Drug-eluting stents for chronic total occlusions make sense, but it is too early to close the discussion

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This editorial refers to 'Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions'† by L. Ge et al., on page 1056

Stent implantation compared with balloon angioplasty alone has proved not only to increase procedural safety but also to reduce elastic recoil and vascular remodelling and to improve immediate and long-term clinical and angiographic outcomes in patients with coronary artery disease.1,2 The use of intravascular ultrasound-guided high pressure stent implantation has reduced the frequency of stent thrombosis.3 However, stents induce a neo-intimal hyperplasia during the initial 9 months after implantation, and this hyperplasia results in a binary restenosis rate of 10–40%. In addition, patient subsets with small vessels, long lesions, multi-vessel disease, diabetics, renal failure, or complex lesions morphology, such as bifurcations or total occlusions have an even higher incidence of in-stent restenosis.

Most large pivotal studies of stent implantation included patients with coronary lesions of non-complex morphology, and the treatment results of these studies cannot necessarily be generalized to patients with more complex lesion morphology.

Smaller studies have demonstrated the effect of stenting in some complex lesions such as stenosis of the proximal part of the left anterior descending coronary artery, restenotic lesions, and recanalized total coronary occlusions, whereas results have been less convincing in long lesions and lesions located in small vessels.

Patients, who have stents implanted seem to fare only marginally better than those with a 'stent-like' result after balloon angioplasty alone.

The survival rate of patients in whom the attempt to re-open a chronic total coronary occlusions fails is lower when compared with that of patients in whom the procedure is successful (10-year survival ~65 and 75%, respectively).4 A challenge in treating total coronary occlusions percutaneously is to successfully force the guide wire through the occluded segment to the peripheral part of the vessel, and procedural success is a combination of gaining this access and obtaining a stable lumen in the vessel segment after the recanalization. Procedural success rates between 50 and 80% have been reported, but the rate seems closely linked to the selection of patients and to the morphology of the lesions. To increase success rates of chronic total occlusions treatment, special wires, and steerable dissecting and ablating devices have been introduced. However, a 'break-through' device is still awaited.

Patients with chronic total coronary occlusion have been studied in randomized studies comparing balloon angioplasty with stent implantation. The restenosis rate was reduced from ~70% in the balloon treated groups to ~30% in the stent groups, with a corresponding reduction in the need for revascularisation and with no increased risk of stent thrombosis. Similar figures have been reproduced in other studies. In one study restenosis rate in the stent group was as high as 55%, which was partially explained by a very high level of lesion complexity.5–7

A key effort in the improvement of clinical outcomes after stent implantation in chronic total occlusions is to foster a device that kills two birds with one stone, i.e. fulfils lesion scaffolding properties necessary after balloon dilatation and allows sufficient but restricted endothelialization of the stented segment. Recently, the macrolide antifungal agent, sirolimus, originally...
produced through natural fermentation by an actinomycete, was found to possess not only immunosuppressive but also antiproliferative abilities. In addition, the microtubule interfering drug, paclitaxel, primarily used as a cytotoxic antineoplastic agent, has proved to be useful as an inhibitor of smooth muscle cell proliferation. Both drugs turned out to have the properties to inhibit neo-intimal hyperplasia after balloon angioplasty and stent implantation. On the supposition that the antiproliferative drug can be released from the stent by local delivery in optimal doses, it might reduce the coronary stent restenosis problem without causing systemic adverse side effects. Incorporated in a synthetic polymer serving as a drug reservoir it appears that these drugs can be released from the stent in a controlled concentration that weakens without totally inhibiting the necessary endothelialization of the stent surface.

In several large trials it was recently demonstrated that both sirolimus- and paclitaxel-eluting stents are superior to identical bare metal stents without drug-eluting properties with regard to angiographic criteria of restenosis and clinical outcome with special reference to target lesion revascularization. No increased risk of stent thrombosis was reported in any of these studies that included patients with simple coronary artery lesions. A few small registries have also indicated that drug-eluting stents may be beneficial in total coronary occlusions.

Ge et al. provide insight into the angiographic and clinical impact of implantation of sirolimus-eluting stents in re-opened chronic total occlusions. The results of the patient group treated with drug-eluting stents were compared with a historical control group treated for the same kind of lesions during an antecedent 2-year period. Coronary enzyme release during the procedures was insignificantly different despite considerably longer stented segments in the sirolimus-stent treated group. All patients were followed clinically, but ~20% declined the re-angiogram. The angiographic results immediately after stent implantation were similar in the two groups, but the minimal lumen diameter in the treated lesion was remarkably higher at 6-month follow-up in the drug-eluting stent group, and the diameter stenosis and frequency of patients with ≥50% diameter stenosis accordingly much lower. Most restenoses in the sirolimus-eluting stent group were focal in contrast to those of the bare metal stent group. These favourable angiographic results were accompanied by similar low rates of re-intervention in the sirolimus-stent group, whereas there were no differences between the groups in the occurrence of death, myocardial infarction, or stent thrombosis in the 6-month observation period.

Although implantation of drug-eluting stents for total occlusions ‘makes sense’, some limitations of the report by Ge et al. deserve attention. A selection bias cannot be ruled out, because the study did not encompass a randomized control group but used historical control cases matched with regard to some, but not all, demographic parameters. It is well known that restenosis depends on stent construction, and Ge et al. used a variety of stent designs in the bare metal stent group. In addition, the analyses of the angiograms were not performed blindly, and a selection bias cannot be excluded because of the limited fraction of patients who accepted follow-up angiography. Even with an ~80% re-angiography frequency, non-randomized patient groups may respond different to the ‘offer’ of having a re-angiography performed.

An interesting aspect of the report of Ge et al. is the differences in procedural characteristics between the groups. The stent length/lesion length ratio in the sirolimus group was 1.8 compared with 1.2 of the bare metal group, and the number of stents per lesion was 1.4 (vs. 1.2) in the sirolimus group. There were no cases of stent thrombosis in the sirolimus-eluting stent group, in which the anti-thrombotic treatment was given for >3 months, so the implantation of long and overlapping stents exceeding the lesion length seems safe. However, to exclude late stent thrombosis in sirolimus-eluting stents, the observation period of stent thrombosis might need extension beyond the 6 months of the present study, and before a stent length/lesion length of 1.8 is widely embraced we suggest to await randomized studies on this topic, which are underway.

References

