Editorials
Lessons from the E-SIRIUS trial

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About 2 million percutaneous coronary interventions are completed worldwide each year, of which approximately 60% involve a new stent. Unfortunately, about 300 000 of these patients will develop recurrent symptoms due to in-stent restenosis. Neointimal hyperplasia induced by vessel wall injury has been identified as the responsible mechanism underlying restenosis after stent implantation[1]. The local delivery of a drug with antiproliferative properties from stents is a new concept introduced into clinical practice in an attempt to reduce the incidence of in-stent restenosis.

Early trials with either sirolimus-eluting stents (RAVEL)[2] or paclitaxel-eluting stents (TAXUS II)[3] have demonstrated the efficacy of this approach in suppressing neointimal hyperplasia, but the protocol and lesion requirements did not represent a "real world" scenario. Both studies recruited patients with short lesions in large vessels, allowed only the use of a single stent, and lesion predilation was mandatory.

SIRIUS[4] was the first pivotal drug-eluting stent trial on *de novo* coronary artery lesions, which enrolled patients with higher comorbidity and more challenging lesions (reference vessel diameter between 2.5 and 3.5 mm, lesion length between 15 and 30 mm), thereby reflecting daily clinical practice more closely. The incidence of target vessel failure at 9 months, the primary endpoint of the study, was significantly reduced from 21% in the bare metal stent group to 8.6% in the sirolimus group ($p < 0.001$). The in-lesion restenosis rate, which includes the stent and the segments of 5 mm outside the stent at both edges, was not as impressively reduced as the restenosis rate within the stent (36.3 vs 8.9% as compared to 35.4 vs 3.2%). The reason for this less pronounced effect within the lesion was due to a lack of inhibition of neointimal hyperplasia at the proximal stent margin, a finding which caused considerable debate about whether this was device-related or the result of a suboptimal stent implantation technique.

E-SIRIUS[5], a European randomized multicenter trial, had a similar study design to that of SIRIUS. However, the lesion length was extended to 15 to 32 mm and the vessel size was restricted to 2.5 to 3.0 mm. In addition, this was the first randomized drug-eluting stent study which allowed direct stenting.

The baseline characteristics of SIRIUS and E-SIRIUS differed and these differences are known to have an impact on the long-term outcome. In E-SIRIUS, there were significantly more patients with a previous myocardial infarction (42.1 vs 30.5%, $p < 0.001$) and significantly more current smokers (33.2 vs 20.8%, $p < 0.001$). More importantly, in E-SIRIUS, there were significantly longer lesions (14.4 vs 15.0 mm, $p = 0.002$) in smaller vessels (2.80 vs 2.55 mm, $p < 0.001$) than in SIRIUS, and significantly more patients received multiple stents (48.3 vs 35.1%, $p < 0.001$).

The minimal lumen diameter at 8 months, which was the primary endpoint of E-SIRIUS, was significantly higher with the sirolimus-eluting stents than with control stents (2.22 vs 1.33 mm, $p < 0.001$). This translated into an in-lesion restenosis rate of 5.9 vs 42.3% ($p < 0.001$). Despite the higher risk profile for the E-SIRIUS patients, a significant effect on neointimal hyperplasia was not only found within the stent, but also at both the distal and – in contrast to SIRIUS – the proximal stent margin (10.3 vs 1.3%, $p < 0.001$, and 8.8 vs 2.1%, $p = 0.018$, for the distal and the proximal margins, respectively). This finding

has important clinical implications, because it clearly demonstrates the effectiveness of the device and points to a suboptimal stent implantation technique in SIRIUS (Schofer J., unpublished data).

How to handle the device?

If predilation is necessary, the balloon should be undersized to avoid dissections beyond the dilated segment. The balloon must be shorter than the projected stented segment length and the exact length of balloon injury must be carefully determined.

The stent must be implanted such that the lesion/balloon-injured segment is completely covered. If postdilation is needed, the balloon must be kept within the stent margins and should not be oversized. The paradigm for a favorable long-term outcome in the era of drug-eluting stents has changed from "the bigger the better" to "the longer the better".

Another option for avoiding margin restenosis is direct stenting, which has been performed in E-SIRIUS in a non-randomized subgroup (26%) of patients[6]. Interestingly, a tendency toward a lower late loss was found for sirolimus patients who underwent direct stenting compared to patients who were predilated. This result was in contrast to the control group, in which late loss was essentially the same for predilated and directly stented patients. A possible explanation for the lack of restenosis at the stent margins in patients who received a sirolimus stent by means of direct implantation is diffusion of the drug beyond the stent edges. A randomized trial may further elucidate the efficacy of direct stenting with the sirolimus-eluting stent.

Who should receive a drug-eluting stent?

Subgroup analyses of the SIRIUS study revealed the effectiveness of the sirolimus-eluting stent irrespective of the lesion length and location, of the vessel size, the gender and the presence of diabetes. Only for the small number of insulin-requiring diabetic patients, no significant reduction in the restenosis – and the target vessel failure – rate was found in SIRIUS. This is in contrast to another landmark study, TAXUS IV, in which a paclitaxel-eluting stent proved to significantly reduce the restenosis rate compared to the bare metal stent in all subgroups tested, including the insulin-dependent diabetics[7]. In E-SIRIUS, the small number of patients did not allow a reliable diabetic subgroup analysis.

Based on evidence, only those patients who meet the inclusion criteria of the above-mentioned trials should receive a drug-eluting stent. Daily practice, however, is different. As evident from the E-Cypher registry, which by September 2003 had enrolled more than 8000 patients worldwide, almost 40% of Cypher stents are currently implanted off-label (Urban P., unpublished data).

There are still key groups of patients, known to be at high risk for restenosis after bare metal stent implantation, who need to be studied. These include patients with bifurcation lesions, saphenous vein grafts, chronic total occlusions and in-stent restenosis including those post-brachytherapy and acute myocardial infarction.

Conclusions

The introduction of drug-eluting stents in cardiovascular medicine has been a major advance, although not a panacea. The potential of this device cannot yet be fully judged. The most important lesson learned from E-SIRIUS, however, is this: to take full advantage of a drug-eluting stent requires thoughtful handling.

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