Drug Delivering Technology for Endovascular Management of Infrainguinal Peripheral Artery Disease

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ABSTRACT

Endovascular intervention has become a well-recognized treatment modality for peripheral artery disease; however, mid- and long-term outcomes have been plagued by limited durability. Plain balloon angioplasty and bare-metal stents have historically suffered from high restenosis rates leading to the need for frequent repeat revascularization procedures. The innovation of locally administered, drug-delivering balloons and stents has been a direct result of technological innovations directed toward prevention and treatment of this limitation. Over the last 5 years, numerous clinical trials investigating the use of drug-coated stents and drug-coated balloons indicate a significant improvement in endovascular treatment durability and outcomes. This review provides an up-to-date assessment of the current evidence for the use of drug-coated stents and drug-coated balloons in the treatment of femoropopliteal and infrapopliteal peripheral artery disease. Additionally, it provides an overview of the development of this technology, highlights landmark ongoing and completed clinical trials, examines evidence to support the use of drug-coated technologies in combination with other modalities, and examines promising new technological developments. Last, it summarizes the challenges and safety concerns that have delayed U.S. Food and Drug Administration approval of these devices. (J Am Coll Cardiol Intv 2014;7:827–39) © 2014 by the American College of Cardiology Foundation.

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Manuscript received January 30, 2014; revised manuscript received April 7, 2014, accepted May 8, 2014.
Abbreviations and Acronyms

BMS = bare-metal stent(s)
BTK = below-the-knee
CLI = critical limb ischemia
DCB = drug-coated balloon(s)
DCS = drug-coated stent(s)
PAD = peripheral artery disease
PES = paclitaxel-eluting stent(s)
POBA = plain old balloon angioplasty
PTA = percutaneous transluminal angioplasty
RCT = randomized controlled trial
SES = sirolimus-eluting stent(s)
SFA = superficial femoral artery
TLR = target lesion revascularization

With an increasingly aging population and a rising incidence of diabetes mellitus in the United States and worldwide, the prevalence and clinical significance of peripheral artery disease (PAD) continues to heighten (1). Endovascular intervention is a well-recognized treatment modality for PAD, especially for patients with multiple comorbidities, such as coronary artery disease and chronic kidney disease (2). Compared with surgical bypass procedures, endovascular intervention is associated with decreased morbidity and a faster recovery time (3). However, the durability of endovascular interventions for PAD has been limited by high rates of restenosis, most notably in the infrapopliteal and infrapopliteal vasculature, after percutaneous transluminal angioplasty (PTA) and bare-metal stent (BMS) implantation (4).

Recently, drug-coated stents (DCS) and drug-coated balloons (DCB) have been the focus of technological innovation in preventing and treating restenosis. In the last 5 years, 6 meta-analyses have synthesized data from many recent clinical trials to examine the efficacy of DCS and DCB compared with BMS and PTA. Overall, the results of 5 meta-analyses, summarized in Table 1, show superior short- and mid-term increased patency and freedom from target lesion revascularization (TLR) for DCS and DCB in the treatment of infrapopliteal and femoropopliteal PAD (5-10). This review provides an overview of the development of drug-eluting technology in PAD and highlights ongoing clinical trials and promising new technologies.

Historically, restenosis after endovascular therapy for PAD has been a major limitation for BMS and PTA (11). The principal mechanism of restenosis for both PTA and BMS is thought to be neointimal hyperplasia due to mechanical injury of the vessel wall (12). And, in the setting of increased biomechanical stress at the femoropopliteal territory, BMS implantation leads to higher rates of in-stent restenosis when used to treat PAD versus coronary artery disease (13). The advent of drug-eluting technology and other technologies such as cutting balloons, atherectomy, and cryoplasty have been a direct result of the desire to decrease restenosis rates.

Restenosis rates are tied to anatomic distribution of PAD, which is itself correlated with disease severity. Critical limb ischemia (CLI), which represents 1% to 2% of PAD and is defined by rest pain, nonhealing or poorly healing ulcers, or gangrene, is the most severe form (14). CLI is associated with long-segment femoropopliteal lesions, multilevel disease, and diffuse infrapopliteal lesions (15). Higher restenosis rates for diffuse, infrapopliteal disease and longer lesions have been borne out by multiple recent studies (16,17). Fortunately, numerous clinical trials investigating the use of DCS and DCB indicate a significant improvement with the use of these technologies in endovascular treatment outcomes in patients with PAD.

The Drugs in Drug-Delivering Technology

Two different drugs have been used in DCS and DCB: paclitaxel, an antineoplastic drug; and sirolimus (and sirolimus analogs such as zotarolimus and everolimus), an immunosuppressant. Paclitaxel inhibits smooth muscle cell proliferation, extracellular matrix secretion, and migration by enhancing the assembly of stable but dysfunctional polymerized microtubules. It also suppresses the release of growth factors such as platelet-derived growth factor, providing an anti-inflammatory effect (4). Higher doses of paclitaxel act at the G2/M phase and cause mitotic arrest and cell death (18). Sirolimus also blocks vascular smooth muscle cell migration and proliferation by arresting the cell at the G1-S checkpoint—a point in the cell cycle that does not cause cell death (19). Both drugs are lipophilic, which enhances tissue uptake; however, determining and efficiently delivering an optimal dose remains a challenge. Drug densities used on DCB are generally higher than those used on DCS because the amount of time available for drug transfer is significantly less with balloon inflation than it is with stent implantation (20).

DCS Technology

A typical DCS consists of 3 elements: a scaffold manufactured using different kinds of metals (such as nickel-titanium, platinum-chromium, or stainless steel), a polymer matrix (consisting of silicone, cellulose esters, and polyurethane), and the drug itself. The drug elutes at a rate proportional to degradation of the polymer matrix, the latter being of particular importance because it has been shown to cause inflammatory responses and late-onset restenosis. Although most first-generation DCS used the polymer coating to control drug elution, newer-generation stents coat the drug directly onto the outer surface of the stent strut without using a polymer (21). To combat the problem of thrombogenic and...
inflammatory responses, a variety of bioabsorbable materials such as polyesters, polycarbonates, bacterial-derived polymers, and corrodeable metals have recently been incorporated into stent design both as the polymer coating and also as the stent scaffold itself (22).

**TRIALS COMPARING DCS WITH BMS IN FEMOROPOPITEAL DISEASE**

Studies evaluating DCS in PAD are summarized in Table 2. Initial DCS trials in PAD tested sirolimus-eluting stents (SES). The SIROCCO (A Clinical Investigation of the Sirolimus Coated Cordis Smart Nitinol Self-Expandable Stent for the Treatment of Obstructive Superficial Femoral Artery Disease) randomized controlled trial (RCT), conducted in 2 phases, studied the effectiveness of SES versus BMS in 93 patients. As shown in Table 2, at 24-month follow-up, Duplex ultrasound-derived in-stent restenosis and TLR rates did not differ significantly between patients treated with SES and BMS. This lack of superior efficacy of SES has been attributed to 2 reasons: 1) lower than expected restenosis rates in the BMS group, probably due to shorter lesion lengths (mean 8.3 cm); 2) a “late catch-up” effect, attributed, in part, to an inflammatory response toward the degraded SES polymer matrix (23,24).

Evololimus, a newer sirolimus analogue, shares much of the same immunosuppressive and anti-proliferative effects as sirolimus, but is more lipophilic and is more rapidly absorbed into the vessel wall (25). The nonrandomized, single-arm trial STRIDES (A Study to Evaluate the Safety and Performance of the Dynalnk-E, Evololimus Eluting Peripheral Stent System for Treating Atherosclerotic de Novo or Restenotic Native Superficial Femoral and Proximal Popliteal Artery Lesions) studied the effects of everolimus-eluting stents in the superficial femoral artery (SFA) in 104 patients. Freedom from >50% restenosis was demonstrated at 6- and 12-month follow-up (26).

The ZILVER-PTX (Evaluation of the Zilver PTX Drug-Eluting Peripheral Stent) RCT (n = 479) compared the efficacy of paclitaxel-eluting stents (PES) with PTA (primary randomization) and BMS (secondary randomization) in patients with femoropopliteal stenosis over 2 years. The Zilver PTX had higher event-free survival than did PTA and BMS, and also had higher patency rates than did the provisional BMS group, at up to 36 months (3,27). To date, the Zilver PTX is the only DCS to have U.S. Food and Drug Administration approval for use during peripheral artery interventions.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>DCS Type, Sample Size</th>
<th>Drug, Dose, $\mu$g/mm²</th>
<th>Control, Sample Size</th>
<th>Arterial Territory</th>
<th>Primary Endpoint</th>
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<th>Secondary Outcomes, DCS vs. Control</th>
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<td>SIROCCO I and II (23), 2006</td>
<td></td>
<td>Smart (Cordis, Bridgewater, New Jersey), 47</td>
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<td>Smart BMS, 46</td>
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<td>6-month in-stent mean lumen diameter stenosis measured by angiography and DUS</td>
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<td>24-month freedom from TLR: 93% vs. 84% (p = 0.30) 24-month in-stent restenosis: 23% vs. 21%</td>
</tr>
<tr>
<td>PARADISE (30), 2010</td>
<td></td>
<td>83% Cypher (Cordis)* 17% Taxus Element (Boston Scientific, Marlborough, Massachusetts),* 106</td>
<td>Sirolimus N/A Paclitaxel N/A</td>
<td>BASIL trial (PTA cohort)</td>
<td>BTK</td>
<td>3-year amputation-free survival and overall survival</td>
<td>36</td>
<td>12-month amputation-free survival: 96% vs. 87% (p = 0.03) 12-month mortality: 13% vs. 18% (p = 0.25)</td>
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<td>DESTINY (29), 2011</td>
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<td>12-month primary patency measured by angiography</td>
<td>12</td>
<td>12-month in-stent diameter stenosis: 21% vs. 47% (p &lt; 0.001) 12-month freedom from TLR: 91% vs. 66% (p &lt; 0.001)</td>
</tr>
<tr>
<td>STRIDES (26), 2011</td>
<td></td>
<td>Dynalink-E (Abbott), 104</td>
<td>Everolimus, 2.25</td>
<td>N/A</td>
<td>FP</td>
<td>6 and 12-month primary patency evaluated by DUS</td>
<td>12</td>
<td>12-month freedom from TLR: 80% ± 3.8%</td>
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<tr>
<td>ZILVER-PTX (3), 2011</td>
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<td>Zilver PTX (Cook Medical, Bloomington, Indiana), 241</td>
<td>Paclitaxel, 3.0</td>
<td>PTA (primary); PTA + Zilver BMS (secondary), 23B</td>
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<td>36</td>
<td>24-month EFS: 87% vs. 78% (p &lt; 0.01) 24-month PP: 81% vs. 63% (p &lt; 0.01) 36-month freedom from TLR: 83% vs. 70%</td>
</tr>
<tr>
<td>YUKON-BTK (28), 2012</td>
<td></td>
<td>Yukon (Translumina, Hechingen, Germany),* 82</td>
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<td>33-month TLR (overall): 97% vs. 88% (p = 0.03) 33-month TLR (claudication): 8% vs. 25% (p = 0.04) 33-month amputation (overall): 99% vs. 95% (p = 0.17) 33-month amputation (CLI): 5% vs. 23% (p = 0.04)</td>
</tr>
</tbody>
</table>

*Coronary stents.

BASIL = Bypass Versus Angioplasty in Severe Ischemia of the Leg; CLI = critical limb ischemia; DESTINY = Prospective Randomized Multicenter Trial Comparing the Implant of a Drug Eluting Stent vs. a Bare Metal Stent in the Critically Ischemic Lower Leg; DUS = duplex ultrasonography; EFS = event-free survival; N/A = not applicable; PARADISE = Preventing Leg Amputations in Critical Limb Ischemia With Below-the-Knee Drug-Eluting Stents; PP = primary patency; SIROCCO = A Clinical Investigation of the Sirolimus Coated Cordis Smart Nitinol Self-Expandable Stent for the Treatment of Obstructive Superficial Femoral Artery Disease; STRIDES = A Study to Evaluate the Safety and Performance of the Dynalink-E, Everolimus Eluting Peripheral Stent System for Treating Atherosclerotic de Novo or Restenotic Atherosclerotic Superficial Femoral and Proximal Popliteal Artery Lesions; YUKON-BTK = Yukon-Drug-Eluting Stent Below-The-Knee-Prospective Randomized Double-Blind Multicenter Study; ZILVER-PTX = Evaluation of the Zilver PTX Drug-Eluting Peripheral Stent; other abbreviations as in Table 1.
TRIALS COMPARING DCS WITH BMS IN INFRAPOPLITEAL DISEASE

The YUKON-BTK (Yukon-Drug-Eluting Stent Below-The-Knee-Prospective Randomized Double-Blind Multicenter Study) compared SES with BMS in 161 patients with below-the-knee (BTK) PAD. At 3-year follow-up, event-free survival and freedom from TLR was higher for the SES group. The results held for subgroup analyses on patients with intermittent claudication and CLI, respectively (8). The DESTINY (Prospective Randomized Multicenter Trial Comparing the Implant of a Drug Eluting Stent vs. a Bare Metal Stent in the Critically Ischemic Lower Leg) (n = 140) compared everolimus-eluting stents and BMS in patients with CLI. Twelve-month follow-up showed that everolimus-eluting stents reduced restenosis and showed superior freedom from TLR (29).

The DESTINY and YUKON-BTK trials were included in 2 recent meta-analyses investigating the efficacy of limus-based DCS versus BMS or PTA for the treatment of BTK disease at 1-year follow-up (Table 1). Antoniou et al. (8) included 4 RCTs and 2 observational studies (n = 544) and demonstrated significantly higher primary patency, freedom from TLR, and clinical improvement for patients treated with DCS. However, no significant differences in limb salvage and overall survival were found (8). Fusaro et al. (10) included 5 RCTs (n = 611) and came to a similar conclusion regarding the superior efficacy of DCS. Overall, compared with BMS or PTA, DCS therapy was found to reduce the risk of reintervention and amputation without an impact on mortality and Rutherford class improvement (10).

The PARADISE (Preventing Leg Amputations in Critical Limb Ischemia With Below-the-Knee Drug-Eluting Stents) trial (30) (n = 106) investigated the use of SES in CLI and compared the results to the BASIL (Bypass Versus Angioplasty in Severe Ischemia of the Leg) trial. Amputation-free survival was greater in the PARADISE trial than in the BASIL PTA group, despite a higher prevalence of CLI patients. This difference in outcomes indicates the potential benefit of PES over PTA in the treatment of BTK lesions in CLI patients.

Along with other SES trials, the PARADISE trial was included in a 2013 meta-analysis (Yang et al. [9]), which pooled outcomes for 16 combined RCTs and non-RCTs comparing DCS, BMS, and PTA in infrapopliteal disease in a total of 3,780 patients (Table 1). The meta-analysis showed that primary BMS implantation had similar restenosis and target vessel revascularization rates as PTA did. Additionally, DCS exhibited superior rates of 1-year primary patency, freedom from target vessel revascularization, and limb salvage.

TRIALS WITH BIOABSORBABLE STENTS

To date, 2 published studies have investigated the use of bioabsorbable stents in PAD. The AMS INSIGHT (Absorbable Metal Stent Implantation for Treatment of Below-the-Knee Critical Limb Ischemia: 6-Month Analysis) trial (n = 117) randomized patients to absorbable stent or PTA for infrapopliteal lesions. At 6 months, angiographic patency for absorbable stents was significantly lower than those treated with PTA (31.8% vs. 58%; p = 0.013) (31). The GAIA (The Evaluation of the Biodegradable Peripheral Igaki-Tamai Stent in the Treatment of De Novo Lesions in the Superficial Femoral Artery) trial (n = 30) observational study implanted a poly-L-lactic acid biodegradable stent in SFA lesions, which showed a 12-month TLR rate of 57.1% and binary restenosis rate of 67.9% (32). The ABSORB (A Clinical Evaluation of the Everolimus Eluting Bioreabsorable Vascular Scaffold System for the Treatment of Subjects with Critical Limb Ischemia from Occlusive Vascular Disease of the Tibial Arteries) BTK study sought to implement AMS in BTK vessels with the hope of achieving similar success to coronary arteries; however, the study has been discontinued due to insufficient enrollment (33).

DCS CONCLUSIONS

Overall, DCS improves mid-term (<2 year) outcomes in femoropopliteal and BTK lesions, reducing restenosis and increasing limb salvage rates. Whereas the 36-month results of Zilver PTX are promising, additional data from the aforementioned and forthcoming trials are necessary to determine whether peripheral DCS will be as impactful as they have been in coronary arteries. DCS may prove to be most useful in shorter BTK lesions (<100 mm), as smaller caliber peripheral vessels may respond similarly to the coronary arteries. Unfortunately, BTK disease and CLI are typically associated with longer lesion length and consequently an increase in difficulty and cost in treatment (9).

The question of whether SES or PES is more effective remains unanswered. Some researchers have suggested that limus-based drugs may have superior outcomes due to fewer late thrombotic complications, as paclitaxel requires 90 days for endothelialization as paclitaxel requires 90 days for endothelialization, whereas the 36-month results of Zilver PTX are promising, additional data from the aforementioned and forthcoming trials are necessary to determine whether peripheral DCS will be as impactful as they have been in coronary arteries. DCS may prove to be most useful in shorter BTK lesions (<100 mm), as smaller caliber peripheral vessels may respond similarly to the coronary arteries. Unfortunately, BTK disease and CLI are typically associated with longer lesion length and consequently an increase in difficulty and cost in treatment (9).

The question of whether SES or PES is more effective remains unanswered. Some researchers have suggested that limus-based drugs may have superior outcomes due to fewer late thrombotic complications, as paclitaxel requires 90 days for endothelialization compared with 30 days for sirolimus (19). A 2009 meta-analysis (Biondi-Zoccai et al. [7]) of 18 mostly non-randomized trials (n = 640) examined the efficacy of provisional stenting with BMS, SES, and PES in
patients with BTK disease and concluded that SES were superior to BMS and PES in 12-month patency (p < 0.001) and that repeat revascularization was less commonly required after treatment with SES as compared with PES (p = 0.014). However, this meta-analysis (7) included only 1 single-arm PES study (34), with 29 patients treated with stents, and a significantly lower primary patency (30%) than what has been demonstrated by other DCS in BTK trials.

DCS in PAD face many of the problems that have been observed in DCS for coronary artery disease, such as late thrombotic complications caused by incomplete endothelialization of the stent (35). The optimal duration of dual antiplatelet therapy to prevent such complications in DCS for PAD remains controversial. DCS have limitations in drug delivery, as the drug affects only the portion of intima in contact with the stent struts. Additionally, stenting in general could reduce future surgical options due to lack of adequate anastomotic bypass sites. It would be preferable to treat lesions without placing permanent implants, such as stents, along with possibly avoiding the concomitant risks such as stent fracture and stent thrombosis. This is particularly desirable in flexion points, such as the common femoral or popliteal arteries. With improving endovascular technologies, many operators increasingly prefer the option of “leaving nothing behind” in the lesion—a strategy bolstered by recent DCB technology.

**DCB TECHNOLOGY**

A DCB consists of a standard balloon catheter coated with an antiproliferative drug and an excipient to control the drug’s release rate. DCB therapy has multiple potential advantages over BMS and DCS: it avoids metal- or polymer-induced restenosis and stent fracture associated with stent implantation in the femoropopliteal arterial territory; it may distribute antiproliferative drugs more homogenously than stents do; and it can be used for in-stent restenosis where avoidance of stent placement is preferred (i.e., tortuous vessels, bifurcation carina, and diffuse disease) (36). The current antiproliferative drug of choice for DCB is paclitaxel due to its lipophilicity and prolonged tissue retention rates (20,36). Yet, interest remains for the use of limus-based DCB. There are some data to support its use and numerous ongoing clinical trials continue to investigate limus-based DCB efficacy in preventing neointimal hyperplasia (37,38). Excipients, which enhance transfer of the drug from balloon to tissue, vary between devices with urea, iopromide, and polysorbate/sorbitol being among the most commonly used (17). Ideally, the drug is released from the balloon and taken up by endothelial tissue after a single inflation that lasts between 30 and 60 s. And, although efficient drug transfer from balloon to tissue remains a challenge, numerous clinical trials, which we will discuss next, are generating promising results.

**TRIALS COMPARING DCBs WITH PLAIN BALLOON ANGIOPLASTY FOR FEMOROPOPLITEAL DISEASE**

Completed studies evaluating DCB in PAD are summarized in Table 3 and currently ongoing studies are listed in Table 4. There is increasing evidence supporting the superiority of DCB over PTA for the treatment of femoropopliteal and BTK artery disease. Four RCTs compared DCB and PTA with a primary endpoint of 6-month late lumen loss measured by angiography and demonstrated significant reductions in late lumen loss, TLR, and binary restenosis (or increased primary patency) (39-42): the THUNDER (Local Taxane With Short Exposure for Reduction of Restenosis in Distal Arteries) trial (n = 154); the FemPac (Paclitaxel-Coated Versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial) (n = 87); the LEVANT I (The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) trial (n = 101); and the PACIFIER (Paclitaxel-Coated Balloons in Femoral Indication to Defeat Restenosis) trial (n = 91). A meta-analysis of the 6-month results of these 4 trials with a total of 381 patients concluded that DCB therapy was associated with lower restenosis rates than was PTA in the treatment of femoropopliteal disease with no significant difference in their safety profiles (6) (Table 1).

The LEVANT 2 (Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries) RCT (43) (n = 476) recently released 6-month follow-up data that demonstrated superior primary patency of DCB over PTA, with a comparable safety profile. Interestingly, the LEVANT 2 trial incorporated 2 elements into its study design in an attempt to reduce bias: controlled pre-dilation with standard PTA prior to randomization to limit the number of bailout stents; and exclusion of bailout stenting from the TLR category. Other multicenter RCTs investigating femoropopliteal stenosis are currently ongoing (44-48): such as the FREERIDE (Freeway Paclitaxel Coated Balloon Catheter to Treat Peripheral Artery Disease) trial; the ADVANCE 18PTX (Treatment of Lesions in Superficial Femoral Artery/Popliteal Artery With a Paclitaxel-coated Balloon) trial; the IN.PACT SFA II (Randomized Trial of IN.PACT Admiral Drug-Eluting Balloon vs. Standard Percutaneous Transluminal Angioplasty for the Treatment of
<table>
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<tr>
<th>Trial, Year</th>
<th>DCB Model/Sample Size</th>
<th>Drug, Dose, g/mm²</th>
<th>Control</th>
<th>Arterial Territory</th>
<th>Primary Endpoint</th>
<th>Primary Outcome, DCB vs. PTA</th>
<th>Longest Follow-Up (months)</th>
<th>Secondary Outcomes, DCB vs. Control</th>
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<tr>
<td>THUNDER (41), 2008</td>
<td>Paccocath (Medrad, Warrendale, Pennsylvania), 48</td>
<td>Paclitaxel-iopromide, 3.0</td>
<td>PTA (n = 54) and PTA + paclitaxel in contrast, 52</td>
<td>FP</td>
<td>6-month LLL measured by angiography</td>
<td>0.4 ± 1.2 vs. 1.7 ± 1.8 vs. 2.2 ± 1.6 mm (all p &lt; 0.001)</td>
<td>60</td>
<td>24-month TLR: 15% vs. 52% (p &lt; 0.001)</td>
</tr>
<tr>
<td>FemPac (42), 2008</td>
<td>PTA coated with paclitaxel (Bavaria Medizin Technologie, Wessling, Germany), 45</td>
<td>Paclitaxel-iopromide, 3.0</td>
<td>PTA, 42</td>
<td>FP</td>
<td>6-month LLL measured by angiography</td>
<td>0.5 ± 1.1 vs. 1.0 ± 1.1 mm (p = 0.031)</td>
<td>24</td>
<td>24-month TLR: 13% vs. 50% (p &lt; 0.001)</td>
</tr>
<tr>
<td>LEVANT I (39), 2010</td>
<td>Lutonix Moxy (BARD, Murray Hill, New Jersey), 49</td>
<td>Paclitaxel-polysorbate/sorbitol, 2.0</td>
<td>PTA, 52</td>
<td>FP</td>
<td>6-month LLL measured by angiography</td>
<td>0.5 ± 1.1 vs. 1.1 ± 1.1 mm (p = 0.016)</td>
<td>24</td>
<td>24-month TLR: 30% vs. 38%</td>
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<td>Schmidt et al. (47), 2011</td>
<td>IN.PACT Amphirion (Medtronic, Minneapolis, Minnesota), 104</td>
<td>Paclitaxel-urea, 3.0</td>
<td>N/A</td>
<td>BTK</td>
<td>3-month binary restenosis measured by angiography†</td>
<td>27%</td>
<td>12</td>
<td>12-month TLR: 17%</td>
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<td>IN.PACT Pacific (Medtronic), 44</td>
<td>FreePac Paclitaxel-urea, 3.0</td>
<td>PTA, 47</td>
<td>FP</td>
<td>6-month LLL measured by angiography</td>
<td>−0.01 ± 0.3 vs. 0.7 ± 0.3 mm (p = 0.0014)</td>
<td>12</td>
<td>12-month TLR: 7% vs. 28% (p = 0.02)</td>
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<tr>
<td>Micari et al. (49), 2013</td>
<td>IN.PACT Admiral (Medtronic), 105</td>
<td>Paclitaxel-urea, 3.0</td>
<td>N/A</td>
<td>FP</td>
<td>12-month primary patency measured by DUS</td>
<td>84%</td>
<td>27</td>
<td>27-month TLR 14%</td>
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<td>DEBATE-BTK (50), 2013</td>
<td>IN.PACT Amphirion (Medtronic), 65</td>
<td>Paclitaxel-urea, 3.0</td>
<td>PTA, 67</td>
<td>BTK</td>
<td>12-month binary restenosis measured by angiography and DUS</td>
<td>27% vs. 74% (p &lt; 0.001)</td>
<td>12</td>
<td>12-month TLR: 18% vs. 43% (p = 0.002)</td>
</tr>
<tr>
<td>DEBATE-SFA (60), 2013</td>
<td>IN.PACT Admiral + BMS (Medtronic), 55</td>
<td>Paclitaxel-urea, 3.0</td>
<td>PTA + BMS, 55</td>
<td>FP</td>
<td>12-month binary restenosis measured by angiography or DUS</td>
<td>17% vs. 47% (p = 0.008)</td>
<td>12</td>
<td>12-month TLR: 17% vs. 33% (p = 0.07)</td>
</tr>
</tbody>
</table>

*Defined as composite of mortality, amputation, and TLR. †Derived from primary patency rates.

DEBATE-BTK = Drug Eluting Balloon in peripheral intervention for Below-The-Knee Angioplasty Evaluation; DEBATE-SFA = Drug Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery; FemPac = Paclitaxel-Coated Versus Uncoated Balloon Femoral Paclitaxel Randomized Pilot Trial; LEVANT I = The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis; LLL = late lumen loss; MAE = major adverse event(s); PACIFIER = Paclitaxel-Coated Balloons in Femoral Indication to Defeat Restenosis; THUNDER = Local Taxane With Short Exposure for Reduction of Restenosis in Distal Arteries; other abbreviations as in Tables 1 and 2.
TABLE 4 Ongoing Trials With DCB

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Patients</th>
<th>Arterial Territory</th>
<th>DCB Model, Drug, Dose, g/mm²</th>
<th>Control</th>
<th>Primary Outcome (months)</th>
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<tbody>
<tr>
<td>LEVANT 2 (44), 476</td>
<td>FP</td>
<td>Lutonix DCB Moxy, paclitaxel-polysorbate/sorbitol, 2.0</td>
<td>PTA</td>
<td>PP (12)</td>
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<tr>
<td>IN.PACT SFA II (45), 450</td>
<td>FP</td>
<td>IN.PACT Admiral, paclitaxel-urea, 3.0</td>
<td>PTA</td>
<td>TLR (12)</td>
<td></td>
</tr>
<tr>
<td>FREERIDE (46), 280</td>
<td>FP</td>
<td>Freeway, paclitaxel-shellac, 3.0</td>
<td>PTA</td>
<td>TLR (6)</td>
<td></td>
</tr>
<tr>
<td>ADVANCE 18PTX (47), 150</td>
<td>FP</td>
<td>Advance 18PTX, paclitaxel, 3.0</td>
<td>PTA</td>
<td>TLR (6)</td>
<td></td>
</tr>
<tr>
<td>ISAR-STATH (48), 150</td>
<td>FP</td>
<td>Paclitaxel + BMS, N/A</td>
<td>PTA + BMS or atherectomy</td>
<td>Percentage of stenosis (6)</td>
<td></td>
</tr>
<tr>
<td>ILLUMINATE Pivotal (49), 350</td>
<td>FP</td>
<td>Stellarex, paclitaxel, 2.0</td>
<td>PTA</td>
<td>TLR (12) and PP (12)</td>
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<tr>
<td>IN.PACT-DEEP (51), 357</td>
<td>BTK</td>
<td>IN.PACT Amphirion, paclitaxel, 3.0</td>
<td>PTA</td>
<td>TLR (12)</td>
<td></td>
</tr>
<tr>
<td>LUTONIX BTK (53), 480</td>
<td>BTK</td>
<td>Lutonix DCB Moxy, paclitaxel-polysorbate/sorbitol, 2.0</td>
<td>PTA</td>
<td>Limb salvage (12)</td>
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<tr>
<td>BAIR (56), 100</td>
<td>BTK ISR</td>
<td>Legflow, paclitaxel-shellac + BMS, 3.0</td>
<td>PTA + BMS</td>
<td>PP (3-12)</td>
<td></td>
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<tr>
<td>FAIR (57), 118</td>
<td>FP ISR</td>
<td>IN.PACT, paclitaxel-urea, 3.0</td>
<td>PTA</td>
<td>Binary stenosis (6)</td>
<td></td>
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<tr>
<td>COPA CABANA (58), 112</td>
<td>FP ISR</td>
<td>Cotavance, paclitaxel-isopridome, 3.0</td>
<td>PTA</td>
<td>LLL (6)</td>
<td></td>
</tr>
<tr>
<td>ISAR-PEBIS (59), 70</td>
<td>FP ISR</td>
<td>IN.PACT, paclitaxel-urea, 3.0</td>
<td>PTA</td>
<td>Percentage of stenosis (6)</td>
<td></td>
</tr>
<tr>
<td>FREEWAY (62), 200</td>
<td>FP</td>
<td>BMS + Freeway, paclitaxel-shellac, 3.0</td>
<td>BMS + PTA</td>
<td>TLR (6)</td>
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<tr>
<td>RAPID (63), 176</td>
<td>FP</td>
<td>Legflow, paclitaxel-shellac + BMS, 3.0</td>
<td>PTA + BMS</td>
<td>Binary restenosis (1-24)</td>
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<tr>
<td>DEFINITIVE AR (64), 125</td>
<td>FP</td>
<td>Cotavance, paclitaxel-isopridome, 3.0</td>
<td>Atherectomy + Cotavance, paclitaxel-isopridome, 3.0</td>
<td>Percentage of stenosis (12)</td>
<td></td>
</tr>
<tr>
<td>ADCAT (65), 80</td>
<td>BTK</td>
<td>IN.PACT, paclitaxel-urea, 3.0</td>
<td>Atherectomy + IN.PACT, paclitaxel-urea, 3.0</td>
<td>PP (6)</td>
<td></td>
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<tr>
<td>REAL PTX (67), 150</td>
<td>FP</td>
<td>Paclitaxel, N/A</td>
<td>Zilver PTX DCS</td>
<td>PP (12)</td>
<td></td>
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<tr>
<td>IDEAS I (68), 50</td>
<td>BTK</td>
<td>Paclitaxel, N/A</td>
<td>DCS</td>
<td>Binary restenosis (6)</td>
<td></td>
</tr>
</tbody>
</table>

Atherosclerotic Lesions in the Superficial Femoral Artery and/or Proximal Popliteal Artery; the ISAR-STATH (Efficacy Study of Stenting, Paclitaxel Eluting Balloon or Atherectomy to Treat Peripheral Artery Disease) trial; and the ILLUMINATE Pivotal (Prospective, Randomized, Single-Blind, U.S. Multicenter Study to Evaluate Treatment of Obstructive Superficial Femoral Artery or Popliteal Lesions with a Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon). Interim and long-term follow-up data examining the durability of DCB therapy are also promising. At 24 months, the THUNDER trial reported that the TLR rate for patients in the DCB arm was one-half that of the patients in the PTA arm (p < 0.001), with results holding at the 5-year mark (p < 0.001). Furthermore, 4% of patients in the DCB arm received additional stents compared with 22% in the PTA arm (40). Two-year results from the FemPac study have also shown a durable TLR benefit of DCB compared with that of PTA (42). Micari et al. (49) conducted another prospective multicenter study (n = 105) investigating the 2-year results of DCB therapy for femoropopliteal disease and revealed a 2-year primary patency of 72.4% and TLR of 14.3% (p < 0.001)—provisional stenting was required in 12.3% of lesions. After 27 ± 3 months of follow-up in 98 patients, the study results demonstrated improvement in absolute claudication distance, Rutherford classification, and quality-of-life functional measures (p < 0.001 for all comparisons with baseline).

TRIALS COMPARING DCB WITH PLAIN BALLOON ANGIOPLASTY FOR INFRAPOPLITEAL DISEASE

In 2011, Schmidt et al. (17) conducted the first single-arm prospective trial using DCB to treat long infrapopliteal lesions and demonstrated superior short- and mid-term outcomes compared with those listed in the historical data using PTA. The DEBATE-BTK (Drug Eluting Balloon in peripheral intervention for Below-The-Knee Angioplasty...
Evaluation) trial (n = 132) reinforced the findings of this trial and other smaller randomized trials with regard to the superiority of DCB therapy versus PTA in the setting of BTK disease in diabetic patients with CLI. Twelve-month angiographic follow-up revealed a significantly lower restenosis rate for DCB versus PTA alone, along with a striking reduction in TLR and occlusion rate (50). However, emergent results from the INPACT-DEEP (Randomized Study of IN.PACT Amphirion Drug Eluting Balloon vs. Standard PTA for the Treatment of Below the Knee Critical Limb Ischemia) RCT (51) (n = 357) showed no significant differences in late lumen loss or TLR, with a slight trend toward higher amputation rates for DCB compared with standard PTA control subjects. Further analysis into the strikingly different outcomes of this trial compared with those of other contemporary DCB RCTs remains speculative due to lack of data (52). The LUTONIX BTK (Lutonix Drug Coated Balloon Versus Standard Balloon Angioplasty for Treatment of Below-the-Knee Arteries) trial (53) is an ongoing RCT with a goal of 480 patients that will further examine the role of DCB therapy in BTK disease in patients with CLI.

**DCB THERAPY FOR IN-STENT RESTENOSIS**

DCB therapy has also been used for in-stent restenosis of femoropopliteal arteries with some degree of success. Stabile et al. (54,55) treated SFA in-stent restenosis with DCB (n = 39) and reported 1- and 2-year primary patency rates of 92.2% and 73.0%, respectively. A number of ongoing RCTs are investigating DCB therapy as a strategy to tackle in-stent restenosis (4). These studies include the BAIR (Paclitaxel-Coated Versus Uncoated Balloon for Treatment of Below-the-Knee In-Stent-Restenosis) trial (56), the FAIR (Femoral Artery In-Stent Restenosis) trial (57), the COPA CABANA (Cotavance Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-Stent Restenosis in SFA and Popliteal Arteries) trial (58), and ISAR-PEBIS (Randomized Trial of Paclitaxel Eluting Balloon or Conventional Balloon for Treatment of In-Stent Restenosis of the Superficial Femoral Artery in Patients With Symptomatic Peripheral Artery Disease) (59).

**TRIALS EXAMINING COMBINATION THERAPIES WITH DCBs**

In light of the somewhat distinct advantages of stent and balloon therapies, there is great interest in therapeutic strategies that combine them. The DEBATE SFA (Drug Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery) RCT (60) (n = 104) compared pre-dilation with DCB versus plain old balloon angioplasty (POBA) prior to BMS implantation. At 12-month follow-up, binary restenosis rates and TLR were significantly lowered. Data from the DEBATE SFA trial also suggests that reduction of restenosis is maintained irrespective of lesion length and recanalization technique.

Post-dilation strategies have also been successfully applied to treat SFA stenosis (61). The FREEWAY (The Freeway Drug-Eluting Balloon for Treatment of De Novo Lesions in the SFA or Popliteal Arteries) RCT is investigating the use of BMS plus post-dilation with either DCB or POBA. Six-month interim results for 79 patients show a TLR rate of 2.5% for BMS + DCB versus 10.2% for BMS + POBA and a higher rate of patency for DCB versus POBA (86.1% vs. 75.7%) (62). Other ongoing RCTs such as the RAPID (Randomized Trial of Legflow Paclitaxel-Eluting Balloon and Stenting Versus Standard Percutaneous Transluminal Angioplasty and Stenting for the Treatment of Intermediate and Long Lesions of the Superficial Femoral Artery) (63) (n = 176) are investigating combination therapy with DCB and stents for the treatment of intermediate and long SFA lesions.

Therapeutic strategies that combine DCB as an adjunct to plaque removal by means of directional atherectomy or photoablation are also being investigated. The ongoing DEFINITIVE AR (Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency) RCT (64) (n = 102) is evaluating the efficacy of directional atherectomy followed by DCB versus DCB therapy alone for the treatment of femoropopliteal de novo stenosis. At the 30-day follow-up assessment, atherectomy achieved higher technical success (90% vs. 64%; p = 0.004) and lowered residual diameter stenosis (18% vs. 28%; p = 0.0002). Similar ongoing RCTs such as the ADCAT (Atherectomy and Drug-Coated Balloon Angioplasty in Treatment of Long Infrapopliteal Lesions) trial (65) (n = 80) and the PHOTOPAC (Photoablative Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis in In-Stent Femoropopliteal Obstructions) trial (66) (n = 50) will continue to investigate the long-term durability of atherectomy or photoablation and specific clinical scenarios that warrant its application.

There are currently no published studies that provide direct comparisons among DCB and other treatment alternatives such as BMS, directional atherectomy, or DCS. An indirect comparison...
between DCB and BMS was performed in a meta-analysis by Fusaro et al. (5) that included 11 RCTs (n = 1,464) investigating DCB versus PTA and BMS versus PTA, the results of which were used to compare DCB versus BMS with PTA as the common comparator (Table 1). Although DCB and BMS performed superiorly to PTA in reducing risk of TLR, restenosis, and adverse events, the indirect comparison found no differences for the same endpoints (5). Two ongoing RCTs (67,68), the REAL PTX (Randomized Evaluation of the Zilver PTX Stent vs. Paclitaxel-Eluting Balloons for Treatment of Symptomatic Peripheral Artery Disease of the Femoropopliteal Artery) trial (n = 150) and the IDEAS-I (Infrapopliteal Drug Eluting Angioplasty Versus Stenting for the Treatment of Long-Segment Artery Disease) (68) (n = 70), are investigating a head-to-head comparison of DCB and DCS and will hopefully provide additional evidence to support a preferred endovascular treatment strategy.

**DCB CONCLUSIONS**

Overall, there is a growing body of evidence indicating significantly lower restenosis with DCB therapy using paclitaxel over PTA for de novo stenosis and in-stent restenosis of the femoropopliteal and BTK PAD. Additionally, review of all current DCS and DCB trials for femoropopliteal PAD interventions do not suggest an advantage of DCS over DCB (Fig. 1). However, definitive, well-powered data are still forthcoming, particularly with regard to long-term clinical outcomes. The comparable efficacy of DCB versus BMS, DCS, and directional atherectomy, both as exclusive treatment modalities and as adjunctive therapies, also awaits data from well-designed, ongoing, and future RCTs.

**LIMITATIONS OF CURRENT DCBs AND REGULATORY CONCERNS**

Irrespective of comparable efficacy, other questions remain about the use of DCBs. The rapid, uniform, efficient, and directed transfer of the drug to the vessel wall during balloon inflation with limited downstream distribution remains the dominant challenge (20). Success of DCB relies on the rapid transfer of a single dose of an antiproliferative agent into the vessel wall. Tissue delivery of the antiproliferative drugs from a DCB is about 8.8 ± 3.9% of the mean percentage of total original catheter load (69). Table 5 depicts antiproliferative drug
concentration on currently-available or under-evaluation DCBs. Moreover, studies reporting plasma levels of paclitaxel following DCB use cannot be deemed conclusive with respect to potential systemic effects of these drugs delivered to patients during peripheral artery interventions (70). Only ≈2% of total drug on the coating and ≈24% of the releasable drug is transferred during 30 s of inflation time (38). Approximately 98% of zotarolimus taken up by the artery was cleared between 5 min and 24 h after 30-s balloon inflation. Yet, resulting arterial levels at 24 h reflect detectable and potentially therapeutic levels of zotarolimus (1.4 ± 0.5 ng/mg) (38). Thus, a lot more work is needed to demonstrate reliable targeted, dose-dependent biological and vascular bed-associated clinical responses. These concerns have been at the heart of the potential U.S. FDA concerns regarding DCB (71).

High diffusivity and vascular wall tissue penetration of lipophilic drugs such as zotarolimus and paclitaxel during balloon inflation are also associated with near immediate clearance after balloon deflation (38,72). Therefore, strategies for targeted drug delivery and binding could play a critical role in DCB therapy. Pre-clinical trials using platelet-mimicking, multiligand nanoparticles have shown enhanced drug uptake by endothelial cells and may ultimately decrease the drug concentration of DCB necessary to obtain beneficial outcomes (73).

An important complication associated with DCB and PTA is acute dissection requiring a bailout stent or, rarely, surgery. The impact of this complication on long-term outcomes remains unclear, but it must be considered when comparing DCB outcomes to those of BMS or DCS trials. Two potential side effects of DCB therapy continue to be analyzed despite the fact that their significance has yet to be borne out in clinical trials: vessel wall toxicity characterized histologically by excess fibrin, and collagen deposition and microparticulate embolization (36). Additionally, an analysis of the cost-effectiveness of DCB therapy is needed, although attempts have been made by Dorenkamp et al. (74) and Zeller (75) provided preliminary results. Optimal duration of dual antiplatelet therapy in conjunction with DCB therapy for PAD also remains widely debated, in contrast to the established clinical guidelines for the use of DES in patients with acute coronary syndrome. Some groups have suggested dual antiplatelet therapy for 1 month, whereas other researchers, citing pre-clinical data, have recommended a duration of 6 months (36). The issue of the preferred antiproliferative drug for DCB is also important. Although pre-clinical and clinical results have been equivocal, it is now believed that the availability of paclitaxel outside of intellectual property protection and the ability to formulate suitable carriers for paclitaxel makes it the preferred choice for most DCBs. Further investigation of a variety of DCB-related issues is clearly necessary; however, there is no question that DCB technology holds a great deal of promise for the treatment of PAD.

The body of evidence demonstrating the superior efficacy of DCS and DCB compared with that of BMS and PTA for PAD is growing. Evidence for the mid- and long-term (>2-year) efficacy of DCS in PAD is promising, but more data from well-powered, multicenter trials are needed. Patterns of success for certain treatment modalities, based on anatomic distribution and disease stage, are starting to emerge. For femoropopliteal disease, the current evidence suggests similar restenosis and TLR outcomes for DCS and DCB. Treatment choice may thus be dictated by rate of stent fracture compared with rate of acute complications associated with balloon angioplasty. For infrapopliteal disease, DCB may ultimately become the treatment of choice due to typically long lesion lengths and diffuse disease. Two studies (DEBATE-BTK and Schmidt et al. [17]) have thus far shown promising outcomes for long concentrations of DCB.

### Types of DCBs

<table>
<thead>
<tr>
<th>DCBs</th>
<th>Manufacturer</th>
<th>Drug Carrier</th>
<th>Drug</th>
<th>Dose Density, μg/mm²</th>
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<tbody>
<tr>
<td>Cotavance</td>
<td>MEDRAD (Warrendale, Pennsylvania)</td>
<td>Paccocath</td>
<td>Paclitaxel</td>
<td>3.0</td>
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<tr>
<td>SeQuent Plexis</td>
<td>B. Braun Melsungen AG (Melsungen, Germany)</td>
<td>Paccocath</td>
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<td>IN.PACT</td>
<td>Medtronic-Invatec (Minneapolis, Minnesota)</td>
<td>FreePac</td>
<td>Paclitaxel</td>
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</tr>
<tr>
<td>Dior, Freeway</td>
<td>Eurocor (Bonn, Germany)</td>
<td>Shellac</td>
<td>Paclitaxel</td>
<td>3.0</td>
</tr>
<tr>
<td>Moxy</td>
<td>Lutonix-Bard (Murray Hill, New Jersey)</td>
<td>Nonpolymeric</td>
<td>Paclitaxel</td>
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</tr>
<tr>
<td>Pantera Lux</td>
<td>Biotronik (Berlin, Germany)</td>
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<tr>
<td>AngioSculpt</td>
<td>Angiodynamics (Fremont, California)</td>
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<tr>
<td>Protege</td>
<td>Blue Medical (Helmond, the Netherlands)</td>
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<td>Elutax</td>
<td>Aachen Resonance (Aachen, Germany)</td>
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<td>Wombat</td>
<td>Avidal Vascular (Halle, Germany)</td>
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<td>Steellarex</td>
<td>Covidien (Mansfield, Massachusetts)</td>
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<tr>
<td>Magic Touch</td>
<td>Concept Medical (San Jose, California)</td>
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<td>Sirolimus</td>
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<tr>
<td>Nanoparticle-coated</td>
<td>In development*</td>
<td>PLGA nanoparticles</td>
<td>Paclitaxel</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Proprietary information of University of Texas Southwestern Medical Center.

DCB = drug-coated balloon(s); PLGA = polylactic-glycolic acid.
Sarode et al.
Infragenicular Drug Delivering Technology


REFERENCES

1. May KK, Robless PA, Sidhu HR, Chua BS, Ho P. Limb salvage in patients with peripheral arterial disease managed by endovascular first approach. Vasc Endovasc Surg 2014;48:129-33.


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**KEY WORDS** drug-coated stents, drug-coated balloons, peripheral artery disease, review