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Why it is preferable to use non-drug-eluting stents

Por qué usar preferentemente stents no farmacoactivos

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Since the introduction in Europe of first-generation drug-eluting stents (DES) in 2002 (the FDA did approved them until 2004), their use quickly grew in Spain and in 2005 exceeded 50 % of all implanted stents (41,352 DES vs. 39,217 conventional stents, Spanish Cardiac Catheterization and Coronary Intervention Registry). According to this registry, there has been a sustained growth until 2011, when 58,211 DES were implanted vs. 36,490 conventional stents (61.47 %). Up until that year (last record available)[1], a total of 428,748 DES had been implemented in Spain. However, variations of use among hospitals and among the autonomous regions, which provide the funds for health, are huge (**Figure**).

Similarly, in 2011, in the Basque Country, 81.49 % of implanted stents were DES, and in Galicia it was 49.08 %. Andalusia remains slightly below average (58.77 %), but at the Torrecárdenas Hospital it only reaches 17.96%. Variability in any aspect of medical practice requires careful analysis.

There are many published studies about the benefits of the DES, usually financed by manufacturers in order to get the approval of agencies for their use (FDA or European market). The following data comes from some registries, such as the Spanish Cardiac Catheterization and Coronary Intervention Registry or, one of great importance, as the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).

In 2007, the first analysis of Swedish registry showed that the use of DES was associated with a higher mortality rate than conventional stents[2]. However, in our environment, the predominant use of first-generation DES was unstoppable. It was not the only study that sounded the alarm[3], the NICE guidelines (The National Institute for Health and Clinical Excellence) of the Great Britain's National Health Service [4] limited the use of DES to lesions less than 3 mm in diameter or with a length greater than 15 mm, and when the difference in price between the DES and conventional stents was under £ 300.00 (about € 345.00). However, the trend in the use of DES

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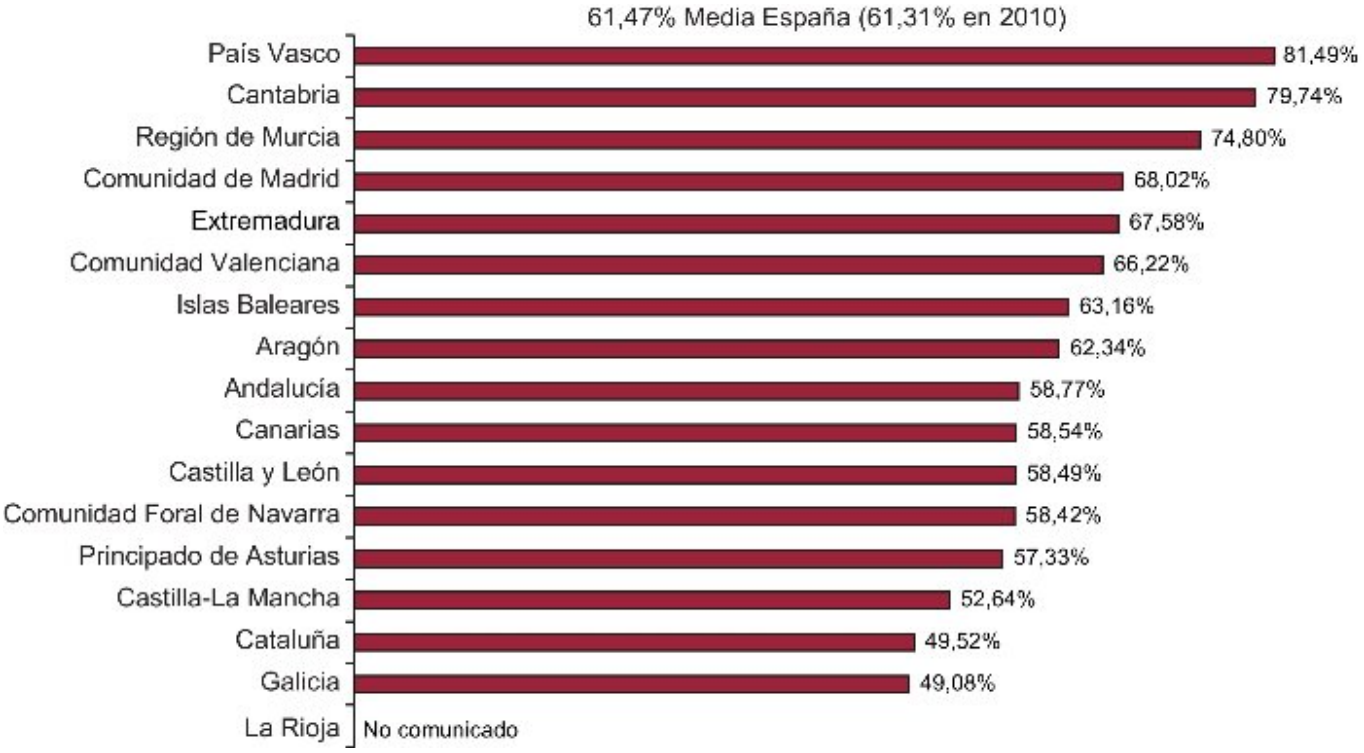

Figure. Percentage of DES in relation to the total number of stents implanted by autonomous regions of Spain. Taken from Diaz JF, et al.[1] with permission from the Revista Española de Cardiología.

followed an upward curve, probably due to the influence of the flurry of studies on their benefits (sometimes with zero rates of adverse events), and supported by marketing strategies showing a new and effective device against what had been singled out as being the main problem, restenosis. In addition, first-generation DES had levels of navigability and flexibility, and therefore a safety of use, much lower than conventional stents (without any reference in the literature).

The DES have shown only one advantage over conventional stents: reducing the rate of restenosis. In the first SCAAR record, the restenosis rates were 4.5 vs. 5.5 %, respectively[2]. However, when analyzing the studies intended for the approval of the various devices, the figures are different: in the RAVEL study published in 2002[5], the sirolimus-eluting stent was compared with conventional stents, and the restenosis rate was 0 vs. 27%. Surprisingly, the stent thrombosis rate was 0 % in both branches.

The Achilles heel of the DES are essentially two:

- Safety: the risk of late and very late thrombosis associated with DES was published immediately[3] and therefore, the need for dual antiplatelet therapy for an indefinite time. Cases of thrombosis with first-generation DES at 6 and 7 years after implantation have been published, and we have witnessed them. This problem explains the higher mortality in early records with this type of stent, compared to conventional stent angioplasty.
- Cost: The price difference when compared with balloon angioplasty or conventional stents, which was initially abysmal (in Spain it was € 2,000 at the time of the monopoly of the first supplier), ruled out the possibility that the marginal benefit generated by the reduction of restenosis would justify the increased cost of an indiscriminate use of DES.

However, all studies that compare something other than the certification of use of stents by state agencies, for example comparing angioplasty with coronary artery bypass surgery in different subgroups, show that the important endpoints of outcomes (mortality, myocardial infarction, stroke) do not differ when surgery was compared with balloon angioplasty, conventional stents, or DES (FREEDOM, BARI, ARTS trials)[6]. It means that there is no ethical dilemma in which the patient's safety is at stake. It has been argued that res-

tenosis is not a trivial phenomenon, and it has been said that it causes myocardial infarction in even up to 20% of cases[7]. All this to put on the same level the important endpoints in comparative analyzes. It is difficult to understand in clinical practice, on the one hand, the variable definition of infarction, used depending on what it is wanted to show, and on the other hand, not to express consternation at the system of care and monitoring of something which in its series has shown such percentage of infarcts as clinical presentation of restenosis.

Moreover, the marginal benefit in this situation does not result in a substantial change in Interventional Cardiology activity, because in the Spanish Cardiac Catheterization and Coronary Intervention Registry the number of interventions in restenotic lesions has continued to rise year after year, with stabilization in 2010 and 2011, despite the massive use of DES since 2005.

In short, the differential cost of the use of DES compared with conventional stents has meant at least 750 million euros over the last decade in our country. In Torrecárdenas Hospital, where Interventional Cardiology activity began in 2004, over 5,500 percutaneous transluminal coronary angioplasties (PTCA) have been performed since then, and over 8,000 stents have been implanted. If DES had been used according to the Spanish average percentage (61.5 %), instead of 18% of this hospital, 4.5 million euros more would have been spent. Yet our health outcomes are no different from those achieved in other hospitals or autonomous regions which use DES indiscriminately. Our activity in the treatment of restenosis has remained around 5% year after year.

If DES were used according to their true value, which is to reduce restenosis in lesions with high risk of restenosis, the rate of use would not exceed 30% (SCAAR).

In our hospital, the use of DES can be summarized as, high risk of restenosis in lesions whose restenosis has clinical significance:

- Long lesions in vessels smaller than 3 mm in diameter, especially in diabetic patients.
- Restenotic lesions.
- Chronic occlusions.
- Great myocardial territory at risk.

It must not be forgotten that angioplasty, in chronic coronary artery disease, improves the quality of life by controlling the symptoms, but does not change survival.

Acute myocardial infarction

Primary angioplasty is an increasingly important part of our activity, both in volume and because it is the Interventional Cardiology procedure with the greatest influence on survival. Recent studies suggest that there is no advantage in using DES in this case[8]. Moreover, it is proposed that in many cases even stent implantation can be avoided after thrombus aspiration, preventing the serious problem of no-reflow after stent implantation[9,10]. Another option, in this case, is the use of micronet mesh-covered stents which prevent thrombus migration with excellent results[11].

Current situation

Fortunately, first-generation DES have been replaced with safer stents. In the latest report from SCAAR[12], the annual rate of revascularization due to restenosis was 4.6 % in the conventional stent group, 3.1% in first-generation DES and 2.2% in new-generation DES. More importantly, the proven intrastent thrombosis rate at 2 years changes from 1.3% in first-generation DES to 0.6 % in new-generation DES. In SCAAR data that were published in PLOS Medicine in February 2013[13], which analyzes the implantation technique (stent inflation pressure and postdilatation) in 93,692 stents (69 % conventional stents) which were implanted since 2008 and followed up for two years, the overall rate of restenosis was 5.09 %, and thrombosis 1.07 %. They were mainly influenced by the implantation pressure (minimal thrombosis with 20 to 21 atmospheres and more restenosis with postdilatation).

Therefore, the new stents, both conventional stents made out of different alloys and various passive coatings, and new DES, are getting increasingly better, safer, easier to implant and with better long-term outcomes.

Improving implantation techniques is increasingly critical for the outcomes. Keeping our practices updated and safe is a daily challenge. And, as it is shown by this saga of the DES, it is necessary to be very critical of technological developments and constantly monitor our results.

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