

Drug-Coated Balloons for Restenosis Prophylaxis

Beschichtete Ballonkatheter zur Restenoseprophylaxe

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Zusammenfassung

Arzneimittel-beschichtete Ballons bewirken eine hohe lokale Arzneistoffkonzentration bei minimalen oder fehlenden systemischen Nebenwirkungen. Durch die Einführung der Arzneimittel-freisetzenden Stents war ihre Entwicklung einerseits verzögert andererseits befördert: Verzögert weil die lange Zeit anhaltende Freisetzung von einer Stent-Plattform als essentiell angesehen wurde und erleichtert weil die bereits existierende Erfahrung mit den Stents bei der Wahl der Prüfmethode und Arzneistoffe eine Hilfe war. Derzeit sind mehrere unterschiedliche arzneimittelbeschichtete Ballonkatheter verfügbar, die grundsätzlich eine Schicht mit ca. 3 µg/mm² Paclitaxel auf der Ballonoberfläche tragen sowie unterschiedliche Zusätze, die die Haftung und Freisetzung des Wirkstoffs beeinflussen, z.B. ein Kontrastmittel, Harnstoff oder verschiedene amphiphile Substanzen. Der Arzneistoff wird während einer einzelnen Inflation von 30–60 sec weitgehend vollständig freigesetzt. Tierexperimentelle Untersuchungen und mehrere unabhängige randomisierte klinische Studien an koronaren und peripheren Arterien zeigen eine wirksame Verminderung der Neointimproliferation, Restenose und Revaskularisierung, ein Effekt, der für mindestens 2, nach einer Studie an Koronarien auch 5 Jahre anhält. Die Einsatzgebiete der arzneimittelbeschichteten Ballone sind vor allem die koronare in-Stent-Restenose sowie de novo und restenotische Läsionen in peripheren Arterien. In klinischen Prüfungen wurden keine der Beschichtung zuzuordnenden unerwünschten Ereignisse registriert. Die anhaltende Wirkung kann durch die lange Verweilzeit von Paclitaxel im Gewebe erklärt werden oder durch die Hemmung eines essentiellen ersten Schrittes in einer Kette von Ereignissen, die zur Neointimproliferation führen.

Abstract

Drug-coated balloons for restenosis prophylaxis provide a high local drug concentration with minimal or no systemic adverse effects. Their development was both delayed and facilitated by the introduction of drug-eluting stents: delayed because sustained release kinetics from stent platforms seemed to be essential and facilitated because prior experience with stents allowed selection of testing methods and drugs. Currently, a variety of drug-coated balloons are available, basically consisting of a coating containing paclitaxel at a dose of about 3 µg/mm² balloon surface, and different additives influencing the adherence and release of the drug, e.g., contrast agent, urea, or various amphiphilic compounds. The drug is almost completely released during a single inflation of 30–60 seconds. Studies in animals and several independent randomized clinical trials in coronary and peripheral arteries demonstrate effective reduction of neointimal proliferation, restenosis, and revascularization persisting for at least 2 years or 5 years according to one study in coronary arteries. Drug-coated balloons are preferably used for treating coronary in-stent restenosis and de novo and restenotic lesions in peripheral vessels. No coating-related adverse events have been observed in clinical trials. Persistent efficacy may be explained by the long residence time of paclitaxel in tissue or inhibition of an essential first step in the chain of events leading to neointimal proliferation.

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Introduction

During the recent decades, percutaneous transluminal angioplasty (PTA), percutaneous trans-luminal coronary angioplasty (PTCA) and related methods like atherectomy have become a standard of care in the treatment of stenotic and occluded arteries [1]. Immediate recoil and dissections are fixed by stent implantation. These methods provide a very high acute success rate and frequently almost immediate relief from symptoms. Excessive formation of neointimal tissue as a response to the unavoidable vessel injury resulting in vessel narrowing remained a major problem [2]. In coronary arteries the incidence of restenosis could be significantly reduced by the implantation of drug-eluting stents suppressing neointimal proliferation due to sustained release of antiproliferative drugs. Preclinical and clinical trials have shown that paclitaxel combined with a suitable excipient coated on the surface of balloons efficaciously inhibits neointimal formation in coronary and peripheral arteries in spite of the short contact time. First products received CE mark and were introduced in clinical practice in countries in which they are available. In the United States the FDA approved clinical trials. Several review articles summarizing the results of studies on drug-coated balloons have been published [3–6].

The current review describes the medical background and history, outlines the rationale for developing drug-coated balloons, and summarizes the preclinical in vivo testing methods and results. A selection of published clinical trials of drug-coated balloons is presented and discussed. Special attention is paid to the reasons why paclitaxel is the only drug so far that has been successfully used on angioplasty balloons for restenosis inhibition and to possible underlying mechanisms of action that may ex-

plain its persistent efficacy in spite of the short contact of the balloons with the vessel wall.

Review criteria

The selection of relevant publications was based on our experience of 13 years in this field. For the overview on preclinical and clinical data, the data had to be published in an accepted peer-reviewed journal.

Local drug delivery for restenosis inhibition

In the seventies angioplasty was introduced as an effective minimally invasive way to re-open stenotic or occluded arteries [7, 8]. The method resulted in almost immediate relief of symptoms caused by ischemia but suffered from a high rate of early and late recurrence. The reasons for the failure to achieve the desired long-term efficacy were renarrowing or reocclusion due to recoil, dissection or thrombus formation already during or shortly after the procedure or late thrombosis, negative remodeling or neointimal proliferation in response to the injury caused by the forceful dilatation of the vessel wall [9].

A variety of approaches to overcome restenosis following balloon dilatation or other methods used to reopen stenotic or occluded arteries have been studied (Table 1).

Several of the approaches mentioned in table 1 are appealing. Some of them may be universally applicable because they do not require stent implantation, and there is no need to change the interventional procedure. However, none of them has yet been

Table 1 Examples of measures aiming at prophylaxis of restenosis.

Tab. 1 Beispiele unterschiedlicher Konzepte zur Restenoseprophylaxe.

method	potential advantages	drawbacks
external and intravascular local radiation therapy [10] using a variety of radiation sources and energies	proven efficacy in scar prevention	late remodeling, narrowing, thrombotic occlusion; radiation protection, multidisciplinary method
improved stent designs and materials [11]	no change in the clinical procedure, no drug or radiation	limited efficacy, only applicable when stenting is performed
choice of inert coating of stents, e. g., gold, silicon carbide, phosphorylcholine [12]	no change in the clinical procedure, no drug or radiation	limited efficacy or even harmful, only applicable when stenting is performed
systemic drug therapy [13]	convenient, can be maintained for six months or more, dose is adjustable; treats all vessels simultaneously	limited efficacy; low local drug concentration, risk of systemic side effects, compliance
injection of drugs into the arterial wall [14] using various kinds of injection catheters	direct access to the treatment site, low systemic exposure	complicated, additional local injury
injection into the pericardium [15]	simultaneous treatment of all coronary arteries, low systemic exposure	complicated, unknown efficacy
permeable balloons [16] which expose the vessel wall to the balloon inflation medium	easy to use, no damage of the vessel, treated segment may be longer than stenotic segment, low systemic exposure	requires an additional device and treatment step; lack of clinical data
double balloon [17] catheters isolating the lumen of the dilated vessel segment for about one minute from blood circulation while flooding the isolated segment with a suitable pharmaceutical preparation, e. g., diluted Taxol™	no damage of the vessel, treated segment may be longer than stenotic segment, low systemic exposure	requires an additional device, pharmaceutical preparation, and treatment step; moderate efficacy
admiring of drugs to contrast media [18, 19]	treats the full length of the artery, does not require additional devices or procedures	dose depends on the need for contrast medium injection, still local but increased systemic exposure; lack of clinical efficacy data

commonly accepted, in most cases because data do not indicate sufficient inhibition of restenosis. Reasons for poor performance may be the lack of an efficacious principle (e.g., inert stent coating [12, 20, 21]), insufficient local drug concentration (e.g., oral administration [13]), or elimination that is too fast for treating a process which continues for months [22]. Furthermore, systemic side effects may be associated with limited acceptance by patients [23].

Before the introduction of drug-eluting stents, cell culture experiments and a few in vivo studies indicated that single local administration of a suitable drug might inhibit vascular smooth muscle cell proliferation for several days to weeks [24]. However, exposure times of 20 min. or more or complicated treatment methods did not fit well with the preferred interventional procedures.

Stents offer a unique platform for slow release formulations of potent drugs. Intuitively, sustained drug release was recognized as the appropriate treatment modality for restenosis inhibition. Initial animal experiments supported the concept of slow release formulations [22]. When fast release formulations of the same drugs on stents subsequently failed to show low restenosis rates, it was universally accepted that the release rate was the key to successful inhibition of persistent neointimal proliferation [25–27].

Early concepts in patent applications

To the best of our knowledge, drug-coated balloons for restenosis inhibition were first mentioned in the literature in 2004 [28]. Nevertheless, when we started coating the first balloon catheters, the concept was not new. Unaware of the later success of drug-eluting stents with sustained release kinetics, several patent applications mentioning drug-coated balloons for restenosis inhibition had been filed between 1989 and 1993. Some of them addressed the discrepancy between single short balloon inflation and slow and long-lasting neointimal proliferation by recommending slowly biodegradable drug carriers or capsules on the surface of the balloons which release the drug over time after transfer to the vessel wall. Obviously, none of these inventions had been tested in animals or reached the stage of clinical trials.

Drugs

Research in restenosis inhibition by drug-eluting stents led to significant advances in the selection of adequate drugs. A variety of drugs had been considered for restenosis inhibition in general and stent coating in particular. Examples were coagulation inhibitors, estrogens, corticosteroids, various cytostatic agents, flavonoids, and antibodies. Only rapamycin (and related macrolides) and paclitaxel were found to be effective [29, 30]. Both are highly lipophilic with a strong tendency to bind to specific cell constituents [31, 32]. Whereas rapamycin and its analogs continue to be the preferred drugs on stents, paclitaxel prevails in drug-coated balloons.

Whether the drug is slowly released from a stent or instantly from a balloon or the vessel wall is exposed to a drug dissolved in an aqueous medium, the problem is similar. To achieve an effective steady-state concentration in the target tissue, the balance between uptake and elimination must be tipped in favor of uptake. If elimination is fast, the small amount of drug that a stent can carry will not be sufficient to make up for the loss to the general circulation. In the case of delivery by injection [18, 19, 33], short perfusion [34], or a coated balloon [28, 33], the desired dose is administered at once. Uptake must be immediate and

loss to the general circulation slow in order to maintain the effective local concentration for long enough [35].

Peculiarities of paclitaxel

Paclitaxel (similar to rapamycin) displays very low water solubility and dissolution rates. This makes it difficult to find physiologically acceptable carriers for liquid preparations as they were used in studies with the double balloon technique [34], permeable balloons [16], direct injection into the vessel wall [14], or selective but free-flowing infusion [19]. The solubility of paclitaxel in aqueous media depends on the physical state of the solid compound but is in the order of 10 to less than 1 μmol (about 8.5 to less than 0.85 $\mu\text{g}/\text{ml}$) [36]. Higher concentrations can be achieved by adding organic solvents, detergents (usually poorly tolerated), or X-ray contrast media [37]. Organic solvents were added to reach high concentrations in cell culture experiments. Controls with solvent (no drug) indicated that toxicity was probably due to the solvent. However, toxic effects of solvent-enhanced “artificial” drug concentrations cannot be ruled out.

Inhibition of human vascular smooth muscle cell proliferation has been observed at very low concentrations in the culture medium (i.e., IC_{50} of 2 nmol/l) if the exposure time was long¹⁰. However, the observation may be misleading because the cells may accumulate the lipophilic drug, resulting in much higher intracellular concentrations over time. Yet, the TaxusTM stent coated with about 100 μg paclitaxel releases only 10% of the drug, indicating a very high potency of the drug [38].

Persistent restenosis inhibition?

Ten years ago it was the common understanding that persistent prevention of restenosis following angioplasty and stent implantation with drugs requires a sustained release formulation [25]. Studies mentioned in this review (► **Tables 2–4**) and additional evidence show that single local administration of paclitaxel is sufficient to protect treated vessel segments from renarrowing for at least two years.

There are two possible explanations:

- Paclitaxel released from a balloon during inflation forms a persistent depot either by firm binding to tissue constituents or as very slowly soluble solid material.
- Persistent neointimal proliferation and vessel narrowing may be initiated by processes occurring as a consequence of vessel injury shortly after angioplasty or stent implantation. Inhibition of these initial processes by the drug may prevent the initiation of neointimal proliferation at a later point in time in the course of healing.

Existing data do not rule out either explanation. Paclitaxel released from a coated balloon persists in the vessel wall for weeks to months [35]. On the other hand, it is known that cell proliferation is fastest during the first week after vessel wall injury [67]. Pharmacological intervention during this phase may be equally effective as a persistent drug supply.

Animal models

The enormous efforts in the preclinical development of drug-eluting stents resulted in standardized animal models of restenosis inhibition which facilitated the selection of effective and well-tolerated balloon coatings in spite of clear differences between

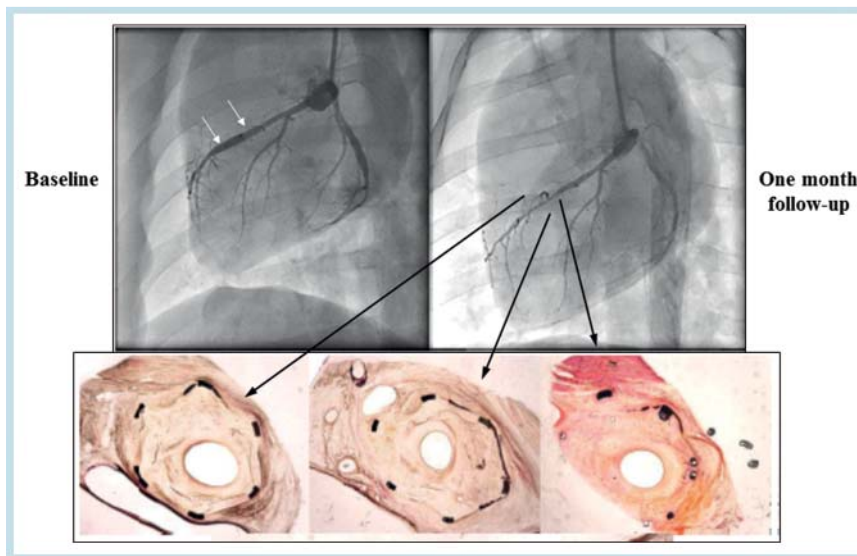


Fig. 1 Porcine coronary arteries following overdistention and stent implantation without drug on balloon or stent: Angiograms show overstretch at baseline and significant narrowing at one-month follow-up; the latter is also visible in the cross sections through the treated segment (arrows); black rectangles are stent struts indicating the original vessel lumen; the white circle is the residual free lumen surrounded by neointima causing stenosis.

Abb. 1 Koronararterien vom Schwein nach Überdehnung und Stentimplantation ohne lokale Medikamentenapplikation. Die Angiografien zeigen die Überdehnung durch den Eingriff sowie eine ausgeprägte Einengung nach einem Monat. Unten: histologische Schnitte des Stents mit deutlicher Neointimabildung.

Table 2 Drug-coated balloons in the porcine overstretch and stent implantation model compared to human clinical trial results (positive ~ tolerated and efficacious; negative ~ no or insufficient inhibition of neointimal proliferation/restenosis).

Tab. 2 Beschichtete Ballonkatheter im Tiermodell sowie klinische Ergebnisse.

balloon investigated	porcine coronaries overstretch + stent	drug transfer to the vessel wall	reference	human randomized clinical trial	reference
Paclitaxel-coated balloon (Paccocath™)	positive	9 – 17 % of dose	Scheller et al., 2004[28]	coronaries, positive femoropopliteal arteries, positive	Scheller et al., 2006 [39] Tepe et al., 2008 [40] Werk et al. 2008 [41]
SeQuent™ Please; B.Braun	positive	same coating composition as Paccocath™	Cremers et al., 2009[42]	coronaries, positive	Unverdorben et al., 2009 [43] Wöhrle et al., 2011 [44] Vajda et al., 2011 [45] Habara et al., 2011 [46] Rittger et al., 2012 [47] Byrne et al., 2012 [48]
In.Pact™; Medtronic	positive	175 µg, ~ 500 µg/g similar to Paccocath™	Kelsch et al., 2011[49] Speck et al., 2012[35]	coronaries, positive femoropopliteal arteries, positive. Below the knee, positive	Latib et al., 2012 [50] Schmidt et al., 2011 [51] Werk et al., 2012 [52]
DIOR I	negative	1.5 – 6 µg/g tissue	Cremers et al., 2009[53] Posa et al., 2008[54]	coronaries, negative	Cortese et al., 2010 [55] Stella et al., 2012 [56]
DIOR II	unclear	170 µg/g tissue	Posa et al., 2010[57]	coronaries, negative	Belkacemi et al., 2012 [58]

balloons and stents and the arterial territories addressed by them, namely primarily the coronary arteries by drug-eluting stents versus peripheral arteries by drug-coated balloons. It is widely accepted that the overstretched and stented coronary artery of young healthy swine is a suitable model of neointimal proliferation in response to injury for angioplasty of human arteries, in spite of the lack of pre-existing pathology [2, 68]. The model was originally developed for the testing of drug-eluting stents but proved to be useful for predicting the clinical efficacy and tolerance of paclitaxel-coated balloon catheters as well (► Fig. 1). Preclinical results from the overstretched and stented coronary artery of young healthy swine have been shown to translate to human applications in the coronaries as well as in the peripheral arteries (► Table 2).

Various attempts to establish animal models that do not include porcine coronary arteries with overstretch and stent placement have failed to show neointimal proliferation, generated question-

able results, or have not yet been tested for reproducibility of the method (► Table 3).

Results of studies in animals

▼ The coating of balloon catheters with drugs requires the selection of a suitable drug, a coating method which provides a sufficient dose, the testing of adherence on the way to the lesion and, different from stents, the immediate release of the drug and transfer into the vessel wall upon balloon inflation. The first report on in vivo testing was published in 2004. It defined the principles of drug-coated balloons that are still valid today: paclitaxel as the drug, a suitable dose range, and dry, predominantly crystalline, coating on a balloon without the need for a protective sheath to prevent premature release, handling similar to the use of plain angioplasty balloons, and an inflation time of 1 minute [28].

Table 3 Recent studies on large animal models applicable to the use of drug-coated balloons (DCB) in peripheral arteries: results and limitations**Tab. 3** Tierexperimentelle Studien zu beschichteten Ballonkathetern in peripheren Arterien.

source	animal model	result	limitation
Albrecht T et al., 2007 [59]	porcine distal femoral arteries, plain balloon or DCB with premounted stents	reduced late lumen loss ($p < 0.05$)	no histology because of problems in retrieving peripheral segments of distal arteries passing joints
Milewski et al., 2011 [60]	porcine iliofemoral arteries, first plain balloon or DCB, then stent	reduced neointimal proliferation at sites treated with 2 DCB	use of 1 DCB not different from plain balloon, no control with 2 plain balloons
Granada et al., 2011 [61]	familial hypercholesterolemic swine, SFA, denudation, no stent, treatment with zotarolimus-coated balloons	less neointimal proliferation in arteries treated with DCB ($p \sim 0.04$)	no clinical data for comparison

The loss of drug from folded balloons on the way to a coronary artery and back was found to be less than 10% of the dose, while approx. 90% of paclitaxel was released during the intervention. Depending on the absence or presence of a stent, 9–17% of the dose was transferred to the vessel wall. This is a moderate yield in absolute terms but surprisingly high considering the topical administration mode and short exposure time. Within 5 weeks the control group (uncoated balloons) developed a thick neointima, resulting in significant lumen narrowing. In the arteries treated with the most efficacious paclitaxel formulation at a dose density of $2.5 \mu\text{g}/\text{mm}^2$ balloon surface, the inhibition of neointimal proliferation was impressive and statistically significant. These formulations contained a small proportion of a hydrophilic contrast agent known to enhance the solubility of paclitaxel [18, 19]. A similar coating using a different solvent without this additive had no impact on neointimal proliferation. Several subsequent studies addressed questions relevant to clinical application:

- ▶ In the same animal model, the coated balloon compared favorably with the clinically proven sirolimus-coated stent (Cypher™, Cordis, USA) with sustained release kinetics and was superior to paclitaxel dissolved in the contrast agent used to visualize the coronary arteries [33].
- ▶ The same coating reduced lumen narrowing in porcine peripheral arteries [59].
- ▶ In the coronary arteries, a short inflation time of 30 or even 10 seconds proved to be sufficient to substantially inhibit neointimal proliferation [42].
- ▶ In the porcine coronary overstretch model, inflation of two fully overlapping balloons with $5 \mu\text{g}$ paclitaxel/ mm^2 did not cause recognizable damage [42].

Using a similar composition but more advanced balloon catheters, B.Braun, Germany, developed SeQuent™ Please for cardiac applications.

The first marketed products were simply coated with paclitaxel, either 2 or $3 \mu\text{g}/\text{mm}^2$. Poor release, very low concentration in the vessel wall, and lack of efficacy in animals and clinical trials were obvious drawbacks [53–55]. Subsequent drug-coated balloon catheters developed in Europe and the USA came closer to the original principle, which is to use $3 \mu\text{g}$ paclitaxel/ mm^2 in conjunction with an additive to protect the drug from premature release while at the same time facilitating fast and complete release upon balloon inflation at the target site. Examples are DIOR™ II (EuroCor, Germany) with the film-forming agent shellac as an additive [36, 57], In.Pact catheters for coronary and peripheral applications (Medtronic, USA) with urea as an additive [49, 51, 69], and Pantera™ Lux (Biotronic, Germany) with the amphiphilic butyryl-tri-hexyl citrate as an additive [70]. Several similar develop-

ments have been presented but no data published in scientific journals are available. Moxy with a paclitaxel dose reduced to $2 \mu\text{g}/\text{mm}^2$ and polysorbate plus sorbitol as additives (Lutonix, USA, recently acquired by Bard, USA) is known from clinical trials [63]. However, as with several other drug-coated balloons, no preclinical data have been published yet. • **Table 5** summarizes the drug-coated balloon catheters with CE mark.

Interestingly, very few studies of balloons coated with drugs other than paclitaxel including sirolimus and related macrolides successfully applied to stents were reported. Cell culture experiments show differential, cell-specific effects after short-term exposure to paclitaxel and sirolimus [81].

The tolerance of local overdose, e.g., due to overlapping inflation of paclitaxel-coated balloons either without stents or combined with premounted bare metal stents, has been addressed in preclinical studies in coronary and peripheral arteries. Whereas the treatment of up to 9 or $10 \mu\text{g}/\text{mm}^2$ vessel wall administered by a single or two overlapping high dose balloons (iopromide or urea – paclitaxel) was tolerated by porcine coronary arteries [42, 49], the treatment of the same vessel segment with 3 high-dose overlapping balloons (urea-paclitaxel-coating) caused thrombotic occlusion of some arteries. Milewski et al. [60] found that 2 overlapping balloons did not cause problems but were required to achieve the desired inhibition of neointimal proliferation in porcine peripheral arteries.

Clinical trials

▼ A survey of published clinical trials is given in table 4. For coronary application, drug-coated balloons are currently being targeted for areas in which drug-eluting stent performance is not optimal, such as bifurcations, in-stent restenosis, long diffuse diseased lesions, and small-diameter vessels. Current clinical trials for peripheral use are focused on the femoropopliteal area, below the knee, and dialysis shunts. Although the number of patients in each trial is limited, the number of independent investigations leaves little doubt about the capability of paclitaxel-coated angioplasty balloons to inhibit neointimal proliferation and diminish binary restenosis rates and the need for repeat treatment of lesions. The safety of the drug coating is also supported by wide-spread use in coronary arteries and a first report on the treatment of intracranial arteries [45].

Coronary trials

The first clinical trials of drug-coated balloons aimed at investigating if the beneficial effect on neointimal proliferation seen in short-lasting experiments in healthy swine would translate to

Table 4 Examples of published clinical trials**Tab. 4** Beispiele publizierter klinischer Studien.

study	catheters tested	indication	# of patients	dual antiplatelet therapy	follow-up	primary endpoint/main results	reference
<i>coronary, randomized trials</i>							
ISR I	Paccocath™ vs. uncoated balloon	ISR	52	1 month	6/12 months	LLL at 6 months/LLL, TLR, and MACE significantly reduced with Paccocath™	Scheller et al., 2006 [39]
ISR I+II			108		5 years		Scheller et al., 2012 [62]
PEPCAD II	SeQuent™ Please vs. Taxus™ DES	ISR	131	3 months (SQP), 6 months (Taxus™)	6/12 months	LLL at 6 months/LLL significantly reduced with SQP compared to Taxus™; TLR and MACE reduced; no additional stent	Unverdorben et al., 2009 [43]
Piccoletto	DIOR™ I vs. Taxus™ DES	de novo lesions	57	1 month (DIOR), 3 months (DIOR + BMS); 12 months (Taxus™)	6/9 months	% diameter stenosis at 6 months/Taxus™-treated group: lower % diameter stenosis (p < 0.05) and strong tendency toward less frequent MACE	Cortese et al. 2010 [55]
DES-ISR	SeQuent™ Please vs. uncoated balloon	Sirolimus DES ISR	50	At least 3 months	6 months	LLL at 6 months/LLL, TLR, and MACE significantly reduced with SQP	Habara et al., 2011 [46]
PERFECT stent	SeQuent™ Please after EPC stent vs. EPC stent alone	de novo lesions	120	3 months	6 months	LLL at 6 months/LLL, TLR, and MACE significantly reduced with SQP™	Wöhrle et al., 2011 [44]
DCB/stent sequence Moxy	Moxy before or after BMS	de novo lesions	27	3 months	6 months	% volume obstruction by OCT/LLL in-stent, 0.53 ± 0.52 mm (DCB first); 0.45 ± 0.57 mm (BMS first)	Gutiérrez-Chico et al., 2011 [63]
PEPCAD IV	SeQuent™ Please followed by BMS vs. Taxus™ DES	de novo lesions, diabetic patients	84	3 months (SQP + BMS), 6 months (Taxus™)	9 months	LLL at 9 months/no difference in LLL, TLR, and MACE between DCB+BMS and DES	Rosli et al., 2011 [64]
BELLO	In.Pact™ Falcon vs. Taxus™ DES	de novo lesions, small vessels	182	1 month (InPact), 3 months (InPact + BMS), 12 months (Taxus)	6 months	LLL at 6 months significantly reduced with InPact	Latib et al., 2012 [50]
PEPCAD DES	SeQuent™ Please vs. uncoated balloon	DES ISR	120	6 months	6 months	LLL at 6 months/LLL, TLR, and MACE significantly reduced with SQP	Rittger et al., 2012 [65]
ISAR-DESIRE III	Sequent™ Please vs. Taxus™ vs. plain balloon	Limus-stent restenosis	402	≥ 6 months	6 – 8 months	diameter stenosis after 6 – 8 months/SQP™ 38 %, Taxus™ 37 %, POBA 54 %	Byrne et al., 2012 [48]
<i>peripheral, randomized trials</i>							
THUNDER	Paccocath vs. uncoated balloon vs. paclitaxel dissolved in contrast medium	Femoropopliteal	154	4 weeks	24 months	LLL at 6 months/significantly lower LLL at 6 months and TLR rate up to 24 months following DCB compared to the other groups	Tepe et al., 2008 [40]
FemPac	Paccocath vs. uncoated balloon	Femoropopliteal	87	not defined	18 months	LLL at 6 months/significantly lower LLL at 6 months and TLR rate up to 18 months following DCB compared to uncoated control catheter	Werk et al., 2008 [41]
PACIFIER	InPact vs. uncoated balloon	Femoropopliteal	85	2 months	12 months	significant reductions in LLL, restenoses, and reinterventions	Werk et al., 2012 [52]
Dialysis shunts	In.Pact vs. uncoated	failing dialysis access	40		6 months	primary patency at 6 months/70 % coated balloon vs. 25 % in the control group, p < 0.001	Katsanos et al. 2012 [66]
<i>peripheral, non-randomized trials</i>							
Pilot infra-popliteal	In.Pact Amphirion	predominantly below-the-knee	104	4 weeks	3 months/12 months	binary restenosis at 3 months/restenosis in 27 %, favorable clinical outcome	Schmidt et al., 2011 [51]
<i>neurovascular, non-randomized studies</i>							
	SeQuent™ Please or uncoated balloon catheters	Intracranial ISR	51	1 year	mean of approx. 7 months	technical success and recurrent stenosis/recurrent stenosis ≥ 50 % after about 3 months in 9 % of patients treated with SQP and 50 % of patients treated with uncoated balloons	Vajda et al., 2011 [45]

ISR = in-stent restenosis; DCB = drug-coated balloon; DES = drug-eluting stent, EPC stent = endothelial progenitor cell capturing stent with human anti-CD34 antibodies, Orbus Neich, Hong Kong; LLL = late lumen loss; MACE = major adverse cardiac event; TLR = target lesion revascularization; OCT = optical coherence tomography; POBA = plain old balloon angioplasty, SQP™ = SeQuent Please, B.Braun.

Table 5 Drug-coated balloon catheters with CE mark: description of the coating, summary of published preclinical and clinical data.**Tab. 5** Zusammenfassung beschichteter Ballonkatheter mit CE-Zulassung.

balloon system	company	coating	preclinical data ¹	clinical data, registry ¹	RCT ¹
<i>coronary</i>					
SeQuent Please	B.Braun	Iopromide + ptx 3 µg/mm ²	+ [28, 33, 42, 53]	+ [45, 71 – 73]	positive [39, 43, 44, 46 – 48, 64, 74, 75]
Dior II	Eurocor	Shellack + ptx 3 µg/mm ²	+ [57]	+ [76]	negative [56, 58]
Pantera Lux	Biotronik	Butyryl-tri-hexyl citrat + ptx 3 µg/mm ²	+ [77]	+ [78]	missing
Elutax	AachenResonance	None + ptx 2 µg/mm ²	+ [70]	–	missing
In.Pact Falcon	Medtronic Invatec	Urea + ptx 3 µg/mm ²	+ [49]	+ [69]	positive [50]
Danubio	Minvasys	Butyryl-tri-hexyl citrat + ptx 2.5 µg/mm ²	–	–	missing
Protégé	Blue Medical	? + ptx 3 µg/mm ²	–	–	missing
<i>peripheral</i>					
Cotavance (SFA)	Bayer Medrad	Iopromide + ptx 3 µg/mm ²	+ [28, 33, 59, 60]	+ [79]	positive [40, 41]
In.Pact Admiral (SFA)	Medtronic Invatec	Urea + ptx 3 µg/mm ²	+ [49]	+ [51, 80]	positive [52]
In.Pact Pacific (SFA)					
In.Pact Amphirion (BTK)					
Freeway (SFA)	Eurocor	Shellack + ptx 3 µg/mm ²	+ [57]	–	missing

Ptx = paclitaxel; RCT = randomized clinical trial; SFA = superficial femoral artery; BTK = below the knee.

¹ published in peer-reviewed journals.

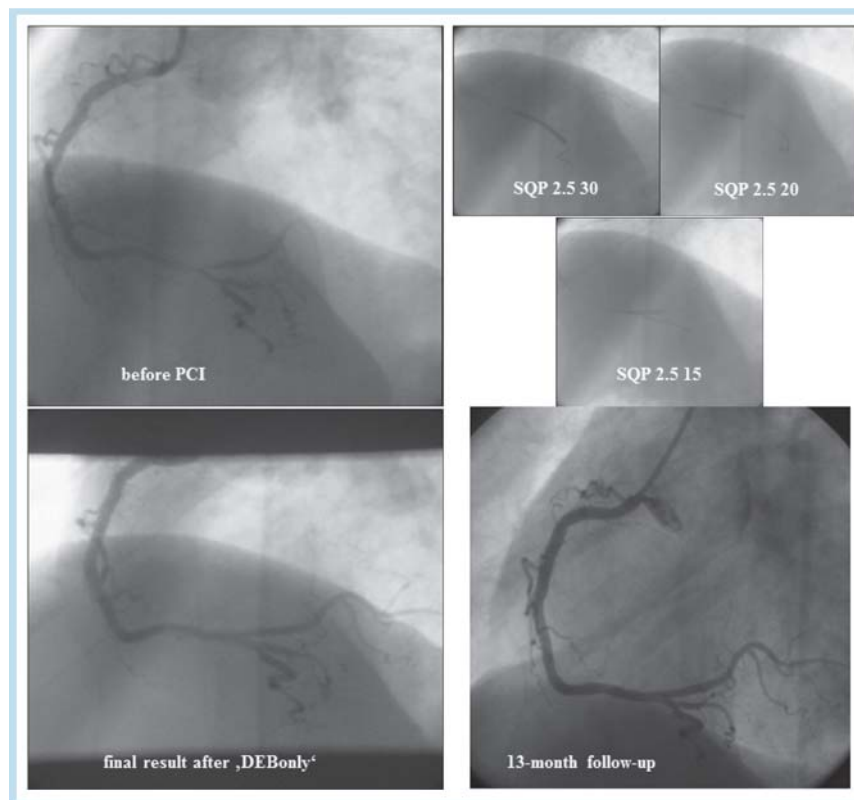


Fig. 2 Trifurcation lesion in the distal right coronary artery treated with 3 drug-coated balloon catheters (SeQuent™ Please, SQP) without stent implantation. Control angiography after 13 months shows increased vessel diameter and restored vasomotion.

Abb. 2 Trifurkationsstenose in der distalen rechten Herzkranzarterie. Behandlung mit 3 beschichteten Ballonkathetern (SeQuent™ Please, SQP) ohne zusätzliche Stentimplantation. Angiografische Kontrolluntersuchung nach 13 Monaten mit verbessertem Gefäßlumen und wiederhergestellter Vasomotion.

persistent restenosis inhibition in patients (Table 4). In these trials, drug-coated balloons were used for treating in-stent restenosis because of the high incidence of recurrent stenosis to be expected in these patients. Randomized treatment comparing uncoated and paclitaxel-coated percutaneous transluminal coronary angioplasty (PTCA) catheters, participation of 5 centers, best possible blinding of the investigators versus the treatment, and quantitative evaluation of angiograms by an independent core lab were intended to dispel doubts that might arise should these studies prove the effectiveness of drug-coated balloons

[39]. Furthermore, reproducibility of the findings was investigated in a second, independently randomized trial with the same study design [74]. Overall, late lumen loss after 6 months was 0.81 ± 0.79 mm in the control group versus 0.11 ± 0.45 mm ($P < 0.001$) in the drug-coated balloon group. Over a period of up to 2 years, target lesion revascularization was performed in 21 of 54 patients treated with the uncoated balloons versus 3 of 54 patients treated with the coated balloons [74]. Meanwhile, long-term data up to 6 years confirms the initial finding with no signs of a late catch-up [75].

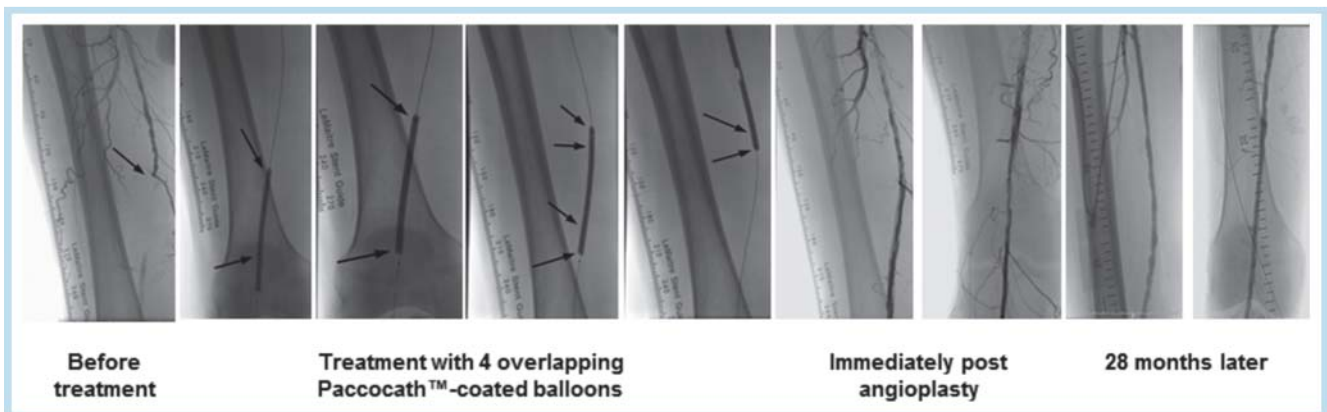


Fig. 3 Long diffuse stenosis and segmental occlusion in the superficial femoral artery, treatment with overlapping balloons, result after two years (random no. 153 of Thunder trial [69]). No signs of aneurysms in the segments treated with overlaps.

Abb. 3 Langstreckige, diffuse Stenose mit einem nachgeschalteten Segmentverschluss der Arteria femoralis superficialis, Behandlung mit 4 beschichteten Ballonkathetern, angiografisches Ergebnis nach 2 Jahren (Patient aus der Thunder Studie [69]). Keine Hinweise auf aneurysmatische Veränderungen im Bereich der Ballonüberlappungen.

Subsequent trials compared a second-generation iopromide-matrix-coated PTCA catheter (SeQuant™ Please) with the Taxus™ stent in the treatment of bare metal stent restenosis (PEPCADII [43]) or investigated the same device in drug-eluting stent restenosis [46, 47] [48]. In these studies beneficial effects of the drug were shown with respect to the restenosis rate and target lesion revascularization. The BELLO study randomized 182 patients with de-novo lesions in small vessels (<2.8 mm) to the drug-coated balloon (In.Pact Falcon™) or Taxus™ stent. In the drug-coated balloon group, 20% of patients required bail-out (spot) stenting. The intention-to-treat analysis showed superiority with respect to the primary endpoint late lumen loss of the drug-coated balloon (0.09 ± 0.38 mm) over the TAXUS stent (0.30 ± 0.44 mm, $p=0.001$) [50].

A proposed coronary “drug-coated balloon only” strategy may reduce the need for drug-eluting stent implantation in coronary arteries and the related long-term dual antiplatelet therapy [82]. This strategy includes predilatation to estimate the risk for dissection followed by low-pressure angioplasty with a drug-coated balloon (► Fig. 3).

Peripheral trials

Arteries in different organs and locations in the body differ significantly from each other. Arteries in the limbs are much longer than coronary arteries, the diameter can be larger, and hemodynamics and mechanical stress are different. Nevertheless, restenosis as a response to injury seems to be similar.

Almost at the same time as the initial coronary studies, two studies of patients with femoropopliteal lesions were initiated [40, 41]. In both studies prototype iopromide-matrix-coated Paccocath™ catheters were tested in comparison to uncoated balloon catheters. In the Thunder trial 54 patients (46% diabetics, 30% restenotic lesions, mean lesion length 7.4 cm) were treated with conventional uncoated balloon catheters, and 48 patients (50% diabetics, 38% restenotic lesions, mean lesion length 7.5 cm) with paclitaxel-coated catheters. The primary endpoint was late lumen loss determined by angiography 6 months after treatment. Late lumen loss was 1.7 mm in the uncoated group versus 0.4 mm in the coated group ($p<0.001$). The restenosis rate at the

6-month follow-up was 44% versus 17% ($p=0.01$), and target lesion revascularization up to 12 months was 48% vs. 10% ($p<0.001$). In the Thunder trial a third group of 52 patients was randomized to angiography with a contrast medium in which paclitaxel was dissolved. The mixture was well tolerated but the results with respect to late lumen loss, restenosis rate and target lesion revascularization did not differ from the control group that received no paclitaxel. Except for the third group, the FemPac trials had a similar design. 42 patients were enrolled in the group treated with uncoated balloons (55% diabetics, 33% restenotic lesions, median lesion length 4.7 cm) and 45 patients were treated with the coated balloons (40% diabetics, 36% restenotic lesions, median lesion length 4.0 cm). Late lumen loss at the 6-month follow-up was 1.0 mm and 0.5 mm, respectively, ($p=0.031$), the restenosis rate was 47% vs. 19% ($p=0.035$), and target lesion revascularization up to 2 years was performed in 50% vs. 13% ($p=0.001$). In conclusion, the results of both studies indicate potent restenosis inhibition and a reduced reintervention rate in the patients treated with the drug-coated balloon (► Table 4). Recently, these results were confirmed using the urea-matrix-coated In.Pact Pacific™ catheter in the same indication [52] and a similar number of patients and patient population per treatment with a mean lesion length of 6.6 cm in the control group and 7.0 cm in the group treated with the coated balloons. Late lumen loss was 0.65 mm and -0.01 mm, respectively, indicating post treatment lumen gain in a significant number of the patients in the coated balloon group, preferably in patients with residual stenosis after angioplasty. In this study restenosis rates determined by blinded evaluation of 6-month angiograms were 32% vs. 9% ($p=0.01$) and the 1-year TLR rate was 28% vs. 7% ($p=0.02$). Further encouraging results regarding the treatment of long infrapopliteal lesions with the In.Pact Amphirion™ catheter were recently reported by Schmidt et al. However, comparison was made to a historical control [51].

An investigation in a different indication is worth mentioning: Katsanos [66] published a randomized study comparing treatment with uncoated or paclitaxel-coated (In.Pact Admiral) balloon catheters in 20 patients each with stenotic or occluded dialysis shunts. At 6 months the primary patency was signifi-

cantly higher ($p < 0.001$) in the patients treated with the paclitaxel-coated balloons and repeat procedures were performed in 4 versus 13 patients ($p = 0.002$).

Coating-related adverse events or problems due to overlapping paclitaxel-coated balloons in long lesions were not reported in any of the published clinical trials. Several years of use of paclitaxel-coated balloons for the treatment of coronary arteries and a report on the treatment of intracranial in-stent restenosis using iopromide-matrix-coated balloons further support the local and regional safety of the coating [45]. The risk of systemic effects due to paclitaxel was addressed in a clinical study on the pharmacokinetics of paclitaxel released from coated balloons in peripheral arteries [79]. Based on this study and the experience with intravenous administration of paclitaxel [83, 84], up to 7 balloon catheters 6.0×120 mm may be used in adult patients during one intervention without reaching the dose known to cause systemic adverse effects.

Conclusion

The persistent patency of blood vessels following initial successful treatment remains an area of concern. Local drug delivery has emerged as the most effective way of preventing restenosis. Initially a large variety of methods and drugs were explored. Restenosis inhibition in coronary arteries is currently dominated by stents providing sustained release of a single class of drugs (so-called "limus" drugs: sirolimus, everolimus etc.), whereas only few studies have addressed restenosis inhibition in peripheral vessels.

In spite of the short contact with the vessel wall, paclitaxel-coated balloons effectively inhibit neointimal proliferation in animal models and have been shown to consistently reduce late lumen loss, restenosis rates and the need for revascularization in coronary and peripheral arteries in several independent randomized clinical trials. Paclitaxel-coated balloons inhibit restenosis without the need for stent implantation. For coronary application, drug-coated balloons are being targeted in bifurcations, in-stent restenosis, long diffuse diseased lesions, and small-diameter vessels. Peripheral use is focused on the femoropopliteal area, below the knee, and dialysis shunts.

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