Paclitaxel-Coated Balloon for Recalcitrant In-Drug-Eluting Stent Restenosis*

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Complete percutaneous revascularization, including the treatment of complex lesions and chronic total occlusions, has become a frequent reality in interventional cardiology. Although the overall need for repeat revascularization due to drug-eluting stent (DES) restenosis remains in single-digit levels, in highly complex forms of coronary artery disease, it may significantly compromise the long-term outcomes (1). Use of a second layer of DES to treat in-DES-restenosis is feasible and efficacious, but safety concerns at very long-term follow-up have been raised (2). Paclitaxel-eluting balloons have been established as an equivalent alternative to repeat implantation of first-generation DES regarding the antirestenotic efficacy within the first year of treatment of in-DES restenosis (3,4).

In this issue of JACC: Cardiovascular Interventions, Rittger et al. (5) report 3-year results of the PEPCAD-DES (Treatment of Drug-Eluting Stent [DES] In-Stent Restenosis With SeQuent Please Paclitaxel Eluting Percutaneous Transluminal Coronary Angioplasty [PTCA] Catheter) study. A total of 110 patients presenting with in-DES restenosis were randomly assigned to be treated with either paclitaxel-coated balloon (PCB) (n = 72) or plain balloon angioplasty (POBA) (n = 38). At 9-month angiographic follow-up, PCB proved superior to POBA regarding the primary endpoint of late lumen loss (0.43 ± 0.61 mm vs. 1.03 ± 0.77 mm, p < 0.001, respectively) (6). At 3-year follow-up, the incidence of target lesion revascularization (TLR) was 19.4% for PCB-treated patients compared with 36.8% for POBA-treated patients (p = 0.046), reflecting the early angiographic results. Cumulative rate of major adverse cardiac events was 20.8%, significantly lower with PCB compared with POBA (52.6%, p = 0.001). Cardiac mortality and myocardial infarction were also lower with PCB compared with POBA (2.8% vs. 10.5%, p = 0.089, and 0% vs. 5.3%, p = 0.049, respectively) (5). Although interesting, the observed differences in safety profile between both treatment groups are difficult to explain. The more frequent need for repeat revascularizations in the same patient observed with POBA (13.2%) compared with PCB (1.4%) may have contributed to these findings. Data coming from larger registries showing an association between presence of restenosis and increased mortality at very long-term follow-up support this hypothesis (7). On the other hand, the small number of patients included and the 2:1 randomization schema used for treatment allocation may have been insufficient to adequately account for cardiac and noncardiac comorbidities.

The PEPCAD-DES study is one among the first studies investigating efficacy of PCB for treatment of in-DES-restenosis (3,4), but it is the only one having more than 50% of patients presenting with recalcitrant restenosis after implantation of at least 2 layers of stent. However, the observed TLR rate with PCB (15.3% at 1 year and 19.4% at 3 years) in this very complex population is still similar to the ones reported in other studies that included mostly patients with first in-DES restenosis (<22% at 1-year follow-up and up to 36% at 3-year follow-up) (2-5,8). In the ISAR-DESIRE 3 (Intracoronary Stenting and
Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 3) trial, 3 treatment strategies for restenosis after implantation of “limus”-eluting stents were compared: PCB, POBA, and paclitaxel-eluting stents. The recently published 3-year results of this study showed that among patients treated with PCB, nearly 30% of repeat TLR occur after the first year compared with only 14% among POBA-treated patients (2). In contrast to this, in the PEPCAD-DES study, only a minority of TLRs occurred after the first year (14% with PCB and 0% with POBA) (5).

There are many possible explanations for these puzzling findings. First, differences in all-cause mortality rates were observed in both studies. Three-year cumulative all-cause mortality was 6.0% with PCB and 9.4% with POBA in the ISAR-DESIRE 3 study, whereas it was 8.3% with PCB and 13.2% with POBA in the PEPCAD-DES study (2). For PCB-treated patients, this means an absolute annual mortality increase of 2% in the ISAR-DESIRE 3 study and of 3.5% in the PEPCAD-DES study. This highlights the poorer risk profile of PEPCAD-DES patients. Second, there were possible differences in the routine follow-up protocols used in centers participating in both studies. It is well known that routine control coronary angiography leads to increased rates of repeat revascularizations due to oculostenotic reflex. We do not know the rate of scheduled repeat angiograms between 1 and 3 years in both studies. However, the fact that the incidence of TLR between 1 and 3 years was 14% with PCB and 9.4% with POBA in the ISAR-DESIRE 3 study and <4% in the PEPCAD-DES study might suggest a higher frequency of scheduled angiographies during this period in the ISAR centers. Third, the mechanisms of late DES failure are very complex. Neointimal hyperplasia is a phenomenon that has been observed very late after implantation of bare-metal stents, but relatively early after DES implantation (within the first year), is one important mechanism of late DES failure in the form of stent thrombosis or in-DES restenosis (9). Neointimal hyperplasia can develop within the restenotic neointimal tissue, and in itself, it can trigger the in-DES neointimal hyperplasia. There are no data about the role of multiple DES layers on the quality of in-DES restenosis, nor are there data about the relative efficacy of paclitaxel on treatment of neointimal hyperplasia or neointimal hyperplasia alone. Because in both of the ISAR-DESIRE 3 and PEPCAD-DES studies no intracoronary imaging was performed, possible differences in the quality of in-DES restenosis at randomization in both studies can only be speculated. Finally, these findings can highlight the differences in the degree of disease severity in both studies, which may lead to different time courses in re-restenosis occurrence.

Focusing on the aggregation of prorestenotic factors, Rittger et al. (5) performed a quantity of subgroup analyses stratifying the population according to the patients’ age, body mass index, presence of diabetes mellitus, type of the original stent (paclitaxel- or limus-based), single or multiple DES layers, and restenosis pattern. The size of subgroups ranged between 13 and 51 patients, which is too small to draw any meaningful conclusions.

Another limitation of the PEPCAD-DES study is the lack of a third treatment arm using the current standard-bearer, the everolimus-eluting stent. Although considering the fact that a great proportion of enrolled patients in the PEPCAD-DES study underwent treatment of recalcitrant restenosis, avoidance of a third metallic layer is conceivable. Evidence is accumulating toward better 1-year efficacy of the everolimus-eluting stent compared with PCB when used for treatment of in-DES restenosis (10). In the RIBS IV (Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloon versus Everolimus-Eluting Stent) trial, which enrolled 309 patients in 23 Spanish centers, the composite of cardiac death, myocardial infarction, and target vessel revascularization was reduced by more than 40% with everolimus-eluting stents compared with PCB, mainly driven by a lower revascularization need (respectively, 8% vs. 16%, p = 0.035). The angiographic parameters of restenosis were reduced in nearly all patients’ subgroups, including the ones defined according to the pattern, time, and location of restenosis (10). Differing from the PEPCAD-DES study, in the RIBS IV study, only 12% of patients underwent treatment of recalcitrant restenosis. Furthermore, considering the reported safety concern at long-term follow-up with the paclitaxel-eluting stent when used for in-DES restenosis (2), longer-term data are required before adopting a strategy of everolimus-eluting stent for treatment of all forms of restenosis.

Adding the findings of the PEPCAD-DES study to the available published evidence, we can conclude that interventional treatment of in-DES restenosis is far away from a “one size fits all” strategy. A better understanding of the patients’ restenosis history and a better characterization of the restenotic tissue by intracoronary imaging is required for tailoring treatment of in-DES restenosis.

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