Editorial Comment

The Use of Drug-Eluting Stents in Everyday Clinical Practice: Can the Results of Randomised Trials be Achieved in the "Real World"?

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The addition of drug-eluting stents (DES) to the cardiologist's therapeutic arsenal has undoubtedly been one of the most important developments in interventional cardiology in recent years. It has been described, with some justification, as the third great revolution in percutaneous coronary procedures, following simple balloon angioplasty and the implantation of metallic stents. The efficacy of these devices in the short, medium and long term, as described in recently published randomised and carefully designed clinical studies, has pushed interventional cardiologists to use them in a variety of anatomical and clinical conditions, many of which have not been investigated or studied adequately before now.

The main benefit from the use of DES in the interventional, non-surgical treatment of coronary artery disease lies in the significant reduction of in-stent restenosis in the lesions being treated. The commercially available DES are the Cypher™ stent, which releases rapamycin locally, and the TAXUS™ stent, which releases paclitaxel. The first randomised, clinical trial of the Cypher stent, the RAVEL study,[1] included 238 patients with single-vessel coronary artery disease and de novo lesions that were selected very carefully (short length <10 mm, low or medium risk, in vessels with reference diameter ≈3.0 mm). The frequency of angiographic restenosis at six-month follow up was 0% in the DES group and 26% in controls who were treated with bare metal stents (BMS). The larger SIRIUS study[2] evaluated the use of Cypher stents in a group of 1058 patients with more complex de novo lesions. That study found that DES had a beneficial effect in patients with higher risk coronary lesions, such as long stenoses in relatively small-diameter vessels, but were less beneficial in diabetic patients, while there was a need for target vessel revascularisation (TVR) in only 8.9% of the DES group, compared with 21% of controls. However, the study population was comprised of patients who underwent angioplasty only in a single vessel, in vessels 2.5-3.5 mm diameter and for lesions 5-30 mm in length. Excluded were patients with stenoses in venous grafts, in bifurcated vessels, with chronic total occlusions or restenotic lesions, as well as patients with acute myocardial infarction, severe unstable angina or chronic renal failure, as was the case in all randomised DES trials. The combined study New-SIRIUS, which included the populations of the E-SIRIUS[3] and C-SIRIUS[4] studies for a total of 452 patients, reported a restenosis rate of 5.1% in the group who received a Cypher stent, compared with 44.2% in controls who received a BMS, in spite of the fact that the former group had longer lesions in smaller diameter vessels.

As far as paclitaxel-eluting stents are concerned, the small first study, TAXUS I,[5] with a population similar to that of RAVEL, found a six-month restenosis rate of 0% in the DES group, compared to 10.3% in controls. The larger TAXUS II study,[6] again with a population similar to that of RAVEL (single-vessel disease with lesions <12 mm in length in vessels 3.0-3.5 mm in diameter) reported a six-month restenosis rate of 2.3-4.7%, depending on the time-mode of drug release, in the DES group, compared to 17.9-20.1% in the control group with BMS. In the TAXUS IV study,[7] where the patient characteristics were similar to those in the SIRIUS study (single-vessel patients with lesions 10-28 mm long in vessels 2.5-3.5 mm in diameter), over a nine-month follow up the in-stent restenosis was 5.5% in DES patients and 24.4% in controls. Recently, the TAXUS VI study,[8] which also had a nine-month follow up period, showed that the use of paclitaxel-eluting stents in a population with lesions of higher risk than in any other published study (single-vessel and multi-vessel, with de novo lesions 18-40 mm long in vessels 2.5-3.5 mm in diameter), was associated with a significant reduction in in-stent restenosis (9.1% versus 32.9% for patients receiving BMS) and in TVR (6.8% versus 18.9%, respectively). A subgroup analysis in this study, as well as in TAXUS IV, (patients with diabetes mellitus, small diameter vessels <2.7 mm, long stenoses) showed that the beneficial results were preserved in all categories of patients and lesions. In none of the above studies, however, was there any difference between BMS and DES as far as the "hard" endpoints of death and acute myocardial infarction were concerned: the benefit from the use of DES lay in the significant reduction in the need for target lesion revascularisation (TLR) and TVR, which resulted in a significant drop in the incidence of major adverse cardiac events (MACE) and an increase in event-free survival time.

The exceptional results of the randomised trials led to the design of large prospective registry studies, which evaluated the use of DES in a wide spectrum of patients with clinical and anatomical characteristics much more complex than in the first studies, from which they had been excluded. The RESEARCH Registry study[9] compared the unrestricted use of Cypher stents in 508 patients from everyday practice with BMS implantation in a group of 663 patients treated during the period immediately prior. More than 60% of the RESEARCH patients would have been excluded from earlier randomised, clinical studies on clinical or anatomical grounds (43% of them had type C lesions, by the ACC/AHA classification). The incidence of in-segment restenosis in 441 patients of the Cypher group who underwent repeat coronary angiography was 7.9%. Overall, the incidence of MACE during a 12-month follow up period was 14.8% in the BMS group and 9.7% in the DES group, representing a risk reduction of 34%. The need for TLR, guided by clinical events, was 10.9% for BMS and 3.7% for DES, representing a risk reduction of 65%.

Another large study, the e-CYPHER Registry,[10] included over 12000 patients from everyday practice, 49% of whom would have been excluded from the first randomised studies. Over a six-month follow up period, MACE-free survival in the patients who received a Cypher stent was 97%, which amounted to an excellent prognosis for these patients, who had risk characteristics that are encountered in daily practice. The WISDOM Registry study,[11] which had a similar design to e-CYPHER, included 778 patients with characteristics corresponding to everyday practice (25% type C lesions by ACC/AHA) in whom TAXUS stents were implanted. The overall incidence of MACE at six months was 4.3%, while the TVR rate over the same period was 3.0%. In all three of the above registry studies, the use of DES under "real world" conditions gave a rate of late thrombosis ranging between 0.4% and 0.8%, which was no different from that seen in large series using BMS. New studies of the use of DES in patients from daily practice, such as the Milestone II Registry, RECIPE, TAXUS-ARRIVE, are currently in progress and their results are awaited with great interest.

The efficacy of Cypher stents in everyday clinical practice in Greece was examined in a study by Dardas et al, published in this issue.[12] This study included patients with coronary atherosclerotic disease who were treated by percutaneous angioplasty and the implantation of Cypher stents. A group of 91 such patients underwent repeat coronary angiography 8 ± 2.4 months after the procedure, either as a routine examination or because of symptoms or signs of recurrence of myocardial ischaemia. Although the baseline clinical and angiographic characteristics of the total patient population treated are not given, those of the patients in the group who underwent repeat angiography indicate a high-risk population who would have been excluded from the historical randomised DES studies and who are representative of the "real world" circumstances prevailing in an interventional cardiology department today. As far as the percentages of patients with unstable angina (43%), diabetes mellitus

(26.7%) and type B or C lesions by the ACC/AHA classification (90.5%) are concerned, the population of this study is similar to that of the RESEARCH, e-CYPHER and WISDOM studies. The diameter of the vessels in which DES were implanted (2.5 ± 0.48 mm) is among the smallest reported in either the randomised or the "real world" studies. Furthermore, 16.1% of the stenoses included a vessel bifurcation (high risk lesions), while overlapping stents were used in 31% of patients.

In the Dardas study the safety of these new stents is reconfirmed. As regards the occurrence of late thrombosis only one case is reported, following the early interruption of clopidogrel treatment, while there were no deaths. Here it is important to stress the need for a combination of antiplatelet treatment with aspirin and clopidogrel or ticlopidine in all patients for at least six months and preferably 12 following the stent implantation, because of the delayed neoendothelisation within the DES. In every study, subacute or late in-stent occlusion was correlated with the discontinuation of antiplatelet treatment. The restenosis rate after the use of DES in the Dardas study was low, although the percentage with angiographic restenosis is not given for each category of patients (routine repeat angiography or recurrence of ischaemia). The late loss of lumen (0.04 ± 0.49 mm) recorded in these patients was exceptionally small and compares only with that reported in carefully designed studies that included selected patients with relatively low risk. The fact that 40% of the patients with confirmed restenosis (4 out of 10) were diabetics, whereas the incidence of diabetes among the patients who underwent repeat angiography was 26.7%, underlines the association between diabetes and restenosis, a finding that was confirmed by the statistical analysis. A higher incidence of restenosis in patients with diabetes mellitus who underwent implantation of Cypher stents was also reported in the SIRIUS study,[2] where a restenosis rate of 17.6% was seen in diabetic patients, with an even higher rate for those who were insulin-dependent (35%). In contrast, in the DIABETES study[13] (exclusively diabetic patients) the restenosis rate was 7.7% and in New-SIRIUS it was 10.8%, while in the e-CYPHER study the frequency of MACE among diabetic patients over a six-month follow up was 6.6%. In the TAXUS IV and VI studies the restenosis rate in diabetic patients was reported to be <6.7%, even for the insulin-dependent. It is clear that more data are needed before sure conclusions can be drawn concerning the efficacy of the Cypher stent in patients with diabetes mellitus, or with regard to the possible superiority of the TAXUS stent in this group of patients. The type of in-stent restenosis following the implantation of a Cypher stent, as reported in the Dardas study, agrees with findings published previously. The focal, short restenosis is the type most commonly found, in contrast to the hyperplastic-proliferative, long type of lesion and the total occlusion that are encountered more often in restenosis following BMS implantation. The treatment of this type of in-stent restenosis with a new plain balloon angioplasty or implantation of a new DES is associated with excellent results, as recorded in this study. The evidence from the Dardas study in this issue indicates that the implantation of Cypher stents in everyday practice for the percutaneous treatment of patients with coronary artery disease is of high immediate and medium term efficacy, while the incidence of MACE is small, even though the study was not designed to show precise percentages or comparisons with the use of BMS.

However, these results should not push interventional cardiologists in the direction of the exclusive use of DES in percutaneous coronary interventions. Even in the RESEARCH study 29% of patients did not receive DES exclusively, because of the unavailability of suitable stents or the physician's choice. These stents may certainly be used safely in patients of everyday practice who have more complex lesions, but in view of their exceptionally high cost, as well as the absence of sure conclusions regarding specific clinical or anatomical conditions (disease of venous grafts, diabetic patients, acute myocardial infarction, large-diameter vessels, stenosis of bifurcations) and their lack of effect on the "hard" endpoints of acute infarction and death, for the time being we should continue to follow faithfully the guidelines and indications for their use in selected groups of patients who have a high risk of restenosis. Their superiority has not been proved in cases of implantation in short lesions, in vessels of diameter >3.0 mm, or in stenoses of bifurcations, which make up a significant percentage of the lesions encountered daily, while issues such as the late creation of local aneurysms and late incomplete apposition, or a late local inflammatory reaction to the polymer, have not been fully investigated. Furthermore, the results from the long term follow up of patients with DES are not yet known, while the late catch-up phenomenon, which tends to reduce their long term efficacy, has already been reported.

In any case, the biggest problem arising from the possible generalisation of the use of DES in the percutaneous treatment of coronary artery disease under

present conditions is the dramatic increase in cost it entails, which would have consequences impinging on the social policies of health care providers. A cost reduction, in combination with the clarification of their long term efficacy and the availability of new devices with active drugs and polymers, are prerequisites for the extension of their use in the future.

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