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LETTERS TO THE EDITOR

The Future Is Now

Comment on a Recent Editorial Suggesting the Need for a New Technology in the Treatment of DES Restenosis

In a recent editorial, John S. Douglas Jr. elegantly describes the issue of drug-eluting stent (DES) restenosis (1). This editorial refers to the RIBS (Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent) III trial, a study whose aim was to compare different strategies for the treatment of DES restenosis, and whose findings revealed that choosing a different DES provides better angiographic outcome than alternative interventional treatments (2). The comments of Douglas are relevant, and we especially agree that a longer follow-up would probably catch more DES restenosis and that post-procedural minimal lumen is generally smaller with balloon angioplasty than with stent implantation, due to acute elastic recoil or tissue prolapse.

However, we believe that the editorial title claiming the need for a new technology for the treatment of DES restenosis is misleading and deserves some comments. Indeed, it is already here. Drug-eluting balloons (DEB) represent a breakthrough technology that has found its land of conquest for the treatment of in-stent restenosis. The advantages related to DEB use are extremely relevant, including local drug delivery with burst paclitaxel release, need for short dual antiplatelet therapy, diffuse and homogeneous rather than strut-related drug distribution, and lack of a further metallic layer.

With regard to DES restenosis, the effectiveness of DEB was first assessed in a small trial recently published in *JACC: Cardiovascular Interventions* that showed significantly lower late lumen loss in patients with sirolimus-eluting stent restenosis who were treated by DEB angioplasty rather than conventional balloon angioplasty (0.18 ± 0.45 mm vs. 0.72 ± 0.55 mm, $p = 0.001$) (3). More robust evidence favoring DEB use in DES restenosis was provided by the PEPCAD (Paclitaxel-Eluting PTCA Balloon Catheter in Coronary Artery Disease) DES trial, which demonstrated the superiority of a DEB strategy compared with plain balloon angioplasty in the treatment of patients with both paclitaxel-eluting and sirolimus-eluting stent restenosis, providing a less-than-one-half late lumen loss value (0.43 ± 0.61 mm vs. 1.03 ± 0.77 mm, $p < 0.001$) and almost 4× less binary restenosis (17% vs. 61%, $p < 0.001$). Moreover, the pattern of restenosis in the plain balloon group was focal in 72% of patients and less complex than in the DEB group (4).

Restenosis after DES implantation has specific morphological patterns and tissue composition, making it particularly challenging to treat. Although a direct comparison is not available, DEB angioplasty for treatment of DES restenosis seems to be associated with lower or at least equivalent need for reintervention when related to DES use. The recurrent use of a DES, however, involves the addition of a further metallic layer and poorly known drug behavior.

So, given DEB sound pathophysiological premises and good preliminary clinical results, we believe that the time of waiting for a new technology is over; we only have to give a glimpse at it on our shelf!

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Reply

The letter of Drs. Cortese and Sgueglia regarding my editorial comment (1) is very much appreciated. They appropriately call attention to the recently published work of Rittger et al. (2), which favorably compared paclitaxel-coated balloon angioplasty (PCBA) with plain balloon angioplasty in the treatment of drug-eluting stent (DES) restenosis. This is the second small randomized trial powered to compare late lumen loss at 6-month angiography. As noted, both studies showed quite significant reduction in late lumen loss, restenosis, target vessel revascularization, and major adverse cardiac events at 6 months following PCBA (2,3). These results along with the report by Scheller et al. (4) that PCBA of bare-metal in-stent restenosis resulted in significantly better event-free survival out to 5 years are indeed encouraging. However, these studies raise some questions: Can a single treatment with paclitaxel influence outcomes months or years later? In the more resistant DES restenosis lesion, will PCBA only delay the appearance of restenosis with "late catch-up" occurring as has been noted with DES and brachytherapy? Are head-to-head direct comparisons of PCBA and second-generation DES required to guide therapy?

With regard to the first question, the lipophilicity of paclitaxel, low water solubility, and binding characteristics contribute to its persistence in the vessel wall following PCBA with a reported half-life of 45 days and about 1% to 2% of the dose being present at 6 months (5). The persistence of drug in the vessel wall for this considerable period may account for inhibition of restenosis for months or even years. Unfortunately, the comparisons that have been reported in DES restenosis (2,3) are only with plain balloon angioplasty in mostly focal lesions with short follow-up. Longer follow-up of PCBA-treated patients is required to ensure that "late catch-up" will not occur, and direct comparisons with second-generation DES will be essential to determine whether PCBA is the "breakthrough" technology that is needed.

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