,¹¹ analysing 4503 patients treated with conventional stents and with dual antiplatelet therapy between 1994 and 2000, the rate of thrombosis was 0.5% per month, 0.8% the first year, and 2% at 10 years (95% confidence interval [CI], 1.5-2.5). Furthermore, mortality in the first month was significant both after a late-stent thrombosis (odds ratio [OR] =22; 95% CI, 3.1-159) as with the very-late-stent one (OR = 40; 95% CI, 15-107) with conventional stents. The most interesting finding is that clinical restenosis at 10 years was 18.1% and in this series presented as acute myocardial infarction in 2.1% of the cases. In the Chen et al¹² series, among the 1186 patients with stent restenosis analyzed, 112 (9.5%) had an acute myocardial infarction as the first manifestation of the restenosis, and 8 (7%) of them died. Based on this, with drug-eluting stents only 5-10 restenoses take place every 100 patients treated, versus 20-25 restenoses in those treated with conventional stents (of which 2%-9% manifests as an acute myocardial infarction, and 7% of these died). Consequently, drug-eluting stents could compensate for at least 10 infarctions related to the restenosis phenomenon/1000 patients treated and, therefore, equal the alleged damage of late stent thrombosis, the incidence of which was 0.5% (5 potential infarctions related to each stent thrombosis per 1000).

It is evident that the fact that restenosis appears as an infarction is associated with an increase in mortality in comparison to the absence of restenosis (OR =2.37; $P<.001$) or with the restenosis that does not manifest as a myocardial infarction (OR =2.42; $P<.001$). I do not intend these considerations to belittle the importance of these adverse events, but I do not believe anybody will find it strange that a late stent thrombosis or a restenosis appearing as an infarction (especially if it affects a vessel with great myocardium at risk) can entail a mortality of 30% (39% in the study referred to in this editorial), just as in the case of any acute myocardial infarction, about which we know that at least 1 in 3 do not reach the hospital alive.¹³

Thirdly, if we take another study¹⁴ reflecting the differences between on-label and off-label use into consideration, with 5541 patients treated with drug-

eluting stents, 2588 (47%) of them being considered off-label, we see that, in fact, the differences are limited to a higher rate of early events (therefore, not related to late or very late stent thrombosis). However, there were no differences at 1 year (adjusted OR =1.10; 95% CI, 0.79-1.54; $P=.57$), and only as it corresponded to a more complex population at greater risk of restenosis (even then it is very low: 7.6%), a greater rate of need for new revascularization was found (adjusted OR =1.49; 95% CI, 1.13-1.98; $P=.005$), which would have been much higher had conventional stents been used.

Fourthly, and from the industry perspective, manufacturers theoretically have the duty to clearly state the indication (on-label) approved for use, to what extent adequate use meets the patients' unmet needs and the results of its use. But it is also true that the indications broaden because of the demand of the market, and it is not uncommon for them to obey the conviction of medical practitioners that a technology can solve problems that have hitherto had no solution for patients, even when there is scant scientific evidence available to date. Consequently, scientific evidence usually arrives in the wake of the use of devices or drugs in contexts that were not initially authorised. Large databases, with more than 408 000 patients, such as the American College of Cardiology National Cardiovascular Data Registry,¹⁵ describe how much drug-eluting stents are used and their results in four indications considered *off-label* (acute myocardial infarction, stent restenosis, lesions in saphenous vein grafts, and total chronic occlusions), which are 24% of the procedures. In this way, it has been shown that the incidence of early events after the use of the drug-eluting stent is even lower than what would be expected to be obtained in a theoretically validated model.

This is how science actually advances, opening new pathways and solving the problems inherent to all new developments. It seems that we are on this pathway, by improving the characteristics of the stents, optimizing their placement, looking for more biocompatible, less thrombogenic polymers, adapting the pharmacokinetic characteristics of the antiproliferative molecule so that it does not induce inflammation, and opening new pathways to the indication of more effective antiplatelet agents. In this respect, the scene is very encouraging. For example, the third-generation antiplatelet agent Prasugrel has been shown to reduce the rate of stent thrombosis by 63% (from 2.31% to 0.84%; $P<.0001$),¹⁶ which will mean preventing at least 10 stent thromboses per 1000 patients treated. Can anybody doubt the impact this will have?

If we really paid more attention to the "alarmists" than to the "constructive critics" we would not be where we are today, Dr Andreas Gruentzig would not have performed the first human angioplasty on September 16, 1977 interventional cardiology would not be what it is today and thousands and millions of patients in the world would not have benefited. Does anyone believe that if percutaneous coronary intervention, with all the limitations

and problems it has experienced since its beginning, and those which we will experienced were not useful for patients, it would have grown in Spain (and in equal proportions in the world) between 1990 and 2005 from 2507 procedures/year to 57 041?¹⁷

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