Drug-eluting stents: effective and safe for every patient and every lesion?

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This editorial refers to 'TAXUS VI 2 year follow up: randomized comparison of polymer-based paclitaxel-eluting with bare metal stents for treatment of long, complex lesions' by E. Grube et al., on page 2578

When Andreas Grünzig performed the first percutaneous transluminal coronary angioplasty in 1978, he did not expect that this procedure would become one of the most often performed interventions in medicine worldwide. The Achilles’ heels of balloon angioplasty were early reocclusions and restenosis. However, >60% of the patients after plain old balloon angioplasty did well without any need for repeat target lesion revascularizations. With the introduction of stents, the procedure became more predictable with respect to early reocclusions and the rate of clinically driven repeat revascularization procedures declined to ~20%, depending on lesion characteristics such as vessel diameter and lesion length and concomitant diseases such as diabetes mellitus and renal insufficiency. However, in randomized clinical trials, no benefit in death and re-infarction was observed with stenting, compared with balloon angioplasty alone. Despite this fact, currently, ~80–90% of the percutaneous coronary interventions (PCIs) are performed with a stent. Soon it became clear that even stents were associated with considerable restenosis rates in some subgroups, namely, diabetics, bifurcation lesions, in-stent restenosis, and long lesions in small vessels.

Benefit of drug-eluting stents

The availability of drug-eluting stents (DESs) represented a major advance for the reduction of restenosis. Very consistently, the two approved DESs, CYPHER and TAXUS, have been shown to reduce the amount of late lumen loss in the months following implantation, compared with bare metal stents (BMSs). This difference was associated with a marked reduction in the rate of restenosis and the need for target vessel revascularization in randomized clinical trials.

Problems of the randomized DES trials

The early DES trials were performed in low-risk populations, and analysing endpoints are viewed as the surrogate of clinical events. The routine angiographic follow-up invariably affected the revascularization rate before any clinical need for repeat procedures could be evaluated. In most of the industry sponsored trials, the comparator of DES was a BMS of similar design of the same manufacturer. However, these BMSs do not necessarily represent the optimal BMS available. Newer BMSs containing cobalt–chrome, for example, with optimized design and reduced thickness of the struts are associated with better results than the BMS used in the randomized DES trials. Consequently, the largest non-industry sponsored trial, the BASKET study using a third generation BMS, did not show these dramatic reductions in target vessel revascularization rates observed in the CYPHER and TAXUS trials.

DES in long, complex lesions

Earlier, DESs were used, at least in Europe, in complex lesions and in lesions with a high risk for restenosis, despite the lack of data from randomized clinical trials. This is due to the fact that an effective reduction of restenosis in this high-risk subgroup is of special interest for the interventionalist. Therefore, the TAXUS VI investigators are to be congratulated because they were the first to evaluate the benefit of DES in patients with a high risk for restenosis. The mean lesion length (21 mm) and the rate of type c lesions (55%) indicate that TAXUS VI included the by far most complex cases when compared with patient selection in other randomized trials studying DES and BMS. At 9 months, the primary endpoint target vessel revascularization was significantly reduced from 19.4 to 9.1%. The TAXUS VI investigators report the 2-year follow-up results. The initial benefit of DES was maintained up to 2 years. The target lesion revascularization rate was reduced from 21 to 10% and the target vessel revascularization rate from 22 to 14%. However, the total MACE (death, myocardial infarction,
and target vessel revascularization) rate at 2 years was not different (25.1 vs. 21.3%, \( P = 0.37 \)). Again, in this high-risk patients with complex lesions, DESs are effective in reducing restenosis but not death and myocardial infarction.

Another high-risk subset of patients was included in the TAXUS V ISR study\(^6\) performed in patients with in-stent restenosis. Here, the use of DES compared with brachytherapy was effective in reducing the clinical and angiographic restenosis at 9 months. Therefore, DESs are clearly preferred to the logistically complex and more expensive brachytherapy.

Taken together, these results, DESs have proven their efficacy not only in simple, short lesions but also in more complex and longer lesions. In these lesions, the desire to use a solid measure to reduce restenosis is certainly highest; therefore, the 2-year results of TAXUS IV are of great value for the interventional community demonstrating the effectiveness of DES during this time period.

**Pending problems with DES**

There is no doubt that DES reduces the rate of angiographic restenosis and the clinical need for repeat revascularization procedures. DESs enable interventionalists to perform procedures in complex lesions, in which surgery would have been the only option before the advent of DES. However, so far, no beneficial effect on death and re-infarction was observed in any of the randomized clinical trials. There are still concerns regarding an increase in the rate of late stent thrombosis. In the TAXUS trials, the definition of stent thrombosis did not include death after 30 days, so that the true rate of late stent thrombosis was underestimated. However, in TAXUS VI, no increase of early or late stent thrombosis was reported with the DES stent. In a recent autopsy study, delayed healing in DES compared with BMS was observed, which might cause late stent thrombosis.\(^7\) The Basket Late study showed an increase in the incidence of late stent thrombosis after the discontinuation of dual antiplatelet therapy after 6 months: 4.9% of the patients with DES experienced cardiac death or myocardial infarction in the subsequent year when compared with 1.3% in those with BMSs (\( P = 0.01 \)). The recent data from the PREMIER registry indicate the problem with stent thrombosis.\(^8\) In the e-CYPHER registry, 42% of the patients with late stent thrombosis died.\(^9\) Clearly, late stent thrombosis is not a benign disease. In a meta-analysis of randomized controlled clinical trials, no increase in the rate of late stent thrombosis for DES compared with BMS was observed.\(^10\) However, this issue is still under investigation and we need more data with longer follow-up for it to be definitively answered. If late stent thrombosis would be significantly higher with DES, then safety concerns might override the effectiveness of DES, reducing the need for target vessel revascularization. To definitively solve this problem, we need more long-term follow-up data from randomized clinical trials and the real-world experience from large registries.

Furthermore, in patients with the need for oral anticoagulation because of the presence of a prosthetic valve or atrial fibrillation, the problem of the duration of a double or triple antithrombotic therapy is not solved. The same is true for the management of patients receiving a DES and awaiting an elective operation elsewhere.

**Future developments**

There are some new devices coming up and will challenge the position of DES. One might be the bioabsorbable stent, another the drug-eluting balloon. The latter seems especially attractive in patients with in-stent stenosis, avoiding the need for another stent and problems with drug release and mechanical complications with the polymer or stent struts.

**Summary**

Certainly, DESs are a step forward in our desire to optimize the results of PCI. The TAXUS VI results have expanded the benefit of DES to more complex and longer lesions. However, before we can recommend a DES for every patient and every lesion, the long-term safety and efficacy issues have to be solved.

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**References**