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Second Generation Drug-Eluting Stents: A Review of the Everolimus-Eluting Platform

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Abstract: Everolimus-eluting stents (EES) represent the next generation of drug-eluting stents (DES). Important design modifications include thin strut stent backbones, less inflammatory and more biocompatible polymers, and lower drug dosing. The cobalt chromium EES fluoropolymer XIENCE V stent has been the most extensively studied of such stents. In animal models, this stent demonstrated minimal vessel inflammation, a biologically active endothelium with strut coverage similar to a bare metal stent, and inhibition of intimal hyperplasia comparable to that seen with sirolimus-eluting stents. The SPIRIT family of clinical trials demonstrated low rates of late loss, and clinical restenosis, as well as low rates of very late stent thrombosis. These excellent clinical outcomes addressed limitations of the 1st generation DES, and substantiated widespread clinical use of the EES platform.

Keywords: drug-eluting stents, coronary artery disease, everolimus

Clinical Medicine Insights: Cardiology 2013;7 115–126

doi: [10.4137/CMC.S11516](https://doi.org/10.4137/CMC.S11516)

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Introduction

In the early 2000s, initial trials of drug-eluting stents (DESs)¹⁻⁵ met with disappointing results. While reductions in target vessel failure (TVF) were clearly achievable in animal models, translation of reductions in restenosis with a successful stent platform in patients would take time. Eventually, through the engineering of better polymers, platforms, and pharmacology, the 1st generation DESs (ie, sirolimus, paclitaxel) demonstrated sustained reductions in rates of restenosis compared to bare metal stents (BMS). In the RAVEL and SIRIUS trials, when compared to BMS, DES improved restenosis rates and late lumen loss, and decreased target lesion revascularization (TLR) from 16.6% to 4.1% ($P < 0.01$),^{6,7} with no significant increase in major adverse cardiovascular events (MACE). The benefits of the 1st generation DESs were demonstrated out to five years, with durable results for significant reduction in target vessel revascularization (TVR) (27.4% vs. 16.9%, $P < 0.0001$).⁸ However the 1st generation DES were not without their own unique limitations. Their thick strut platforms (Fig. 1) made deliverability limited, while a growing concern for late stent thrombosis was fueled by in vitro studies demonstrating an indirect relationship between thickness and the extent

of endothelialization. Additionally, clinical studies showed bare metal thinner strut platforms achieving less angiographic restenosis when compared to thick strut DES platforms.^{9,10} Due to concern over the demonstrated increase in stent thrombosis and increased TVR/TLR, the TAXUS (paclitaxel) stent platform was abandoned. The goal of better endothelial coverage with less inflammation and enhanced delivery fueled the development of 2nd generation DESs. The following is an in-depth review of the everolimus-eluting stent platform (EES), the most widely used and studied of these 2nd generation DESs.

Drug Kinetics

Everolimus is a semi-synthetic macrolide immunosuppressant, obtained through chemical modification of rapamycin. It is part of the olimus family of drugs that induces cell cycle arrest in the late G1 phase by inhibiting the target FRAP1 (FK506 binding protein 12-rapamycin associated protein 1), or mTOR (mammalian target of rapamycin).¹¹ mTOR is a serine/threonine protein kinase that regulates cell growth, proliferation, motility, survival, protein synthesis, and transcription. Everolimus prevents migration of proteins to the nucleus, down regulating the p27 gene and cell proliferation. Because of

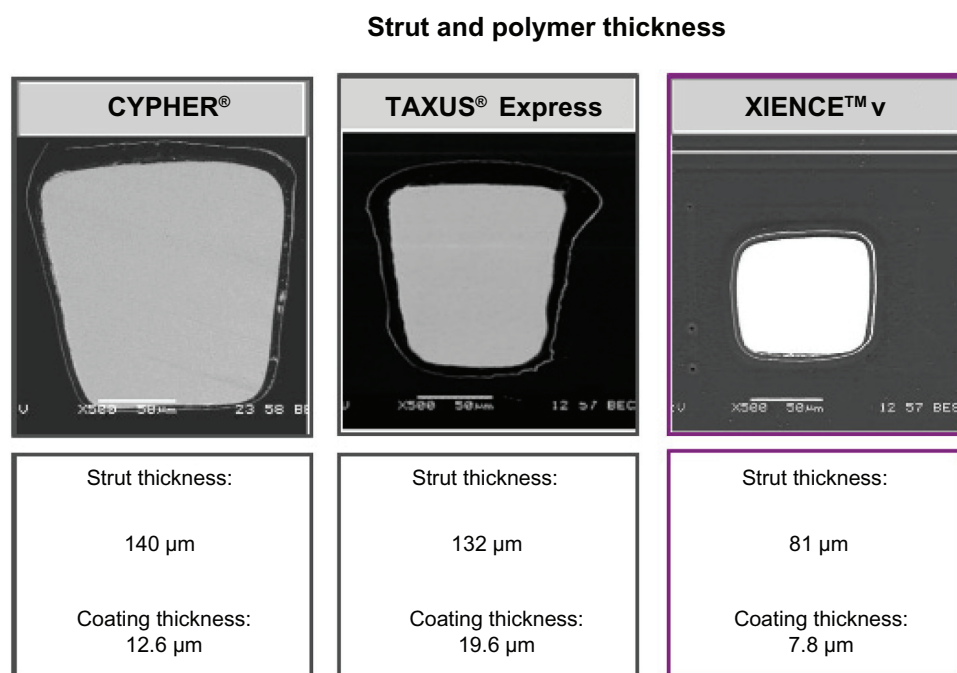


Figure 1. Photomicrographs of strut and polymer, thickness of 1st and 2nd generation drug-eluting stents.

its effectiveness, it is currently used for immunosuppression in cardiac, renal, and lung transplant patients worldwide (Fig. 2).

Stent Platform and Polymer

The EES platforms include a Multilink™ vision cobalt chromium thin strut stent backbone (81 μm compared to the 1st generation DES stents of >130 μm strut thickness) mounted on a Vision balloon (Fig. 3). This stent was commercially available as the Xience™ V (Abbott Vascular, Illinois) or Promus™ (Boston Scientific, Mattick, MA) as part of a co-marketing agreement. The stent itself consists of two layers, a drug polymer (containing the primer and a matrix) and the stent back bone. The polymer is a non-inflammatory ultra-pure fluorinated co-polymer (vinylidene fluoride and hexafluoropropylene) coating, which provides both elasticity and toughness. This chemical make-up provides a stable molecular weight and mass, thereby allowing for superior biocompatibility and outstanding stability. This design is key in maintaining the polymer's integrity during deployment and providing a predictable controlled release of drug at lower

total doses than those in previous DESs (100 μg vs. 140 μg). Additionally the fluorinated copolymer enhances the ease with which the delivery balloon is withdrawn after stent implantation because of the lack of webbing seen with other polymers.

Preclinical Studies

Original porcine coronary artery injury models compared the EES to BMS from 28 days to two years. The EES was associated with lower amounts of hyperproliferation in cross sectional samples and comparable overall inflammation scores at two years, with subsequent decline over time. Electro-micrographs obtained from the same porcine models demonstrated complete endothelialization of the arteries in both BMS and EES at two years. Finally, studies were performed in rabbit iliac injury and stenting models to determine whether the endothelium present over the surface of the stent struts was biologically active. Joner et al used platelet-endothelial cell adhesion molecule or PECAM1 expression as a marker for biologically active endothelium activity to test for activity above and between stent struts. At 14 and

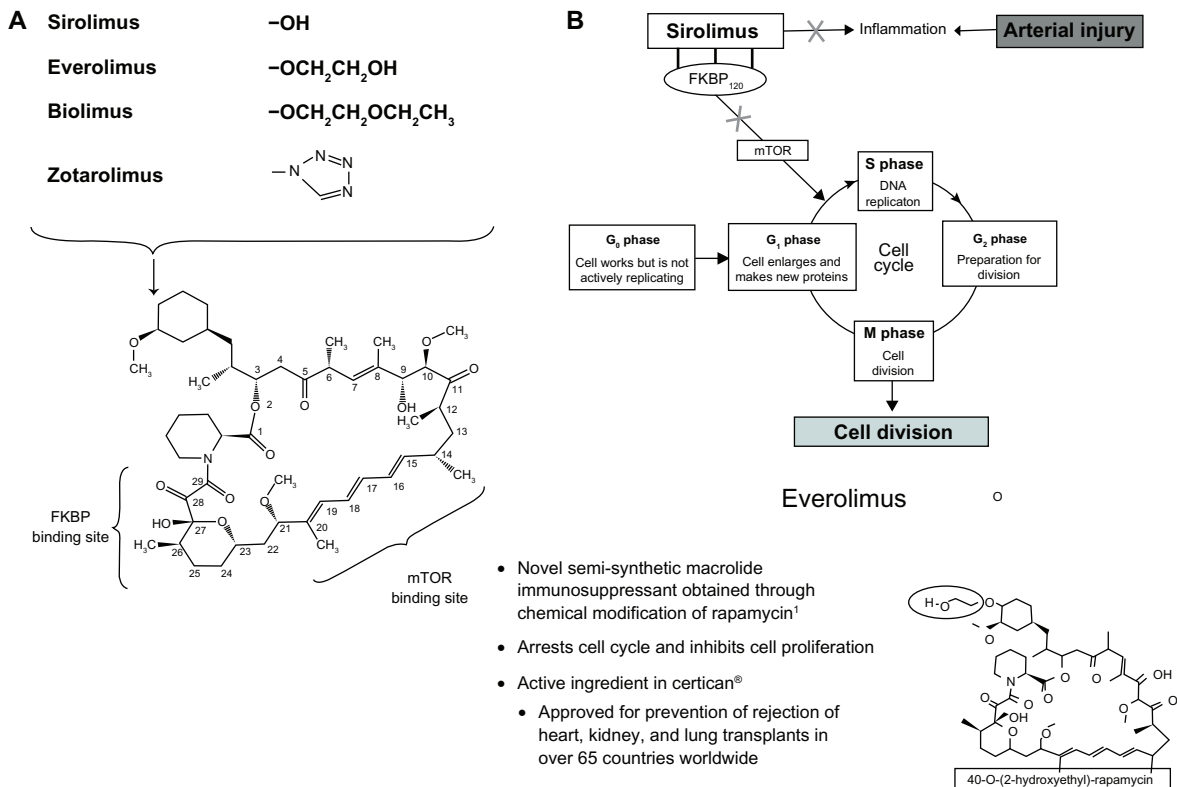


Figure 2. Schematic depiction of the mechanism of action of the olimus family of drugs.

Adapted from: Coronary Stents: Current Status Scot Garg, and Patrick W. Serruys J. *Am Coll Cardiol.* 2010;56:S1–42.

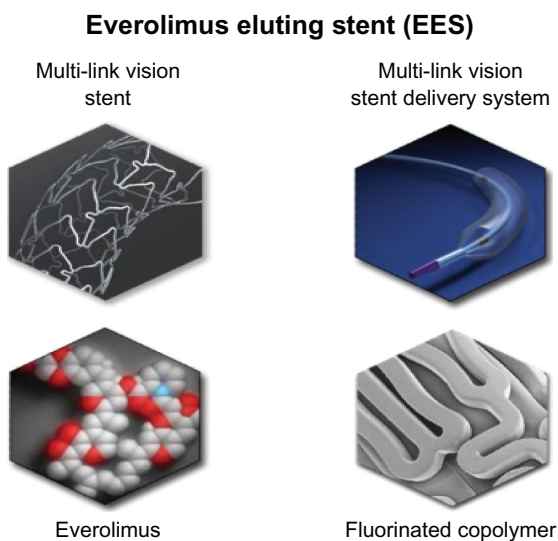


Figure 3. Key elements of the everolimus-eluting stent platform. Accessed Dec 31, 2012 from www.abbottvascular.com.

28 days there was no significant difference in the PECAM1 expression between the BMS and the EES.¹² This study demonstrated a functional, biologically active endothelium above and between stent struts in both types of stents.

Clinical Studies

The SPIRIT clinical trials were responsible for escalating the everolimus second generation DES into a status as the preferred stent platform among interventional cardiologists. The trials began with SPIRIT I through SPIRIT IV (one of the largest randomized clinical trials of DES platforms to date) and included a real world registry experience with SPIRIT V. Perhaps one of the most important features of the SPIRIT trials is their long-term data.

SPIRIT I, the first in-man comparison of the XIENCE V™ EES to the Multi-link™ Vision BMS, demonstrated a lower incidence of ischemia-driven TLR (8.3% vs. 28%) and no significant increase in stent thrombosis at five years.¹³

The SPIRIT II trial compared 1st generation TAXUS EXPRESS™ paclitaxel-eluting stent with the 2nd generation XIENCE V™ EES. This trial focused on patients with de novo single lesion coronary artery disease (CAD), with a primary endpoint of in-stent late loss (late loss defined as occurring between 6–12 months). At six months the XIENCE V™ platform had an in-stent late loss of 0.11 mm compared to 0.36 mm for the TAXUS™ platform ($P < 0.0001$).¹⁴ While three-year data has also been published on

cardiac death, MI, TLR, and MACE rates, this trial was not designed to evaluate these clinical endpoints, although it did demonstrate a decrease in MACE rates by 55% ($P < 0.05$). While provocative, it served as evidence to provide the European mandatory conformity mark or CE mark, allowing for the stent's commercial availability.

In the United States it was not until the publication of the SPIRIT III randomized clinical trial data that the Food and Drug Administration (FDA) approved the XIENCE V™ EES for commercial use. This trial of over 1,000 patients in 65 US cities included patients with up to two de novo lesions (≤ 28 mm) in different epicardial coronary vessels. It randomized them in a 2:1 fashion to the XIENCE V™ EES and the TAXUS EXPRESS™ paclitaxel-eluting stent. Patients were stratified by diabetes and intent for one vs. two lesion treatment; they were then followed for up to five years. Before randomization, all patients received ≥ 300 mg of aspirin and ≥ 300 mg of clopidogrel; they were then maintained on ≥ 80 mg of aspirin and 75 mg of clopidogrel for at least six months. The primary endpoint of in-segment loss at eight months met the criteria for both non-inferiority and superiority in the XIENCE V™ EES group (0.14 mm vs. 0.28 mm, $P = 0.004$),¹⁵ and these findings were consistent with the previous published SPIRIT II trial results. TVF defined as cardiac death, MI, or ischemia-driven TVR represented the major secondary endpoint of the SPIRIT III trial and occurred at nine months in 8.6% of the XIENCE V™ EES group, compared to 11.3% in the TAXUS EXPRESS™ paclitaxel-eluting stent group, meeting the criteria for non-inferiority.¹⁵ This definition of TVF would later be modified to target lesion failure (TLF) and became the primary endpoint for future DES trials. As noted earlier, this trial followed patients for up to five years and at year three TVF was significantly reduced (Fig. 4), occurring in the XIENCE V™ EES group 13% of the time compared to 19.2% in the TAXUS EXPRESS™ paclitaxel-eluting stent group. These findings demonstrated a relative risk reduction of 30% of TVR at three years ($P = 0.03$).¹⁶ Additional one, two, and three-year follow-up findings included a 43% reduction in TLF for all time points, including cumulative events at three years ($P = 0.01$, $P = 0.004$, $P = 0.005$ respectively).¹⁶ Specifically, ischemia driven TLR was lower in the XIENCE V™ EES group between

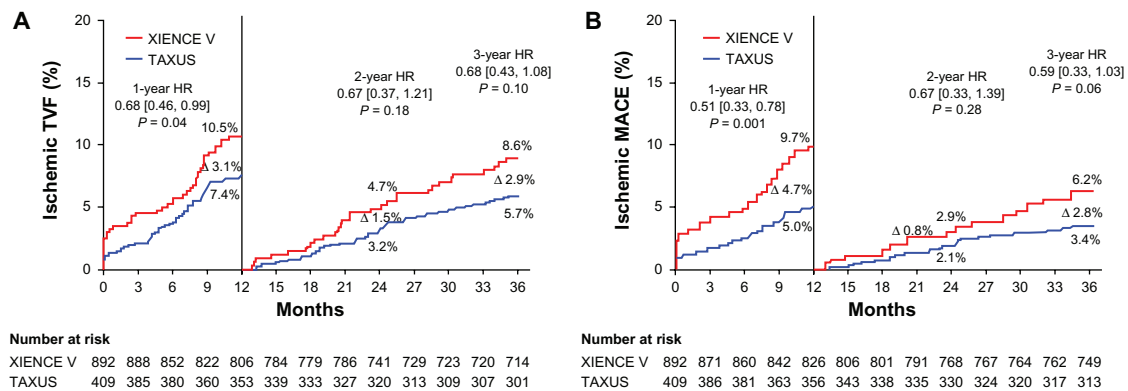


Figure 4. Kaplan-Meier plots to three years, showing ischemic target vessel failure (TVF), left panel, and ischemic major adverse cardiac events (MACE), right panel, from the SPIRIT II randomized clinical trial.

Adapted from: Garg S, Serruys P, Onuma Y, et al. SPIRIT II Investigators. 3-year clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT II trial. *J Am Coll Cardiol Interv.* 2009;2:1190–8.

one to three years, with a small but increasing gap as time went on. This was accompanied by a trend towards higher all cause death of 1.5% in the TAXUS EXPRESS™ paclitaxel-eluting stent group. Perhaps the most important result in the long term outcomes of this trial was that of stent thrombosis. During the early and late periods, where patients are typically still taking dual antiplatelet therapy and where in this trial it was mandated for at least six months, the overall incidence of stent thrombosis was 1.3% for XIENCE V™ and 1.7% for TAXUS EXPRESS™, which was not statistically different. However, for very late stent thrombosis (>12 months) the incidence with the XIENCE V™ stent was 0.3% compared to 1.0% for TAXUS EXPRESS™ stent. Although not statistically significant, the 0.3% very late stent thrombosis in XIENCE V™ group was lower than that of rates reported for the 1st generation CYPHER™ and TAXUS EXPRESS™ stents.

SPIRIT IV randomized over 3,000 patients and was powered for clinical endpoints specifically to address the issue of, and frequency of, stent thrombosis. Similar to the previous SPIRIT trials, SPIRIT IV compared the XIENCE V™ EES platform to the TAXUS EXPRESS™ paclitaxel-eluting stent platform; however, it was designed to have only clinical follow-up in hopes of preventing a bias for revascularization in the previous coronary imaging based protocols. This study randomized patients in a 2:1 fashion stratified by diabetes and the presence of complex lesions. At 12 months there was a 39% reduction in the primary endpoint of TLF (cardiac death, target vessel MI, or ischemia-driven TLR) seen in 3.9% of XIENCE V™

stent compared to 6.6% of TAXUS EXPRESS™ stents (HR 0.61, 95% CI 0.46–0.82, $P = 0.0008$).¹⁷ These results were driven by a 46% reduction in the HR of ischemia-driven TLR, 2.3% vs. 4.5% in favor of the XIENCE V™ EES platform (HR 0.54, 95% CL 0.38–0.78, $P = 0.0008$) (Fig. 5).¹⁷ Of note is a trend towards an increase in cardiac death or target vessel MI ($P = 0.08$) in patients receiving TAXUS EXPRESS™ stents, as well as a significant increase in risk of stent thrombosis at one year, 1.06% vs. 0.29% (HR 0.27, 95% CI 0.11–0.67, $P = 0.003$).¹⁷ This increase in stent thrombosis seen with TAXUS EXPRESS™ stents was particularly concerning due to the fact that dual antiplatelet therapy with aspirin and clopidogrel was mandated by study protocol for a minimum of 12 months. Besides a lower risk of the primary endpoint and stent thrombosis, sub-clinical analysis also demonstrated the superiority of XIENCE V™ EES over TAXUS EXPRESS™ stents in patients with hypertension, hyperlipidemia, a body mass index ≥ 30 , and those with multiple lesions.

The PLATNIUM trial was a non-inferiority trial designed to evaluate the safety and effectiveness of the PROMUS Element™ EES compared to the Xience V™ EES.¹⁸ This multicenter prospective randomized controlled trial of over 1,400 non-ACS patients had a primary endpoint of TLF. TLF was defined as any ischemia-driven revascularization of the target lesion, myocardial infarction (Q-wave and non-Q-wave) related to the target vessel, or cardiac death related to the target vessel. At 12 months, comparing the Xience V™ stent system versus the PROMUS Element™ stent system, the rate of TLF was 3.2% vs. 3.5% ($P = 0.72$),

**Table 1.** Important clinical studies on EES.

Trial	Treatments	Patients
SPIRIT I 2005 n = 28/32 Follow-up: 6 months/5 years SPIRIT II 2006 n = 223/77 Follow-up: 6 months/3 years	Xience™ everolimus eluting sent, versus MULTI-LINK VISION bare metal stent Xience V™ EES versus TAXUS EXPRESS 2 paclitaxel eluting stent	De novo native coronary artery lesions De novo lesions (maximum two)
SPIRIT III 2008 n = 669/333 Follow-up: 12 months SPIRIT IV 2010 n = 2458/1229 Follow-up: 1–2 years	Xience V™ EES versus Taxus PES Xience V™ EES versus TAXUS EXPRESS 2 Paclitaxel Eluting stent	Lesions 28 mm or less in length, vessel diameter 2.5 to 3.75 mm De novo lesions vessel 2.5 mm to 4.25 mm and lesion lengths ≤ 28 mm
SPIRIT V 2010 n = 2700 Follow-up: 2 years Platinum 2011 n = 1530 Follow-up: 3 years	Xience V™ EES PROMUS Element™ EES compared to the Xience V™ EES	De novo lesions, vessel 2.5 mm to 4.0 mm, lesion length ≤ 28 mm Non ACS patient's, with De novo lesion, in coronary vessel ≥ 2.50 to ≤4.25 mm, ≤24 mm length
Compare 2010 n = 1800 Follow-up: 1 year ISAR-TEST 4 2009 n = 2600 Follow-up: 1 year SCAAR 2012 n = 8375 Follow-up: 1 year ReSolute All Com 2011 n = 1788 Follow-up: 2 year	Xience V™ EES versus TAXUS Liberté™ Xience V™ EES versus CYPHER™ sirolimus-eluting stent PROMUS Element™ versus All available DES RESOLUTE™ stent versus XIENCE V™ EES	All comers with lesions amendable to PCI All comers with evidence of ischemia and de novo coronary lesion > 50% All patients included in a national registry that received a DES All comers with coronary artery lesion eligible for treatment with drug eluting stents

cardiac death or MI was 2.5% vs. 2.0%, ($P = 0.56$), TLR 1.9% vs. 1.9%, ($P = 0.96$), and incidence of stent thrombosis was 0.4% vs. 0.4% ($P = 1.00$), respectively.¹⁸ These results demonstrated that the PROMUS Element™ EES was non-inferior to the Xience V™ EES, with non-significant differences in measures of safety and efficacy through the 12 month follow-up period after PCI.

Observational and Registry Studies

As with most registry and observational studies, the cited DES trials tend to have broad inclusion criteria and they often include patients that were ineligible for randomized clinical trials. The fifth SPIRIT trial, aptly named SPIRIT V, was a single arm registry trial of all comers outside the United States of America that included a randomized control trial sub study of

diabetics and that examined the XIENCE V™ EES platform and TAXUS Liberté™ thin strut stainless steel platform. The primary composite endpoint of all cause death, non-fatal MI, and TVR, was found to occur at one year in 5.3% and at two years in 7.5% of patients with XIENCE V™ stents. To put this into perspective, in the SPIRIT III clinical trial, at two years the TLF rate was 6.9%. These observations suggest that the efficacy of the EES platform can be translated to a general population outside of a clinical trial without a significant loss of efficacy. On top of these results the incidence of late stent thrombosis (six months to one year) in the SPIRIT V registry was comparable to the previous SPIRIT IV incidence of less than 1%; additional data at two years demonstrated an incidence of very late stent thrombosis (>1 year) occurring in only 0.12% of XIENCE V™ stents. Notably, at the



Design and location	Primary endpoints	Main findings
Parallel groups single-blind International non-USA	In-stent late loss	Xience™ EES with significant decrease in primary endpoint at 6 months ($P = 0.01$)
Parallel groups single-blind (patient) International non-USA	In-stent late loss	Xience V™ EES with significant decrease in primary endpoint at 6 months ($P \leq 0.0001$)
Parallel groups single-blind USA	In-segment loss at eight months	Non-inferiority and superiority for XIENCE V™ EES group ($P = 0.004$)
Parallel groups 270 days (5 years) USA	TLF (cardiac death, target vessel MI, or ischemia-driven TLR)	Xience V™ EES with significant decrease in TLF ($P = 0.0008$) and stent thrombosis ($P = 0.003$)
Non-randomized, registry International non-USA	Composite endpoint of all cause death, non-fatal MI and TVR	Similar results to previous SPIRIT studies
Randomized single blinded, non-inferiority trial International/USA	TLF (ischemia-driven revascularization of the target lesion, MI or cardiac death related to the target vessel)	No difference in TLF or stent thrombosis
Single center randomized Safety/Efficacy Study Netherlands	All cause death, non-fatal MI and target vessel revascularization	Xience V™ EES with significant decrease in MACE ($P = 0.02$) and stent thrombosis ($P = 0.0002$)
Randomized open label Efficacy study Germany	Target lesion revascularization	Trend towards lower TLR ($P = 0.11$) and definite stent thrombosis ($P = 0.25$) for Xience V™ EES
Non-randomized: Safety/Efficacy Study Registry Sweden	Restenosis and stent thrombosis	Promus Element™ was not significantly different from the overall DES group for either outcome
Randomized single blinded Safety/Efficacy Study Switzerland	Target lesion failure (cardiac death, target vessel MI, clinical TLR)	No difference in TLF, but Angiographic late loss ($P = 0.04$) favored XIENCE V™ EES

two-year follow-up period only 49% of patients were on dual antiplatelet therapy. The COMPARE study included all patients undergoing stent therapy at a single center and randomized 1,800 patients to XIENCE V™ EES platform versus TAXUS Liberté™ thin strut stainless steel stent platform. The primary endpoint was all cause death, non-fatal MI and TVR. The XIENCE V™ EES platform maintained superior efficacy by again demonstrating a significant decrease in MACE (9.1% vs. 6.2%; $P = 0.023$), TLR (4.8% vs. 1.7%; $P = 0.0002$), and stent thrombosis (2.6% vs. 0.7%; $P = 0.002$) (Fig. 6).¹⁹ Based on the results of the SPIRIT II, III, IV and the COMPARE trial, a clear association has been identified between discontinuation of dual antiplatelet therapy and stent thrombosis in the 1st generation DES, even out to 24 months (Fig. 7).

One of the most notable randomized control trials comparing the 1st generation CYPHER™ sirolimus-eluting stent to the XIENCE V™ EES platform was the ISAR-TEST 4 substudy. At 12 months, both clinical and angiographic results were obtained. TLR was observed in 10.7% of CYPHER™ treated patients compared to 8.1% of the XIENCE V™ treated patients, but failed to reach statistical significance ($P = 0.11$).²⁰ There was an observed decrease in definite stent thrombosis, 0.7% vs. 1.3% in favor of XIENCE V™, but again it failed to reach statistical significance ($P = 0.25$).²⁰

The safety and efficacy of the Promus Element™ stent has been recently demonstrated in a selected clinical trial population.¹⁸ The SCAAR registry is a real world experience of DES implants in Sweden from November 2009 to March 2011. This registry

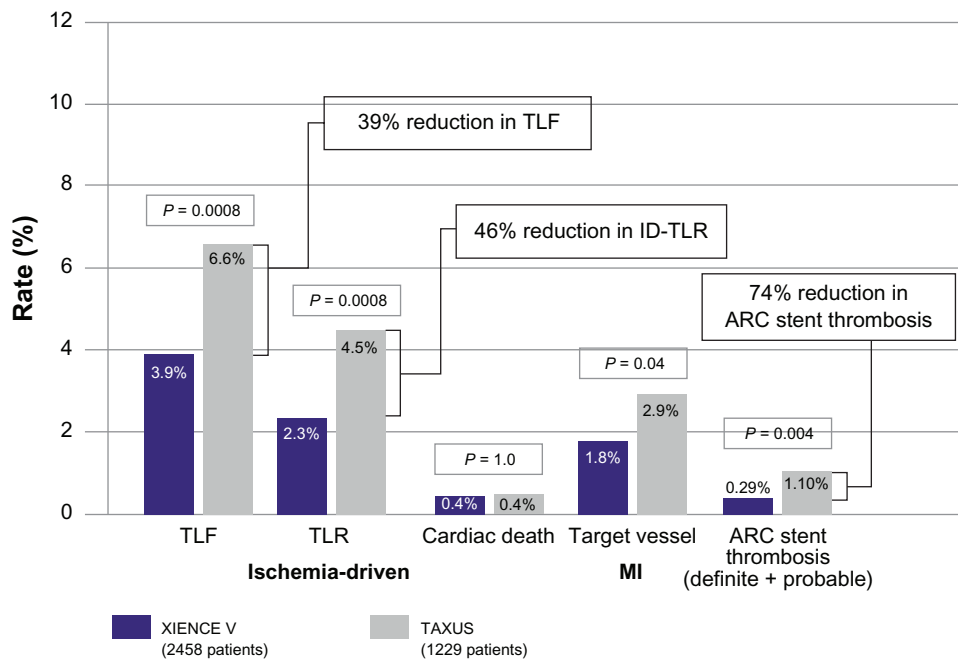


Figure 5. Bar graphs depicting the key study endpoints from the SPIRIT IV randomized clinical trial. Adapted from SPIRIT IV 1-year results, Gregg Stone, TCT 2009.

compared the PROMUS Element™ EES (n = 2,724) to the available DES platform at the time. Along with the PROMUS Element™, the Cypher™ (n = 782), Endeavor™ (n = 747), TAXUS Liberté™ (n = 1,393), XIENCE V™/Promus™ (n = 4,832), Resolute™ (n = 1,566), and XIENCE Prime™ (n = 4,832) were implanted in 8,375 procedures. At one year

the restenosis rate in the Promus Element™ was not significantly different from the overall DES group (2.8% vs. 2.7%, HR: 1.17, 95% CI: 0.75–1.75). A significantly lower restenosis (2.8% vs. 5.8%; HR: 0.44; 95% CI: 0.26–0.74) and stent thrombosis (0.2% vs. 0.8%; HR: 0.24; 95% CI: 0.08–0.6) rates were observed in the Promus Element™ when compared

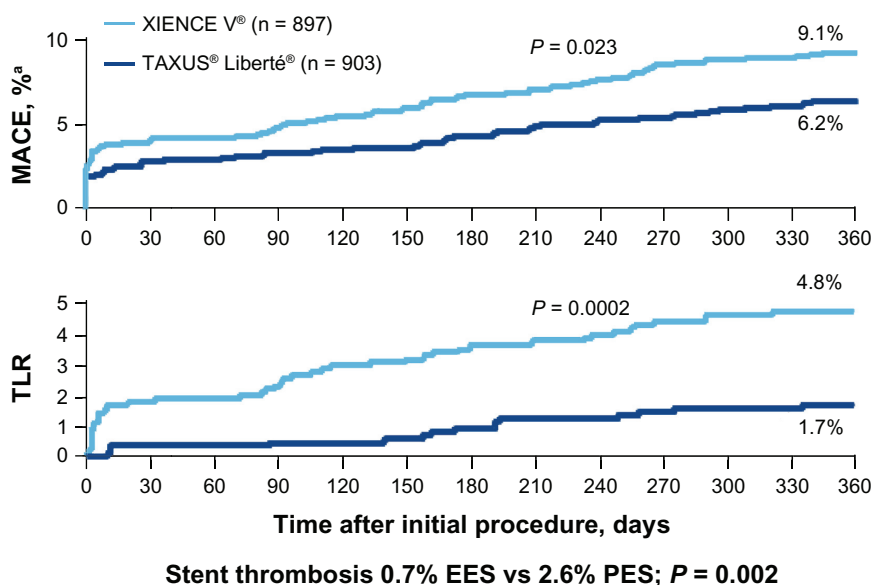


Figure 6. Kaplan-Meier plots to one year from the COMPARE single center randomized trial, showing major adverse cardiac event rates (MACE) (top panel), and target lesion revascularization (TLR) (bottom panel). Adapted from: Kedhi et al. *Lancet*. 2010;375:201–9.

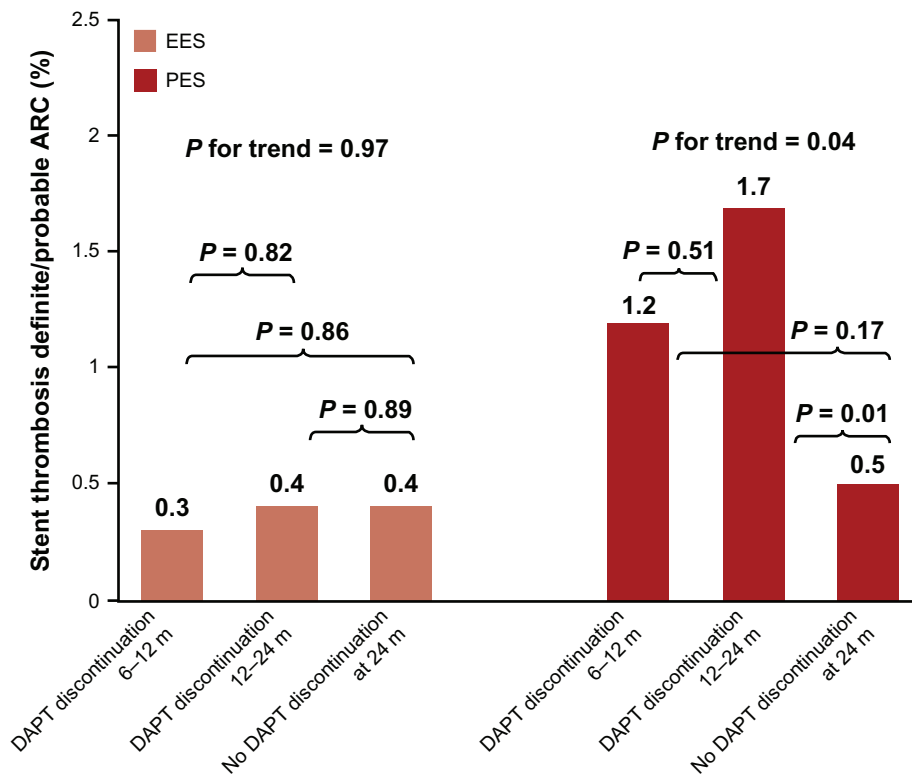


Figure 7. Bar graphs showing rates of definite and probable ARC stent thrombosis pooled from four randomized trials of everolimus-eluting stents vs. paclitaxel-eluting stents.

Adapted from: EuroIntervention 8(5), Kedhi et al, Stent thrombosis: Insights on outcomes, predictors and impact of dual antiplatelet therapy interruption from the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE trials. 599–606, Copyright 2012, with permission from Europa Digital & Publishing.

with Endeavor™. Of note, the stent thrombosis rate at one year was not significantly different in the Promus Element™ group as compared with the overall DES group (0.2% vs. 0.5%; HR: 0.59; 95% CI: 0.25–1.40).²¹ Two additional registry studies (SPECIALIST and IRIS-ELEMENT) are currently either enrolling patients or have completed enrollment and should have preliminary results in the upcoming year. The RESOLUTE™ all comers trial was one of the first to compare a zotarolimus-eluting stent platform to the XIENCE V™ EES platform. This trial randomized 2,300 patients in a 1:1 fashion to the RESOLUTE™ stent of the XIENCE V™ EES platform. The trial included patients with acute MIs, chronic total occlusions, and diabetes. The overall baseline characteristics were well matched and enrollment was completed in just six months. At one year the individual clinical outcomes for the primary endpoint of TLF (cardiac death; $P = 0.61$, target vessel MI; $P = 0.92$, clinical TLR; $P = 0.50$) and the pre-specified subgroups (STEMI; $P = 0.17$ and multivessel; $P = 0.55$) were all similar.²² At 13 months, angiographic late loss favored the XIENCE V™ EES platform. Specifically, in-stent

late loss (millimeters) was 0.19 vs. 0.27 ($P = 0.08$) and in-segment late loss (millimeters) was 0.06 vs. 0.15 ($P = 0.04$). At one year both platforms demonstrated a low event rate for definite/probable stent thrombosis, 1.6% for the RESOLUTE™ and 0.7% for the XIENCE V™ EES platform ($P = 0.05$). The two-year follow-up for the RESOLUTE trial is now available. There continues to be no difference in the components of TLF (cardiac death; $P = 0.58$, target vessel MI; $P = 0.84$, clinical TLR; $P = 0.58$).²³ With regards to definite or probable stent thrombosis at two years, the RESOLUTE™ stent was 1.9% compared to 1.0% for the XIENCE V™ EES platform ($P = 0.08$). Very late stent thrombosis, defined as after 360 days, was 0.3% for both platforms.

Patient and Selected Lesion Subsets

Left main

Since the results of the Syntax trial,²⁴ wherein TAXUS EXPRESS™ stents were compared to coronary artery bypass grafting (CABG) and demonstrated equivalent outcomes in those patients with scores ≤ 32 , the opinion of left main stenting has evolved to the point



where it is considered an option in specific patient subsets. To further expand its role, the EXCEL study is currently enrolling 4,000 non-ACS patients with left main disease and a syntax score < 32 . These patients will be randomized to either PCI with XIENCE Prime™ stents or CABG; they will then be followed for up to five years. This study should provide important information concerning the optimal treatment for this patient subset.

Diabetics

Other high risk patients that should be mentioned in this setting are those with diabetes. These patients have emerged as a subgroup that may benefit from individual DES platforms. A subset meta-analysis of diabetics in the SPIRIT II and III trials demonstrated that in-stent late loss remained consistent (0.33 mm) in patients with and without diabetes who received TAXUS EXPRESS™ stents.²⁵ However, among diabetics treated with XIENCE V™ stents, in-stent late loss was 0.20 mm compared to 0.12 mm in non-diabetics. SPIRIT IV included a one year follow-up subset of diabetics looking at TLF. XIENCE V™ outperformed TAXUS™ in non-diabetics 3.1% vs. 6.7% (RR 0.47; 95% CI 0.32–0.68, $P \leq 0.0001$), but there was no significant difference in patients with diabetes 6.4% vs. 6.9% (RR 0.94; 95% CI 0.59–1.49, $P = 0.80$).¹⁷

Small vessel disease ≤ 2.5 mm

In-segment and in-stent late loss are always of concern when treating small vessel disease with stents. Pooled data from SPIRIT II and SPIRIT III demonstrated these outcomes were lower for the XIENCE V™ platform compared to the TAXUS EXPRESS™ platform; these findings mirrored the results in the overall patient cohort. When looking at clinical endpoints, there were decreases in stent thrombosis, MI, TLR, and MACE (51% reduction; P log rank = 0.03) in small vessels with the XIENCE V™ platform compared to the TAXUS EXPRESS™ platform.²⁵ Thus, the weight of these studies in subsets of patients treated in the SPIRIT family of trials or clinical trial with broad patient inclusions indicate that the XIENCE V™ EES retains an excellent efficacy and safety profile when used in patients and lesions commonly encountered in routine clinical practice.

Utilization and Cost Effectiveness of EES

Overall, PCI procedures in the US fell from 2004 onward due to several factors including concerns about safety of DESs and the benefits of elective PCI.²⁶ From 2005 to 2006, in the United States use of DES reached its peak at 86% of PCI procedures, and then declined to 65% from 2007 to 2008.^{27,28} By contrast, DES utilization as a percentage of total stent usage was 90% by 2008 in regions of Asia, eg, Japan, Korea and China, and has remained at similarly high levels.²⁹ As of 2013, global DES use has rebounded to 73% of total stent usage.³⁰ EES represents 60% and 70% of the global and US markets, respectively.³¹ The cost effectiveness of EES compared to PES was evaluated as part of the SPIRIT IV trial out to two years of follow-up.³² In the primary analysis using target vessel revascularization as the endpoint and costs calculated from the United States healthcare system, EES was an economically attractive strategy when compared to PES, with cost savings of \$273 per patient. Using bootstrap simulations, the authors also found that EES was economically dominant in 64.8% of simulations; the incremental cost effectiveness ratio remained $< \$50,000$ per QALY gained in 85.7% of simulations. These data support the concept that EES is an economically viable stent therapy in contemporary practice.

Bioresorbable Vascular Scaffold (BVS) Coronary Devices

The BVS EES system consists of a bioresorbable stent mounted on a Multilink™ Vision balloon system. The system has a bioresorbable polymer coating, including everolimus, allowing controlled release of the drug in a fashion similar to the XIENCE V™ permanent implant. The BVS stent itself is composed of a polylactic acid polymer. This material has been used in numerous medical applications and is fully resorbed without polymer or without the stent being left behind in the coronary vessel. The polylactic acid polymer of the stent undergoes hydrolysis via the Krebs cycle to lactic acid, and finally to its end products of carbon dioxide and water. The stent is resorbed 18–24 months after implantation. The first in-man experience with the BVS EES was evaluated in the ABSORB trial. This study included 30 patients with single discreet



de novo lesions and was designed to provide proof of concept that the bioresorbable vascular scaffold could be successfully deployed in patients and provide sustainable reduction in ischemia driven TLR. At 6, 12, and 24 months, there were no repeat revascularization procedures and only one non-Q wave MI suffered at the time of implant.³³ During the two year follow-up, there was no evidence of stent thrombosis, with dual antiplatelet therapy being required for at least three months and thereafter left to the discretion of the primary physician. However, the initial six month angiographic follow-up showed there was a 0.44 mm in-stent late loss due to slight recoil of the vessel and the stent site. This demonstration of less than excellent radial stent strength prompted manufacturing enhancement to reduce the unsupported scaffold areas along with a small change to the polymer. These changes resulted in a significant increase in radial stent strength. A new second generation BVS cohort B was created and the results of late loss were presented at Euro PCR 2010, and then published the following year.³⁴ Both cohorts outperformed the Vision BMS from SPIRIT I and the BVS cohort B. Furthermore, they appeared to parallel that of the permanent XIENCE V™ EES implant, suggesting the modifications to the BVS system had achieved the goal of providing less recoil and a result comparable to the permanent implant. It is anticipated that a randomized clinical trial evaluating a comparison of clinical outcomes with the BVS and a permanent implant will begin enrolling within the next year.

Author Contributions

Conceived and designed the experiments: MGW, RJA. Analyzed the data: MGW, RJA. Wrote the first draft of the manuscript: MGW, RJA. Contributed to the writing of the manuscript: MGW, RJA. Agree with manuscript results and conclusions: MGW, RJA. Jointly developed the structure and arguments for the paper: MGW, RJA. Made critical revisions and approved final version: MGW, RJA. All authors reviewed and approved of the final manuscript.

Funding

Author(s) disclose no funding sources.

Competing Interests

RJA discloses remuneration from Abbott Vascular for board membership and consultancy, and grants made

to RJA's institution. MGW discloses no competing interests.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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