Remise in the treatment of in-stent restenosis

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This editorial refers to “Treatment of in-stent restenosis using a paclitaxel-eluting stent: acute results and long term follow-up of a matched-pair comparison with intracoronary \(\beta\)-radiation therapy”\textsuperscript{1} by P.W. Radke et al. on page 920.

For patients and interventional cardiologists, restenosis has been a major disappointment in the field of percutaneous, transluminal coronary angioplasty (PTCA) and patients with restenosis have suffered both physically as well as emotionally. The early spectacular results of treatment gradually faded away within three months and 6–12 months since the introduction of the intra-coronary stent. It is difficult to find a cardiologist who does not have patients that have been psychologically affected by one or more restenotic events. For the physician, the mechanism and potential prevention of the problem remains obscure although many approaches have been developed to protect treated vessels from excessive wound healing that leads to eventual luminal diameter reduction and clinical symptoms of angina. Many pharmacological, and even gene therapy, trials were extremely successful in animal models, but failed to deliver in the atherosclerotic human coronaries. The potential genetic predisposition and co-morbidity have been analysed in order to identify patients at risk from this serious complication, with variable outcome (GENDER: GENetic DEterminants of Restenosis Dutch Multicenter study). Although, the introduction of stents have reduced and delayed the development of restenosis, the problem has not been solved.

Potentially, the problem might be minimised by the introduction of the drug-eluting stents (DES) that are currently being used on a large scale in the US, but in a selected number of cases in Europe for various reasons. Among the reasons to restrict the use of DES are economical considerations and a modest increase in subacute and late in-stent thrombosis. Although the occurrence rate of DES thrombosis is low, the presentation of this acute problem is impressive as electively treated patients develop an acute myocardial infarction with a high rate of anterior wall infarctions.

These considerations cause in-stent restenosis (ISR) to remain a serious problem that deserves our on-going attention and research efforts. The study reported by Radke et al.,\textsuperscript{1} is therefore an important contribution addressing the treatment of ISR. In this study, two comparable populations are described, treated either with DES (paclitaxel) or intra-coronary \(\beta\) brachytherapy (ICBT). Both approaches appeared to be equipotent and rather successful for the treatment of ISR, therefore remise is the outcome here.

The current treatment modalities for ISR include repeat balloon angioplasty, repeat stenting, cutting balloon angioplasty, directional coronary atherectomy, rotational coronary atherectomy, brachytherapy, and DES. To judge a study on its merits, the first question is whether the most optimal treatment strategies were compared. Therefore, it is important to determine which DES has the best results in ISR. Paclitaxel-coated stents are available in a moderate and slow-release form. Only one release form and stent coated with sirolimus is available. Although DES are being used in clinical practice to treat ISR successfully, no direct comparison is available that shows superiority of one stent.\textsuperscript{2,3} For radiation therapy \(\gamma\) and \(\beta\) sources are available and both have been successfully applied to treat ISR with comparable outcome.\textsuperscript{4} No important differences were reported in the routine clinical application of \(\gamma\) or \(\beta\) radiation in single centre registries.\textsuperscript{5}

Based on these studies, the approach of comparing radiation therapy with DES by Radke et al., appears to be rational. An important limitation of the study, however, is its size and design as patients were retrospectively matched from two databases and the angiographic analysis performed after 6 months, whereas another clinical evaluation was performed after 12 months. A significant difference was observed for the minimal luminal diameter (\(P < 0.01\)) and in-stent net gain.
favouring DES. Other parameters also hinted at a trend, both morphological and clinical, towards better results after DES implantation. The fact that the DES is easy to use and does not require any special adjustments in the catheterisation laboratory would also support its use in ISR. Fortunately, we are moving from high recurrence rates after percutaneous transluminal rotational ablation of 64.9% and 51.2% after rePTCA in the ARTIST study to values of 20% after DES and 16% after ICBT, but it is obvious that 20% recurrence of ISR is still a major clinical problem. Potentially, the combined approach (DES with ICBT) could reduce the recurrence rates even further. This will depend on whether different molecular targets can be reached with drugs interfering in the cell cycle and the exact effect of radiation on tissue healing.

Therefore, our focus must be on the prevention of ISR through risk stratification and tailored therapy for PTCA patients, within the limits of budget constraints. A potential quick and inexpensive solution could have been the introduction of direct stenting. However, the published results are disappointing as they show near identical ISR rates compared directly with conventional stenting. The feasibility of using DES in patients with increased risk for ISR has already been reported by several groups with clinical events in <5% of the cases. Another approach is to compare different treatments in the high risk patients for preventive measures such as ICBT or DES. One example of a recently completed randomised trial is the BEGUT (The BEta versus Gamma Utrecht Trial)-Cypher study.6 In this single centre prospective trial, patients were included if they had a high risk for restenosis >40%, or ISR. ISR risk assessment is based on treatment for diabetes and/or type C-lesions according to AHA/ACC classification. In the trial, high risk patients were randomised to either DES (sirolimus), β (P32-Galileo-Guidant) or γ-irradiation using the Checkmate (Cordis J & J, Miami, USA) device. Forty patients were included in all arms. All three systems were used as they have been shown to provide excellent acute results. These techniques have also been shown to induce positive remodelling and inhibition of (in-stent)-hyperplasia/tissue growth at 6-month follow-up in earlier studies. Such direct comparative studies should help us select the correct therapy for each individual patient. Further tailoring will require the re-evaluation of potential additional pharmaceutical treatment looking at anti-coagulant therapy, and AT1 blockers, ACE inhibitors, statins and calcium antagonists.

In the near future, patients will have to be classified on the basis of biochemical markers of inflammation, genotype, co-morbidity and lesion characteristics to determine the risk of ISR in one individual patient. The outcome of the classification will determine which therapy is most appropriate and also where coronary bypass surgery has to be considered. Before we can make definite therapy choices for the best initial treatment, additional studies are required on the long-term outcome with respect to angiography and clinical end-points of high risk patients for the development of ISR. In the meantime, it is comforting that the risk for a recurrence of ISR has been reduced by more then 50% and that we have devices that can be used in every centre to improve our treatment in the unfortunate patients with symptoms due to in-stent tissue growth.

References