

Current Use of Coronary Drug-Coated Balloons

A review of technical considerations and clinical applications and a discussion of what's next in drug-coated balloon technology.

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In 1977, coronary angioplasty revolutionized the approach to coronary revascularization. The clinical benefits of a minimally invasive approach to coronary revascularization were immediately recognized; however, the limitations of balloon angioplasty, including vessel dissection, elastic recoil, constrictive remodeling, and intimal hyperplasia, were also acknowledged. Coronary stents later successfully addressed the acute complications of vessel dissection, as well as the problems of elastic recoil and constrictive remodeling. Bare-metal stents (BMSs) did not affect the development of intimal hyperplasia but led to the creation of a new clinical problem—intense restenosis (ISR), which continues to occur with a frequency of 20% to 35% in real-world application of BMSs. This led to the important development of drug-eluting stents (DESs), with local delivery of antiproliferative agents to the vessel wall, which have been successful in reducing the incidence of proliferative ISR to <5%.¹ However, antiproliferative drugs also delay endothelialization of the stent, with the consequence of an increased risk of late stent thrombosis, which currently necessitates longer-term use of dual-antiplatelet therapy (DAPT) with balloon angioplasty or application of BMSs.

Around the time that the first coronary DES (Cypher, Cordis Corporation) was introduced in Europe in 2002, Ulrich Speck, PhD, and Bruno Scheller, MD, set out to develop a novel method for local antiproliferative drug delivery that was not stent-based in order to overcome some the limitations of DESs. This would also broaden the applications of local antiproliferative drug delivery to coronary lesions not suited for stenting and for other vascular applications where stenting had been problematic (eg, infrainguinal lower extremity vessels). Prof. Speck, who developed the contrast agent iopromide (Ultravist, Bayer HealthCare) in 1979,

collaborated with Prof. Scheller to use iopromide as a vehicle to deliver paclitaxel on coronary balloons and completed a series of animal experiments that proved that the contrast agent facilitated drug delivery, tissue uptake, and reduced reactive hyperplasia in a porcine coronary stent model. They also completed important dose range experiments that confirmed that a paclitaxel dose of $\geq 3 \mu\text{g}/\text{mm}^2$ was optimal for inhibition of neointimal proliferation.

Subsequently, they developed the Paccocath coronary drug-coated balloon (DCB) (Bayer HealthCare/Medrad), and the first coronary application was in coronary ISR lesions (PACCOCATH ISR I) in 2003. The PACCOCATH ISR I trial demonstrated significantly better angiographic results with the Paccocath DCB as compared to uncoated balloons (in-segment late lumen loss [LLL] of 0.48 mm vs 0.86 mm; $P = .002$).² The subsequent trial, PACCOCATH ISR II, validated these findings in a larger series of patients and also demonstrated the continued benefit of the Paccocath DCB at 2 years.³ The positive findings of the PACCOCATH ISR I and II trials berthed the industry of paclitaxel DCBs with dosing of 2 to 3 $\mu\text{g}/\text{mm}^2$ and a number of different excipients for drug retention and delivery. Currently, there are nine different coronary DCBs that have CE Mark approval in Europe (Table 1).⁴

TECHNICAL CONSIDERATIONS

Lesion Preparation

The principal advantage of a DCB is the ability to deliver antiproliferative drugs without a stent, which is advantageous in ISR where multiple stent layers are not desirable, in cases in which DAPT is not desirable or cannot be tolerated, and when the need for repetitive treatments is anticipated. The main disadvantage of DCBs is that because there is no stent scaffold, the

TABLE 1. DCBs CURRENTLY CE MARK APPROVED AND MARKETED IN EUROPE

Manufacturer	Product Name	Drug, Dose	Excipient
Aachen Resonance GmbH	Elutax	Paclitaxel, 2.2 µg/mm ²	Dextrane
B. Braun Interventional Systems, Inc.	SeQuent Please Neo	Paclitaxel, 3 µg/mm ²	Iopromide
Biosensors International Group, Ltd.	Biostream	Paclitaxel, 3 µg/mm ²	Shellac
Biotronik	Pantera Lux	Paclitaxel, 3 µg/mm ²	Butyryl-tri-hexyl citrate
Boston Scientific Corporation	Agent	Paclitaxel, 2 µg/mm ²	Citrate ester
Cardionovum GmbH	Restore DEB	Paclitaxel, 3 µg/mm ²	Safepax
Eurocor GmbH	Dior	Paclitaxel, 3 µg/mm ²	Shelloic acid
iVascular	Essential	Paclitaxel, 3 µg/mm ²	Organic ester
Medtronic	In.Pact Falcon	Paclitaxel, 3 µg/mm ²	Urea

acute results are the same as those of percutaneous transluminal angioplasty (PTA), with more elastic recoil, less acute gain, and a higher incidence of dissection than with a stent platform. For this reason, lesion preparation becomes critically important to optimize acute gain before application of a DCB.

In 2011, the German Drug-eluting Balloon Consensus Group published their recommendations for use of DCBs in a variety of clinical situations, including ISR, small vessels, and bifurcation lesions.⁵ The recommendation was to predilate in all cases with a balloon-to-vessel ratio of 0.8:1 of the reference vessel diameter to achieve a residual percent diameter stenosis of ≤ 30% before application of a DCB. This recommendation has been applied to most clinical trials of DCBs that have been subsequently performed. Further support of this recommendation was demonstrated by a retrospective study of long-term clinical outcomes of 166 patients with ISR treated with DCBs, in which inadequate predilation (defined as a ≥ 30% diameter stenosis, < TIMI 3 flow, or major dissection) was found to be an independent predictor of subsequent target lesion revascularization (TLR), which only became apparent after the first year of treatment.⁶

Given the importance of adequate vessel preparation prior to DCB application, attention has also been paid to the use of focal and/or scoring balloons prior to applying a DCB. The RESCUT trial⁷ established the benefit of cutting-balloon PTA in reducing balloon slippage and the need for unplanned stenting in ISR lesions. The ISAR DESIRE IV trial evaluated use of the AngioSculpt scoring balloon (Spectranetics Corporation) versus a standard PTA balloon for predilation prior to application of a DCB

in ISR lesions. This trial demonstrated a better percent diameter stenosis and a lower restenosis rate at 6- to 8-month angiographic follow-up.⁸ The SQP SVD Japan trial randomized patients to the Lacrosse NSE scoring balloon (Goodman Co., Ltd.) or a standard PTA balloon prior to applying a DCB in de novo small vessel disease. This trial demonstrated a lower percent diameter stenosis and need for acute bailout stenting in vessels 2 to 2.1 mm in diameter.⁹ There is also some evidence that devices that cut or score the intima may facilitate drug delivery and uptake, which could further enhance DCB effectiveness. Use of focal and/or scoring balloons for vessel preparation prior to DCB is increasing, and research is being conducted on drug-coated versions of these balloons.

Dissections and Bailout Stenting

Endovascular use of DCBs in non-flow-limiting dissections does not negatively impact the effectiveness of DCBs in terms of LLL.¹⁰ In coronary applications, most non-flow-limiting dissections heal and do not negatively affect clinical outcomes if they are left untreated after application of a DCB.¹¹ Bailout stenting of non-flow-limiting dissections after DCB use is therefore discouraged. However, when bailout stenting is needed for the treatment of a flow-limiting dissection after applying a DCB, use of a BMS significantly increases LLL, restenosis, and the need for subsequent reinterventions.^{12,13} As a result, if a flow-limiting dissection occurs during vessel preparation, then application of a DES is recommended.⁵ If a flow-limiting dissection occurs after use of a DCB, another study suggests the application of a DES is safe and associated with supe-

rior outcomes, perhaps as a result of the synergistic actions of two antiproliferative drugs.¹⁴

Anticoagulation and Stent Thrombosis

The German Drug-eluting Balloon Consensus Group recommends 4 weeks of DAPT for patients undergoing a stand-alone procedure with a DCB and 6 to 12 months of DAPT for patients who receive either a bail-out BMS or DES.⁵ Clinical trials of coronary DCBs have largely followed the recommended 4-week course of DAPT in the DCB arms, and there has been no signal to suggest a safety concern, which makes the use of a DCB a good strategy in cases in which prolonged DAPT is not desirable or contraindicated. Rates of stent thrombosis with DCBs has been very low in the ISR trials, ranging from 0% to 1.4% (average, 0.4%).¹⁵ By comparison, the Resolute DES (Medtronic) has the lowest long-term stent thrombosis rates: 2.1% at 1 year and 2.5% at 2 years in ISR applications.¹⁶

Moreover, the PEPCAD China ISR trial reported higher all-cause mortality, all-cause mortality or myocardial infarction, and cardiovascular death or myocardial infarction at 2 years with a paclitaxel DES as compared to a paclitaxel DCB in ISR lesions.¹⁷ The BELLO trial reported a lower overall major adverse cardiovascular event rate with a paclitaxel DCB as compared with a paclitaxel DES at 3 years in small vessels.¹⁸ Based on these long-term observations, use of DCBs appears safer than paclitaxel DESs despite having a recommended duration of DAPT that is considerably shorter. However, more data are needed to determine if DCBs are safer than second-generation everolimus-eluting stents (EESs).

CLINICAL APPLICATIONS

In-Stent Restenosis

Coronary ISR was the first obvious application of DCBs. Given the favorable findings of the Paccocath DCB as compared to uncoated balloons and coronary artery ISR, as well as two subsequent positive trials of DCBs versus uncoated balloons in DES restenosis, the field rapidly evolved to compare DCBs to DESs in ISR lesions. Three randomized clinical trials have compared DCBs to DESs in BMS restenosis lesions (PEPCAD II ISR,¹⁹ RIBS V,²⁰ and Pleva et al²¹), and three randomized trials have compared DCBs to repeat DES in DES restenosis (RIBS IV,²² ISAR-DESIRE 3,²³ and PEPCAD China ISR²⁴). In the randomized trials comparing DCBs to DES in BMS restenosis, PEPCAD II ISR demonstrated equivalent outcomes at 1 and 3 years, and the most recently published trial by Pleva et al demonstrated lower LLL and equivalent clinical

outcomes as compared to an EES. Only the RIBS V trial demonstrated better outcomes with a DES. Of the three randomized trials comparing DCBs to DESs in DES restenosis, ISAR-DESIRE 3 showed equivalent clinical outcomes up to 3 years, and PEPCAD China ISR showed superior clinical outcomes with DCBs at 2 years. Only RIBS IV showed better outcomes with repeat DES. The RIBS IV and V trials were criticized for accepting up to a 50% stenosis prior to application of the DCB and for having a disproportionately high TLR rate in patients with restenosis in the DCB arm (ratio of TLR to restenosis, 74% in DCB arm vs 47% in the EES arm), suggesting differing thresholds for reintervention, depending on whether there were one or two layers of stent already present.²⁵

Several meta-analyses of coronary ISR clinical trials have been performed, with the most recent and inclusive performed by Siontis et al.²⁶ All treatment strategies for coronary ISR lesions were reviewed, and the authors concluded that “two strategies should be considered for treatment of any type of coronary ISR: PCI [percutaneous coronary intervention] with EES because of the best angiographic and clinical outcomes, and DCB because of its ability to provide favorable results without adding a new stent layer.” This analysis was performed prior to the publication of the study by Pleva et al in BMS restenosis that showed less LLL and equivalent 1-year clinical outcomes with scoring balloons to predilate, followed by the SeQuent Please DCB (B. Braun Interventional Systems, Inc.) as compared to the Promus Element stent (Boston Scientific Corporation). Nonetheless, evidence suggests equivalent clinical outcomes with DCBs as compared to repeat DES use, especially when optimal lesion preparation is performed prior to DCB application. DCBs now have a level IA indication for treating coronary ISR in Europe.²⁷

De Novo Lesions

Vessel diameter and lesion length remain the two most powerful predictors of restenosis after PCI. Small vessels have posed challenges to treatment with stents, which makes the concept of using DCBs in this setting attractive if the acute problems of elastic recoil and dissection with PTA can be managed with better vessel preparation. The BELLO trial randomized patients with vessels < 2.8 mm in diameter and < 25 mm in length by visual estimates to either a paclitaxel DCB or a paclitaxel DES.²⁸ Treatment of small vessel disease with a paclitaxel DCB was associated with less angiographic LLL and similar rates of restenosis and revascularization as compared with a paclitaxel DES at 6 months,²⁸ and

TABLE 2. SIROLIMUS DCBs

Company	Product	Drug	Concentration	Delivery Agent
Abbott Vascular	NA	Zotarolimus	6–7 µg/mm ²	Iopromide matrix
Caliber Therapeutics, Inc.	Virtue DCB*	Sirolimus nanoparticles	3 mg	Porous balloon
Concept Medical Inc.	Magic Touch DCB,* Xtreme Touch DCB	Sirolimus nanoparticles	1.3 µg/mm ² 3 µg/mm ²	Phospholipid excipient
M.A. Med Alliance SA	Selution DCB*	Sirolimus nanoparticles	1 µg/mm ²	CAT
Sahajanand Medical Technologies Pvt. Ltd.	NA	Sirolimus	0.7 µg/mm ²	PLGA/PVP 50/50 coating

*The Virtue, Magic Touch, and Selution DCBs are currently in human clinical trials.
Abbreviations: CAT, cell adherence technology; NA, not available; PLGA, poly(lactic-co-glycolic acid); PVP, poly(vinyl pyrrolidone).

at 3 years, the composite major adverse cardiovascular event rate was significantly lower in the DCB arm (14.4% vs 30.4%; $P = .0015$).¹⁸

A network meta-analysis of published PCI outcomes in small vessels concluded that early-generation sirolimus-eluting stents (SESs) yielded the most favorable angiographic and clinical outcomes for the treatment of stenoses in small coronary arteries.²⁹ Whether DCBs have equivalent outcomes to SESs or EESs in small vessels is now the subject of significant research and is being evaluated in the BASKET-SMALL2 trial (NCT01574534), which is randomizing 750 patients with vessels < 3 mm to either the SeQuent Please DCB or the Xience EES (Abbott Vascular). Other potential applications of DCBs are in bifurcation lesions, especially side branch lesions that are normally treated with PTA, but further research is needed to determine if there is benefit in this lesion subset.

WHAT'S NEXT?

Scoring and Focal DCBs

Combining a scoring or focal balloon with drug delivery makes intuitive sense, and the positive effect of using the AngioSculpt balloon prior to a DCB on angiographic percent diameter stenosis and restenosis in the ISAR DESIRE IV trial sparked the development of drug-coated scoring and focal balloons. The PATENT-C trial randomized patients with coronary ISR to the AngioSculpt scoring balloon or to a paclitaxel-coated AngioSculpt and demonstrated superior angiographic outcomes in the paclitaxel-coated AngioSculpt group at 6 months, with LLL of 0.17 ± 0.40 mm, restenosis rate of 7%, and a TLR rate of 3% compared with an LLL of 0.48 ± 0.51 mm, 41% restenosis rate, and 32% TLR rate in the uncoated AngioSculpt group.³⁰

At 2 years, clinically driven TLR was still only 3.3%.³¹

The Chocolate focal balloon is also now coated with paclitaxel (Chocolate Heart, QT Vascular Ltd.). The first-in-human trial of the Chocolate Heart demonstrated an average LLL of 0.01 mm and a TLR rate of 5% at 6 months. These early findings were sufficient for CE Mark approval in Europe, and a US Food and Drug Administration investigational device exemption has been approved to begin enrollment in the United States. These early results are encouraging, and there is promise that combining scoring and focal balloon technologies with drug delivery will lead to superior DCB outcomes in the future. Both the AngioSculpt and Chocolate DCB devices are also being developed for peripheral applications.

Sirolimus DCBs

Thus far, paclitaxel has been the only drug used for local balloon delivery. By virtue of its lipophilicity and stability, paclitaxel is more readily transferred to the vessel wall and penetrates vessel tissue layers more readily, allowing for easier drug delivery. On the other hand, paclitaxel is less effective in suppressing reactive hyperplasia, is associated with more LLL and more restenosis than limus drugs, and as a cytotoxic drug, has a much narrower therapeutic window, which may be one of the reasons it has been difficult to demonstrate similar effectiveness to SES and EES in coronary applications and safety in critical limb ischemia. For these reasons, there is a growing movement to develop an effective limus DCB. The challenge has been how to deliver therapeutic doses of sirolimus to vascular tissues for a sufficient period of time, as tissue absorption of sirolimus is slow and retention is short. The solution appears to be to encapsulate sirolimus in extended-

release nanoparticles that facilitate rapid transfer and sustained drug release. Of the five different formulations of sirolimus DCBs, three are now in human clinical trials (Table 2).

The SABRE trial evaluated the Virtue sirolimus-eluting balloon (Caliber Therapeutics, Inc.) in 50 patients with coronary ISR and demonstrated a 6-month LLL of 0.10 ± 0.31 mm in BMS restenosis lesions and an LLL of 0.20 ± 0.38 mm in DES restenosis lesions, with corresponding 12-month TLR rates of 0% and 2.8%, respectively.³² The Nanolute Registry evaluated the MagicTouch DCB (Concept Medical Inc.) in 167 patients with coronary ISR and reported a 12-month TLR rate of 5.3%.³³ This trial did not use angiographic follow-up for determination of LLL, but based on the clinical results, a larger-scale all-comers trial of the MagicTouch (EASTBOURNE Registry) is planned. Patient enrollment has begun for a first-in-human trial evaluating the Selution DCB (M.A. Med Alliance SA) in the superficial femoral artery; a coronary ISR and a small vessel trial is also planned to begin next year. Although the results of sirolimus-coated DCBs are very early, there is great promise that these technologies will be successful and lead to better DCB outcomes, as well as potentially expanded applications to other vascular territories, including below the knee and cerebrovascular, where paclitaxel DCBs have not been effective. ■

- Kereiakes DJ, Meredith IT, Windecker S, et al. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II randomized trial. *Circ Cardiovasc Interv.* 2015;8:pice002372.
- Scheller B, Speck U, Schmitt A, et al. Addition of paclitaxel to contrast media prevents restenosis after coronary stent implantation. *J Am Coll Cardiol.* 2003;42:1415-1420.
- Scheller B, Hehrlein C, Bocksch W, et al. Two year follow-up after treatment of coronary in-stent restenosis with the paclitaxel coated balloon catheter. *Clin Res Cardiol.* 2008;97:773-781.
- Latib A. Methods and technologies to improve DCB outcomes: does the data support their use? Presented at Transcatheter Cardiovascular Therapeutics 2016; November 1, 2016; Washington, DC.
- Kleber FX, Mathey DG, Rittger H, Scheller B; German Drug-eluting Balloon Consensus Group. How to use the drug-eluting balloon: recommendations by the German consensus group. *EuroIntervention.* 2011;7(suppl K):K125-K128.
- Tanaka A, Latib A, Jabbari RJ, et al. Impact of angiographic result after predilatation on outcome after drug-coated balloon treatment of in-stent coronary restenosis. *Am J Cardiol.* 2016;118:1460-1465.
- Albiero R, Silber S, Di Mario C, et al. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the restenosis cutting balloon evaluation trial (RESCUT). *J Am Coll Cardiol.* 2004;43:943-949.
- Byrne RA, Kufner S, Joner M, et al. Neointimal modification with scoring-balloon and efficacy of drug-coated balloon therapy in patients with restenosis in drug-eluting coronary stents: results of the Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis 4 (ISAR-DESIRE 4). Presented at Transcatheter Cardiovascular Therapeutics 2015; October 11-15, 2015; San Francisco, CA.
- Funatsu A. SQP small vessel disease Japan trial. Presented at Complex Cardiovascular Therapeutics; October 29-31, 2015; Kobe, Japan.
- Tepe G, Zeller T, Schnorr B, et al. High-grade, non-flow-limiting dissections do not negatively impact long-term outcome after paclitaxel-coated balloon angioplasty: an additional analysis from the THUNDER study. *J Endovasc Ther.* 2013;20:792-800.
- Cortese B, Silva Orrego P, Agostoni P, et al. Effect of drug-coated balloons in native coronary artery disease left with a dissection. *JACC Cardiovasc Interv.* 2015;8:2003-2009.
- Unverdorben M, Kleber FX, Heuer H, et al. Treatment of small coronary arteries with a paclitaxel-coated balloon catheter. *Clin Res Cardiol.* 2010;99:165-174.
- Wöhrlé J, Zadura M, Möbius-Winkler S, et al. SeQuent Please World Wide Registry: clinical results of SeQuent please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. *J Am Coll Cardiol.* 2012;60:1733-1738.
- Basavarajah S, Latib A, Hasegawa T, et al. Assessment of efficacy and safety of combining "paclitaxel" eluting balloon and "limus" eluting stent in the same lesion. *J Interv Cardiol.* 2013;26:259-263.
- Scheller B. Debate: DCB for in-stent restenosis: does the current data support broad adoption? Yes! The data is solid and DCB should be the treatment of choice! Presented at Transcatheter Cardiovascular Therapeutics 2016; November 1, 2016; Washington, DC.
- Richardt G, Leschke M, Abdel-Wahab M, et al; RESOLUTE All Comers and RESOLUTE International Investigators. Clinical outcomes of the Resolute zotarolimus-eluting stent in patients with in-stent restenosis: 2-year results from a pooled analysis. *JACC Cardiovasc Interv.* 2013;6:905-913.
- Xu B, Qian J, Ge J, et al. Two-year results and subgroup analyses of the PEPCAD China in-stent restenosis trial: a prospective, multicenter, randomized trial for the treatment of drug-eluting stent in-stent restenosis. *Catheter Cardiovasc Interv.* 2016;87(suppl 1):624-629.
- Latib A, Ruparella N, Menozzi A, et al. 3-year follow-up of the Balloon Elution and Late Loss Optimization Study (BELLO). *JACC Cardiovasc Interv.* 2015;8:1132-1134.
- Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation.* 2009;119:2986-2994.
- Alfonso F, Pérez-Vizcaino MJ, Cárdenas A, et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V clinical trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol.* 2014;63:1378-1386.
- Pleva L, Kukla P, Kusnierova P, et al. Comparison of the efficacy of paclitaxel-eluting balloon catheters and everolimus-eluting stents in the treatment of coronary in-stent restenosis: the treatment of in-stent restenosis study. *Circ Cardiovasc Interv.* 2016;9:e003316.
- Alfonso F, Pérez-Vizcaino MJ, Cárdenas A, et al. A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the RIBS IV randomized clinical trial. *J Am Coll Cardiol.* 2015;66:23-33.
- Byrne RA, Neumann FJ, Mehilli J, et al; ISAR-DESIRE 3 investigators. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet.* 2013;381:461-467.
- Xu B, Gao R, Wang J, et al; PEPCAD China ISR Trial Investigators. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. *JACC Cardiovasc Interv.* 2014;7:204-211.
- Scheller B, Ong P, Kleber FX. Drug-coated balloon treatment as default strategy for DES-ISR. *J Am Coll Cardiol.* 2016;67:346-347.
- Siontis G, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. *Lancet.* 2016;386:655-664.
- Windecker S, Kolh P, Alfonso S, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-2619.
- Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study [published erratum appears in *J Am Coll Cardiol.* 2013;61:1660]. *J Am Coll Cardiol.* 2012;60:2473-2480.
- Siontis GM, Piccolo R, Praz F, et al. Percutaneous coronary interventions for the treatment of stenoses in small coronary arteries: a network meta-analysis. *JACC Cardiovasc Interv.* 2016;9:1324-1334.
- Scheller B, Fontaine T, Mangner N, et al. A novel drug-coated scoring balloon for the treatment of coronary in-stent restenosis: results from the multi-center randomized controlled PATENT-C first in human trial. *Catheter Cardiovasc Interv.* 2016;88:51-59.
- Scheller B, Chamíé D, Mangner N, et al. TCT-414: a novel drug-coated scoring balloon for the treatment of coronary in-stent restenosis: two years follow-up results from the PATENT-C first in human trial. *J Am Coll Cardiol.* 2015;66(15_S_).
- Stella P. Sirolimus angioplasty balloon for in-stent restenosis (SABRE) trial: 6-month angiographic and 1-year clinical follow-up. Presented at Transcatheter Cardiovascular Therapeutics 2016; November 1, 2016; Washington, DC.
- Cortese B. Nanoparticle sirolimus-coated balloon for the treatment of in-stent restenosis: results from the Nanolute Registry. Presented at Transcatheter Cardiovascular Therapeutics 2016; November 1, 2016; Washington, DC.

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