Optimal treatment for in-stent restenosis after BMS—DES, coated balloon, or scalpel?

Debabrata Mukherjee*

Gill Heart Institute, University of Kentucky, Lexington, KY 40536-0200, USA

Online publish-ahead-of-print 13 June 2008

This editorial refers to ‘Two-year clinical outcomes after paclitaxel-eluting stent or brachytherapy treatment for bare metal stent restenosis: the TAXUS V ISR trial†’ by S.G. Ellis et al., on page 1625

The year 2007 saw a significant decrease in the usage of drug-eluting stents (DES)1 and a commensurate increase in the usage of bare metal stents (BMS) primarily because of concern about stent thrombosis with DES. As a result of increased use of BMS, we are likely to see more patients presenting with in-stent restenosis (ISR) after BMS, and determining the optimal treatment of these individuals becomes clinically relevant.

During the last decade, numerous modalities have been used to treat ISR after BMS, with only modest intermediate-term efficacy. These devices, including balloon angioplasty, atherectomy (directional, rotational, and laser), and repeat stenting (stent-in-stent), provided a high rate of immediate technical success and a low rate of ischaemic events; yet 30–60% of patients required another target vessel revascularization (TVR) in the subsequent months.2,3 The initial therapy that was proven to be effective in treating ISR was vascular brachytherapy as an adjunct to successful repeat balloon angioplasty. Several randomized, placebo-controlled studies testing β- and γ-radiation in the setting of ISR revascularization demonstrated a sharp and clinically significant reduction in TVR (to 15–30%) with brachytherapy.2,3 Given the procedural logistics (need for multiple personnel, expensive specialty equipment, radiation barriers), and concerns about stent-edge restenosis, thrombosis, and a late TVR catch-up phenomenon with brachytherapy, interventional cardiologists turned to DES for the management of ISR even before prospective data became available. Small non-randomized pilot studies5,6 initially suggested that DES may be more effective than brachytherapy for ISR. Subsequently, larger randomized studies, the TAXUS V ISR study6 and the Sirolimus eluting stent with vascular brachytherapy for the treatment of in-STENT restenosis from bare metal stents (SISR) trial,7 reported randomized comparisons of vascular brachytherapy vs. a paclitaxel-eluting stent and a sirolimus-eluting stent, respectively, as treatment for ISR within a BMS. Both trials randomized ~400 patients to either radiation therapy or a DES. Despite some differences in trial design, the results of these two trials were remarkably consistent and suggested roughly a halving of the risk of restenosis with either DES compared with brachytherapy.8

Ellis et al.9 report on the 2-year clinical outcomes of the TAXUS V trial. They report that follow-up analysis through 2 years after randomization demonstrates the durability of paclitaxel-eluting stents for ISR after BMS and continued superiority over brachytherapy. The data suggest that the efficacy of an paclitaxel-eluting stent in preventing restenosis relative to brachytherapy is enhanced with continuing long-term follow-up, due largely to mitigation of the restenosis ‘catch-up phenomenon’ described after radiation therapy. Placement of a paclitaxel-eluting stent for ISR after BMS also appears safe, with low long-term rates of death, myocardial infarction, or target vessel thrombosis. This, together with previous data and the current lack of availability of brachytherapy, suggests that DES should be the primary modality of therapy in patients developing ISR after BMS.

Recently another novel approach has been described for the treatment of ISR in a pilot study with paclitaxel-coated balloon catheters.10 In this study, treatment of coronary in-stent restenosis with paclitaxel-coated balloon catheters significantly reduced the incidence of restenosis.10 These pilot data suggested that the inhibition of restenosis by local drug delivery may not require DES implantation, but needs to be confirmed in a larger adequately powered study.

The study by Ellis et al., while proving the superiority of DES over brachytherapy for ISR, also raises some concern and challenges. One concern is that the overall TVR rate of 18.1% at 24 months after paclitaxel-eluting stent implantation for ISR still remains high, and we need to continue to strive forward to minimize the TVR rate after ISR. We also do not know if the ISR rate will plateau after 24 months or if we will see a catch-up phenomenon at a later time point, i.e. at 3–5 years, with even higher TVR rates. In an open-label, small randomized trial conducted at two centres in Germany, sirolimus-eluting stents had significantly
lower TVR compared with paclitaxel-eluting stents (8% vs. 19%, \(P = 0.02\)) for treatment of ISR.\(^{11}\) Additional larger trials are needed to confirm whether sirolimus-eluting stents may be the preferred DES for ISR. Another reasonable approach, particularly for the 35% of patients with left anterior descending artery (LAD) ISR in this study, may be robotic mammary takedown and off-pump bypass surgery,\(^{12}\) and may potentially be a more durable solution with lower TVR. Robotic technology has evolved to facilitate the least invasive approach for coronary artery bypass surgery and now offers patients the opportunity for shorter hospital stays, lower complication rates, and more rapid return to full activity, and may be applicable to patients with ISR involving the LAD who could be eligible for this approach. Integrated revascularization treatment plans may also provide minimally invasive options for patients who have multivessel ISR with robotic left internal mammary artery (LIMA) to LAD and DES evolution to facilitate the least invasive approach for coronary artery bypass surgery and now offers patients the opportunity for shorter hospital stays, lower complication rates, and more rapid return to full activity, and may be applicable to patients with ISR involving the LAD who could be eligible for this approach. Integrated revascularization treatment plans may also provide minimally invasive options for patients who have multivessel ISR with robotic left internal mammary artery (LIMA) to LAD and DES implantation for the circumflex and right coronary arteries.\(^{13}\) Future studies may want to compare robotic LIMA with LAD, or hybrid revascularization strategies with DES-only therapies with 4–5 years follow-up to determine the optimal therapy for ISR. The current study also excluded patients with renal dysfunction with serum creatinine \(>2.0 \text{mg/dL}, \) vessels \(<2.5 \text{mm}, \) and lesion length \(>46 \text{mm}, \) and we do not know the optimal therapy for ISR in these individuals. In the future, bioabsorbable stents may provide a platform for drug delivery\(^{14}\) for neointimal suppression without inducing more neointimal hyperplasia, but this needs to be evaluated in prospective randomized trials.

Finally, although we currently only have sirolimus-eluting stents and paclitaxel-eluting stents available on our shelves, newer DES will be available in the next few months, namely the everolimus-eluting Xience V stent (Abbott Laboratories, Abbott Park, IL, USA) and the zotarolimus-eluting Endeavor stent (Medtronic, Medtronic Parkway, Minneapolis, MN, USA). Ideally the choice of DES for ISR should be driven by a head to head comparison of the four DES devices in a prospective multicentre adequately powered randomized trial, but such a trial is unlikely to happen for logistical reasons. The ongoing choice of a DES for ISR then will probably depend on multiple factors which will include safety, efficacy, deliverability, physician preference, and, given recent cuts in reimbursement, cost of the device. In the final analysis, optimal therapy for ISR after BMS should be individualized, with the choice of optimal medical therapy for some patients, DES implantation for the majority of patients, and bypass surgery for a few patients especially those with LAD involvement. The future question we will have to answer is how to manage patients with ISR after either de novo DES placement or DES placement for ISR after BMS. Such a group, although small, may be particularly difficult to treat.

Conflict of interest: none declared.

References