Editorial Comment

Stent, drug, polymer--benefits, risks, and opportunities

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It has been well established that use of drug-eluting stents has resulted in marked reduction in neointimal proliferation following stenting and that this is reflected clinically in a very significant decrease in late lumen loss, in-stent restenosis, and target lesion revascularization. This benefit occurs, however, in the setting of delayed endothelial and vascular wall healing with its potential for continuing thrombogenicity requiring more prolonged use of dual antiplatelet therapy to prevent stent thrombosis. Large series of patients receiving sirolimus-eluting and paclitaxel-eluting stents have indicated the absence of any increase in adverse cardiac events up to one year following stenting. Questions have been raised, however, as to whether there may be any late “catch-up” in restenosis or in late stent thrombosis.

Recently published data regarding the Cypher and Taxus stents with 2-3 year follow up have confirmed continuing significant decrease in in-stent restenosis and target lesion revascularization with no increase in late thrombosis or other adverse cardiac events. In these series, clopidogrel was prescribed for 3-6 months after Cypher and six months after Taxus stenting. Although there is, to date, no evidence of an increase in early or late stent thrombosis with drug-eluting stents compared with bare metal stents, when this does occur, cessation of clopidogrel, with or without continuation of aspirin, is the most important contributing factor. Thus, adverse late events seem low but at the expense of continuing dual antiplatelet therapy for periods of at least six months with need for longer duration presently uncertain. Unpublished data suggest similar favorable outcomes with Cypher to four years.

Much attention has been paid to the antiproliferative drug as a cause for delayed vessel healing with less to the polymer used for binding the drug to the stent. Absence of complete endothelialization and of inflammatory changes have been documented long after complete release of the drug from the stent, raising concern that the polymer itself may play a role in possible late stent restenosis and thrombosis. A case of autopsy-proven hypersensitivity reaction at the site of a sirolimus-eluting stent 18 months after implantation has been reported by Virmani with a subsequent autopsy series showing four similar allergic reactions with drug-eluting stents but not with bare-metal stents. Although these events seem rare and reaction to the stent itself cannot be excluded, occurrence in these cases long after complete drug elution suggests the polymer to be the culprit. In vitro studies have shown that a variety of stent polymers induce marked inflammatory changes and intimal thickening.

With this in mind, several approaches are being taken in stent technology including avoidance of any polymer and development of new polymers both non-erodable and bioabsorbable. Studies with a non-polymer-based paclitaxel-eluting stent (DELIVER) compared with a bare metal stent have shown a decrease in neointimal proliferation but without a significant improvement in restenosis or target vessel failure at nine months. A non-polymer-based rapamycin-eluting stent (ISAR-TEST) compared to the Taxus stent showed only non-inferiority at nine months. Likely the greatest problem with absence of any polymeric binding is providing reliable absorption and release kinetics for the drug.

Development of a bioabsorbable polymer may have the advantage of eliminating long-term polymer presence with its inflammatory effects. Unknown, however, are the possible interactions between such a polymer and the eluting drug, the effects of the polymer resorption on drug release kinetics and even any possible inflammatory response due to the resorption itself. A small series of patients receiving an everolimus-eluting stent with a bioabsorbable polylactic acid polymer showed no restenosis or stent thrombosis to one year.

The study reported by Zhang et al. in this issue of Journal of Geriatric Cardiology evaluates the use of a new sirolimus-coated coronary stent with an innovative biodegradable polymer. This stent appears similar to the Cypher in stent material, strut thickness, and sirolimus dose, differing in an open-loop construction, somewhat longer release kinetics of the sirolimus and use of the biodegradable polymer applied in a thinner layer and with the polymer/sirolimus coating only on the outer vessel wall surface. In a group of 60 patients receiving in a non-randomized manner either the new stent or a Cypher stent, major adverse cardiac events and angiography-assessed late lumen loss and diameter stenosis were similar at six months in the two groups. Angiographic follow up was high (84%) in the new stent group and less in the Cypher group (36%) but findings in the latter were similar to those reported in other studies. Patients included a high proportion with diabetes mellitus, hypertension, hyperlipidemia, unstable angina, and non-A lesions and multivessel disease. While these are
encouraging results, they are limited by the small number of patients and lack of follow up beyond six months as acknowledged by the authors.

Issues related to the significance of any effect of present stent polymers and whether they play a role in delayed endothelialization and/or late stent thrombosis remain unresolved. There is consensus that present drug-eluting stents markedly decrease the incidence of restenosis and need for repeat revascularization with no convincing evidence of late adverse events. Because of delayed endothelialization, it is known that longer-term use of dual antiplatelet therapy is required for prevention of late stent thrombosis. The goal in the design of new stent technology should be a balance of inflammatory and proliferative response and endothelialization and vessel wall healing. Polymer design would seem an important component in this process. Any polymer to be used must be relatively inert and biocompatible with predictable drug-release kinetics. Its composition, as well as thickness and application to stent struts, will need to be determined. The authors of this study and manufacturers of the stent should be congratulated on their work in developing their novel approach. We will need to await longer-term results in more patients before concluding its benefits.

References