Circulation
Cardiovascular Interventions
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Drug-Eluting Balloon : The Comeback Kid?

Ron Waksman and Rajbabu Pakala

Circ Cardiovasc Interv 2009;2;352-358;
DOI: 10.1161/CIRCINTERVENTIONS.109.873703
Circulation: Cardiovascular Interventions is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-7640. Online ISSN: 1941-7632

Drug-Eluting Balloon
The Comeback Kid?

Ron Waksman, MD; Rajbabu Pakala, PhD

Balloon angioplasty revolutionized coronary revascularization; however, elastic recoil and restenosis caused by cellular proliferation are major drawbacks of angioplasty. Intracoronary stenting, which could tackle dissections and eliminate elastic recoil, became the next mode of intervention but was limited by stent thrombosis and increased neointimal hyperplasia, leading to in-stent restenosis. Drug-eluting stents significantly attenuate the cellularity and reduce the need for repeat revascularization; however, late stent thrombosis, dependency on prolonged dual antiplatelet therapy, and continued restenosis led to a quest for new treatment modalities. In recent years, drug-eluting balloons (DEB) have emerged as a potential alternative to combat restenosis. Paclitaxel was identified as the primary drug for DEB because of its rapid uptake and prolonged retention. DEB technology demonstrated safety and efficacy in preclinical and in randomized clinical trials for patients with in-stent restenosis. Further studies for de novo lesions in small vessels, for lesions in the superficial femoral artery, and those for below the knee signal its safety and efficacy for broader indications. This review will discuss the rationale, concept, and available DEB technologies, along with preclinical and clinical data, to support the DEB as a new technology for endovascular intervention. It will also assess the potential of the balloon to become the "comeback kid" of percutaneous coronary intervention in the form of DEB.

The use of percutaneous balloon angioplasty to recanalize narrowed coronary arteries and endovascular vessels revolutionized revascularization.[1] Balloon angioplasty, however, was associated with subintimal dissection, abrupt vessel closure, and restenosis. Stents tackle dissection, eliminate the elastic recoil and late negative vessel remodeling,[2] but increase inflammation, thereby leading to more intimal hyperplasia resulting in in-stent restenosis (ISR).[3] The major limitation of stents is stent thrombosis, which is controlled with antiplatelet therapy. Drug-eluting stents (DES) are another breakthrough in stent technology because of their ability to minimize cellular proliferation and to reduce restenosis rates to single-digit levels.[4,5] DES carry with them the new phenomena of late and very late stent thrombosis, with a hazard ratio of up to 0.6 per year as a result of delayed healing, local inflammation, and impaired endothelial function, which lead to prolonged dual antiplatelet therapy.[6] Restenosis is also reported with DES, especially in complex subsets of patients and lesions.[7] These DES limitations prompted innovation for improved solutions, such as the local delivery of drugs via nonstent-based platforms, including drug-eluting balloons (DEB). This review will discuss the rationale, concept, and available DEB technologies, along with the preclinical and clinical data available to support the DEB as a new technology for endovascular intervention.

Rationale

Rationale for the development of DEB derives mainly from the limitations of DES. Nonstent-based local drug delivery using DEB maintains the antiproliferative properties of DES, but without the limitations of DES. Moreover, DEB may be used in subsets of lesions where DES cannot be delivered or where DES do not perform well, such as in torturous vessels, small vessels, or long diffuse calcified lesions, which can result in stent fracture; or perhaps when scaffolding obstructs major side branches or in bifurcated lesions. The discovery that sustained drug release is not a requisite for the long-lasting antiproliferative effect of paclitaxel and the fact that the uptake of paclitaxel by vascular smooth muscle cells is rapid and can be retained up to 1 week, resulting in prolonged antiproliferation, have given rise to the concept of local paclitaxel delivery through coated balloons.[8] The most appealing indication for paclitaxel-eluting balloons would be for the treatment of ISR.

Additional potential advantages of DEB include (a) homogenous drug transfer to the entire vessel wall; (b) rapid release of high concentrations of the drug sustained in the vessel wall no longer than a week, with little impact on long-term healing; (c) absence of polymer could decrease chronic inflammation and the trigger for late thrombosis; (d) absence of a stent allows the artery's original anatomy to remain intact, notably in cases of bifurcation or small vessels, thereby diminishing abnormal flow patterns; and (e) with local drug delivery, overdependence on antiplatelet therapy could be curtailed (Table 1).

However, DEB cannot overcome the mechanical limitation of acute recoil seen postballoon angioplasty. Furthermore, it is not clear whether DEB can eliminate the late negative remodeling seen with noncoated balloons. The efficacy and safety parameters when using DEB as adjunct therapy to bare metal stents (BMS) must also be determined. Other potential

From the Division of Cardiology, Department of Internal Medicine, Washington Hospital Center, Washington, DC.
Correspondence to Ron Waksman, MD, Washington Hospital Center, 110 Irving Street, NW, Suite 4B-1, Washington, DC 20010. E-mail ron.waksman@medstar.net

(*Circ Cardiovasc Intervent*. 2009;2:352-358.)

Circ Cardiovasc Intervent is available at http://circinterventions.ahajournals.org DOI: 10.1161/CIRCINTERVENTIONS.109.873703

Table 1. DES Versus DEB

	DES	DEB
Platform of drug delivery	Stent scaffolding	Balloon
Retention	Polymer based	Embedded imprinted
Drug dose	Low: <100 to 200 μg	High: 300 to 600 μg
Release kinetics	Slow and controlled	Fast release
Distribution	Strut-based vascular penetration	Balloon surface homogenous distribution
Advantages	Mechanical support	Leave no implant
	Abluminal trapping	Larger surface area
	Less drug spillage into the circulation	Less drug localization in the vessel wall
	Proven efficacy in many indications	Accessible to complex lesions and long segments
	No acute recoil tackled dissection	May not require prolonged DAPT

DAPT indicates dual antiplatelet therapy.

limitations of the DEB include the variability of pharmacokinetics and control of dosing.

Technologies

Multiple approaches are proposed for local drug delivery to the vessel wall—injection of nanoparticles loaded with drug, dissolution of the drug in suitable media (contrast media), and drug transfer through drug delivery balloons or DEB. Targeted drug delivery using nanoparticles was validated in preclinical[9] and clinical studies.[10] Injection catheters allow high concentrations of the drug to be delivered locally.[11] Contrast media adheres to the vessel wall for a few seconds, which could serve as a matrix for local drug delivery.[12] However, these methods deliver only a small amount of the drug to the target area, whereas larger amounts are washed away. Porous balloons[13] and double balloons[14] are also used for local drug delivery. The former has multiple holes for drug delivery; the latter uses 2 balloons inflated at proximal and distal ends of the lesion while the occluded area is filled with the drug. Most of these systems were developed before the introduction of DES, with little knowledge about sirolimus and its analogues, and paclitaxel, the only drug proven to reduce restenosis with DES. What we know about DEB is seen in the recent work done with paclitaxel, which includes a series of preclinical[15–21] and clinical[22–27] studies.

Methodologies to load the drug to the balloon include spraying, dipping, nanoparticles, and imprinting the drug on the rough surface of the balloon. Controlling the release of the drug into the vessel wall during inflation without losing it during the delivery of the balloon to the target lesion is important. Furthermore, the release kinetics of the drug to the vessel wall is critical to the efficacy and safety of the procedure. With a strong lipophilic nature for retention to the vessel wall, paclitaxel is the drug of choice for DEB.

Drug-Eluting/Delivery Balloon Systems

There are 3 main types of technologies for drug-eluting or delivery balloon systems (Table 2). The Paccocath technology is a proprietary drug matrix applied to the balloon of an angioplasty catheter. It is developed by Ulrich Speck and Bruno Scheller; Bayer Schering Pharma AG (Berlin, Germany) is the owner of the Paccocath technology and is developing it for market through Bayer affiliate, MEDRAD, Inc. Paclitaxel is embedded in hydrophilic iopromide, which increases the solubility and transfer of paclitaxel to the vessel wall. More than 80% of the drug is retained during balloon

Table 2. Drug-Eluting or Delivery Balloon Systems

Name	Manufacturer	Principle
Paccocath	Bayer (Bavaria Medizin Technologie, Oberpfaffenhofen, Germany)	Paccocath technology (paclitaxel embedded in hydrophilic iopromide coating)
SeQuent Please	B. Braun Melsungen AG (Melsungen, Germany)	Improved Paccocath technology
Coroflex DEBlue	B. Braun Melsungen AG	Drug-eluting balloon with a thin strut CoCr stent
DIOR	Eurocor (Bonn, Germany)	Paclitaxel coated onto microporous balloon surface and folded
MAGICAL	Eurocor	Folded balloon in combination with stent
Elutex	Aachen Resonance (Aachen, Germany)	Folded balloon
GENIE	Acrostak Corporation (Winterthur, Switzerland)	Liquid drug delivery catheter
IN.PACT Amphirion	INVAtec (Italy)	FreePac, a proprietary coating that balances hydrophilic and lipophilic properties
IN.PACT Falcon	INVAtec	FreePac
Advance PTX	Cook Medical (Bloomington, Ind)	DEB
N/A	Lutonix Inc (Maplegrove, Minn)	DEB

delivery to the target lesion, and 10% to 15% of the initial dose is delivered to the vessel wall on 60-second inflation. Paccocath coating is stable during ethylene oxide sterilization, and the balloon has >1 year shelf life. B. Braun Melsungen AG (Berlin, Germany) has licensed the technology for use in its SeQuent Please DEB catheter, but with an improved coating procedure and better balloon technology. Coroflex DEBlue is comprised of a paclitaxel-eluting balloon in combination with a thin strut CoCr BMS.

IN.PACT Amphirion is a drug-eluting percutaneous transluminal angioplasty balloon catheter designed to treat atherosclerosis in arteries located below the knee. It features the Amphirion percutaneous transluminal angioplasty balloon with FreePac, a proprietary, natural coating. FreePac reduces the total drug elution time to 30 to 60 seconds; balloon inflation beyond 60 seconds can be maintained without additional drug release. IN.PACT Falcon is a drug-eluting percutaneous transluminal coronary angioplasty balloon catheter designed specifically to treat atherosclerosis in the coronary arteries. It features the Falcon percutaneous transluminal coronary angioplasty balloon platform with FreePac. In clinical evaluation is the Advance PTX, a drug-eluting percutaneous transluminal angioplasty balloon designed to increase long-term patency. Lutonix, Inc is also developing DEB for coronary and small vessel use.

DIOR uses folded balloon technology that prevents early wash-off during insertion and tracking. DIOR can be inflated up to 60 seconds for full drug release or less for partial release. The first inflation for 20 seconds will release 35% of the drug and subsequent inflation of 20 seconds will release another 35%. Another DEB using the same coating method as Dior is Elutex, which releases 20% of the drug per inflation. MAGICAL is a system in which a BMS can be delivered using DIOR. GENIE is a liquid drug delivery catheter available in various diameters and shaft lengths. After determining the vessel diameter and lesion length, the balloons are inflated with diluted paclitaxel. The GENIE therapy can include the whole vessel, stent edges, and adjacent vessel segments.

Nonpaclitaxel DEB Preclinical Studies

Sheiban et al[28] tested the efficacy of a genistein-coated balloon (anti-inflammatory falconoid, 0.7 $\mu g/mm^2$) in a porcine coronary artery stent model. They reported that at 4 weeks, peri-stent inflammatory cell count (mononucleocytes) was significantly less in vessels treated with genistein-coated balloons compared with those treated with noncoated balloons (39 ± 32 versus 96 ± 29 mm^2, $P=0.019$). However, at 6 to 8 weeks, the reduced inflammatory cell count did not translate into reduced neointimal hyperplasia (0.13 ± 0.11 versus 0.14 ± 0.09, $P=0.835$).

Tharp et al[29] tested $Ca2^+$-activated K^+ channel (KCa3.1) inhibitor TRAM-34-coated balloon (20 mg/mL in acetone) in a porcine coronary artery angioplasty model. In vessels treated with control balloons, KCa3.1, c-jun, and c-fos mRNA levels were increased 2 hours postangioplasty, whereas repressor element 1-silencing transcription factor expression decreased. Smooth muscle myosin heavy chain expression was unchanged at 2 hours but decreased 2 days postangioplasty. Use of TRAM-34-coated balloons prevented KCa3.1 upregulation and repressor element 1-silencing transcription factor downregulation at 2 hours, smooth muscle myosin heavy chain and myocardin downregulation at 2 days, and attenuated subsequent restenosis 14 and 28 days postangioplasty.

Paclitaxel DEB: Preclinical Trials

Mori et al[30] demonstrated that when cells are exposed to paclitaxel, the drug is retained up to 6 days. Herdeg et al[14] demonstrated that a short, single-dose application of paclitaxel on human smooth muscle cells had a sustained antiproliferative effect up to 14 days.

In a porcine model, Scheller et al[15] have shown that after a 60-second dilatation most of the drug is released from the balloon (≈90%), and 40 to 60 minutes later, they could still detect 10% to 15% of the drug in the vessel wall, thus suggesting that paclitaxel is rapidly transferred from the balloon and retained by the tissue for a long time. They also demonstrated that treatment with a paclitaxel-coated balloon led to a dose-dependent reduction in stent neointimal area (up to 63%), without any effect on re-endothelialization of stent struts. A dose-dependent inhibitory effect was demonstrated only when paclitaxel was dissolved in acetone with iopromide, but no effect was demonstrated when dissolved in ethyl acetate, suggesting that the use of proper dissolution agents is important. In another porcine coronary artery study, Speck et al[16] have shown that treatment with a paclitaxel-coated balloon reduced in-stent neointimal area by 54%, whereas sirolimus-eluting stents reduced it by only 26%. In a balloon overstretch and stented porcine peripheral artery model, Albrecht et al[17] have shown that the use of a 480-μg paclitaxel-coated balloon allowed a 68% decrease in diameter stenosis and a 56% decrease in late lumen loss.

Recently, Cremers et al,[20] using balloons coated with paclitaxel (5 $\mu g/mm^2$) dissolved in acetone with iopromide, have shown that 10-second and 60-second inflations yielded similar results. They also demonstrated that multiple 60-second inflations using a single balloon or multiple balloons yielded results similar to that of single 10-second inflation, suggesting that a short inflation time of a single balloon seems equally effective as multiple or prolonged inflations, which may be used occasionally in conditions at higher risk of recurrence of ISR. In a head-to-head comparison of Paccocath and DIOR DEB, Cremers et al[21] have shown that matrix-coated Paccocath led to a highly significant ($P<0.01$) reduction of all parameters, including neointimal proliferation, compared with both the uncoated control and the roughened DIOR balloon.

Paclitaxel DEB: Clinical Studies

DEB for ISR

In a small study of 5 patients (11 segments with lesion length 16.5 ± 7.0 mm and $67\pm15\%$ stenosis) with at least second episode of ISR within the same stent using a Remedy delivery catheter, Buszman et al[31] administered 100 μg of paclitaxel diluted in 2 mL of 0.9% NaCl over 60 seconds, repeating the dose for each 10 mm of the lesion. In all patients, a lower rate of target vessel revascularization was achieved compared with a

Table 3. Angiographic and Clinical Results From Paccocath ISR and PEPCAD II Trials

Trial	Group, No. Patients	6-mo Late Loss In-Stent, mm	6-mo Late Loss In-Segment, mm	6-mo Restenosis In-Segment, n (%)	6-mo TLR, n (%)	TLR (% at mo)	MACE (% at mo)
Paccocath ISR I	Rx (n=26)	0.09±0.49	0.03±0.48	1 (5)	0	0 (0% at 24)	1 (4% at 24)
	Control (n=26)	0.76±0.86	0.74±0.86	10 (43)	6 (23)	6 (23% at 24)	9 (35% at 24)
Paccocath ISR II	Rx (n=28)	0.19±0.43	0.18±0.41	2 (8)	2 (8)	3 (11% at 24)	5 (18% at 24)
	Control (n=28)	0.74±0.86	0.86±0.73	15 (58)	14 (50)	14 (50% at 24)	16 (57% at 24)
PEPCAD II	Rx (n=66)	0.19±0.38	0.17±0.42	4/57 (4)	2/64 (3.1)	4 (6% at 12)	6 (9% at 12)
	Taxus (n=65)	0.47±0.71	0.38±0.61	12/59 (20)	10/60 (16.7)	10 (15% at 12)	15 (22% at 12)

MACE includes TLR, myocardial infarction, acute and subacute stent thrombosis, stroke, and death.

control. No adverse events were observed in the peri-procedural period or during the 6-month follow-up. Follow-up angiography at 6 months revealed ISR in 3 segments (27.2%) and in-stent late lumen loss of 0.2±0.93 mm.

In the randomized, double-blind, multicenter Paclitaxel-Coated Balloon Catheter for In-Stent Restenosis (PACCOCATH ISR I) trial, Scheller et al[22] enrolled 52 patients with a clinical evidence of stable or unstable angina and a single restenotic lesion in stented coronary artery. The primary end point was angiographic late lumen loss in-segment. Secondary end points included binary restenosis and major adverse cardiovascular events (MACE). Patients were randomly assigned to either paclitaxel-coated balloon (3 $\mu g/mm^2$) or uncoated catheter (Bavaria Medizin Technologie, Oberpfaffenhofen, Germany). At 6 months, the in-segment late lumen loss was significantly less in the coated balloon group ($P=0.002$). The coated balloon group had 5% binary restenosis and 4% MACE compared with 43% and 31%, respectively, in the uncoated balloon group ($P=0.002$ and 0.02; Table 3).

PACOCATH ISR I and II pooled data after complete 2-year follow-up confirmed these results.[26] A total of 108 patients were enrolled in both studies. Quantitative coronary angiography revealed no differences in baseline parameters. After 6 months, in-segment late lumen loss was less in the drug-coated balloon group compared with the uncoated balloon group ($P<0.001$), resulting in a binary restenosis rate of 25/49 versus 3/47 ($P<0.001$). Until 12 months postprocedure, 20 patients in the uncoated balloon group compared with 2 patients in the coated balloon group required target lesion revascularization (TLR; $P=0.001$). From 12 to 24 months, only 2 MACE, 2 stroke in the uncoated group, and 1 TLR in the coated balloon group were recorded (Table 3).

PEPCAD II was a prospective, randomized, multicenter, 2-arm phase II pilot study.[32] The objectives were to examine the safety and efficacy of the SeQuent Please DEB in the treatment of ISR in native coronary arteries for procedural success and preservation of vessel patency compared with the Taxus DES. The primary end point was angiographic late loss at 6 months, and the secondary end points were procedural success (≤30%), 6-month binary restenosis rate, MACE, and MACE at 1 and 3 years. The SeQuent Please was safe and had a high procedural success rate. At 6-month follow-up, in-segment late lumen loss was 0.38±0.61 mm in the DES group versus 0.17±0.42 mm ($P=0.03$) in the DEB group, resulting in a binary restenosis rate of 12/59 (20%) versus 4/57 (7%; $P=0.06$). At 12 months, MACE rates were 22% and 9% ($P=0.08$). This difference was primarily due to the need for TLR in 4 patients in the DEB group compared with 10 patients in the DES group ($P=0.15$; Table 3). The difference between SeQuent Please and Taxus is not surprising. The use of SeQuent Please in the treatment of ISR confirms the results of Paccocath ISR I and II, in that the restenosis rate with Taxus is similar to that in other trials using this DES for the treatment of BMS restenosis.

DEB for de Novo Lesions

DEB for de novo lesions is less studied. The only registry available is PEPCAD I, which targeted small vessels.[33] This was a prospective, nonrandomized, multicenter, 1-arm phase II pilot study. The primary end point was late loss at 6 months, with secondary end points of binary restenosis and MACE at 6 months, and MACE at 1 and 3 years. Of the 114 patients treated with DEB, 32 required stenting postprocedure. The results were quite different between the balloon-alone group and the DEB with BMS group. Although the late loss in the DEB-alone group was only 0.18±0.38 mm and the binary restenosis 5.5%, the DEB with BMS had higher late loss and restenosis of 0.73±0.74 mm and 44.8%, respectively. In addition, the rate of stent thrombosis in the DEB and BMS group was 6.3%. The authors attributed the poor results of the DEB with BMS to geographic miss and concluded that the paclitaxel-eluting balloon catheter, SeQuent Please, was safe, was associated with a high procedural success rate in small de novo lesions, and exhibited low late lumen loss after 6 months in small vessel disease. The question of DEB in conjunction with BMS remains a concern because of high restenosis rates.

DEB for Bifurcation Lesions

In a short-term study of only 3 patients, Herdeg et al[34] used the GENIE catheter for treatment of ISR of coronary artery bifurcation lesions. They delivered liquid paclitaxel into whole bifurcation lesions without repeating stent implantation, using the kissing balloon technique. At 6 months, they reported no MACE and angiographically patent vessels.

In the Drug Eluting Balloon in Bifurcation Utrect (DEBIUT) Fanggiday et al[23] tested the safety and efficacy of the Dior balloon in 20 patients with bifurcation lesions. They sequentially treated main and side branches with the Dior balloon, followed by provisional stenting of only the main branch with a BMS. At 4-month follow-up, no major coronary events or vessel closure was reported. There were no angiographic data in the report.

Table 4. Angiographic and Clinical Results From the FemPac and THUNDER Trials

	FemPac	THUNDER
No. of patients		
Uncoated	42	54
Coated	45	48
Angiographic follow-up, %		
Uncoated	81	89
Coated	69	85
6-mo late lumen loss, mm		
Uncoated	1.0±1.1	1.7±1.8
Coated	0.5±1.1	0.4±1.2
6-mo angiographic restenosis, %		
Uncoated	47	44
Coated	19	17
6-mo % TLR		
Uncoated	33	37
Coated	9	4
18–24 mo % TLR		
Uncoated	48	52
Coated	20	15
6-mo deaths		
Uncoated	0	1
Coated	2	2
6-mo major amputations		
Uncoated	2	0
Coated	0	2

DEB for Peripheral Artery Disease

In the Local Taxan with Short Exposure for Reduction of Restenosis in Distal Arteries (THUNDER) multicenter trial, Tepe et al[24] randomly assigned 154 patients with stenosis or occlusion of a femoropopliteal artery to treatment with paclitaxel-coated catheters, uncoated catheters with paclitaxel dissolved in the contrast medium, or uncoated catheters (control). The primary end point was late lumen loss at 6 months. They reported no adverse events. At 6 months, the mean late lumen loss was significantly less with paclitaxel-coated catheters compared with control or contrast medium groups ($P<0.001$). The rate of revascularization of target lesions at 6 months was 20/54 in the control group, 2/48 in the paclitaxel group ($P<0.001$), and 15/52 in the contrast medium group ($P=$NS); at 24 months, the rates increased to 28/54, 7/48, and 21/52, respectively (Table 4).

In the Femoral Paclitaxel (FemPac) pilot trial, Werk et al[25] randomly assigned 87 patients with femoropopliteal peripheral artery disease to uncoated or paclitaxel-coated catheters. The primary end point of angiographic late lumen loss at 6 months was significantly reduced in patients treated with the paclitaxel-coated balloon (31 of 45). Patients treated with the paclitaxel-coated balloon also had a significant reduction in TLR at 6 months, which was maintained up to 24 months (Table 4).

Thus, the THUNDER trial and FemPac trial demonstrated a signal of biological efficacy. Unfortunately, both investigations were limited in design. Both FemPac and THUNDER examined small sample sizes, enrolled heterogeneous populations, provided incomplete follow-up, and were designed to evaluate short-term angiographic primary end points. Enrollment criteria included variable clinical indications, de novo, balloon angioplasty related, and in-stent restenotic lesions. Lesions were long, and 15% to 27% of patients had total occlusions. Neither trial established complete blinding. Although each trial described the Rutherford clinical class at baseline, it was not available in 25% of the subjects at 6 months or in 43% of the subjects at 18 to 24 months. "Proof of principle" was claimed for paclitaxel delivery by balloon alone and, if true, constitutes a very exciting development in endovascular therapy (Table 4).

Latif and Hennebry[35] report 2 cases where, despite the failure of multiple revascularization techniques, local delivery of 1.7 mg of paclitaxel diluted in 10 cc of normal saline at the lesion site, using a 10-mm vascular clearway irrigation balloon, yielded good short-term results. A list of clinical studies is provided in Table 5.

Regulatory Considerations

The Food and Drug Administration perspective on DEB as presented at Cardiovascular Research Technologies 2009 in Washington, DC, is that the DEB is a hybrid product of balloon and drug. It is a class III device likely to be regulated by Center for Devices and Radiological Health (CDRH) as the lead center, with consultation to Center for Drug Evaluation and Research (CDER). The device requires characterization on: (1) drug dosage and release profile; (2) drug absorption into tissue versus released into bloodstream versus remains on the balloon; (3) how the balloon is coated; (4) consistency and uniformity across a range of sizes; (5) indication of ISR versus de novo coronary versus peripheral; (6) DEB use for multiple inflations; and (7) the presence of coatings or polymers.

The following concerns and challenges are also present: (1) the potential for higher drug doses in vivo than with DES and (2) higher doses of drug released into the bloodstream when the drug-coated balloon is inflated versus what remains in the DES. Testing should not simply evaluate when the DEB is in vitro because the drug remains in vivo longer than that of the balloon. There is a need for specific characterization of the drug, despite existing knowledge on the drug. Among the recommended testing is bench testing to support an indication. Testing should evaluate expected worst case scenarios in clinical use and encompass product matrix, coating integrity, and particulates. Preclinical assessment and clinical trials should be discussed with the Food and Drug Administration before initiation.

Clinical Considerations and Unresolved Issues

DEB is an emerging technology undergoing evaluation to find its role in the combat against restenosis, and it is expected to add value to the available technologies for the prevention of restenosis. The immediate comparator for DEB is the DES, which is currently used in >70% of coronary interventions in the United States. DES technology has high success and low restenosis rates but has very late stent

Table 5. Clinical Trials

Trial	Principal Investigator	Device Used	Treated Lesion	No. of Patients	Trial Results
Coronary					
Recurrent ISR	P. Buszman	Remedy catheter	ISR	5	Late lumen loss of 0.21+/−0.93 mm
PACOCATH ISR I	B. Sheller	Paccocath vs uncoated balloon	ISR	52	Superiority of Paccocath at 2 y
PACOCATH ISR II	B. Sheller	Paccocath vs uncoated balloon	ISR	56	Superiority of Paccocath at 2 y
PEPCAD II ISR	M. Undeverborden	SeQuent Please vs Taxus	ISR	131	Superiority of DEB at 6 mo
PEPCAD I SVD	M. Undeverborden	SeQuent Please	De novo, small vessels	120	Binary restenosis at 6 mo of 6%
PEPCAD III	C. Hamm B. Scheller	Coroflex DEBlue vs Cypher	Complex, de novo lesions	600	Ongoing
PEPCAD IV DM	M.A. Rosli	SeQuent Please+Corflex Blue vs Taxus	De novo lesions in diabetics	128	Ongoing
PEPCAD V	D. Mathey F.X. Kleber	SeQuent Please+Coreflex	Bifurcation	25	Ongoing
PEPCAD VI	J. Woehrle G. Werner	SeQuent Please+Corflex Blue	CTO	48	Ongoing
DEBIUT	J.C. Fanggiday	Dior	Bifurcation	20	No events at 4 mo
Peripheral					
Thunder	G. Tepe	Control IV Paclitaxel Paccocath	SFA lesions	154	Reduction of TLR with Paccocath at 2 y
FemPac	M. Werk	Uncoated vs coated-balloon	SFA, popliteal, de novo and ISR	87	Reduction of TLR with coated balloon at 2 y
Piccolo	G. Tepe	Paccocath vs uncoated-balloon	Below-the-knee lesions	114	Ongoing

CTO indicates chronic total occlusion; SFA, superficial femoral artery.

thrombosis and long-term dependency on dual antiplatelet therapy. DEB technology is proven to be effective with paclitaxel in preclinical trials and clinically for the treatment of ISR. The DEB has also shown low restenosis and TLR rates when used as the sole modality, without a stent for the treatment of de novo lesions in small vessels. Additionally, 2 randomized studies proved safety and efficacy of DEB in superficial femoral and popliteal arteries. However, many unanswered issues remain. Will it work with drugs other than paclitaxel? How consistent and homogenous is the drug elution? Will it work as adjunct therapy to BMS in the case of suboptimal angioplasty? Current results suggest higher restenosis and TLR rates when stents are implanted post-DEB angioplasty. Nearly 30% of patients undergoing balloon angioplasty will have to crossover to stenting if the results are not favorable when these technologies are coupled, which will rule out the option of using DEB for de novo lesions. Perhaps, stents should be placed before the DEB but, if so, what is the advantage over DES? Finally, the amount of drug on the balloon is excessive, given that 80% of it is washed into the blood stream primarily for long peripheral lesions when longer balloons are used, which could result in potential systemic toxicity. The current data support the use of DEB only for the treatment of ISR, although more studies are needed to confer advantage of this technology over DES for this indication. Although the peripheral trials, THUNDER and FemPac, demonstrated proof of biological concept, well-powered randomized clinical trials are required before we can accept the DEB as a viable technology for peripheral artery disease. Dose findings and release kinetics are tricky when it comes to balloon technology, which is known to be less predictive when compared with stents. The DEB technology must be compatible with stenting because we cannot predict who will need a stent. Therefore, before we tout the comeback of the balloon, we must continue to explore this technology's potential in the armamentarium of devices.

Disclosures

None.

References

1. Gruentzig A. Results from coronary angioplasty and implications for the future. *Am Heart J*. 1982;103:779–783.
2. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med*. 1994;331:489–495.
3. Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AD, Satler LF, Kent KM, Griffin J, Leon MB. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation*. 1996;94:1247–1254.
4. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315–1323.
5. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME; TAXUS V Investigators. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA*. 2005;294:1215–1223.
6. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation*. 2007;115:1440–1455.
7. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007;356:998–1008.
8. Axel DI, Kunert W, Goggelmann C, Oberhoff M, Herdeg C, Küttner A, Wild DH, Brehm BR, Riessen R, Koveker G, Karsch KR. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation*. 1997;96:636–645.
9. Kolodgie FD, John M, Khurana C, Farb A, Wilson PS, Acampado E, Desai N, Soon-Shiong P, Virmani R. Sustained reduction of in-stent neointimal growth with the use of a novel systemic nanoparticle paclitaxel. *Circulation*. 2002;106:1195–1198.
10. Margolis J, McDonald J, Heuser R, Klinke P, Waksman R, Virmani R, Desai N, Hilton D. Systemic nanoparticle paclitaxel (nabpaclitaxel) for in-stent restenosis I (SNAPIST-I): a first-in-human safety and dose-finding study. *Clin Cardiol*. 2007;30:165–170.
11. Tian W, Kuhlmann MT, Pelisek J, Scobioala S, Quang TH, Hasib L, Klocke R, Jahn UR, Nikol S. Paclitaxel delivered to adventitia attenuates neointima formation without compromising re-endothelialization after angioplasty in a porcine restenosis model. *J Endovasc Ther*. 2006;13:616–629.
12. Speck U, Scheller B, Abramjuk C, Grossmann S, Mahnkopf D, Simon O. Inhibition of restenosis in stented porcine coronary arteries: uptake of paclitaxel from angiographic contrast media. *Invest Radiol*. 2004;39:182–186.

13. Oberhoff M, Kunert W, Herdeg C, Küttner A, Kranzhöfer A, Horch B, Baumbach A, Karsch KR. Inhibition of smooth muscle cell proliferation after local drug delivery of the antimitotic drug paclitaxel using a porous balloon catheter. *Basic Res Cardiol*. 2001;96:275–282.
14. Herdeg C, Oberhoff M, Baumbach A, Blattner A, Axel DI, Schröder S, Heinle H, Karsch KR. Local paclitaxel delivery for the prevention of restenosis: biological effects and efficacy in vivo. *J Am Coll Cardiol*. 2000;35:1969–1976.
15. Scheller B, Speck U, Abramjuk C, Bernhardt U, Böhm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation*. 2004;110:810–814.
16. Speck U, Scheller B, Abramjuk C, Breitwieser C, Dobberstein J, Boehm M, Hamm B. Neointima inhibition: comparison of effectiveness of non-stent-based local drug delivery and a drug-eluting stent in porcine coronary arteries. *Radiology*. 2006;240:411–418.
17. Albrecht T, Speck U, Baier C, Wolf KJ, Böhm M, Scheller B. Reduction of stenosis due to intimal hyperplasia after stent supported angioplasty of peripheral arteries by local administration of paclitaxel in swine. *Invest Radiol*. 2007;42:579–585.
18. Scheller B, Kühler M, Cremers B, Mahnkopf D, Böhm M, Boxberger M. Short- and long-term effects of a novel paclitaxel coated stent in the porcine coronary model. *Clin Res Cardiol*. 2008;97:118–123.
19. Posa A, Hemetsberger R, Petnehazy O, Petrasi Z, Testor M, Glogar D, Gyöngyösi M. Attainment of local drug delivery with paclitaxel-eluting balloon in porcine coronary arteries. *Coron Artery Dis*. 2008;19:243–247.
20. Cremers B, Speck U, Kaufels N, Mahnkopf D, Kühler M, Böhm M, Scheller B. Drug-eluting balloon: very short-term exposure and overlapping. *Thromb Haemost*. 2009;101:201–206.
21. Cremers B, Biedermann M, Mahnkopf D, Böhm M, Scheller B. Comparison of two different paclitaxel-coated balloon catheters in the porcine coronary restenosis model. *Clin Res Cardiol*. 2009;98:325–330.
22. Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, Böhm M, Speck U. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med*. 2006;355:2113–2124.
23. Fanggiday JC, Stella PR, Guyomi SH, Doevendans PA. Safety and efficacy of drug-eluting balloons in percutaneous treatment of bifurcation lesions: the DEBIUT (drug-eluting balloon in bifurcation Utrecht) registry. *Catheter Cardiovasc Interv*. 2008;71:629–635.
24. Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwälder U, Beregi JP, Claussen CD, Oldenburg A, Scheller B, Speck U. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med*. 2008;358:689–699.
25. Werk M, Langner S, Reinkensmeier B, Boettcher HF, Tepe G, Dietz U, Hosten N, Hamm B, Speck U, Ricke J. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation*. 2008;118:1358–1365.
26. Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, Böhm M, Speck U. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol*. 2008;97:773–781.
27. Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, Werner GS, Antoni D, Kleber FX, Bocksch W, Leschke M, Ackermann H, Boxberger M, Speck U, Degenhardt R, Scheller B. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119:2986–2994.
28. Sheiban I, Anselmino M, Moretti C, Biondi-Zoccai G, Galloni M, Vignolini C, Mattoni M, Sciuto F, Omedè P, Trevi GP. Effect of a novel drug-eluted balloon coated with genistein before stent implantation in porcine coronary arteries. *Clin Res Cardiol*. 2008;97:891–898.
29. Tharp DL, Wamhoff BR, Wulff H, Raman G, Cheong A, Bowles DK. Local delivery of the KCa3.1 blocker, TRAM-34, prevents acute angioplasty-induced coronary smooth muscle phenotypic modulation and limits stenosis. *Arterioscler Thromb Vasc Biol*. 2008;28:1084–1089.
30. Mori T, Kinoshita Y, Watanabe A, Yamaguchi T, Hosokawa K, Honjo H. Retention of Paclitaxel on cancer cells for 1 week in-vivo and in-vitro. *Cancer Chemother Parmacol*. 2006:58:665–672.
31. Buszman P, Zurakowski A, Gruszka A, Szkróbka I, Peszek-Przybyła E, Radwan K, Milewski K, Barteczko Z, Tendera M. Local paclitaxel delivery as a treatment of persistent, recurrent in-stent restenosis - safety assessment. *Kardiol Pol*. 2006;64:268–272.
32. Rosenkranz S, Maier LS, Maack C, Böhm M. Hotline update of clinical trials and registries presented at the German Cardiac Society Meeting 2007: 2L-Registry, Kardio-Pro, EVER, AFFECT, VTACH, ARTS II, OPTAMI, PEPCAD I, PEPCAD II, GERSHWIN, SPICE, FIX-CHF and CREDIT. *Clin Res Cardiol*. 2007;96:457–468.
33. Maier LS, Maack C, Ritter O, Böhm M. Hotline update of clinical trials and registries presented at the German Cardiac Society meeting 2008. (PEPCAD, LokalTax, INH, German ablation registry, German device registry, DESDE registry, DHR, Reality, SWEETHEART registry, ADMA, GERSHWIN). *Clin Res Cardiol*. 2008;97:356–363.
34. Herdeg C, Geisler T, Goehring-Frischholz K, Zuern C, Hartmann U, Haase KK, Gawaz M. Catheter-based local antiproliferative therapy in kissing balloon technique for in-stent stenosis of coronary artery bifurcation lesions. *Can J Cardiol*. 2008;24:309–311.
35. Latif F, Hennebry TA. Successful revascularization of re-stenosis of lower extremity arteries with localized delivery of paclitaxel. *Catheter Cardiovasc Interv*. 2008;72:294–298.

KEY WORDS: in-stent restenosis ■ drug-eluting balloon ■ paclitaxel ■ peripheral artery disease