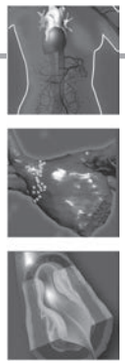

What are the barriers to the use of drug-eluting balloons?

"...there are certain limitations to drug-eluting balloons ... such as the relatively high rate of bail-out stenting in case of unsatisfactory angiographic results, significant heterogeneity among different drug-eluting balloons and limited data from clinical trials."

KEYWORDS: coronary artery disease ■ drug-eluting balloon ■ percutaneous coronary intervention ■ stents

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In percutaneous coronary interventions the main risk of restenosis and, despite the advent of drug-eluting stents, it still poses a significant problem [1]. The concept behind drug-eluting balloons (DEBs) is local drug administration and sustained release of antiproliferative drugs without a permanent stent and with homogenous transfer of drugs to the vessel wall [2]. This shorter duration of drug release and the avoidance of implanting a permanent 'foreign body' may facilitate vascular healing, reduce hypersensitivity reactions to the foreign body, reduce the risk of stent thrombosis [3] and, thus, reduce the duration of intensive antiplatelet therapy, which is needed after a stent implantation.

However, there are certain limitations to DEBs that we will discuss in the article, such as the relatively high rate of bail-out stenting in case of unsatisfactory angiographic results, significant heterogeneity among different DEBs and limited data from clinical trials.

Lack of class effect

Early animal models of DEB have demonstrated that paclitaxel had better tissue retention levels than sirolimus [4]. The unique lipophilic characteristics of paclitaxel results in the rapid adsorption at the site of delivery, even after short balloon expansion duration. In addition, the sustained drug effect, even without the use of a permanent delivery scaffold (stent) [5], is making paclitaxel the drug of choice for DEBs [5].

Controlling the release of paclitaxel onto the vessel wall during inflation, while avoiding washout during the advancement of the balloon over the coronary lesion, is key for effective delivery.

There are currently different groups of DEB technologies. The Paccocath® DEB technology is developed by Bayer Schering Pharma AG (Berlin, Germany) and involves paclitaxel being embedded in hydrophilic iopramide, which increases the solubility and transfer of the drug to the vessel wall. However, only approximately 10–15% of the drug is delivered to the vessel wall during a 60-s inflation. DIOR uses folded balloon technology to protect the drug upon delivery, and first inflation for 20 s will release 35% of the drug and subsequent inflation of 20 s will release another 35%. Another DEB using the same coating method as DIOR® (Eurocor Gmbh, Bonn, Germany) is Elutax® (Aachen Resonance GmbH, Aachen, Germany), which releases 20% of the drug per inflation. Cremers *et al.* have demonstrated that the Paccocath DEB significantly reduces neointimal thickening compared with the DIOR, balloon and uncoated balloons [6]. The Swedish Coronary Angiography and Angioplasty Registry/Swede heart registry data have also shown that a second-generation Paccocath DEB with hydrophilic carrier was associated with a significantly lower risk of restenosis compared with the Elutax DEB [7].

Even though these comparisons are based on small studies or nonrandomized data, it is very likely that there are relevant differences in the performance of different DEB types and that we cannot expect a 'class effect'.

Lack of regulatory approval in the USA

The use of DEBs are an established treatment option for in-stent restenosis and recommended by current European guidelines [8]. However, the role of *de novo* coronary lesions has not being well defined. In the USA, however, DEBs are not approved by the US FDA, although several companies, including Medtronic (MN, USA),

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are submitting their initial applications this year. Although most of the currently available DEBs for coronary applications are based on similar principles using similar paclitaxel doses, specific elution kinetics differ owing to the coating/carrier and drug deposition characteristics and may result in differing tissue retention characteristics. Moreover, these drug-elution profiles have not yet been defined in certain pathologies, such as acute myocardial infarction with high thrombus burden.

> *"...it is very likely that there are relevant differences in the performance of different drug-eluting balloon types and that we cannot expect a 'class effect'."*

Compared to conventional drug-eluting stents, the release of cytotoxic drugs from DEBs has the potential to adversely affect microvascular endothelial function, which could lead to detrimental vascular effects, as well as undocumented effects of macroparticle drug loss to systemic circulation potentially causing effects at end organs and systemic toxicity. These will need to be better characterized before FDA approval can be given.

High bail-out stenting

Among the limitations reported for DEB use for *de novo* lesions is the rather high proportion of 'bail-out stenting' owing to suboptimal angiographic results, such as dissections [9]. However, this rate is very variable. The reported bail-out stenting requirements range from 3 [10] to 20% [11,12]. There is a certain learning curve involved; DEB angioplasty should be done slightly differently than standard percutaneous coronary intervention.

Ideally, the stenosis should first be adequately predilated with an uncoated balloon, as the DEB is only used for drug delivery. To prepare the lesion, the diltation should be done gently to avoid significant dissections, followed by DEB inflation. Predilation is thought to create important microdissections, which facilitate drug transfer through the intima and media. However there is also the potential to cause shear stress and trauma with a high-dissection rate, elastic recoil and abrupt closure.

Conclusion

DEB has been proven to be effective in treating in-stent restenosis, especially for bare-metal stent and slightly less so for drug-eluting stents restenoses [10,13]. For *de novo* lesions, limited data suggest a potential benefit (either standalone or with bare-metal stent) compared with bare-metal stent alone; however, so far, superiority has not been proven [14–16].

> *"The use of drug-eluting balloons are an established treatment option for in-stent restenosis and recommended by current European guidelines."*

The exact role of DEB is not clear. It is an evolving field owing to new developments, including the adoption of new carriers to enhance drug transfer, as well as the use of new antiproliferative drugs, which need further investigation. Thus far, initial trials have been rather encouraging; however, larger randomized clinical trials in distinct clinical populations are required to further characterize the role of this technology.

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