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Drug Eluting Stents

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With the introduction of DES technology, a reduction in coronary restenosis rates was supposed to improve the incidence of myocardial infarction and mortality at least in more complex patient populations, such as those with long lesions, multiple vessel disease, diabetics, etc. However, after over seven years of systematic use in countries across the world, the angiographic and clinical improvements of restenosis have not translated into a reduction in myocardial infarction and death. Also, some adverse side-effects were associated with first generation DES, e.g. inflammation, delayed healing with poor re-endothelisation, late stent mal apposition, and endothelial dysfunction, described as “collateral side-effects” in preclinical and clinical studies with this early technology. Durable polymers and the drug itself have been associated with the above unfavourable effects. Furthermore, besides their initial advantages in the reduction of TVR and TLR over BMS therapy, we don’t know how these rewards would be maintained at long-term follow-up.

Long-Term Outcomes in First DES Designs

As a result I would like to review some recent experiences with the long-term outcome of these first DES designs, which raised concerns about the safety/efficacy of these devices. In the pooled data from SIRIUS trials with the first Cordis/Johnson & Johnson sirolimus eluting stents (SES), at five years follow up, a significant reduction of TLR compared to BMS was reported, but they also showed a significant increase in overall and cardiac mortality over the entire follow-up period in the subgroup of patients with diabetes, a well-known difficult patient subset to be treated with PCI.

The concerns increase even further, when the higher mortality and Q myocardial infarction was observed beyond the first year, suggesting a specific device effect in these findings. In our ERACI III Registry, we compared first generation SES (Cypher, Cordis/J&J) and paclitaxel eluting stents (Taxus, Boston Scientific) with BMS and CABG in patients with multivessel coronary artery disease, and at five years of follow-up, there was a complete loss of the 1 year initial DES advantage over either BMS or CABG groups. Furthermore, there was a concern with the significantly greater incidence of noncardiac death and myocardial infarction in the DES group after the first year of follow up compared with the other two groups.

The diabetic subgroup was at higher risk for hard cardiac events. Therefore, according to these long-term results, first DES generation do not have any protective effects in this traditionally complex cohort of patients to PCI procedures. A clear pathologic explanation is as yet unknown. However, diabetic patients have lesions, which are more lipid-rich, softer, with more endothelial dysfunction and prone to plaque rupture than the non-diabetic population.

An Explanation for Questionable Safety/Efficacy?

All of the above can induce progression of atherosclerosis and may lead to an enhanced inflammatory and thrombotic reaction, which can potentially be more pronounced with coated drugs and polymers stents. All can lead to processes that could end in late/very late thrombosis, where diabetes was identified in several registries as an independent predictor of stent thrombosis. Additionally, the ARTS 2 registry compared old BMS with first SES generation, at five years of follow up. Although the TVR rate with SES was significantly lower compared to BMS, it was ineffective in comparison to the TVR rate reported by the CABG group. It also reported a higher incidence (9.4 percent) of stent thrombosis in the SES treated group. Though this finding had no impact on late mortality in the study, it was responsible for over a third of Major Adverse Cardiac Events (MACE) rate in that trial.

TAXUS Confirms Loss of Initial Advantages

The TAXUS VI study also reported a complete loss of their initial advantage to BMS in patients treated with complex and long lesion subsets. All these long-term data raised concerns about the results of ongoing randomised trials comparing first DES generation versus CABG in the above cohort of patients with diabetes or complex multiple vessel disease. If we are going to achieve long-term negative results in trials such as SYNTAX, FREEDOM, CARDIA etc, we should ask if these harmful results would be linked to an inadequate patient selection, since PCI practitioners are treating patients/lesions beyond boundaries or because we are comparing a well established revascularisation technique such CABG versus an almost obsolete first DES generation in which safety advantages over old BMS technology is controversial. Besides that, there are new randomised trials with the latest DES generation that are showing significant improvement in safety/efficacy.

During these years, we also understood the complex process to build the ideal DES design, where a combination of safety and efficacy should be the main goal of any DES technology. Moreover, we clearly recognised that minimal luminal diameter loss at follow up should be reduced to improve late outcome, although degree of such reduction is contentious and debatable. Some of the side effects with the first DES designs were related to durable polymers, essential in the first DES generation for a controlled release of the immunosuppressive agent. New technologies are coming with biocompatible polymers, biodegradable polymers or complete biodegradable DES design, all of them trying to avoid or minimise the undesirable side effects linked to durable polymers. Therefore, we now have positive randomised clinical trials with newer DES versus older generation head-to head comparison. This means that the industry is working hard to solve many of these problems.

Other Limitations

Other limitations for the widespread use of DES are the requirements for long-term dual antiplatelet therapy, which was one of the major restrictions for first DES technology. There are subgroups of patients with limited compliance to that therapy, such as older age, upper and lower digestive tract bleeding, non responsiveness to clopidogrel, patients under oral anticoagulation therapy or unable to take dual antiplatelet therapy either at short or long term for concomitant non cardiac illness; all these clinical conditions, 30 percent of current PCI candidates, should be considered contraindications or restrictions for DES deployment. Hence, DES with biodegradable polymers, dedicated antithrombotic BMS designs with antithrombotic coating layers and paclitaxel coating balloon catheters are potential solutions for the above clinical circumstances. In addition to all these technology improvements, we also have new tools beyond DES, to reduce or prevent coronary restenosis.

Oral Therapies More Cost-Effective?

During the last decade, results from randomised clinical trials using systemic oral therapies after BMS implantation systematically reported positive results using either oral sirolimus, oral prednisone, oral thiazolidinediones or oral cilostazol. One of these trials also found a cost saving advantage of this therapy over DES. Perhaps these later groups of drugs in conjunction with the new DES designs should be tested in future trials searching frontiers in the most complex subsets of patients with coronary heart disease. Improving survival in the diabetic population should be the main research goal for interventional procedures, and amulti-therapeutic instead of single approach appears to be the most reasonable option.

Conclusions

With the introduction of the first DES generations, the market for coronary stents is slated to exceed 7.2 billion dollars by 2012. Backed by a greater number of PCI procedures and penetration, the U.S. represents the largest market for coronary stents worldwide. Collectively, the U.S, Europe and Japan account for about 85 percent of the global coronary stent market. The DES is forecast to reach a value of 5.7 billion dollars in 2012. However, manyphysicians, federal health agencies and insurance companies have a greater focus on long-term safety and closer assessmentof late-stent thrombosis after DES implantation. New DES designs introduce new groups of actors to the market, like DES with absorbable polymers and completely absorbable coated stents, although long term safety/efficacy is needed. Furthermore, current DES designs need mandatory dual antiplatelet therapy, opening other alternatives with medical or interventional therapies during PCI, either alone or in combination with the latest generation of DES.

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