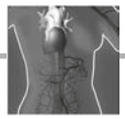
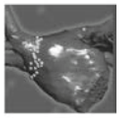


The use of the Xience nano™ coronary stent system for the treatment of small vessels coronary artery disease

Drug-eluting stents have proven long-term safety and effectiveness for the treatment of coronary artery disease especially due to their marked efficacy in reducing restenosis rates. Nevertheless, the rates of late and very late stent thrombosis, especially in first-generation systems, have raised some concerns. Moreover, percutaneous coronary intervention to small vessels (especially <2.5 mm) remains challenging. The Xience nano™ drug-eluting stent system was developed to improve coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤28 mm) with reference vessel diameters of ≥2.25 to <2.50 mm. In this article, we describe the components of the Xience nano drug-eluting stent system presenting clinical data of this current stent.

KEYWORDS: coronary artery disease ■ everolimus ■ long lesions ■ next-generation drug-eluting stents

Elad Asher[1] & Marco A Costa*[1]

[1]Harrington Heart & Vascular Institute, Case Western Reserve University, 11100 Euclid Avenue, LKS 3001, Cleveland, OH 44106-5038, USA
**Author for correspondence:*
Tel.: +1 216 844 5840
Fax: +1 216 844 8954
marco.costa@uhhospitals.org

Small-vessel coronary angioplasty encompasses all the potential difficulties of percutaneous coronary interventions (PCIs): guide-wire manipulation, lesion crossing, device sizing, stent delivery due to frequently high tortuosity of the vessel proximal to the lesion and risk of dissection, perforation and abrupt closure. Even after a successful procedure, long-term outcomes are affected by higher incidences of restenosis or thrombosis [1]. In the past, small-vessel interventions had a higher incidence of myocardial infarction, vessel dissection and perforation, acute vessel closure and emergent coronary artery bypass grafting. Furthermore, these lesions are usually technically difficult. They are often calcified, noncompliant and tortuous. Their predominant distal location makes device delivery and expansion more difficult. Together with poorer outcomes, there is also a high restenosis rate, which can lead to repeat intervention or bypass surgery. Intravascular ultrasound has demonstrated that some of the angiographically small vessels can be in fact 'pseudo-small'. This is due to both angiographically undetected diseases in the reference vessel segment and/or positive remodeling at the lesion. Furthermore, independent predictors of more than a 1.0 mm discrepancy between intravascular ultrasound and angiography included small vessel size (<3.0 mm), proximal lesion and diabetes mellitus. This might suggest that intravascular ultrasound in an angiographically small vessel in a proximal location or in diabetic patient may help to ensure optimal treatment [2]. Newer technologies such as optical coherence tomography appears to be a very attractive tool providing interesting information regarding whether the vessel is a true or a pseudo-small vessel, and enable an optimal result after a PCI capable of obtaining the largest possible cross-sectional areas [3]. The definition and treatment of small vessels has evolved over the years and is reflective of advancements in PCI. Early PCI trials identified small-vessel treatment as vessels ≤2.9 [4], <2.80 [5] or ≤2.75 mm in diameter [6], resulting in mean reference vessel diameters of 2.50, 2.20 and 2.40 mm, respectively. For this kind of disease, stenting was found to be superior compared with balloon angioplasty. In a meta-analysis of more 4383 patients with a median follow-up time of 8 months, death and myocardial infarction rates did not differ significantly between groups; however, stenting showed an overall significant reduction of the risk of repeat revascularization when compared with balloon angioplasty [7]. Furthermore, drug-eluting stents (DES) with antiproliferative agents emerge as an important new technology to minimize the long-term risks associated with small-vessel PCI. DES treatment compared with bare-metal stents treatment in smaller diameter vessels (≤2.75 mm) has resulted in significantly lower late loss, percentage diameter stenosis (DS), binary restenosis rates and major adverse cardiac event rates, due to less target-lesion revascularizations [8]. Despite these favorable outcomes, in-stent restenosis in small vessels remains relatively high in the DES era [9]. Another element that plays a major rule in small-vessel disease is strut thickness, which was found to be an independent predictor of angiographic restenosis in

Future Medicine part of fsg

small coronary vessels (2.75–2.99 mm); stents with thinner struts were associated with lower incidence of restenosis compared with thicker-strutted stents [10]. In the small-vessel subgroup of patients, recommendations on optimal stent deployment remain critical to decrease the likelihood of restenosis and thrombosis. The details on both Xience nano™ DES systems (Abbott Vascular, CA, USA), a 2.25-mm diameter stent for small vessels, and results from recent clinical small vessels trial are presented below.

Xience nano eluting coronary stent system

The 2.25 mm diameter Xience nano is a device–drug combination product composed of an L-605 cobalt chromium (CoCr) alloy balloon expandable stent platform coated with two polymer layers, poly-*N*-butyl methacrylate – a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of polyvinylidene fluoride and hexafluoropropylene monomers as the drug–matrix layer containing everolimus, and a drug layer mounted on a rapid exchange delivery system [101]. The 2.25 mm Xience nano has the same stent design, including struts thickness (81 µm), delivery system, drug (everolimus) and coating materials as the 2.5, 2.75 and 3.0 mm diameter Xience V® Everolimus Eluting Coronary Stent System (EECSS). Differentiating features of the 2.25 mm Xience nano are the balloon diameter (2.25 mm) and nominal stent inner diameter when expanded [102].

Drug component

Like the Xience V stent, the Xience nano stent is a coated stent, with the active ingredient everolimus. This material is embedded in a nonerodible polymer which is the inactive ingredient. The everolimus is a novel semisynthetic macrolide immunosuppressant, synthesized by chemical modification of rapamycin. The everolimus chemical name is 40-*O*-(2-hydroxyethyl)-rapamycin [103]. Once the stent is implanted in the artery, the stent releases as much as 80% of the everolimus material within 30 days. The maximum time after the stent procedure to undetectable blood everolimus concentrations is 168 h. In all studies, the C_{max} never reached a concentration of 3 ng/ml, which is necessary for systemic immunosuppression [11,12].

Clinical studies

The PERSEUS trial was design to evaluate the safety and efficacy of the Taxus™ (Boston Scientific, MA, USA) Element™ Stent compared with first-generation Taxus Express2™ Stent in 1262 patients with *de novo* lesions [13]. The patients mean age was 63 years old, approximately 70% were male, and 25% had diabetes mellitus. The study was a prospective, randomized (3:1) trial. The primary end point was noninferiority for target-lesion failure (TLF) at 12 months and the secondary end point was in-segment percentage DS at 9 months. The Taxus Element Stent was found to be noninferior to the Taxus Express2 Stent with respect to the incidence of TLF (5.57 vs 6.14%, respectively; Bayesian posterior probability of noninferiority = 0.9996) and percentage DS (3.09 vs 3.12, respectively; Bayesian posterior probability of noninferiority = 0.9970). No differences in clinical outcomes at 12 months were observed between stent treatments, and stent thrombosis. The PERSEUS Small Vessel study was a single-arm study that compared the Taxus Element Stent to the Express2 bare-metal stent [14]. The Taxus Element Stent was placed in 224 patients with small vessels (≥2.25 to <2.75 mm in diameter) and the Taxus Express2 Stent in 125 patients. The trial met its primary end point of superiority for in-stent late loss at 9 months (unadjusted values of 0.38 mm for the Taxus Element Stent and 0.80 mm for the Express2 Stent [$p < 0.001$]). The trial also met its secondary end point of superiority for TLF at 12 months, with 7.3% TLF in the Taxus Element's group compared with the prespecified performance goal of 19.5% that was derived from the bare-metal stents and DES results in the previous Taxus trials. The Element was also superior to the bare-metal stents after propensity adjustment to account for the nonrandomized design of the small-vessel analysis. The 1-year stent thrombosis rate for the Taxus Element was 0.3% compared with 0.6% in the control group. Another small-vessel trial was the PLATINUM small-vessel trial that was designed to compare the platinum chromium Promus (Boston Scientific) Element™ Stent to match a predefined performance based on historical Taxus Express2 results in small vessels [15]. The trial enrolled 94 patients with *de novo* lesions ≥2.25 to <2.5 mm in diameter and ≥28 mm in length. The primary end point was met with a 12 month TLF of 2.4% compared with the performance goal of 21.1% ($p < 0.001$). Furthermore, the technical and procedural success was 96.8%. There were three cardiac deaths, but no myocardial infarctions or stent thrombosis. Nevertheless, the differences in outcome can be partly explained by the fact that the Taxus Express2 stent has a stainless steel stent

platform which has thicker struts (132 µm) than the Promus Element Stent (81 µm).

Data regarding 2.25 mm DES treatment and outcomes still remain limited. The SPIRIT SV trial [16], which investigated the safety and efficacy of the 2.25 mm Xience nano EECSS, further contributed to the understanding of small-vessel treatment. The Xience nano EECSS is a line extension to the commercially approved Xience V EECSS. The SPIRIT SV trial was a prospective, open-label, US multicenter single-arm study designed to evaluate the safety and efficacy of the 2.25 mm diameter Xience V EECSS in up to two *de novo* coronary artery lesions in vessels (≥2.25 to <2.5 mm) in stable or unstable angina or silent ischemia patients. The trial was designed to enroll a total of 150 subjects and allowed for target and nontarget lesion treatment, in which there was an angiographic cohort of 69 subjects. The SPIRIT SV trial allowed for a single target lesion or two lesion treatments (two target lesions or one target and one nontarget lesion) in separate epicardial vessel regions with a required lesion length of ≤28 mm. As many as 39.2% of patients were diabetic, and approximately 40% were insulin dependent. Lesion length was 13.4 mm, and the mean reference vessel diameter was only 2.13 mm. The SPIRIT SV trial was designed to support the approval of the Xience nano stent system. The Xience nano EECS has been commercially approved outside the USA; however data on the performance of the Xience nano™ EECS have not been publicly available. After 1 year, the rate of cardiac death was 1.5%, the target-vessel myocardial infarction rate was 1.5%, and definite/probable stent thrombosis rate was 1.5%. Furthermore, the Xience nano EECS was associated with a TLF rate of 8.1% in which the upper 95% confidence limit was 13.03%, meeting the performance goal of 20.4% ($p < 0.0001$). The 1-year TLF rate was mainly the result of target-lesion revascularization rate of 5.1%. In the angiographic cohort, the in-stent and in-segment late loss was 0.20 and 0.16 mm, respectively, and in-stent segment and in-segment stent DS percentage was 12.86 and 20.85, respectively. The SPIRIT SV trial was nonrandomized with no comparator; however, the SPIRIT SV trial included more patients who were female (38.2%) and diabetic (39.2%), than have been typically represented in the 'all comers' stent trials who traditionally included only 30% female and 25% diabetic patients. Hence, the outcomes were considered appropriate based on the complexities and the high restenosis risk associated historically with the treatment of small coronary vessels, long lesions and a high percentage of diabetics.

Device status

Xience nano EECS has been approved in the USA since 24 May 2011 and available in Europe since 2008. Currently the Taxus Element, the Promus Element Stent and some drug-eluting balloons are available to treat small-vessel disease lesions.

Conclusion & future perspective

While the safety and efficacy of the Xience nano stent system for treatment of small vessels has been demonstrated by the SPIRIT SV trial, further randomized clinical trials are required to further understand the complexity of small-vessel disease. The small-vessel disease and the small-vessel coronary angioplasty and PCI with all its complexity remain a true challenge. To date, coronary intervention was limited to the, relatively large coronary arteries. Small-vessel disease, on the other hand, has traditionally been treated with medication and lifestyle modification, and only in

Executive summary

Stent & delivery system platforms

- Balloon-expandable cobalt–chromium (L-605) stent.
- Available in diameters from 2.25 to 2.5 mm and lengths from 8 to 28 mm.

Polymers

- Xience nano™ stent (Abbot Vascular, CA, USA) is a coated stent, with the active ingredient everolimus. This material is embedded in a nonerodible polymer that is the inactive ingredient.

Clinical studies

- The Xience nano safety and effectiveness information is derived from the SPIRIT Small Vessel Registry (SPIRIT SV trial). The SPIRIT SV trial evaluated the Xience nano stent in improving coronary luminal diameter in subjects with symptomatic heart disease in small vessels (≥2.25 to <2.50 mm).
- The results of the SPIRIT SV trial showed that the primary composite end point (cardiac death, target vessel myocardial infarction and clinically-indicated target lesion revascularization) at 1 year was 8.1%, for which the upper limit of the one-sided 95% CI was 13.03%, which met the prespecified performance goal of 20.4% ($p < 0.0001$). This composite end point contains both safety and effectiveness components.

recent years have stents and balloons been another treatment option. The next frontier might be the treatment of very small vessels (<2.25 mm) and the data from the SPIRIT SV trial suggest that this might be an achievable goal.

Financial & competing interests disclosure

M Costa is on the speaker bureau and is a consultant for BSC, Sanofi Aventis, Eli Lilly and Medtronic, and is on the speaker bureau and a member of the scientific advisory board for Abbot, Cordis, St Jude medical and Scitech. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- of interest

1 Meier B. How to treat small coronary vessels with angioplasty. *Heart* 79, 215–216 (1998).

2 Moussa I, Moses J, Di Mario C *et al.* Does the specific intravascular ultrasound criterion used to optimize stent expansion have an impact on the probability of stent restenosis? *Am. J. Cardiol.* 83(7), 1012–1017 (1999).

3 Bezerra HG, Costa MA, Guagliumi G *et al.* Intracoronary optical coherence tomography: a comprehensive review clinical and research applications. *J. Am. Coll. Cardiol. Cardiovasc. Interv.* 2(11), 1035–1046 (2009).

- **One of the first reviews about clinical use of optical coherence tomography.**

4 Doucet S, Schalij MJ, Vrolix MC *et al.* Stent placement to prevent restenosis after angioplasty in small coronary arteries. *Circulation* 104(17), 2029–2033 (2001).

5 Elezi S, Dibra A, Mehilli J *et al.* Vessel size and outcome after coronary drug-eluting stent placement: results from a large cohort of patients treated with sirolimus- or paclitaxel-eluting stents. *J. Am. Coll. Cardiol.* 48(7), 1304–1309 (2006).

6 Ardissino D, Cavallini C, Bramucci E *et al.* Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. *JAMA* 292(22), 2727–2734 (2004).

- **Key publication showing successful treatment of small-vessel disease with drug-eluting stents to prevent in stent restenosis.**

7 Agostoni P, Biondi-Zoccai GG, Gasparini GL *et al.* Is bare-metal stenting superior to balloon angioplasty for small vessel coronary artery disease? Evidence from a meta-analysis of randomized trials. *Eur. Heart J.* 26(9), 881–889 (2005).

8 Pocock SJ, Lansky AJ, Mehran R *et al.* Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J. Am. Coll. Cardiol.* 51(1), 23–32 (2008).

9 Kastrati A, Dibra A, Mehilli J *et al.* Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation* 113(19), 2293–2300 (2006).

- **Key publication showing the predictors of in-stent restenosis.**

10 Briguori C, Sarais C, Pagnotta P *et al.* In-stent restenosis in small coronary arteries: impact of strut thickness. *J. Am. Coll. Cardiol.* 40(3), 403–409 (2002).

11 Kukreja N, Onuma Y, Serruys PW. Xience V everolimus-eluting coronary stent. *Expert Rev. Med. Devices* 6, 219–229 (2009).

12 Butt M, Connolly D, Lip GY. Drug-eluting stents: a comprehensive appraisal. *Future Cardiol.* 5, 141–157 (2009).

13 Kereiakes D, Cannon L, Feldman R *et al.* Clinical and angiographic outcomes after treatment of *de novo* coronary stenoses with a novel platinum chromium thin-strut stent. *J. Am. Coll. Cardiol.* 56(4), 264–271 (2010).

14 Cannon LA, Kereiakes DJ, Mann T *et al.* A prospective evaluation of the safety and efficacy of Taxus Element paclitaxel-eluting coronary stent implantation for the treatment of *de novo* coronary artery lesions in small vessels: the PERSEUS Small Vessel trial. *EuroIntervention* 6(8), 920–927 (2011).

15 Meredith I. PLATINUM Small Vessel: 12-month outcomes. Presented at: *EuroPCR 2011*. Paris, France, 17–20 May 2011.

16 Canon LA, Simon DI, Kereiakes D *et al.* The Xience nano™ everolimus eluting coronary stent system for the treatment of small coronary arteries: the SPIRIT small vessel trial. *Catheter. Cardiovasc. Interv.* 80(4), 546–553 (2012).

■ Websites

101 The Xience V® and Xience nano™ Everolimus Eluting Coronary Stent System instructions for use. www.abbottvascular.com/static/cms_workspace/pdf/ifu/coronary_intervention/XIENCE_V_Everolimus_Eluting_Coronary_Stent_System.pdf

102 Summary of safety and effectiveness data. www.accessdata.fda.gov/cdrh_docs/pdf7/P070015S054b.pdf

103 Drug Eluting Stents In The Critically Ischemic Lower Leg 2 (DESTINY 2). http://clinicaltrials.gov/ct2/show/NCT01442636