

## Drug-eluting balloons for percutaneous coronary interventions

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The simple and originally naïve idea of dilating a coronary stenosis to restore unobstructed coronary flow through percutaneous transluminal coronary angioplasty (PTCA) (1) has been a major advance in the treatment of acute coronary syndromes and is currently also commonly used in stable coronary artery disease (2). However, there is no such thing as a "free lunch", and the vascular injury caused by the balloon-induced barotrauma elicits an initial inflammatory response in the vessel wall that leads to vessel restenosis in 30–40% of cases through two major processes: a) negative vascular remodeling (used to designate late vessel shrinking after the acute dilation) and b) cellular proliferation. While the former is abolished by the use of stents, acting as metal scaffolds, such metal devices themselves actually increase the risk of the latter, leading to neointimal hyperplasia often more severe than when the plain "old" balloon angioplasty was used (3). Interventions with balloon angioplasty and/or the use of stents are now unanimously referred to as percutaneous coronary interventions (PCI). Drug-eluting stents (DES) were seen as the final solution of the problem, since they dramatically reduce in-stent restenosis by inhibiting cellular proliferation (Fig. 1).

The initial enthusiasm for DES, however, has been recently tempered by the concern for the occurrence of late stent thrombosis (4), caused by an incomplete endothelialization of the stent struts and an inflammatory response to the polymer (5). We have therefore lately witnessed some revival for the use of bare-metal stents (BMS), which will be probably accompanied by a predictable re-increase in the rate of in-stent restenosis.

Because of this, there is currently uncertainty on the optimal selection of stents. As dual antiplatelet therapy is recommended for at least 12 months after DES (6), patients at higher risk of bleeding (the elderly, patients with cancer, candidates to oral anticoagulant and to any type of surgery) or subjects with expected lack of adherence or inability to tolerate an extended course of dual antiplatelet therapy are undoubtedly better candidates to receive BMS. On the other hand, most conditions frequently occurring in the "real world" and usually considered "off-label" indications for DES share a higher risk of both, late thrombosis and restenosis: such are diabetes mellitus, chronic

total occlusions, small ( $\leq 2.5$  mm) coronary arteries, very long ( $> 30$  mm) stenoses and bifurcation lesions. Therefore, interest in alternative strategies of PCI using "biocompatible" devices and aiming at the reduction of restenosis has recently resumed.

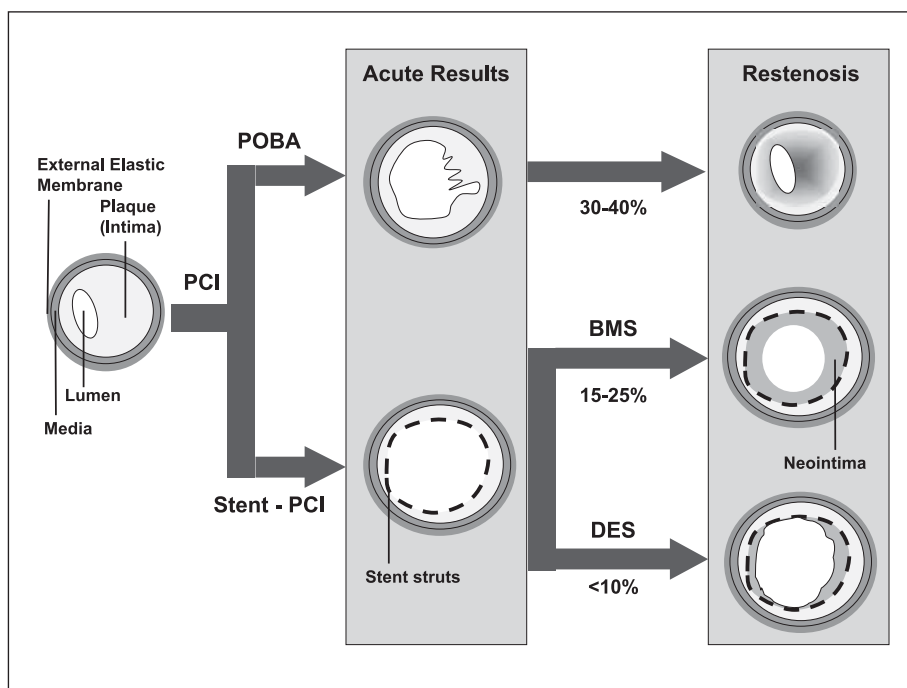
From the finding that vascular cells (endothelial and smooth muscle cells mostly) retain antiproliferative drugs for up to one week after contact exposure to the drugs themselves, and that this contact causes a prolonged inhibition of vascular smooth muscle cell proliferation, the concept and later the development of drug-eluting balloons were born (7). As an alternative to DES, where only about 15% of the stented surface is covered by struts, drug-eluting balloons allow a wider and more homogeneous distribution of the antiproliferative compound. Paclitaxel is well suited for this purpose because its lipophilic properties account for satisfactory penetration and persistence in the tissue; moreover, in the coating preparation, its solubility is enhanced by adding a small amount of the hydrophilic X-ray contrast medium iopromide (Ultravist®) (8).

In experimental studies Scheller et al. extensively documented that paclitaxel-eluting balloons (PEB) effectively inhibited neointimal proliferation after BMS deployment (9). These positive findings were confirmed in a small pilot study among patients with in-stent restenosis after BMS (10): patients treated with a balloon coated with a paclitaxel dose of  $3 \mu\text{g}/\text{mm}^2$  and inflated for 60 seconds featured a significantly lower six-month late lumen loss and need for target-lesion revascularization compared with the uncoated balloon group. In the absence of data about the efficacy and tolerability of higher drug dosages and of the optimal inflation times, Cremers et al. went back to a much awaited experimental study, the findings of which are reported in the present issue of *Thrombosis and Haemostasis* (11). The authors deployed 56 BMS into left anterior descending and circumflex coronary arteries of 28 domestic pigs, and randomized them to five different strategies: i) control, with uncoated balloon; ii) PEB with 10 seconds inflation time; iii) PEB with 60 seconds inflation time; iv) PEB with two consecutive 60 seconds inflations performed with the same balloon; v) PEB with two consecutive 60 seconds inflations performed with two balloons. After four weeks, angiographic and histomorphometric analyses

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Received: November 27, 2008  
Accepted: November 27, 2008

Prepublished online: December 4, 2008  
doi:10.1160/TH08-11-0770



**Figure 1: Mechanisms of lumen enlargement and restenosis after percutaneous coronary interventions (PCI).** A coronary lesion (on the left) can be effectively treated with plain “old” balloon angioplasty (POBA) or stent-PCI, and both techniques obtain most of the gain with a stretching of the entire vessel, with POBA disrupting the plaque and frequently causing dissections. Angiographic restenosis occurs at a higher rate after POBA, due to vessel remodeling and cellular proliferation (grey area), and to a lower rate after bare-metal stents (BMS) (here only through the neointimal component). Such neointima formation is dramatically reduced by drug-eluting stents (DES). DES however also cause incomplete or delayed strut endothelialization, which can be responsible for even late (>1 month) thrombosis and acute vessel occlusion.

showed a statistically significant increase in lumen diameter and luminal area and a corresponding decrease in maximum neointimal thickness and neointimal area in the vessels treated with PEB. Reduction in neointimal hyperplasia ranged between 57–61% and was comparable in all the PEB arms; inflammation scores were similar in treated groups, and significantly higher than controls. No edge effect was detected. A satisfactory endothelialization was documented in all samples. Therefore, a short inflation time of a single balloon seems equally effective as multiple or prolonged inflations, which might be occasionally used in conditions at higher risk of recurrence of in-stent restenosis (e.g. diabetes or renal dysfunction). Higher local doses of paclitaxel also appeared well tolerated.

PEB reduces cellular proliferation inside the stent and seems in principle, therefore, extremely well suited for the treatment of in-stent restenosis (10). PEB angioplasty cannot be actually proposed as a stand-alone therapy for *de novo* coronary lesions, since paclitaxel effectively inhibits cellular proliferation, but does not reduce vascular recoil, which is a major component of post-balloon-only angioplasty restenosis. In-stent restenosis, conversely, is characterized by an extremely high rate of recurrence (30–80%) with traditional percutaneous treatments. Currently, the deployment of a DES inside the previous restenotic BMS is considered the best option for this subset of patients, and proved better than intravascular brachytherapy (12). However, a stent “sandwich” cannot be viewed as the ideal solution of this cumbersome problem because – as pointed out above – the local concentrations of the drug at variable distance from the stent struts are likely dishomogeneous, and also because such a solution is not optimal for treatment of bifurcation lesions.

In the search of the “ideal” device to restore coronary patency, fully bioabsorbable stents seem also extremely promising: they are able to acutely scaffold the artery, tackling dissections and counteracting vessel recoil, and later to “magically disappear” from the vascular wall. However, in the first-in-man experience, the four-month degradation of magnesium struts produced a late vessel recoil, and this translated into an unacceptable rate of 45% target-vessel revascularization at one year (13). More promising results were recently obtained with the first experience of a fully bioabsorbable everolimus-eluting stent (14), for which at one year the rate of major adverse cardiac events was 3.3%, with only one patient having a non-Q wave myocardial infarction. Neither target lesion revascularisations nor late stent thromboses were here recorded.

We must acknowledge the limited power of the present study to detect low frequency events, such as stent thrombosis, and therefore a final statement about safety cannot be given; this limitation is, however, common in preclinical studies. Endothelialization, a possible surrogate for safety, was here documented to be uniform on the stent surface, without any evidence of platelets or fibrin deposition surrounding stent struts, which form the substrate underlying stent thrombosis in both animals and humans. We would wish to see many more studies like this meticulously testing PEB (and newer PCI devices in general) in a suitable animal model, and therefore welcome the device as an effective strategy for the treatment of in-stent restenosis. However, preclinical studies cannot be shortcuts for carefully performed clinical trials. The study presented here will likely be the solid background for one or more multicenter clinical trials testing the full therapeutic potential of PEB.

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