DRUG-COATED BALLOONS 2008 PERSPECTIVE

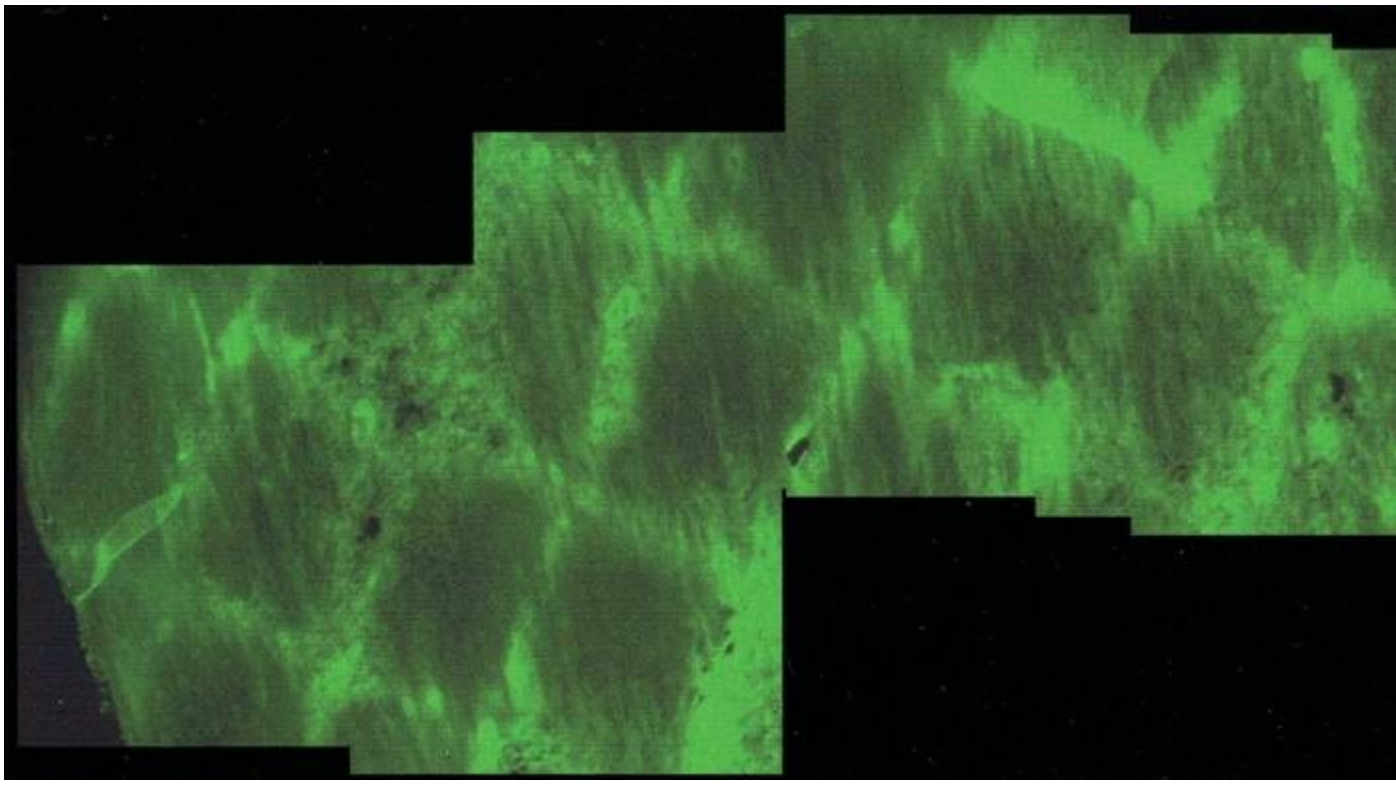
ABSTRACT

Numerous, initially promising, approaches using systemic antiproliferative agents have so far failed to prevent restenosis after percutaneous coronary interventions. Thus, restenosis prevention continued to be a challenge to interventional cardiology. Some years ago, intracoronary radiation therapy was considered a breakthrough treatment against in-stent restenosis, but the method crucially relies on the availability of the radiotherapeutic armamentarium. Another major limitation of brachytherapy is late thrombosis, especially when combined with stent implantation. The advent of drug coated stents has improved the scenario but has limitations especially in stent restenosis . The drug-coated balloon has the potential to improve the limited results of drug-eluting stents.

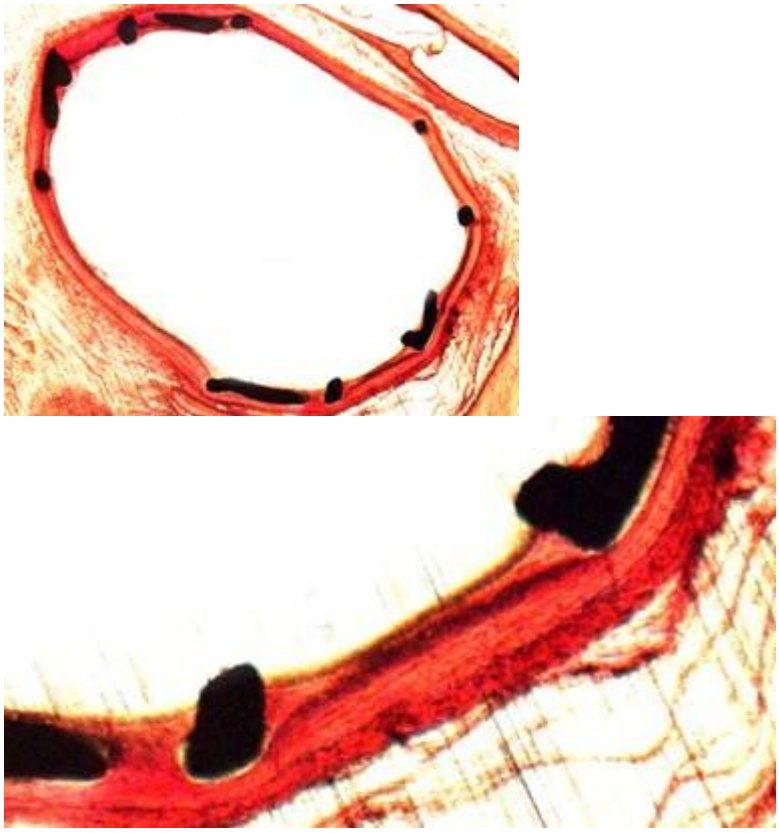
BACKGROUND

The development of drug eluting stents (DES) as an answer to restenosis is now about 6 years old in clinical use and we have come to understand the limitations of the technology as well as the potential deleterious effects. The key factor in DES drug delivery is understanding the fact that about 85% of the vessel wall is not covered by stent struts resulting in inhomogenous drug delivery as the drug has to diffuse from the stent struts into the vessel wall . This necessitates the loading of drug in a high dose at the stent struts, polymer coating to hold the drug and slow release kinetics to enable drug diffusion into those parts of the vessel in between the stent struts.

New concepts to overcome the limitations of DES should avoid a sustained drug release from stent struts to allow for earlier endothelialisation. There should be no use of polymers or other sustained release technology capable of inducing inflammation. Non-stent-based local delivery of antiproliferative drugs may offer additional flexibility and efficacy in the entire range of applications.It may allow for a homogenous drug distribution to the arterial wall.



Scanning Photomicrograph showing inhomogenous drug distribution following stent implantation.



Photograph showing non endothelisation of stent struts 28 days following DES implantation

EMERGING NOVEL TECHNOLOGY- DRUG-COATED BALLOONS

The drug-eluting balloon is a regular angioplasty balloon requiring no special handling. It is a novel option for the treatment of coronary and peripheral arteries. Once exposed, cells retained paclitaxel in vivo for 6 days even if plasma levels were far below the detection limit[1] The basic research leading to the development of this device after the surprising discovery that sustained drug release is not a precondition for long lasting restenosis inhibition. Preclinical studies have shown that brief contact between vascular smooth muscle cells and antiproliferative drugs can result in prolonged inhibition of neointimal proliferation.[2–5] Initial high drug concentration as achieved by the drug-eluting balloon is a substitute for sustained release. The drug is administered only during the short inflation time of the balloon, and is subject to rapid dilution and elimination. Endothelial cells and their precursor cells migrate to the injured vessel segment. Re-endothelialisation should not be inhibited because these cells entering the lesion from distant locations had no previous exposure to the drug and, therefore, maintain their capability to

proliferate. The innovative coating technique of balloons using Acetone as a solvent and Iopromide (a commonly used contrast agent) as an additive to hold the drug, enables a controlled dose of paclitaxel to be released during dilatation, as soon as the balloon is inflated inside the stenotic artery.[4] Drug-coated balloons are currently the most advanced and possibly superior alternative to stent-based local drug delivery.

CLINICAL TRIALS

The Paccocath ISR trial : was a controlled, randomised, blinded, first-in-man study that investigated the use of paclitaxel-coated balloon catheters for treatment of coronary in-stent restenosis. Patients who were treated with the coated balloon had significantly better angiographic results and concomitant improvement in 12-month clinical outcomes compared with patients treated with an uncoated balloon. The mean (SD) in-segment luminal loss was reduced from 0.74 (0.86) mm in the uncoated balloon group to 0.03 (0.48) mm in the coated balloon group ($p = 0.002$) (fig 1). There were no coating-related adverse events. Clopidogrel was given for only 4 weeks in both groups.[6]

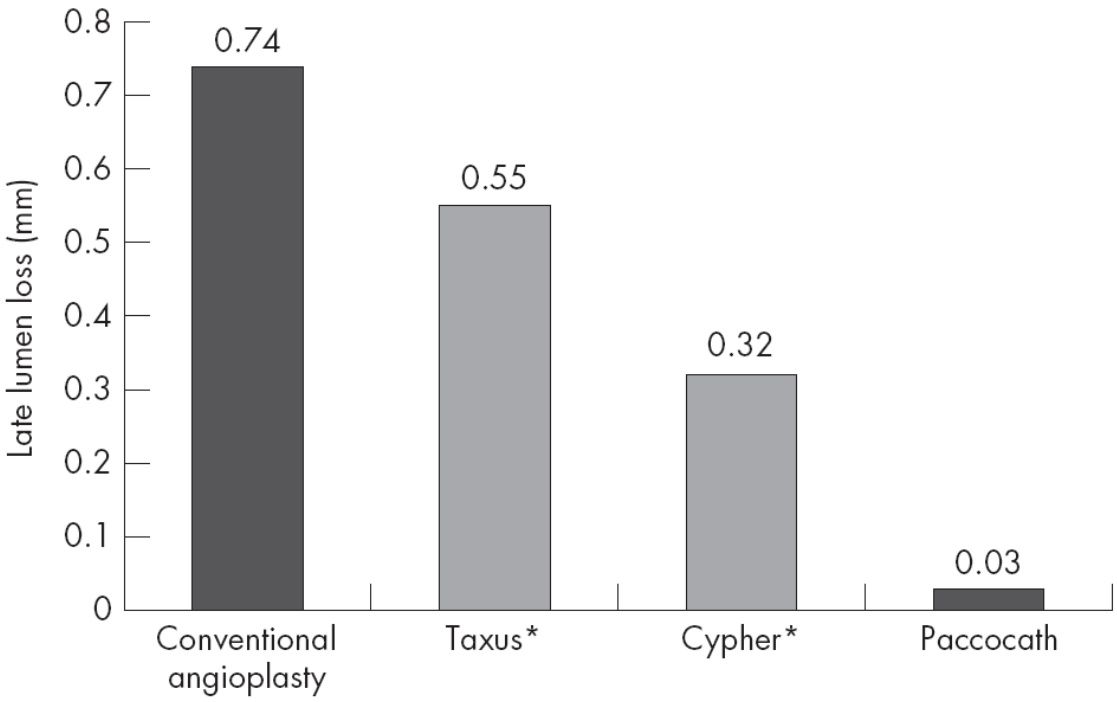


Figure 1 Late lumen loss in-segment after treatment of coronary in-stent restenosis. Comparison of conventional balloon angioplasty, implantation of a Taxus stent, Cypher stent, and angioplasty with the drug-coated balloon (Paccocath). Data from the Paccocath ISR I trial (conventional angioplasty and Paccocath)[6] and the ISAR-DESIRE study (Taxus stent and Cypher stent).[7]

PEPCAD 2 Trial : This is a trial that assessed the efficacy and safety of the Sequent drug coated balloon versus the Taxus DES in treating BMS restenosis. In approximately 120 patients in the trial , those randomized to Paccocath , late lumen loss measured 0.19mm versus 0.45 mm in the Taxus group, resulting in binary restenosis of 3.75 versus 20.8% in the Taxus group and a TLR rate of 3.2% versus 18.6%.

The conclusions drawn were that the drug eluting balloon was more effective than the Taxus stent in preventing restenosis , and was safe as no event of stent thrombosis wa reported despite >200 patient years of follow up and dual anti platelet therapy for 3 months only. Follow ups are still in progress for this trial

	DEB (N=66)	**DES (N=60)**	**P=**
Follow-up [months]	**6.2 ± 0.8**	**6.2 ± 0.8**	**0.7**
Follow-up: clinical	**62 (93.9%)**	**59 (98.3%)**	**0.4**
Follow-up: angiographic	**54 (81.8%)**	**53 (83.3%)**	**0.5**
Late lumen loss [mm]	**0.19 ± 0.39**	**0.45 ± 0.69**	**0.01**

Binary restenosis in segment	**2/54 (3.7%)**	**11/53 (20.8%)**	**0.02**
Total MACE	**3/62 (4.8%)**	**13/59 (22.0%)**	**0.007**
TLR	**2/62 (3.2%)**	**11/59 (18.6%)**	**0.008**
Myocardial infarction	**0/62 (0.0%)**	**1/59 (1.7%) 2**	**1**
Death	**1/62 (1.6%)3**	**1/59 (1.6%) 4**	**1**

PEPCAD 1 Trial : This trial assessed the safety and efficacy of drug eluting balloon versus DES in native small vessel disease. In about 120 patients with small vessel disease (vessel size rangin between 2.2 mm - 2.8mm) drug eluting balloon alone versus drug eluting balloon followed by deployment of BMS was assessed : At the end of 6 months late lumen loss was 0.18mm in drug eluting balloon group versus 0.67mm in drug eluting balloon followed by BMS group. This resulted in a binary restenosis of 5.5% versus 39.3%. this resulted in TLR rates of 4.9% versus 30%. In drug eluting balloon group dual anti platelet therapy was given for 1 month only. Follow ups are still in progress for this trial.

	DEB Only (N=82)	**DEB & BMS (N=32)**
Follow-up clinical [months]	**6.7 ± 1.9**	**6.2 ± 1.3**
Follow-up: clinical [N]	**82 (100%)**	**30 (93.75%)**
Follow-up: angiographic	**73 (89%)**	**28 (87.5%)**
Late lumen loss [mm]	**0.18 ± 0.38**	**0.67 ± 0.67**
Binary restenosis in segment	**4/73 (5.5%)**	**11/28 (39.3%)**
Binary restenosis in lesion	**4/73 (5.5%)**	**10/28 (35.7%)**
Total MACE	**5/82 (6.1%)**	**10/30 (33.3%)**
TLR	**4/82 (4.9%)**	**9/30 (30.0%)**
Myocardial infarction	**1/82 (1.2%)**	***1/30 (3.3%)**
Death	**0/82 (0 %)**	**0/30 (0 %)**

Ongoing Clinical Trials : PEPCAD 3 is a trial assessing efficacy in complex lesions of drug eluting balloon followed by Coroflex Blue stenting in large vessels compared to Cypher Select stent. Recruitment of patients is ongoing.

INDICOR is an Indian multicentric study with angiographic follow up comparing drug coated balloon and stenting with Cobalt chromium stent in reverse order.

CONCLUSIONS

The drug-coated balloon has the potential to improve the limited results of DES—for example, in patients with coronary in-stent restenosis, in bifurcations, in small vessels, or in other circumstances where stent implantation is not desirable or possible. With the drug-coated balloon there is no need for a stent. However, the combination with modern, flexible, thin bare metal stents is another promising application. The treatment of peripheral arteries, where DES have shown limited efficacy, may become a future domain of the coated balloon.

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