EuroIntervention 2012;7:1011-1013

It's time to say goodbye... (to the first-generation drug-eluting stent era)

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Today, for the large number of patients who are living with a first-generation drug-eluting stent, it is mandatory that we continue to perform long-term observations of these patients now that these first generation devices are being replaced by a new generation. So now is the time to say goodbye to the era of the first generation of drug-eluting stents. In this issue of the journal, three papers attempt to answer important unresolved questions concerning first-generation drug-eluting stents, focusing on long-term clinical outcomes in patients who have stents implanted for coronary artery disease. Does treatment with an alternative stent, including a short duration of dual antiplatelet therapy, match that of first-generation stents? What are the predictors of cardiac events after implantation of first- and second-generation drug-eluting stents? Were first-generation drug-eluting stents safe to implant in patients with ST-segment elevation myocardial infarction?

Limacher et al describe comparable 3-year clinical outcomes of propensity matched patients treated with the titanium-nitride-oxide coated Tinox stent, the sirolimus-eluting Cypher stent and the paclitaxel-eluting Taxus stent.[1] Although experimental studies have shown that titanium-nitride-oxide coating reduces platelet adhesion and neointimal hyperplasia, late lumen loss in Tinox stents is only slightly less than in a thin-strutted bare-metal stent when used in humans. Therefore, it should be safe to shorten the duration of dual antiplatelet treatment after implantation of the Tinox stent, which is supported by the study. Unfortunately, the patient groups are propensity matched rather than randomised, which is acceptable in case the data are consecutively collected, which they are only in part, and the inherent problems with group matching and selection bias result in differences in important lesion and procedural characteristics. Still, we support the authors' statement, that Tinox stent treatment might be considered in patients unsuitable for long-term treatment with dual antiplatelet therapy. On the other hand, the study leaves us with a question that can only be answered by a large randomised trial: Does the shorter duration of dual antiplatelet therapy with Tinox stent implantation outweigh its higher late lumen loss compared with drug-eluting stents with regard to clinical outcome, including target lesion revascularisation, bleeding complications, late stent thrombosis, reduced costs etc.? This comparison should, in all fairness, be performed with second-generation drug-eluting stents, stents which in unselected patients result in a low incidence of cardiac events, including a very low stent thrombosis rate.[2]

Both logistic and Cox regression analyses of the Spirit III study demonstrate that the strongest independent predictor of cardiac events through three years is the number of vessel treated.[3] Of less, but significant importance are a high blood concentration of HbA1c and total cholesterol in addition to female gender. Confirming the findings of the Spirit II trial, patients who had the

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PCR online

DOI: 10.4244/EIJV7I9A161

everolimus-eluting thin-strutted Xience V stent implanted fared considerably better than those with the thick-strutted Taxus stent with the exception of diabetics, an unexplained finding that was confirmed in the Spirit IV trial.[4] Of interest, Applegate et al demonstrate that the HbA1c-level rather than the presence of diabetes is associated with a higher event rate. We find it noteworthy to stress that the primary endpoint of the Spirit III trial was the angiographic assessment of late lumen loss at eight months examined in a fraction of the patients and, that despite inclusion of 1,000 patients, an excess of unstable patients were included in the Taxus group, and that the report by Applegate et al is a *post hoc* analysis of secondary endpoints in a study of a selected low-risk population not powered to evaluate differences in clinical events. Their findings should be interpreted accordingly and not extrapolated to patients at higher risk or with complex coronary anatomy. A comment on the importance of stent strut thickness is warranted at this place, since the Taxus Express rather than the Taxus Liberté with thinner stent struts, was used as the control stent in Spirit III (and IV).

The decision to reduce stent strut thickness was originally based on a reduction in late lumen loss to values <1.0 mm with thinner struts of a stainless steel stent.[5] Both angiographic and clinical restenosis rate were reduced considerably, independent of stent design.[6] Later it appeared that the relatively high late lumen loss induced by the bare metal Bx Velocity (and Zonic) counterpart of the Cypher stent appeared to be unimportant, with the drug on board even in very complex lesions. Thus, an efficient antiproliferative drug with an optimal release profile seems to surpass the importance of strut thickness.[7,8] Interestingly, a reduction in restenosis rate related to strut thickness has not been demonstrated in a randomised setting with the cobalt nickel or chromium stents.

It is well known that drug-eluting stents reduce the need for revascularisation compared with bare-metal stents in patients with ST-segment elevation myocardial infarction, and although there are some indications of late adverse events,[9-11] meta-analyses of hard endpoints find no increase in the risk of death and reinfarction, when drug-eluting stents are preferred.[11,12] The 5-year clinical data of the small dimensioned MISSION! trial indicate a trend towards a higher rate of (very) late stent thrombosis in the Cypher group as compared to a bare-metal stent group of different design. Stent thrombosis may occur in patients with ST-segment elevation myocardial infarction due to late stent strut malapposition as a result of resolution of thrombus material on the abluminal stent border, as well as undersizing of stents due to relative vessel constriction in the acute phase of the disease. Again, it should be stressed that long-term data so far are only available for first-generation drug-eluting stents. Newer stents with optimal release profiles of antiproliferative drugs with and without bioabsorbable polymers, in addition to new self-expanding stents, are currently being evaluated, and the next step to implant completely resorbable scaffolds is just around the corner. These devices should be studied in properly sized trials against the above-mentioned second-generation stents. Until then, we are forced to perform long-term observations and meta-analyses pooling data from trials not powered to detect differences in clinical endpoints.

Conflict of interest statement

The authors have no conflict of interest to declare.

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