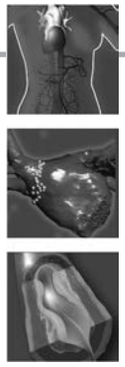

SPIRIT clinical trial program

Percutaneous coronary angioplasty started a revolution by providing a mechanical means of relieving angina. Abrupt vessel closure and restenosis emerged as its major limitations. Bare-metal stents dramatically reduced acute vessel closure, but restenosis, although significantly reduced, remained a clinical problem. Drug-eluting stents mitigated the problem of restenosis to a large extent. However, a small but significant increase in very-late stent thrombosis rates have been noted. Newer stents have been introduced in order to improve the efficacy and safety of stent implantation. The everolimus-eluting Xience V™ stent has been extensively evaluated in the SPIRIT clinical trial program. This article summarizes the various studies of this program and their impact on clinical practice.

KEYWORDS: in-stent late loss ■ SPIRIT clinical trial ■ SPIRIT registry ■ Taxus™ ■ Xience V™

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Coronary artery stenting has emerged as a major technique of coronary revascularization during the past decade. Drug-eluting stents (DESs) have significantly reduced the problem of restenosis inherent to bare-metal stents (BMSs), while their limitation relates to the increased risk of very-late stent thrombosis (ST) [1]. Improvement in the safety of DESs continues to be pursued through changes in platform stent design, development of safer polymers and administration of the appropriate drugs. Keeping these issues in mind, the second-generation DESs were developed. One of these stents that has extensive clinical research data is the Xience V™ (Abbot Vascular, CA, USA) everolimus-eluting stent. The First Use To Underscore Reduction in Restenosis With Everolimus (FUTURE) I and II trials were the first small randomized trials evaluating the feasibility of an everolimus-eluting stent in comparison with a BMS in coronary artery disease (CAD) and the preliminary data supported the safety of the everolimus-eluting stent with a bioabsorbable polymer [2–4]. The SPIRIT clinical trial program is the SPIRIT series of studies evaluating the Xience V stent for the treatment of CAD.

Xience V stent system

Xience V consists of the Multi-Link Vision™ coronary stent system, which is made from cobalt–chromium alloy [101]. It is a low profile stent with a strut thickness of only 81 µm. The drug is embedded in a biocompatible, durable fluorocarbon copolymer [5]. The copolymer elutes everolimus, an analog of rapamycin, at a dose of 100 µg/cm^2 in a controlled fashion, 80% in 1 month and the remainder within 4 months. The key improvement in design is its high flexibility and excellent deliverability. It was launched in Europe and Asia–Pacific in 2006 and received US FDA approval in July 2008 [6].

Xience Prime everolimus-eluting stent is the next modification of the Xience stent wherein the drug and the polymer are retained, but the stent design and delivery system are altered in order to improve flexibility and deliverability.

SPIRIT clinical trial program

This program is the major source of evidence behind the Xience V stent and includes 12 studies (randomized controlled trials as well as registries) (**Box 1 & Table 1**).

■ SPIRIT FIRST

This is the first-in-man study of Xience V [7]. The study examined the safety and efficacy of the Xience V stent compared with an identical Multi-Link Vision BMS. A total of 60 patients were enrolled in a prospective, randomized single-blind trial in nine European centers between December 2003 and April 2004. The patient population included patients with stable/unstable angina (excluding acute myocardial infarction [MI]) who had a single *de novo* coronary lesion (50–99% stenosis) and a vessel diameter of 3.0 mm that could be covered with a single 18 mm stent. Postprocedure dual

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Box 1. SPIRIT clinical trial program: randomized controlled trials and registries.

- SPIRIT FIRST (FIM; RCT, Xience V™ vs Multi-Link™ Vision)
- SPIRIT II (RCT, 3:1 Xience V vs Taxus™)
- SPIRIT III
  - RCT (2:1 Xience V vs Taxus)
  - 4.0 mm Xience stent registry
  - Xience V Japan registry
- SPIRIT IV (RCT, 2:1 Xience V vs Taxus)
- SPIRIT V
  - Diabetic study (RCT, 3:1 Xience V vs Taxus)
  - Registry (prospective, multicenter registry)
- Xience V SPIRIT Women
  - Registry (female-only multicenter study)
  - RCT (2:1 Xience V vs Cypher®)
- Registries
  - XIENCE V USA (postapproval, prospective, multicenter data)
  - XIENCE V INDIA (postapproval, prospective, multicenter data)
  - XIENCE V EXCEED (Xience V use in the catheterization laboratory)
  - Small-vessel IDE registry (2.25 mm Xience V use in small vessels)

FIM: First-in-man; IDE: Investigational device exemption; RCT: Randomized controlled trial.

antiplatelet therapy (DAT) was recommended for 3 months. Follow-up was clinical and angiographic. The primary end point was in-stent late lumen loss at 6 months (by quantitative coronary angiography). The results of this study showed that the mean in-stent late lumen loss was significantly lower in the Xience V group (0.1 vs 0.87 mm; $p < 0.001$). The 1-year major adverse cardiac event (MACE) rate was 15.4% in the Xience V arm and 21.4% in the BMS arm [8]. The MACEs included cardiac death, Q-wave or non-Q-wave MI and clinically driven surgical or percutaneous revascularization of the target lesion. In the Xience V arm, no additional death, MI, clinically driven target lesion revascularization (TLR) or clinically driven target vessel revascularization (TVR) events were observed between 1- and 5-year follow-up. No ST events were observed in the Xience V arm or the control arm after up to 5 years of follow-up (Table 2) [9].

■ SPIRIT II

After demonstrating the safety and efficacy of Xience V versus the BMS, the next step was to compare Xience V with an established first-generation DES.

The SPIRIT II trial evaluated Xience V in comparison with a paclitaxel-eluting stent (Taxus™ Express 2 or Liberté; Boston Scientific, MA, USA) [10]. A total of 300 patients were randomized in a prospective single-blind noninferiority study in a 3:1 ratio to the Xience V arm (n = 223) and the Taxus arm (n = 77). Patients included had ischemia-demonstrated CAD with one or maximum two *de novo* coronary lesions (50–99% stenosis) and a vessel diameter of 2.5–3.75 mm with lesion length less than 28 mm. All patients received at least 75 mg aspirin daily for a minimum of 1 year after the procedure. Clopidogrel was administered in a loading dose of 300 mg to all patients followed by a maintenance dose of 75 mg for at least 6 months. Follow-up angiography was performed at 6 months. A subset of 152 patients also underwent intravascular ultrasound (IVUS) and angiography at 6 months and 2 years. The primary end point was in-stent late loss at 180 days. Results demonstrated that the primary end point of in-stent late loss in a single lesion per patient at 6 months met the criteria for noninferiority (and also superiority) for the Xience V group compared with the Taxus group (0.11 mm for everolimus vs 0.36 mm for paclitaxel; $p < 0.001$ for both noninferiority and superiority). Clinical secondary end points in the SPIRIT II trial included ischemia-driven MACEs (death, MI or ischemia-driven TLR) and rates were nonsignificantly different at 27% (6/22) in the Xience V arm and 6.5% (5/77) in the Taxus arm. At 1-year follow-up, lower rates of MACEs were observed for Xience V compared with Taxus (2.7 vs 9.2%; $p = 0.04$) [11]. However, at 2-year follow-up, this difference of late loss was not statistically significant (0.33 mm for

Table 1. SPIRIT randomized controlled trials.

Study	Study population	Study groups	Design	Primary end point	Findings	Ref.
SPIRIT I	Low-risk Single *de novo* lesions	Xience V™ vs Multi-Link™ Vision	Prospective, multicenter RCT	In-stent LL at 6 months	LL in favor of Xience V ($p < 0.001$)	[7]
SPIRIT II	CAD patients with one or two lesions (non-ACS)	3:1 Xience V vs Taxus™	Prospective multicenter RCT	In-stent LL at 180 days	LL in favor of Xience V ($p < 0.0001$)	[10]
SPIRIT III	Similar to SPIRIT II	2:1 Xience V vs Taxus	Similar to SPIRIT II	In-segment LL at 8 months	Xience V superior to Taxus ($p < 0.001$)	[15]
SPIRIT IV	More complex population. Up to three lesions (non-ACS)	3:1 Xience V vs Taxus	Prospective, multicenter RCT	Composite TLF at 1 year	TLF in favor of Xience V ($p < 0.001$)	[23]

ACS: Acute coronary syndrome; CAD: Coronary artery disease; LL: Late loss; RCT: Randomized controlled trial; TLF: Target lesion failure.

Table 2. SPIRIT I 5-year clinical outcomes.

End points	Xience V™ arm (n = 27)	Multi-Link Vision™ arm (n = 29)
Late loss (6 months)	0.10 ± 0.23 mm	0.84 ± 0.36 mm
Late loss (12 months)	0.23 ± 0.29 mm	0.81 ± 0.44 mm
Cardiac death	0%	0%
MI	8.30%	0%
Stent thrombosis (protocol)	0%	0%
Stent thrombosis (ARC)	0%	0%
Ischemic TLR	8.30%	28%
Major adverse cardiac events	16.70%	28%

Both MIs were not device-related; one Q-wave MI was in a nontarget vessel and one non-Q-wave MI occurred during a follow-up intravascular ultrasound procedure.
ARC: Academic Research Consortium; MI: Myocardial infarction; TLR: Target lesion revascularization.

Xience V vs 0.34 for Taxus; p = 0.61) in the subset of patients with 2-year data [12]. In-stent percentage diameter of stenosis was lower in the Xience V group at 6 months (16 vs 21%; p < 0.001), but not at 2 years (19.2 vs 18.8%; p = 0.9). MACE at 2 years occurred in 6.6% of the Xience V group and 11.0% of the Taxus group (p = 0.31). The rate of ST at 2 years was 0.9 and 1.4% in the two arms, respectively (p = nonsignificant). At 3-year follow-up, the incidence of MACEs was numerically lower with Xience V compared with the Taxus stent (7.2 vs 15.9%; p = 0.05) [13]. Target vessel failure (TVF; 11.8 vs 17.4%; p = 0.30), MI (3.6 vs 4.3%; p = 0.72), all-cause mortality (4.4 vs 9.6%; p = 0.14) and ST (1.0 vs 2.9%; p > 0.05) were similar between the two arms at the end of the 3 years. SPIRIT II 4-year outcome data have been reported (Table 3), showing a consistent reduction in end points as compared with Taxus [14].

Thus, the SPIRIT II trial showed that the early benefit of late loss noted with the Xience V was not observed at 2 years. At 3 years, the outcomes were numerically lower in the Xience V arm, although they did not reach statistical significance. However, the findings confirm that Xience V is noninferior to Taxus for late loss at 2 years and shows outcomes trend in favor of Xience V at 3 and 4 years.

■ SPIRIT III

Following the favorable results of SPIRIT FIRST and II trials in Europe, the pivotal SPIRIT III trial was started in the USA.

This was a larger randomized controlled study conducted in the USA and Japan involving 1002 patients of similar background to the patient population of SPIRIT II, comparing Xience V with Taxus in a 2:1 ratio [15]. The premise was that the everolimus-eluting stent will be similar or superior to the paclitaxel-eluting stent in reducing angiographic in-segment late loss. A subset of patients underwent repeat angiographic follow-up at 8 months (n = 564). Among the repeat angiographic cohort, a proportion of patients also underwent IVUS. As per protocol, patients received at least 80 mg aspirin daily indefinitely and 75 mg clopidogrel daily for a minimum of 6 months after the procedure. Left anterior descending artery was involved in 42% of patients. The primary end point of in-segment late lumen loss at 8 months was lower in the Xience V group than the Taxus group (0.14 vs 0.28 mm; p < 0.001 for noninferiority and p = 0.004 for superiority). In-segment binary restenosis was also lower (4.7% of the Xience V group and 8.9% of the Taxus group; p = 0.07). On IVUS, neointimal hyperplasia volume was 10.1 mm^3 in the Xience V group and 20.9 mm^3 in the Taxus group (p = 0.04). There was no difference in the major secondary end point of TVF at 9 months. However, Xience V did reduce the risk of MACEs at 9 months and 1 year compared with Taxus. ST rates were low and similar in the two groups. Subgroup analysis of diabetic patients revealed a 1-year MACE rate of 8.8% for diabetics undergoing Xience V implantation versus 4.3% for Taxus implantation. At 2-year follow-up, TLR, TVR and MACE were significantly lower in the Xience V group compared with the Taxus group [16]. Similar to the 2-year results, at 3 years, TVF, TLR and MACEs were all significantly lower in the Xience V group versus Taxus group [17]. The comparative 3-year data of SPIRIT II and III are shown in Table 4. In the subgroup of patient with diabetes mellitus, however, no difference in outcomes was observed between Xience V and Taxus. This study complements the SPIRIT II data and the patients will be followed for 5 years.

Table 3. SPIRIT II 4-year clinical outcomes.

End points	SPIRIT II	
	Xience V™ arm (%; n = 195)	*Taxus™ arm (%; n = 67)*
MACE†	7.7	16.4
Cardiac death	0.5	4.5
Myocardial infarction	3.6	7.5
QMI	0	0
NQMI	3.6	4.3
ID-TLR	5.1	10.4
Non ID-TLR	1.5	5.6
All TLR	5.9	12.7
Total stent thrombosis (ARC)	1	3

†Cardiac death, MI, ID-TLR by coronary artery bypass graft or percutaneous coronary intervention.
ARC: Academic Research Consortium; ID: Ischemia-driven; MACE: Major adverse coronary event; MI: Myocardial infarction; NQMI: Non-Q-wave myocardial infarction; QMI: Q-wave myocardial infarction; TLR: Target lesion revascularization.
Data taken from [14].

A *post hoc* gender subset analysis has been performed on SPIRIT III. Women in this trial had inherently higher MACE and TVF rates than men. At 1 year, rates of MACEs (11.1 vs 5.7%; p = 0.004) and TVF (13.7 vs 7.5%; p = 0.003) were higher in women compared with men. However, women with Xience V stents had significantly lower MACE (8.2 vs 16.1%; p = 0.04) and TVR (3.1 vs 8.9%; p = 0.03) compared with those treated with Taxus stents. Thus, women in general benefit by receiving Xience V compared with Taxus [18].

A pooled analysis of the 2-year clinical data from the SPIRIT II and III trials comparing the long-term outcomes of Xience V and Taxus has been recently published. Xience V reduces the rates of MI and TLR compared with Taxus, with lower overall TVF and MACE [19].

■ SPIRIT Small Vessel trial

This category includes a subgroup analysis of SPIRIT III patients with small vessel disease and an ongoing 250-patient multicenter US SPIRIT Small Vessel trial, examining the safety and effectiveness of 2.25 mm Xience V (for small coronary vessels).

In the SPIRIT III small vessel subgroup analysis (patients treated with a 2.5 mm stent system and an average reference vessel diameter of 2.36 mm), the following results were obtained: an observed 80% reduction in in-stent late loss compared with Taxus at 8 months (p = 0.011), an observed 74% reduction in MACEs compared with Taxus at 9 months (p = 0.017), an observed 68% reduction in the risk of TVF compared with Taxus at 9 months (p = 0.019) and an observed 90% reduction in TLR compared with Taxus at 9 months (p = 0.002) [20].

Table 4. SPIRIT II and SPIRIT III 3-year outcomes.

End points	SPIRIT II		SPIRIT III	
	Xience V™ arm (n = 195)	*Taxus™ arm (n = 69)*	*Xience V™ arm (n = 669)*	*Taxus™ arm (n = 333)*
MACE†	6.4	14.9	9.7	16.4
All death	4.4	9.6	2.6	4.1
Cardiac death	0.5	4.2	1.4	1.6
Noncardiac death	3.9	5.5		
MI	3.6	7.2	3.7	6.3
QMI	0	0		
NQMI	3.6	4.3		
ID-TLR	4.2	9.4	5.4	8.9
TVF‡			14.3	19.2
TLF§			8.9	14.4
Total stent thrombosis (protocol definition)			0.9	1.6
Total stent thrombosis (ARC)	0.9	2.8	1.2	1.6

†Cardiac death, MI or ID-TLR by coronary artery bypass graft or percutaneous coronary intervention.
‡Cardiac death, MI or ID-TVR; MACE = cardiac death, MI or ID-TLR.
§Cardiac death, target vessel MI or ID-TLR.
ARC: Academic Research Consortium; ID: Ischemia-driven; MACE: Major adverse coronary event; MI: Myocardial infarction; NQMI: Non-Q-wave myocardial infarction; QMI: Q-wave myocardial infarction; TLF: Target lesion failure; TLR: Target lesion revascularization; TVF: Target vessel failure.
Data taken from [13,17].

■ SPIRIT III 4.0 mm registry

This study evaluated the safety and efficacy of the Xience V 4.0-mm stent for the treatment of *de novo* native coronary artery lesions [21].

During enrollment in the SPIRIT III randomized trial, 69 patients with lesions less than 28 mm in length and reference vessel diameter of 3.75–4.25 mm were enrolled and treated with the 4.0-mm diameter Xience V. The primary end point was 8-month in-segment late loss. The 4-mm Xience group was compared with the Taxus 8-month angiographic follow-up cohort of the SPIRIT III trial (188 patients). In-segment late loss was 0.17 ± 0.38 mm in the 4.0-mm Xience V registry compared with 0.28 ± 0.48 mm in the Taxus arm ($p < 0.0001$ for noninferiority). The 1-year rates of ischemia-driven TVF (cardiac death, MI or TVR) and MACEs (cardiac death, MI or TLR) were numerically, but not statistically, lower in the Xience V 4.0-mm patients compared with the randomized Taxus patients (5.9 vs 11.3%; $p = 0.27$, and 5.9 vs 10.3%; $p = 0.36$, respectively). There was no difference in 8-month late loss or 1-year TVF or MACEs between the 4.0-mm Xience V and randomized Xience V patients in the SPIRIT III Trial. In large coronary arteries, the 4.0-mm Xience V results in low rates of late loss (at 8 months) and adverse clinical events at 1 year.

■ SPIRIT III Japan registry

The SPIRIT III Japan registry of 88 patients demonstrated similar angiographic and clinical results to the favorable outcomes from the SPIRIT III US trial (8% MACE rate and no cases of ST at 1 year) [22]. Xience V demonstrated consistent safety and effectiveness up to 2 years in Japan, comparable with US patients with no ST.

■ SPIRIT IV

Earlier SPIRIT trials (FIRST, II and III) demonstrated the safety and efficacy of the Xience V for the treatment of CAD, with the end point being angiographic late lumen loss.

SPIRIT IV is a large-scale trial seeking to compare clinical end points between Xience V and Taxus in a more complex patient population [23]. A total of 3687 patients were enrolled in this single-blind, prospective, multicenter US trial randomizing patients to Xience V or Taxus in a 2:1 fashion. DAT was prescribed by protocol for at least 1 year and compliance was monitored. Baseline characteristics were fairly similar between the two groups. Approximately 32% had diabetes, 21% had prior MI and 28% presented with unstable angina. Patients included had stable/unstable angina (excluding acute MI) with up to three *de novo* coronary lesions (maximum two lesions per vessel). The left anterior descending artery was involved in 40% of patients and 25% had multivessel CAD. The mean reference vessel diameter was 2.75 mm, mean lesion length was 14.7 mm and the mean stented length per lesion was 22 mm. The primary end point of this trial was target lesion failure (TLF) at 1 year (defined as cardiac death, target-vessel MI or ischemia-driven TLR). Patients will be followed for 5 years. Results of this trial showed that Xience V was superior to Taxus with respect to the primary end point (Figure 1), showing a significant 38%

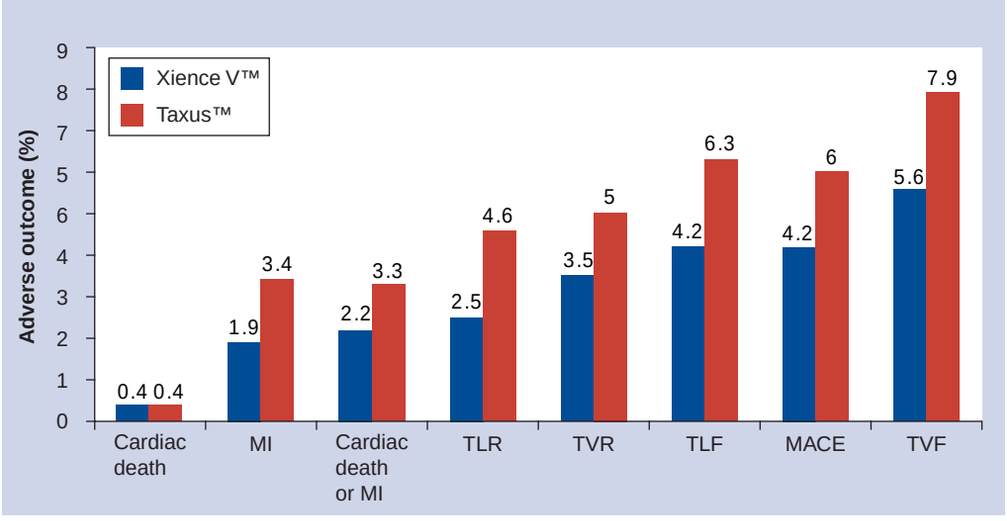

Figure 1. SPIRIT IV: 1-year outcomes.
MACE: Major adverse coronary event; MI: Myocardial infarction; TLF: Target lesion failure; TLR: Target lesion revascularization; TVF: Target vessel failure; TVR: Target vessel revascularization.

relative reduction in TLF in favor of Xience V (p = 0.001), mainly driven by a significant 45% relative reduction in the key secondary end point of ischemia-driven TLR (p = 0.001). A significant 73% reduction in ST at 1 year was observed in favor of Xience V (p = 0.004). In the subset of patients with diabetes, however, no difference in the clinical end points was noted between Xience V and Taxus. In the diabetic subgroup, the TVF rate was 6.4% in the Xience V group versus 6.9% in the Taxus group (relative risk [95% CI]: 0.94 [0.59–1.49]).

Similar results have been reported in the recently published Randomized Trial Comparing Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice (COMPARE; Xience V vs Taxus Liberté in a real-world all-comer population of 1800 patients, end points being all-cause mortality, MI and TLR within 12 months) [24]. The results of this study corroborate those of the SPIRIT IV trial: nonfatal MI: 2.8% (Xience V) versus 5.4% (Taxus; p = 0.007); TVR: 2.4 versus 6.0% (p = 0.0001); MACE at 1 year: 6.2 versus 9.1% (p = 0.023); and ST: 0.7% (Xience V) versus 2.6% (Taxus; p = 0.002), mainly due to a reduction in early ST.

■ SPIRIT V

SPIRIT V is an international postapproval study consisting of two concurrent studies, SPIRIT V diabetic study and SPIRIT V registry. SPIRIT V registry is a prospective, single-arm, multicenter registry evaluating the performance of Xience V in 2663 patients in real world settings, per its instructions of use. The registry includes CAD patients with demonstrated ischemia who were allowed up to four planned Xience V stents in *de novo* target lesions with a reference vessel diameter of 2.5–4.0 mm and a lesion length less than or equal to 28 mm. The enrolled patients included 30% with diabetes, 42% with multivessel CAD and 82% having highly complex lesions (lesion type B2 or C). Calcified lesions were seen in 29%, long lesions in 28% and small vessels in 35%. The primary end point of the study is a composite end point of all-death, MI and TVR at 30 days. The following results were obtained in this study [25].

The composite primary end point at 30 days occurred at a rate of 2.7%. At 1-year follow-up, TLR occurred at a rate of 1.8%, definite/probable ST. 0.75%, MACE rate (cardiac death, MI [target vessel] and TLR) at 5.1% and cardiac death rate at 1.1%. SPIRIT V 2-year results were presented at the EuroPCR 2010 [26]. MACEs occurred in 7.5%, cardiac death in 1.9%, MI in 4.4%, ST in 0.8% and TLR in 3.0%. These data suggest that Xience V is safe and effective in more complex patient and lesion subsets and the event rates are comparable with those of the more controlled SPIRIT II and III trials.

■ SPIRIT V diabetic study

Data were presented at EuroPCR 2010 on the SPIRIT V diabetic study [27], an international randomized clinical trial comparing Xience V with the Taxus Liberté in 324 patients with diabetes. In the trial's primary end point of in-stent late loss at 270 days, Xience V demonstrated superiority to Taxus (0.19 mm for Xience V vs 0.39 mm for Taxus; p < 0.0001). However, a trend of higher clinically indicated TLR was noted in the Xience V arm at 12 months (8.4 vs 3.8% for Taxus; p = 0.16). The study was not powered for clinical outcomes.

Xience V SPIRIT Women

It is an 'all comers' multicenter study of 2000 female patients conducted outside the USA. A total of 1550 female patients will be followed for 1 year in a single-arm registry assessing patient and disease characteristics specific to women as well as treatment outcomes (a composite end point of death, MI and TVR) including ST. In addition, 450 patients will participate in a randomized trial of Xience V versus Cypher® in a 2:1 ratio, with a 9-month end point of angiographic late loss. Results are pending.

Postapproval registries

■ Xience V USA

Xience V USA is a postapproval prospective, open-label, multicenter, single-arm registry of 5025 patients in the USA, designed to evaluate continued safety and efficacy of the Xience V in real-world settings and patients will be followed for 5 years. Primary outcome measures include ST levels per Academic Research Consortium (ARC) definition measured annually over 5 years and the composite end point of cardiac death and MI at 1 year. Compliance with DAT will also be evaluated. Data presented at the EuroPCR 2010 on Xience V USA demonstrated a low rate of ST at 1 year (0.84% per ARC definition). In less complex CAD ('standard risk'), the 1-year ST rate was 0.34% per ARC definition [28].

■ Xience V INDIA

This ongoing study is similar to Xience V USA involving 1000 patients in India with similar end points and follow-up.

■ Xience V EXCEED

This real-world study of 2488 patients looked at how catheterization laboratories and physicians are using the Xience V stent in real practice [29]. The study examined the performance of the stent during the procedure (i.e., stent deliverability, catheterization laboratories resource utilization, procedure times and procedural success). The primary end point of EXCEED was overall operator- or physician-determined deliverability and performance of the Xience V stent, assessed by a performance evaluation questionnaire. Physicians answered 13 questions immediately after the case was over, relating to details about how the stent performed during the case. In addition, procedural success was also indicated by the physician if the lesions treated had a final stenosis of less than 50% without any major complications during the procedure. EXCEED looked at all comers and had virtually no exclusion criteria. The acute procedural success rate was 99.3%, with no differences observed among patient subgroups. In addition, in 99.2% of cases, the operators rated the acute performance and deliverability as 'excellent' when compared with first-generation DESs. Also of importance, the in-laboratory rate of serious adverse events was only 0.8%. Data were then compared with the American College of Cardiology National Cardiovascular Data Registry (NCDR) database (NCDR data from the same time period that the EXCEED trial was taking place). A 30% reduction in the amount of contrast used in the EXCEED cohort and a 26% reduction in fluoroscopy exposure time in the patients receiving the Xience V stent in EXCEED was observed compared with those that were obtained by a first-generation DES.

Impact of SPIRIT clinical trial program

First-generation DESs, in comparison with BMSs, succeeded in reducing restenosis and the need for TLR but were found more likely than BMS to be associated with very-late ST. The extensive integrated data from the SPIRIT program of trials and registries have demonstrated the improved safety and efficacy of Xience V compared with first-generation DESs (mainly Taxus).

Efficacy of Xience V

The SPIRIT FIRST study demonstrated the clinical safety and efficacy of the Xience V in comparison with BMSs at 5-year follow-up. SPIRIT II and SPIRIT III involved the randomized comparison of Xience V with Taxus in patients with a maximum of two *de novo* coronary artery lesions. In both studies, there was a significant reduction MACEs with Xience V compared with Taxus at 12-month follow-up, and at 3-year follow-up of SPIRIT II, the favorable clinical outcomes of Xience V continued, consistent with the results from earlier studies with shorter follow-up. SPIRIT III complemented the SPIRIT II data, demonstrating a reduction in late-lumen loss with the Xience V stent compared with Taxus in a low-risk, elective percutaneous coronary intervention population.

The SPIRIT IV trial indicated that revascularization of CAD with Xience V is superior to that with Taxus in reducing TLF, MI and ST at 1 year. The 1-year clinical results in the SPIRIT V registry show that the use of the Xience V stent in complex lesions in a real-world population results in 1 year MACE, ST and TLR rates that are comparable with those of the more controlled SPIRIT II and SPIRIT III trials.

The reasons for improved outcomes with Xience V could be several fold. A more flexible stent frame, a more efficacious drug or a thinner biocompatible polymer could account for its superiority compared with Taxus [30].

One of the limitations of the SPIRIT program is the lack of comparison with the Cypher stent. Despite better results with Cypher and higher late loss with Taxus, the sponsors chose Taxus as a comparator in the SPIRIT trials. Indirect data suggest that Xience V is comparable with the Cypher [31]. The Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting (EXCELLENT) trial [32] will prospectively enroll 1400 patients and compare Xience with Cypher.

The Zotarolimus-Eluting Stent From Medtronic (RESOLUTE) 'all-comers' trial has recently been published [33]. This trial is a multi-center, open-label, noninferiority, randomized controlled trial comparing the efficacy and safety of Resolute™ (Medtronic, MN, USA) zotarolimus-eluting stent with Xience V in 2292 'real-world' patients (chronic stable angina or ACS including MI with or without ST elevation). As the trial was an all-comers study, the use of stents was unrestricted, with minimum patient exclusion (66.3% stent use off-label). Aspirin was to be taken indefinitely and clopidogrel was prescribed for a minimum of 6 months after the procedure. All patients received a SYNTAX score [34] at baseline. The primary end point of TLF (cardiac death, MI or clinically-indicated TLR) at 12 months was similar in the two stent groups (8.2% for Resolute vs 8.3% for Xience V; $p < 0.001$ for noninferiority). The ST rate was 2.3% for Resolute and 1.5% for Xience V ($p = 0.17$). This study finds Resolute and Xience V similar in terms of safety and effectiveness in 'real-world' patients.

Xience V in diabetic patients

Outcomes in diabetic patients are not improved by Xience V compared with Taxus. Perhaps the mechanisms of restenosis or the vascular response to limus drugs differ in diabetic patients compared with nondiabetic patients.

■ Safety

The SPIRIT studies were not powered to detect differences in rare events such as ST but mortality was similar and MI rates similar or lower in the Xience V group compared with Taxus. The low rates of late and very-late ST with Xience V are encouraging.

In the X-SEARCH registry [35], patients treated with Xience V had a higher risk profile and had more complicated lesions compared with patients treated in the past with BMS, Cypher and Taxus. At 6 months, after adjustment, Xience V was superior to BMS for TVR and MACEs and had similar clinical outcomes to Cypher and was more effective than Taxus. Similar to the SPIRIT trials, Taxus had a higher risk of MACEs compared with Xience V, extending the findings to a high-risk, all-comers population.

Conclusion

The results of the SPIRIT family of trials published to date suggest both improved safety and efficacy of the Xience V compared with both the Multi-Link Vision BMS and the Taxus. Trials in the future need to compare it with the third-generation stents with bioabsorbable polymers like Biomatrix®. Outcomes in diabetics are not improved by Xience V compared with Taxus. Overall, the favorable data of Xience V have made it a global stent market leader.

Future perspective

The antirestenotic superiority of DES across the spectrum of CAD patients stands well established. The current concerns with DES relate mainly to the risk of ST and delayed endothelialization. Manufacturers are continuously striving to improve the safety of DES without compromising efficacy. The drug, polymer and platform are all targets for modification.

Ongoing or planned studies of Xience V are examining the performance of this stent in complex subsets of patients such as multivessel disease, saphenous vein graft lesions or bifurcation disease. Some of the ongoing or planned studies are listed in Table 5.

The concept of vascular restoration therapy at present appears very attractive and promising and has been termed the fourth revolution in interventional cardiology (after balloon angioplasty, BMS and DES) [36]. The key to this concept is the fully bioabsorbable stent (e.g., the bioresorbable vascular scaffold stent: Abbott Laboratories). A couple of years after implantation, the fully biodegradable stent gets absorbed and integrated into the vessel wall. The vessel positively remodels and the endothelial structure and function are restored. Perhaps this is the future of percutaneous coronary intervention [37].

Table 5. Some ongoing and planned clinical studies with Xience V™.

Study	DES compared	End points	Patients (n)
SERIES III RUN-IN	Supralimus vs Xience V™	9 months LL	360
EXCELLENT	Xience V vs Cypher®	9 months LL	1372
LONG-DES-III	Sirolimus vs Xience V	9 months LL	500
STACCATO	Xience V vs Biomatrix®	9 months LL	60
ZEPPELIN	ZES Resolute and Xience V	6–8 months LL	2600
COVER OCT-II	ZES Resolute and Xience V	OCT at 3 months	40
PLATINUM Trial	Promus™ Element™ vs Xience V/Promus	Clinical FU	1728
TWENTE	ZES Resolute vs Xience V	Clinical FU	1380
LEFT-MAIN-2	Xience V and ZES Resolute	Clinical FU	600
ISAR-TEST6	Nobori® vs Xience V	Clinical FU	2010
ROBUST	Xience V vs Biomatrix	Clinical FU	400
BASKET-PROVE-II	Prokinetic Energy™ vs Nobori vs Xience V	Clinical FU	2400
RESOLUTE AC	Endeavour® Resolute vs Xience V	Clinical FU	2300
BASE-ACS	Bioactive stent vs Xience V	Clinical FU	1050
TEST-6-OCT	Nobori vs Xience V	OCT at 3 months	45

DES: Drug-eluting stent; FU: Follow-up; LL: Late loss; OCT: Optical coherence tomography.

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Executive summary

Background

- The SPIRIT clinical trial program consists of a number of randomized controlled trials as well as registries evaluating the Xience V™ stent system for the treatment of coronary artery disease.

Xience V

- Xience V stent system is based on the Multi-link Vision™ stent. It is made of cobalt–chromium alloy with very thin struts that allow it high flexibility and deliverability.
- The stent is embedded in a durable fluorocarbon copolymer that elutes the antiproliferative drug, everolimus.
- Xience V Prime is the next modification of the Xience V stent system. The polymer and the drug are the same, but the stent design has been modified for further improvement in flexibility and deployment.

SPIRIT clinical trials

- SPIRIT FIRST is the first-in-man randomized controlled trial of Xience V (n = 60). It showed that the primary end point (mean in-stent late loss) was significantly lower in the Xience V group compared with Multi-link Vision group, and Xience V was safer than the bare-metal stent.
- At 5-year follow-up, no additional major adverse cardiac events have been reported in the Xience group.
- The SPIRIT II, SPIRIT III and SPIRIT IV are randomized controlled trials directly comparing the second-generation stent Xience V with the first-generation paclitaxel-eluting stent, Taxus™.
- The SPIRIT II trial (n = 300) demonstrated not only noninferiority but also superior in-stent late loss at 6 months with the Xience V stent compared with Taxus.
- The SPIRIT III trial (n = 1002) demonstrated a significant reduction in the primary angiographic end point of in-segment late loss with Xience V stent compared with Taxus at 8 months and noninferiority to Taxus for the clinical end point of target vessel failure at 1 year, and resulted in a significant reduction in major adverse cardiac events.
- The SPIRIT IV is a large-scale randomized controlled trial (n = 3687) that compared the Xience V stent with Taxus in a more complex patient population without routine angiographic follow-up. The primary end point was target lesion failure rate at 1 year.
- Xience V was found to be superior to Taxus with respect to the primary end point as well as the secondary end point, of 1 year target lesion revascularization rate.

Diabetes & Xience V

- Patients with diabetes have not been shown to achieve significant reduction in composite outcomes with Xience V compared with paclitaxel-eluting Taxus. This has been seen in SPIRIT IV and the diabetic subgroups of SPIRIT III and the COMPARE trials.
- The SPIRIT V diabetic study is a prospective randomized controlled trial comparing Xience V with Taxus Liberte (n = 300) and showed a significantly lower late loss with Xiance V.

SPIRIT registries

- The SPIRIT V registry evaluated a more complex and global population of patients with coronary artery disease (n = 2663). A primary end point (composite of all-cause death, myocardial infarction and target vessel revascularization) at 30 days occurred at the rate of 2.7%. The 1-year results show the maintainance of the safety and efficacy data in more complex patient and lesion subsets.
- The Xience V SPIRIT Women is the first clinical study to evaluate women for the safety and efficacy of drug-eluting stents (n = 2000).
- The Xience V INDIA and Xience V USA are postapproval registries and are ongoing and evaluating Xience V for safety and efficacy in real-world settings.

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