Review of the everolimus-eluting coronary stent system

Drug-eluting stents have been demonstrated to improve outcomes for coronary artery disease patients. Introduction of the new-generation everolimus-eluting stent into Japanese clinical practice has raised expectations of further enhancement in the field of percutaneous coronary intervention. This article will evaluate this device by systematically reviewing its mechanical characteristics and associated clinical trials that consider device usage.

KEYWORDS: coronary artery disease ▪ drug-eluting stent ▪ everolimus ▪ percutaneous coronary intervention

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Since balloon angioplasty was first introduced in a clinical setting, the Achilles' heel of percutaneous coronary intervention (PCI) has been restenosis. To overcome this problem, technical considerations, such as spot stenting and stent deployment after debulking plaque, have been introduced with some success [1,2]. In addition, technical advancements have been made with the devices themselves, including the release of antirestenotic drugs from the stents. Trials using sirolimus-eluting stents (SESs) and paclitaxel-eluting stents (PESs) have clearly demonstrated that drug-eluting stents (DESs) result in a marked reduction of neointimal proliferation and target lesion revascularization compared with bare-metal stents (BMSs) [3–6]. Soon after the introduction of DESs, they became a mainstay in PCI and have led to the treatment of more complex lesion morphology in varied clinical settings. However, concern has been raised regarding the risk of late and very late stent thrombosis [7,8]. Pooled data analyses of randomized clinical trials and registry studies provide evidence supporting this safety issue in first-generation DESs [9–11]. The increase in very late stent thrombosis with DESs also remains a concern because of the required long duration of treatment with dual antiplatelet drugs [12].

With the goal of further enhancing the safety and efficacy of DESs, a next-generation DES was developed. The everolimus-eluting stent (EES; Xience V® [Abbott Laboratories, IL, USA]/Promus® [Boston Scientific, MA, USA]) is a newer-generation DES that was approved in Japan in March 2010 as the fourth DES following the SES, the PES and the zotarolimus-eluting stent (ZES; Endeavor®, [Medtronic, MN, USA]). The efficacy and safety of EES have been

demonstrated in the SPIRIT trial series [13–15]. However, the current body of real-world clinical practice data is currently not sufficient to confirm the promising randomized trial data. Therefore, outcomes from such ongoing trials as the EXECUTIVE trial are anticipated, which is assessing the efficacy of the EES compared with the PES in 200 patients, to substantiate the efficacy and safety of the EES. Simultaneously, more attention should be paid to the characteristics of DES components. To improve the efficacy of EESs, they must be used optimally. Each DES has a different stent delivery system and, although procedural technique has been underestimated, it has been directly linked to outcomes of safety and efficacy, having a marked impact on the prevention of intimal proliferation [16,17]. In this article, we comprehensively review EESs, with a special focus on technical aspects.

Everolimus-eluting stent overview
▪ Stent design
The rationale behind the design and choice of polymer for the EES is beyond the scope of this article. In brief, the EES consists of a stent platform, polymer and drug, in a similar manner to the SES and the PES. The lipophilic antiproliferative drug, everolimus, is released from a thin, durable polymer applied to a low-profile stent. The EES platform used is the MULTI-LINK® VISION® (Abbott Laboratories, IL, USA) coronary stent, which is characterized by an open-cell, nonlinear link design made from an L-605 cobalt–chromium alloy. This material and stent design have resulted in a thinner and more flexible DES compared with first-generation DESs made of

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stainless steel (**Table 1**). These qualities of the stent platform have resulted in improved deliverability and conformability of the stent. The performance of the MULTI-LINK VISION stent has previously been demonstrated in clinical practice and this stent is among the most commonly used worldwide [18–20].

Everolimus is a semisynthetic macrolide immunosuppressant drug, synthesized by chemical modification of rapamycin. This drug has been demonstrated to inhibit vascular smooth muscle cell proliferation and to function through the formation of a complex with the cytoplasmic FK 506 binding protein. This complex binds and interferes with the mTOR protein, resulting in the inhibition of cell metabolism, growth and proliferation by arresting growth at the G_1 stage of the cell cycle. Everolimus has increased solubility in organic solvents compared with sirolimus, in conjunction with a similar ability to inhibit smooth muscle cell proliferation, despite having a two- to three-fold lower affinity for FK 506 binding protein [21]. To minimize polymer loading in the vessel, an absorbable composite coating is used on the EES, consisting of two durable layers: a primary and reservoir layer. The primary layer is a nonerodable polymer made of poly-*N*-butyl methacrylate (PBMA) and plays a role in adhering the drug coating to the stent. The reservoir layer, made of vinylidine fluoride and hexafluoropropylene monomers, contains and releases everolimus. The drug load is 100 µg/cm² for all stent sizes. The formulation of drug and polymer results in controlled elution of 80% of the drug within 1 month and the remainder within 4 months [22]. The integrity of the EES polymer has been shown in scanning electron microscope studies evaluating the coating integrity of DESs after failed implantation in calcified and/or tortuous vessels [23], and of the expanded stent

at 14 atm in a water bath [24]. Although the extensive methodological limitations of the process of harvesting DESs hinder the ability to draw conclusions, these studies demonstrate the continued integrity of the EES as well as differences in the degree of coating integrity among DESs.

Preclinical studies

The polymer coating of a stent system plays an important role in drug delivery to the vessel wall. However, the coating itself may also increase the risk of inducing inflammation and promoting thrombus formation. Furthermore, incomplete endothelialization of stent strut surfaces and endothelial dysfunction may be essential components of stent thrombosis formation, although the exact mechanisms through which thromboses form are still poorly understood. Therefore, the properties of an ideal coating would include biocompatibility, healing of stent implants and continued integrity of the coating. Joner *et al.* addressed the recovery of endothelialization after stent implantation in a rabbit iliofemoral artery stenting model [25]. They focused on between- and above-stent strut endothelial coverage and relevant mitogenic and antithrombotic properties among leading polymer-based stent platforms. Notable differences among the stents were observed after 14 days. Endothelial coverage occurred more rapidly in the EES (>70% above-stent strut) relative to the SES, PES and ZES at 14 days (**Figure 1**). Reduced expression of platelet endothelial cell-adhesion molecule-1 in conjunction with increased mRNA levels and secretion of VEGF 14 days after stent implantation were found in those arteries treated with the EES compared with first-generation SESs or PESs. Nonetheless, by 28 days, endothelial function had recovered – as represented by the weak or absent expression of the antithrombotic cofactor – in all DESs tested.

Stent design	Strut thickness (µm)	Polymer	Polymer thickness (µm)	Drug (dose)
Cypher®	140	PEVA + PBMA	12.6	Sirolimus (1.4 µg/mm²)
Taxus Liberté®	97	SIBBS	16	Paclitaxel (1.0 µg/mm²)
Endeavor®	91	PC	5.3	Zotarolimus (1.60 µg/mm²)
Promus®/Xience V®	81	Fluoropolymer	7.6	Everolimus (1.0 µg/mm²)
MULTI-LINK® VISION®	81	–	–	–
BioMatrix®	112	PLA	10	Biolimus A-9 (1.0 µg/mm²)

Table 1. Comparison of components of comparator drug-eluting stents.

PBMA: Poly-N-butyl methacrylate; PC: Phosphorylcholine; PEVA: Polyethylene-co-vinyl-acetate; PLA: Polylactic acid; SIBBS: Poly(styrene-b-isobutylene-b-styrene).
Reproduced with permission from [25].

Clinical review

The efficacy and safety of the EES has been mainly demonstrated in the SPIRIT I, II, III, IV and V clinical trials. SPIRIT I consisted of 60 patients in Europe who were randomized to receive either a bare-metal MULTI-LINK VISION stent or an EES. Mean in-stent late loss (EES: 0.10 vs BMS: 0.87 mm; p < 0.001) [13] and major adverse cardiac event (MACE) rates (EES: 15.4% vs BMS: 21.4%; p = 0.59) were lower in the EES group at 1 year compared with the BMS group [26]. The SPIRIT II trial was a 300-patient randomized clinical trial enrolling patients in the Asia–Pacific region and Europe. Patients were randomized 3:1 to receive the EES (n = 223) or the first-generation Taxus® Express²™ stent (Boston Scientific; n = 77). Even though there were no significant differences in MACE rates (EES: 2.7% vs PES: 6.5%), angiographic late loss and intimal hyperplasia, as evaluated by intra-vascular ultrasound (IVUS), were significantly smaller in the EES group versus the PES group at 6 months [14]. However, at 1 year, clinical outcomes were numerically higher in the EES arm compared with the PES group [27], and a catch-up phenomenon was noted as similar rates of angiographic late loss and similar rates of volume

of intimal hyperplasia were observed between the EES and the PES after a 2-year follow-up [28]. SPIRIT III was a randomized trial that also compared the EES and Taxus Express² stent. A total of 1002 patients were randomized 2:1 to an EES (n = 669) or a PES (n = 333) at centers in the USA. In this trial, significantly lower late loss and binary restenosis rates were observed in the EES group at 8 months [15]. There was no difference in target vessel revascularization but the rate of MACE was reduced in EES-treated patients at 9 months and, in contrast to the outcomes of SPIRIT II, this comparative reduction was sustained at 2 years (**Figure 2**) [29]. The reduction in procedure-related myocardial necrosis observed with EESs may be the result of less side branch compromise due to the thinner polymer and stent strut width compared with the first-generation PES. Discontinuation of dual anti-platelet therapy after 6 months did not result in increased stent thrombosis, thus supporting the safety of the EES. SPIRIT IV was a 3687-patient trial evaluating the safety and efficacy of the EES compared with the PES in patients with more complex lesion morphology. Target lesion revascularization and stent thrombosis rates were significantly lower in the EES arm at 1 year
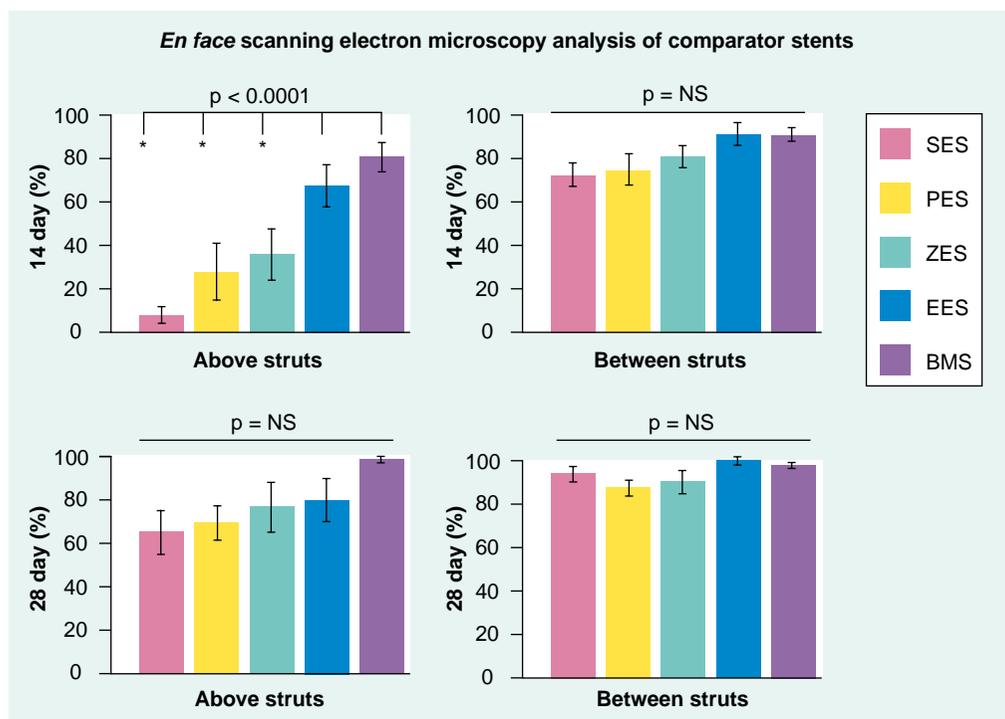

Figure 1. Quantitative analysis of endothelial coverage between and above drug-eluting stent struts after 14 and 28 days in an animal model, respectively. Asterisks indicate a statistically significant difference versus the bare-metal MULTI-LINK® VISION® stent (p < 0.001). BMS: Bare-metal stent; EES: Everolimus-eluting stent; NS: Not significant; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent. Data taken from [25].
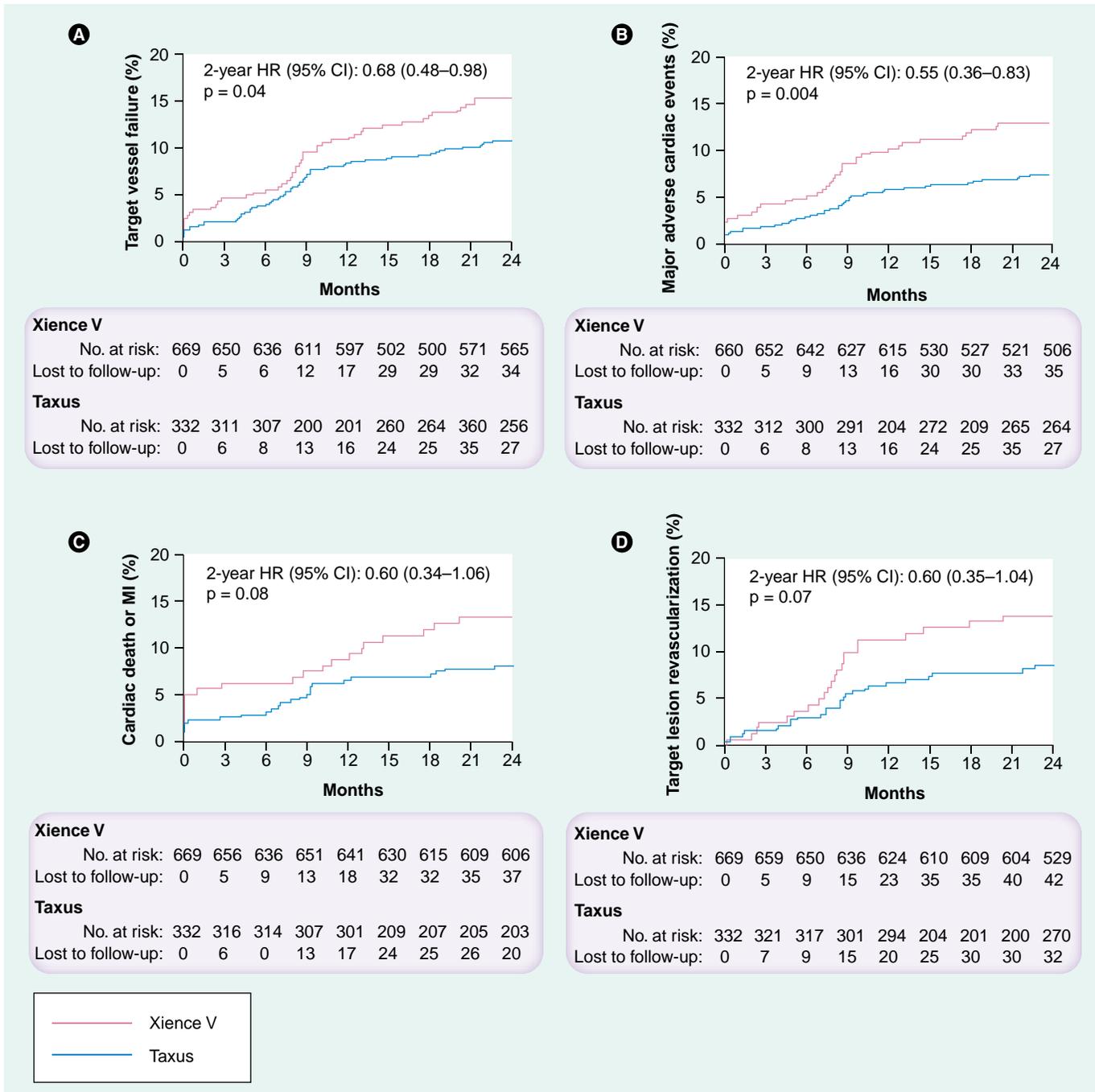
Figure 2. Time-to-event curve for patients treated with everolimus-eluting stents or paclitaxel-eluting stents for up to 2 years. (A) Target vessel failure rate. **(B)** Major adverse cardiac events rate. **(C)** Cardiac death or MI rate. **(D)** Target lesion revascularization rate. These are expressed in the vertical axis of each figure.
HR: Hazard ratio; MI: Myocardial infarction.
Data taken from [29].

compared with the PES arm [30]; however, in the subset of patients with diabetes mellitus (DM), no differences in MACE or target vessel failure were observed between the treatment arms [30]. These data support the clinical benefit of the EES compared with the Taxus Express² stent in high-risk patients and lesions [30]. However, these benefits do not appear to extend to patients with

DM [30]. The safety and efficacy of the EES in real-world practice has recently been reported. In the single-center Xience Stent Evaluated at Rotterdam Cardiology Hospital (X-SEARCH) registry [31], Onuma *et al.* demonstrated the outcomes of the EES in an all-comers population [31]. A total of 649 patients were enrolled and outcomes were analyzed at 6 months [31].

The EES was compared with three historical controls (BMS: n = 450; SES: n = 508; PES: n = 576). Even though EESs were implanted in a patient population with a more complex clinical background, with older patients and those suffering more frequent acute myocardial infarction, the EES demonstrated a comparable safety profile with the other stents and revealed improved efficacy compared with BMSs and PESs [31]. Latib *et al.* published clinical outcomes with the EES in an unrestricted population that included treatment for off-label indications [32]. In this study, 573 lesions in 345 patients treated with the EES were analyzed [32]. The majority of patients (71.9%) were treated for one or more off-label indications [32]. After a mean follow-up period of 378 days, MACEs had occurred in 10.6% of patients overall and target lesion revascularization (TLR) in 7.9% of patients [32]. Off-label EES deployment was associated with slightly higher MACE and TLR rates than were seen in the SPIRIT trials, but not with a statistically increased risk of MACE compared with on-label EES usage within this registry [32]. Previous bypass surgery and DM were independent predictors of MACE in a multivariate analysis of these registry patients [32]. This study was underpowered to detect differences in TLR rates [32]; therefore, the TLR rate may be higher in patients treated for off-label compared with on-label indications [32]. An important point to mention is that the mortality and myocardial infarction rates were similar in patients receiving off-label compared with on-label EES implantation [32]. Further evaluation, including long-term follow-up data, will be mandatory in order to draw any final conclusions regarding the safety and efficacy of the EES. In the SPIRIT III trial, IVUS data showed no significant difference in the rate of incomplete stent apposition either at the completion of procedure or after 8 months follow-up when comparing EESs and PESs; however, the outcome was somewhat different in the SPIRIT Japan registry [33]. The SPIRIT Japan registry consisted of 82 lesions; all target lesions were followed up by means of coronary angiography at 8 months [33]. A subset of lesions was evaluated by IVUS at 8 months [33], and follow-up data were analyzed by the same core laboratory as in the SPIRIT III randomized trial. Comparing the SPIRIT III randomized arm (in the USA) with SPIRIT III Japan provided interesting information about differences in stenting procedures and patient populations between the USA and Japan. The Japanese cohort consisted of an older population with a reduced prevalence of obesity (defined as BMI >30) and dyslipidemia compared with the US cohort (EES arm of the randomized cohort) [33]. There were no significant differences in the prevalence of DM or hypertension [33]. Angiographic parameters were similar between the Japanese and US arms; however, procedural characteristics were different [33]. Maximal dilatation balloon pressure was greater (Japan: 17.9 atm vs USA: 15.7 atm; p = 0.0003) and postprocedure dilatation was more frequently performed in the Japanese arm (65.9 vs 48.7%; p = 0.02) [33]. These procedural differences are likely to influence the underlying differences in IVUS findings. For example, postprocedural incomplete stent apposition was significantly more frequently observed in the US arm (**Table 2**) and the volume of in-stent neointimal hyperplasia was also significantly reduced in the Japanese arm (**Table 3**) [33]. During clinical follow-up over 2 years, stent thrombosis was not observed in any Japanese patient. It should be noted that owing to the small sample size, drawing conclusions about the relationship between perceived safety issues and procedural characteristics is difficult. Nonetheless, it seems reasonable to consider that stent apposition is

Table 2. Comparison of the rate of postprocedure, persistent and late-acquired incomplete stent apposition.

Variable	Japan (n = 82)	USA (n = 117)	p-value
Dissection	2 (2.4%)	2 (1.7%)	0.72
• Proximal edge/distal edge	0/2	1/1	
Intraluminal tissue prolapse	14 (17.1%)	24 (20.5%)	0.54
Incomplete stent apposition:			
After procedure	13 (15.9%)	39 (33.3%)	0.006
• Persistent	12 (14.7%)	24 (20.5%)	
– Proximal edge/stent body/distal edge	8/3/1	13/7/4	
• Resolved	1 (1.2%)	15 (12.8%)	
– Proximal edge/stent body/distal edge	1/0/0	10/2/3	
Late acquired	1 (1.2%)	2 (1.7%)	0.78

Data taken from [33].

Table 3. Comparison of the rate of in-stent neointimal hyperplasia volume and percentage volume obstruction.

Variable	Japan		p-value	USA (n = 71)		p-value
	After procedure	*Follow-up*		*After procedure*	*Follow-up*	
Vessel volume index	13.0 ± 4.5	13.0 ± 4.3	0.83	12.4 ± 3.8	12.5 ± 3.6	0.53
Peri-stent plaque volume index	6.2 ± 2.5	6.3 ± 2.5	0.62	6.3 ± 2.7	6.3 ± 2.3	0.71
Lumen volume index	7.0 ± 2.4	6.8 ± 2.4	0.002	6.2 ± 1.7[†]	6.0 ± 1.9[†]	0.009
Stent volume index	7.0 ± 2.4	7.0 ± 2.3	0.61	6.3 ± 1.7[†]	6.4 ± 1.8	0.005
Minimum lumen area	5.8 ± 2.2	5.4 ± 2.3	0.0003	5.1 ± 1.5[†]	4.7 ± 1.8[†]	0.0008
Neointimal volume index		0.2 ± 0.2			0.4 ± 0.4[‡]	
Percentage neointimal obstruction		3.5 ± 4.2			6.8 ± 6.4[‡]	
Maximum percentage cross-sectional narrowing		15.1 ± 14.1			21.3 ± 15.5[†]	

[†]*p < 0.05 for Japan versus USA.*
[‡]*p < 0.001 for Japan versus USA.*
Data taken from [33].

important, not only for efficacy but also for safety. The findings of the SPIRIT III Japan registry data seem to be consistent with those reported by Latib *et al.*, which were previously mentioned [32].

A technical note & discussion

Optimization of stent expansion is considered to be an important element in accomplishing favorable short- and long-term outcomes. It is important to expand the stent optimally in order to prevent suboptimal stent deployment and to reduce the likelihood of clinical adverse events. How can one obtain optimal stent apposition? The possible underlying reasons for suboptimal deployment are multifactorial; for example, one cause is underexpansion. In addition, one must take into account the mechanical characteristics of the DES. As with BMSs, the main function of the stent is to support the vessel wall and prevent elastic recoil. In previous studies, acute stent recoil ranged between 3 and 15% [34–36]. These variable data were based, in part, on the difference in stent material and design and, in part, on differences in the definition of recoil. Tanimoto *et al.* found that acute absolute stent recoil of the EES was 0.13 ± 0.21 mm and the acute percentage recoil was 4.3 ± 7.1% [37], suggesting that acute recoil is still encountered with second-generation DESs. Tanimoto *et al.* also reported that smaller reference diameter and lower maximum balloon pressure led to a higher percentage recoil [37]. Another important mechanical consideration is understanding the characteristics of the dilatation balloon and the initial dilatation pressure of the EES. The stent delivery system of the EES is designed with a semicompliant material (polyether block amide) with short tapers to prevent endothelial

and vessel injury, which are adjacent to the stented segment. According to the directions for use and our personal examination, this delivery balloon is able to dilate the EES more quickly and begins to dilate at a lower pressure compared with other DES delivery systems. However, the semicompliant nature of the balloon, especially that of the 2.5-mm size, has higher compliance compared with other DESs, which may lead to an increased risk of severe complications such as a dissection at the stent edge. Such behavior may be due, to some extent, to the balloon material, stent strut thickness and stent material.

To overcome these problems and to achieve optimal stent deployment, not only for the EES but for all DESs, there are some measures that physicians are able to take. As suggested by the SPIRIT III Japan registry, postdilatation with an adequate high-pressure atmosphere may be one option for obtaining optimal EES expansion. The use of an IVUS modality may also help in confirming proper stent expansion. IVUS guidance during PCI has been suggested to potentially reduce adverse clinical events. Both Tanimoto *et al.* and Latib *et al.* pointed out the usefulness of IVUS [32,37]. Another interesting finding was recently published by Kawasaki *et al.* The authors investigated the degree of stent expansion with different stent-deployment methods [38]. The authors concluded that prolonged stent dilatation is an effective method to optimally expand a stent [38]. Stent expansion was significantly greater after 60-s dilatation compared with 20-s dilatation [38]. Furthermore, repeated dilatation with the same pressure resulted in better expansion (**Figure 3**) [38]. Therefore, to obtain optimal EES expansion, one has to keep in

mind the importance of dilatation duration and repetition. In addition, to prevent severe complications such as stent dissection at the edge, maintaining a low pressure over a long duration is a useful strategy, as this leads to gradual EES expansion.

Taken together, our recommended EES dilatation procedure can be summarized as follows: first, start dilatation from a low pressure (<10 atm) for a sufficient duration (20 s); second, incrementally increase the dilatation pressure; third, repeated dilatation with long inflation times (at least three times); fourth, use a noncompliant balloon if this is not sufficient; and, fifth, use IVUS modality during

complex procedures. Although these practices need to be further investigated relative to clinical outcomes, these options may contribute to improved EES clinical outcomes.

Alternative devices

Currently, the first-generation Cypher® SES (Cordis Corporation, NJ, USA), and the second-generation Taxus® Liberté® PES System (Boston Scientific Corporation, MA, USA) and Endeavor® ZES (Medtronic, USA) are available in the Japanese market. Promus/Xience V is the fourth regulatory-approved DES in Japan, which has been available in the rest of the world for several years.
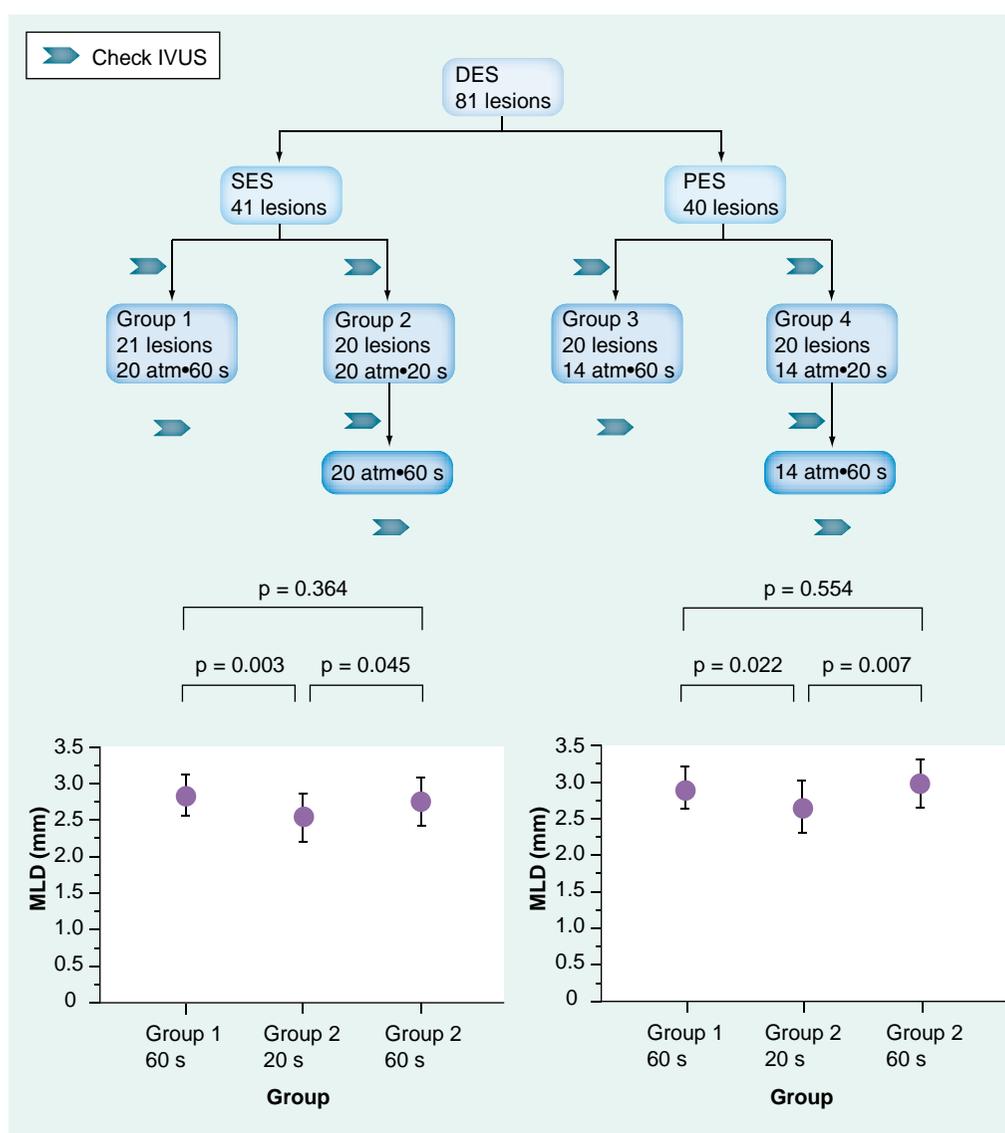

Figure 3. Comparison of postprocedural minimum lumen diameter. Prolonged and repeated stent dilatation with the same pressure provided a bigger stent area.
DES: Drug-eluting stent; IVUS: Intravascular ultrasound; MLD: Minimum lumen diameter;
PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent.
Data taken from [38].

Conclusion & future perspective

The everolimus-eluting Promus/Xience V stent consists of three DES components: everolimus as the drug, vinylidine fluoride and hexafluoropropylene monomers with a primary PBMA polymer coating and the MULTI-LINK VISION stent platform. Its thinner stent platform provides enhanced stent deliverability and stent flexibility. Recent clinical trial outcomes with the EES raise expectations regarding the safety and efficacy of this DES. Meanwhile, given that real-world data are currently limited, EES safety and efficacy should be reinforced by more evidence both from randomized trials and registries. Procedural and mechanical issues are also important elements to be considered. In order to achieve optimal EES expansion, adequate stenting strategies should be used, hopefully resulting in improved DES outcomes for the future.

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Executive summary

- The everolimus-eluting stent (EES) consists of everolimus as a drug, MULTI-LINK® VISION® as a stent platform and a thin polymer made of two layers.The MULTI-LINK VISION stent is made from an L-605 cobalt–chromium alloy and resulted in a thinner and more flexible platform compared with earlier-generation stents.
- Everolimus is a semisynthetic macrolide immunosuppressant drug synthesized by chemical modification of rapamycin, which has increased solubility in organic solvents.
- The EES polymer coating showed the recovery of endothelial function in a preclinical study.
- The efficacy and safety of the EES has been demonstrated mainly in the SPIRIT trial series, suggesting promising clinical outcomes, although long-term follow-up data need to be evaluated.
- The mechanical characteristics of the drug-eluting stent should be taken into account in order to obtain optimal stent apposition
- Dilatation pressure and duration, noncompliant balloon usage and the use of an imaging modality are recommended to optimize EES implantation.

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