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REVIEW

Update on the everolimus-eluting coronary stent system: results and implications from the SPIRIT clinical trial program

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Abstract: Drug-eluting stents (DES) have had a major impact in interventional cardiology. Compared to bare metal stents, they significantly reduce restenosis and the need for target vessel revascularization. Four DES are available in the US, the first-generation sirolimus-eluting (Cypher®) and paclitaxel-eluting (Taxus®) stents and later approved second-generation everolimus-eluting (Xience V®) and zotarolimus-eluting (Endeavor®) stents. The Xience V stent was approved on the basis of clinical efficacy and safety data from 3 studies in the SPIRIT clinical trial program. Within this trial series, the Xience V was superior to its bare metal stent counterpart, the Vision® stent, and noninferior to the paclitaxel-eluting stent for target vessel failure at 9 months. This review provides a comprehensive assessment of the data derived from both the pre- and post-approval randomized controlled trials and registry studies of Xience V that comprise the SPIRIT clinical trial program including recently published mid-term outcomes. The implications of the results in terms of interventional practice will be discussed.

Keywords: cobalt-chromium, drug-eluting stent, everolimus, percutaneous coronary intervention, Xience V

Introduction

Stenting is the default strategy in percutaneous coronary interventions due to superiority over balloon angioplasty in acute technical success and the subsequent need for target vessel revascularization. There are currently two broad categories of stents available: bare metal (BMS) and drug-eluting (DES). Bare-metal stents prevent coronary artery elastic recoil but restenosis may occur due to intimal hyperplasia. Drug-eluting stents are associated with a marked reduction in restenosis and target vessel revascularization compared to BMS.[1,2] After the US approval of the first two DES, the sirolimus-eluting stent (Cypher®) in 2003 and paclitaxel-eluting stent (Taxus®) in 2004, concern was raised about the safety of the devices due to the occurrence of late and very late stent thrombosis. Pooled analyses of available randomized trails at the time, however, showed similar rates of death and myocardial infarction in patients treated with one of these DES compared to the BMS counterpart in randomized clinical trials.[3] Registry studies also supported the safety of DES in unselected patients and off-label type lesions.[4,5] Nonetheless, knowledge of delayed healing in DES and concern for stent thrombosis led to the recommendation to increase the duration of dual anti-platelet therapy with aspirin and clopidogrel in patients treated with a DES to 12 months.[6] The sirolimus-eluting and paclitaxel-eluting DES are often referred to as the first-generation DES.

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More recently, two additional DES were approved in the US, the everolimus-eluting stent (Xience V®) in 2007 and the zotarolimus-eluting stent (Endeavor®) in 2008. These two newer DES have similar basic components to the initially approved DES, with a stent platform, polymer and anti-restenotic drug. Due to advances in stent platforms, delivery systems and polymer biocompatibility coupled with the later time of approval, they are referred to as second-generation DES. These DES are designed from a cobalt–chromium alloy and are thinner and more flexible than the first-generation DES. In addition to advantages in deliverability, the second-generation DES may have superior long-term safety with similar or greater clinical efficacy. More head-to-head randomized controlled trials are needed, however, before conclusions can be made. The purpose of this review is to highlight the stent design and clinical trials that led to the approval of the everolimus-eluting stent, herein referred to as Xience V, and to provide a comprehensive update on the status of the SPIRIT clinical trial program. The timing of this review coincides with the release of mid-term study outcomes and the results will be discussed in relation to stent selection and patient outcomes.

Xience V stent design

The Xience V® Everolimus Eluting Coronary Stent System (Abbott Vascular, Santa Clara, CA, USA) is composed of a stent delivery system coated with a formulation containing the anti-restenotic drug everolimus embedded in a durable biocompatible polymer. The Xience V stent was approved by the US Food and Drug Administration (FDA) and launched in July 2008.[7] The rationale for the design and polymer selection of the Xience V was the subject of a recent review.[8] In brief, the stent is the MULTI-LINK VISION Coronary Stent System which is manufactured from a medical grade cobalt–chromium alloy. The stent has favorable characteristics such as a low profile and excellent deliverability that are due to a strut thickness of only 81 μm and an open cell non-linear link design. The stent delivery balloon is designed with a semi-compliant material (polyether block amide) with short tapers to prevent endothelial and vessel injury adjacent to the stented segment. The Xience V is contraindicated in patients with a hypersensitivity or adverse reaction to the components including: everolimus, cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers.

Everolimus is the active pharmaceutical ingredient in the Xience V stent. It is a semi-synthetic macrolide immunosuppressant drug, synthesized by chemical modification of rapamycin (sirolimus). Everolimus is a proliferation signal inhibitor that acts on several cell types including vascular smooth muscle cells. The antiproliferative properties of the drug inhibit in-stent neointimal growth in experimental models and coronary vessels following stent implantation.[9,10] At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 rapamycin associated protein) also known as mTOR (mammalian target of rapamycin), leading to inhibition of cell metabolism, growth, and proliferation by arresting growth at the G1 stage.[11] Everolimus is highly lipophilic, potent, and rapidly absorbed into tissue making it a desirable drug for intravascular delivery.

The Xience V stent contains the nonerodable polymer ingredients poly (n-butyl methacrylate) (PBMA), a polymer that adheres to the stent and drug coating (primer layer), and vinylidine fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus (reservoir layer). The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA-coated stent surface. The drug load is 100 μg/cm^2 for all stent sizes, for a nominal everolimus content of 37 to 181 μg depending on the stent size. No topcoat layer is used. The copolymer elutes everolimus in a controlled fashion, 80% in 1 month and the remainder within 4 months.

Clinical studies

Safety and effectiveness data on the Xience V everolimus eluting stent (EES) is derived primarily from the SPIRIT Clinical Trial Program, which consists of 12 studies and will evaluate more than 18,000 patients. The initial studies, prior to FDA approval, were SPIRIT FIRST, SPIRIT II, and SPIRIT III. The SPIRIT III trials included three studies: the SPIRIT III randomized controlled trial versus Taxus, a registry of the 4.0 mm Xience, and the Japan Registry. The post-approval trials are in various stages of completion and include: SPIRIT IV, SPIRIT V, XIENCE V SPIRIT WOMEN, and post- approval registries XIENCE V USA, India, and EXCEED, and the small vessel investigational device exemption registry. For the purposes of this review, we will describe the most recent data publicly available regarding each of the SPIRIT trials as of the time of this writing. Additional selected studies, including COMPARE trial, will also be discussed. A summary of the randomized trials with primary endpoint data available is presented in Table 1.

Table 1 Randomized clinical trials of the Xience V everolimus eluting stent

Study (reference)	Design	Primary endpoint	Results
SPIRIT I N = 60[12]	Prospective, multicenter RCT versus Vision bare metal stent	In-stent LL at 6 months	In-stent LL was significantly lower in the Xience group versus Vision (0.10 mm versus 0.87 mm, $P < 0.001$)
SPIRIT II N = 300[15]	Prospective, multicenter RCT versus Taxus PES	In-stent LL at 180 days	In-stent LL was significantly lower in the Xience arm versus Taxus (0.11 ± 0.27 mm versus 0.36 ± 0.39 mm, $P < 0.0001$)
SPIRIT III N = 1002[19]	Prospective, multicenter RCT versus Taxus PES	In-segment LL at 8 months	In-segment LL was lower in the Xience V group versus Taxus (0.14 mm versus 0.28 mm, $P < 0.001$ for noninferiority and $P = 0.004$ for superiority)
SPIRIT IV N = 3687*	Prospective, multicenter RCT versus Taxus PES	Ischemia-driven target vessel failure (cardiac death, target vessel MI, ischemia driven TLR) at 1 year	Target lesion failure was significantly lower in the Xience V arm versus Taxus (4.2% versus 6.8%, HR 0.62, 95% CI 0.46–0.82, $P = 0.001$ for superiority)
COMPARE trial N = 1800**	Prospective, single-center, RCT versus Taxus PES in unselected patients	Death, MI and target vessel revascularization at 12 months	Primary endpoint was significantly lower in the Xience group versus Taxus (6.2% versus 9.1%, RR 0.69 0.5–0.95, $P = 0.023$)

*1-year results were presented by Dr Gregg Stone at the Transcatheter Cardiovascular Therapeutics Meeting (September 2009, San Francisco, CA).
**1-year results were presented by Dr Peter C. Smits at the Transcatheter Cardiovascular Therapeutics Meeting (September 2009, San Francisco, CA).
Abbreviations: CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk; LL, late loss; PES, paclitaxel-eluting stent; MI, myocardial infarction; TLR, target lesion revascularization.

SPIRIT FIRST

The successful use of the Xience V EES was initially reported in the SPIRIT FIRST trial. This prospective, single-blinded, randomized, multicenter trial conducted in European evaluated the safety and efficacy of the Xience V versus an identical Multi-Link Vision bare metal stent in the treatment of patients with a single de novo coronary artery stenosis of ≥50% and <100% and a vessel diameter of 3.0 mm as assessed by on-line quantitative coronary angiography that could be covered by a single 18 mm stent. Dual antiplatelet therapy was recommended for three months. The primary endpoint of the study was in-stent late lumen loss at 6 months by quantitative coronary angiography. Sixty patients were randomized and at 2-year follow-up, clinical data were available in 96% and 97% of patients in the everolimus and control arm, respectively. Four patients were excluded due to protocol violations and 2 patients withdrew consent. The mean in-stent late loss was significantly lower in the everolimus group (0.10 mm versus 0.87 mm, $P < 0.001$) as was neointimal hyperplasia as assessed by intravascular ultrasound (IVUS).[12]

The SPIRIT FIRST trial was not powered for clinical endpoints; however, the 1-year major adverse cardiac event (MACE) rate was 15.4% in the everolimus arm and 21.4% in the bare stent arm.[13] At 2 years the MACE rate for the everolimus arm remained 15.4%, but 2 patients in the control arm had target lesion revascularization for an overall MACE rate of 25.0%.[14] Under the Dublin/Academic Research Consortium (ARC) definition of late stent thrombosis, there were zero late stent thromboses in the Xience V arm of the SPIRIT FIRST Trial up to 3 years of clinical follow-up. Unpublished 5-year follow-up data from SPIRIT FIRST presented by Eberhard Grube, MD at EuroPCR May 21, 2009 indicate no additional MACE since 1-year follow-up in the Xience V group. Data from this trial and extended follow-up confirm the safety and efficacy of Xience V EES compared to the BMS platform.

SPIRIT II

SPIRIT II is a 300-patient randomized, single-blind, prospective clinical trial evaluating the Xience V EES versus the Taxus Paclitaxel-Eluting Coronary Stent System (TAXUS EXPRESS2 or Liberté, Boston Scientific, Nadic, MA) (PES) in Europe and Asia Pacific. Patients with de novo coronary artery lesions of 50% to 99% stenosis and demonstrated ischemia were randomized 3 to 1 to receive either the Xience V (n = 223) or a Taxus (n = 77) stent. The primary endpoint of SPIRIT II was in-stent late loss at 180 days. Percentage in-stent volume obstruction was obtained by IVUS in a subset of 152 patients, who also underwent serial angiographic follow-up at 6 months and 2 years. At 6 months, the in-stent late loss was significantly lower in the Xience V

arm compared to the Taxus arm (0.11 ± 0.27 mm versus 0.36 ± 0.39 mm, $P < 0.0001$). Percentage volume obstruction in the Xience V arm was also significantly lower. Thus, Xience V met the primary endpoint and was found to be superior to Taxus with respect to late loss. Clinical secondary endpoints in SPIRIT II included ischemia driven MACE and rates were non-significantly different at 2.7% (6/222) in the Xience V arm and 6.5% (5/77) in the Taxus arm.[15] Although not a primary endpoint, 1-year clinical follow-up results demonstrated lower rates of MACE for Xience V compared to Taxus (2.7% versus 9.2%, $P = 0.04$). As defined in SPIRIT II, the MACE rate included death, myocardial infarction (MI) or clinically driven target lesion revascularizations. Under the ARC definition, the late-stent thrombosis rate up to 1 year was 0% with Xience V and 1.3% for Taxus.[16] In a post-hoc analysis of SPIRIT II angiographic outcomes in high-risk patients including those with diabetes, left anterior descending artery lesions, lesions longer that >20 mm, vessels smaller than <3.0 mm and type B2 and C lesions, the in-stent late loss results were consistent with the findings in the overall SPIRIT II trial population.[17] In all, the primary outcome and 1-year clinical data favored Xience V.

Recently, 2-year clinical, angiographic, and IVUS follow-up of patients in the SPIRIT II trial was published.[18] After 2 years, target lesion failure defined as cardiac death, MI, and ischemia-driven target lesion revascularization rates were numerically but not statistically lower at 6.6% in the Xience V group and 11% in the Taxus group respectively ($P = 0.31$). Additionally, in the 115 patients with serial angiography, the initial 6-month benefit of Xience V over Taxus in terms of in-stent late loss (Xience V 0.33 ± 0.37 mm versus Taxus 0.34 ± 0.34 mm, $P = 0.84$) and percent volume obstruction (5.18 ± 6.22% versus 5.80 ± 6.31%, $P = 0.65$) was lost at 2 years. The incidence of stent thrombosis was low and similar in both groups (Xience V 0.9%, Taxus 1.4%). Therefore, at two-year follow-up in SPIRIT II, there were no significant differences between Xience V and Taxus in clinical, angiographic, and IVUS outcomes. The findings confirm, however, that Xience V is noninferior to Taxus for late loss at 2 years.

SPIRIT III

SPIRIT III is a randomized clinical trial comparing the Xience V to the Taxus stent system in 1,002 patients in the United States and Japan. Patients were randomized 2:1 to Xience V (n = 669) or Taxus (n = 333). A subset of patients underwent repeat angiographic follow-up at 8 months (n = 564), some of whom also had IVUS. Lesion location was the left anterior descending in 42% of patients. The baseline angiographic characteristics were well matched in terms of reference vessel diameter, lesion length, and the mean number of stents per patient. The primary endpoint of in-segment late lumen loss at 8 months was lower in the Xience V group than the Taxus group (0.14 mm versus 0.28 mm, $P < 0.001$ for noninferiority and $P = 0.004$ for superiority). In-segment binary restenosis occurred in 4.7% of the EES group and 8.9% of the PES group ($P = 0.07$). On IVUS, neointimal hyperplasia volume was lower in the Xience V compared to the Taxus group (10.1 mm^3 versus 20.9 mm^3, $P = 0.04$). There was no difference in the major secondary endpoint of target vessel failure at 9 months (7.2% Xience V versus 9.0% Taxus; $P < 0.001$ for noninferiority and $P = 0.31$ for superiority). The Xience V did, however, reduce the risk of MACE at 9 months (4.6% versus 8.1%; relative risk, 0.56 [95% confidence interval (CI), 0.34 to 0.94]; $P = 0.03$) and 1 year compared to Taxus (6.0% versus 10.3%; relative risk, 0.58 [95% CI, 0.37 to 0.90]; $P = 0.02$), with fewer MIs and target lesion revascularizations. Stent thrombosis occurred in 0.8% of the Xience V group and 0.6% of the Taxus group ($P > 0.99$).[19]

In SPIRIT III at 2 years, the individual outcomes of cardiac death occurred in 1.1% and 1.3% ($P = 0.75$), MI in 3.3% and 5.9% ($P = 0.08$), target lesion revascularization occurred in 6.1% and 11.3% ($P = 0.006$), and target vessel failure occurred in 11.3% and 16.4% ($P = 0.04$), respectively for Xience V versus Taxus. MACE defined as cardiac death, MI, or target lesion revascularization occurred in 7.7% and 13.8% ($P = 0.005$), respectively for Xience V and Taxus. Cumulative stent thrombosis at 2 years occurred in 1.0% and 1.7% ($P = 0.35$), whereas very late thromboses (>1 to 2 years) occurred in 0.2% and 1.0% ($P = 0.10$), respectively, for Xience V and Taxus. Among 360 patients who discontinued dual antiplatelet therapy after 6 months there were numerically fewer stent thrombosis events in Xience V-treated patients compared to Taxus (0.4% versus 2.6%, $P = 0.10$).[20] A pooled analysis of the 2-year follow-up of SPIRIT II and III confirmed these findings.[21]

The three year SPIRIT III results were presented at the Transcatheter Cardiovascular Therapeutics Meeting (San Francisco, CA, September 2009) by Dr Gregg Stone and further support the Xience V EES. Similar to the 2-year results, target vessel failure, target lesion revascularization, and MACE were all significantly lower in the Xience V group

versus Taxus group. In the subgroup of patient with diabetes mellitus, however, no difference in outcomes was observed between Xience V and Taxus.

There were two small registries that enrolled concurrently with the SPIRIT III randomized trial, the SPIRIT III 4.0 Registry and SPIRIT Japan. The SPIRIT III 4.0 Registry consisted of 69 nonrandomized patients with lesions ≤28 mm in length and reference vessel diameter 3.75 to 4.25 mm treated with a 4.0 mm Xience V. In-segment late loss was 0.17 ± 0.38 mm and similar to the randomized Xience V cohort. In-segment binary angiographic restenosis at 240 days occurred in only 1 patient receiving a 4.0 mm Xience V (2.0%). Ischemia-driven target vessel failure at 1 year occurred 5.9% of patients in the 4.0 mm Xience V cohort. The SPIRIT III 4.0 Registry is one of the few studies evaluating outcomes for de novo lesions >3.75 mm in diameter treated with DES.[22] The SPIRIT III Japan is a prospective, multicenter, nonrandomized arm using EES in Japan. IVUS of 79 Japan patients at 8 months follow-up was compared to 115 Xience V and 45 Taxus patients in the randomized SPIRIT III trial. Significant suppression of neointimal hyperplasia in the Japanese population was observed demonstrating the effectiveness of the Xience V stent in this population.[23]

SPIRIT IV

SPIRIT IV is an ongoing, prospective, 3687-patient, post-approval trial evaluating the safety and efficacy of the Xience V stent system for the treatment of coronary artery disease in a more complex patient population. Similar to the SPIRIT II and III trials, this large-scale randomized trial will further assess the differences between the Xience V and Taxus platforms. The details of the trial design were recently published.[24] This single-blinded, randomized, multicenter US study will randomize patients with up to 3 *de novo* native coronary artery lesions, with a maximum of 2 lesions per vessel to Xience V or Taxus in a 2:1 fashion. The primary endpoint of the trial is ischemia-driven target vessel failure (cardiac death, target vessel MI, ischemia-driven TLR) at 1 year and patients will be followed out to 5 years. The trial is powered for sequential noninferiority and superiority testing. The absence of routine angiographic follow-up in this trial may allow a more accurate assessment of the absolute differences in the clinical safety and efficacy profile between Taxus and Xience V. The number of patients in the trial may also permit insights into the relative performance of the 2 stents in subgroups of patients including those with diabetes mellitus.

SPIRIT IV enrollment began in August 2006 and the 1-year results were presented by Dr Gregg Stone at the Transcatheter Cardiovascular Therapeutics Meeting (September 2009, San Francisco, CA); publication of results in the peer-reviewed medical literature is presently awaited. A total of 2458 were randomized to Xience V and 1229 to Taxus. Baseline characteristics were similar between the two groups, with a mean patient age of 63.3 years and 32% female. Approximately 32% of patients were diabetics, including 9% insulin-dependent. About 21% had prior myocardial infarction and 28% presented with unstable angina pectoris. The mean reference vessel diameter was 2.75 mm, lesion length 14.7 mm, and stented length per lesion was about 22 mm. The primary endpoint of target lesion failure was significantly lower in the Xience V arm compared with the Taxus arm (4.2% versus 6.8%, hazard ratio [HR] 0.62, 95% CI, 0.46 to 0.82, $P = 0.001$ for superiority). This was driven primarily by a significant reduction in ischemia-driven TLR (2.5% versus 4.6%, HR 0.55, 95% CI 0.38 to 0.78, $P = 0.001$). Cardiac death or target vessel MI were similar between the two arms (2.2% versus 3.2%, $P = 0.09$). All-cause mortality was similar (1.0% versus 1.3%, $P = 0.61$), but Xience was associated with a significant reduction in MI (1.9% versus 3.1%, $P = 0.05$). In addition, Xience was associated with a significant reduction in stent thrombosis at 1 year, as compared with Taxus (0.29% versus 1.06%, HR 0.27, 95% CI 0.11 to 0.67, $P = 0.003$). In the subset of patients with diabetes mellitus, however, no difference in MI, target lesion revascularization or the composite endpoints of MACE and target vessel failure was observed between Xience V and Taxus.

SPIRIT V

SPIRIT V is an international post-approval trial that will provide additional clinical experience with Xience V in approximately 2663 patients at approximately 100 sites clinical sites throughout Europe, Asia, Canada and Latin America. The SPIRIT V Clinical Evaluation consists of two concurrent studies, the Diabetic Study and the Registry. The SPIRIT V Diabetic Study is a prospective, randomized, active-controlled, single-blind, parallel two-arm multicenter study comparing the Xience V to the Taxus Liberté in the treatment of diabetic patients with coronary artery lesions, and the SPIRIT V Registry, a prospective, single arm, multicenter registry evaluating performance of the Xience V in real-world clinical settings, per its instruction for use. The trial is currently enrolling patients. Real-world clinical settings may include up to 4 planned Xience V stents in de novo target lesions with a reference diameter between

2.5 and 4 mm and a lesion length less than or equal to 28 mm. Enrolled patients will be followed for 5 years and clopidogrel is recommended for at least 3 months. Initial results were presented at the EuroPCR Meeting by Prof. Eberhard Grube (May 21, 2009, Barcelona, Spain). The 1-year rates of target lesion revascularization, definite/probable stent thrombosis, and MACE were 1.8%, 0.7%, and 5.1% respectively. The results suggest that Xience V is safe and effective in more complex patient and lesion subsets than were examined in the pre-approval trials.

XIENCE V SPIRIT WOMEN

The XIENCE V SPIRIT WOMEN trial will evaluate the characteristics of 2000 women undergoing stent implantation as well as the performance of Xience V in those patients in Europe, Asia-Pacific, Canada, and Latin America. The study, which is currently enrolling, will evaluate patient and disease characteristics specific to women as well as treatment outcomes such as rate of death, MI and target vessel revascularization and potential risk of stent thrombosis.

Additional post-approval registries and trials

XIENCE V USA is a 5000-patient, prospective, open-label, multicenter (108 sites in the US); observational, single-arm registry designed to evaluate continued safety and efficacy of the Xience V stent in real world settings, and will evaluate outcomes such as late stent thrombosis, death, MI and revascularization with follow-up out to 5 years. Primary outcome measures include: stent thrombosis rates as defined by ARC annually through 5 years and the composite endpoint of cardiac death and MI at 1 year. The study also will evaluate patient compliance with antiplatelet therapy. The study started in July 2008, with final data collection for the primary outcome measures expected in June 2009 (clinicaltrials.gov). Data from the XIENCE V USA Registry are presently awaited.

XIENCE V India is a 1000-patient, prospective, open-label, multicenter (16 sites in India), observational, single-arm registry to evaluate Xience V continued safety and effectiveness during commercial use in real world settings, with follow-up planned through 5 years. Primary outcome measures include: stent thrombosis rates as defined by ARC annually through 5 years and the composite endpoint of cardiac death and myocardial infarction at one year. XIENCE V India follow-up will document patient adherence and persistence with adjunctive antiplatelet drug therapy at several time points throughout the study. The study started in June 2008, is expected to be completed in June 2013, with final data collection for the primary outcomes expected to be completed in June 2010 (clinicaltrials.gov).

XIENCE V EXCEED (Evaluation of Xience V Catheterization Lab Endpoints and Excellence in Delivery) is a 2517-patient, observational, prospective, multicenter (44 sites in the US) cohort study designed to assess physician-determined Xience V acute performance, deliverability and resource utilization in the catheterization lab during commercial use by various physicians with a range of coronary stenting experience. The study started in October 2008, with estimated completion in March 2010, with final data collection for primary outcome in March 2009 and data are presently awaited (clinicaltrials.gov).

SPIRIT Small Vessel trial is designed to study the use of a 2.25 mm Xience V stent in 250 patients at approximately 50 centers in the United States. The primary endpoint is a composite measure of cardiac death, MI and TLR at one year.

COMPARE trial

The COMPARE trial is a physician-initiated, single center, prospective, randomized trial comparing the Taxus Liberte against the Xience V EES in an all-comer real-world population. The study enrolled 1800 patients and used a 1:1 randomization to Taxus Liberte (n = 903) or Xience V (n = 897) with the operator blinded to stent type. The 1-year results were presented by Dr Peter C. Smits at the Transcatheter Cardiovascular Therapeutics Meeting (September 2009, San Francisco, CA). The groups were well-matched relative to baseline variables and approximately 60% of patients presented with an acute coronary syndrome. The primary endpoint of death, MI and TVR at 12 months was observed in 9.1% of patients in the Taxus group and 6.2% in the Xience V group (relative risk 0.69 [0.5 to 0.95], $P = 0.023$). Secondary endpoints of MACE, ARC definite and probable stent thrombosis, and nonfatal MI were also statistically significantly lower the Xience V group. Longer follow-up is not yet available.

Next generation Xience

The XIENCE Prime EES System is the next generation Xience stent. The XIENCE Prime stent, currently an investigational device, uses the same drug and polymer as Xience V; however the stent design and delivery system have been modified to improve flexibility and deliverability. Similar to Xience V, the stent will be cobalt chromium and

the design based on the MULTI-LINK family of stents. The XIENCE Prime will be evaluated in the SPIRIT Prime study, a prospective, multicenter, nonrandomized trial of 500 patients at 75 hospital centers. SPIRIT Prime will have 2 arms: the Core arm will follow 400 patients who will be treated with a stent from 2.25 mm to 4.0 mm in diameter and from 8 mm to 28 mm in length, and the Long Lesion arm will follow 100 patients who will receive a stent from 2.5 mm to 4.0 mm in diameter and either 33 mm or 38 mm in length. The primary endpoint is MACE and TLR at one year. The recently announced EXCEL trial, a randomized trial of CABG versus DES in 2500 patients with left main disease, will also use the XIENCE Prime stent.

Clinical implications of the SPIRIT clinical trial program

The Xience V EES is a second-generation DES that is effective at inhibiting neointimal hyperplasia, with less late loss compared to its BMS equivalent the Vision stent. The stent has favorable characteristics such as a deliverable cobalt–chromium stent platform and the lipophilic antiproliferative drug everolimus, which is completely released from a durable reservoir polymer over several months. In the US, the Xience V was the third DES to be approved, after the first-generation Cypher and Taxus DES, and prior to the Endeavor DES. Each DES differs in stent platform, drug, and polymer, which may result in differences in stent performance in terms of efficacy in preventing intimal hyperplasia and safety from stent thrombosis due to delayed healing. Substantive comparative data, however, among the four DES are lacking.

The SPIRIT program evaluated Xience V compared to Taxus in a series of studies. In patients with simple lesions and low-risk profiles, the Xience V results in reduced late loss at 6 to 8 months and noninferior rates of 9-month target vessel failure compared to the Taxus. A catch up phenomenon, with similar rates of late loss at 2 years, however, was noted in subset of SPIRIT II patients that underwent serial angiography. Despite these findings, a reduction in clinical events was observed with Xience V in SPIRIT III, including significantly lower rates of target lesion revascularization and MACE. The benefits of EES may, to some degree, have been influenced by protocol driven routine angiographic follow-up. The preliminary results of SPRITI IV support the clinical benefits of Xience V compared to Taxus in higher-risk patient and lesion subsets; however, these benefits do not appear to extend to patients with diabetes mellitus. The findings of the COMPARE trial suggest an even greater benefit of Xience V compared to Taxus when used in unselected patients with potentially more complex lesion types than examined in the SPIRIT trials. Longer follow-up is needed to determine if the initial benefits seen with Xience V will persist.

In terms of safety, the SPIRIT studies were not powered to detect differences in rare events such as stent thrombosis, but mortality was similar and MI rates similar or lower in Xience compared to Taxus. Although the rates of stent thrombosis were numerically lower in the Xience V patients, the relative safety compared to Taxus in patients on or off dual anti-platelet therapy is not certain. The low rates of late and very late stent thrombosis with Xience are encouraging. Pre-clinical studies of stent healing suggest that endothelialization, a surrogate for stent thrombosis risk, is more rapid with Xience than the other 3 DES but that by 28 days strut coverage is similar.[25]

The Xience V Stent Evaluated at Rotterdam Cardiac Hospital (X-SEARCH) registry is a single-center registry of 649 consecutive patients treated with EES. Patients treated with EES were compared with patients who were treated in the past with BMS, SES (RESEARCH registry) and PES (T-SEARCH registry). In this registry, patients treated with EES were older; more often had MI, and had more complicated lesions compared to the other groups. At 6 months, after adjustment, EES was superior to BMS for target vessel revascularization and MACE, and had similar clinical outcomes to SES. Similar to the SPIRIT trials, PES had a higher risk of MACE compared to EES, extending the findings to a high risk, all-comers population.[26]

Currently, no randomized trials are comparing the Xience V to the other FDA-approved DES, the Cypher or Endeavor. The RESOLUTE-III trial was designed to compare the Endeavor-Resolute Zotarolimus-Eluting stent system with the XIENCE V EES system with respect to cardiac death, MI, and TLR at 1 year in a real-world patient population. The study started in April 2008 and is a prospective, multicenter, randomized, two-arm, international, noninferiority, open-label study with 2300 patients. The Principal Investigator is Dr Patrick Serruys and final data collection for the primary outcome measure is expected in May 2010 (clinicaltrials.gov). The clinical results of the Xience V versus the Cypher sirolimus-eluting stent were evaluated by means of an indirect comparison meta-analysis. Using this analytical method, the Xience V was found to be at least as effective as Cypher in preventing TLR ($P = 0.12$).[27] Whether this will hold true in a randomized study will be determined by future trials. The study design and

rationale for a randomized trial comparing the Xience V to the Cypher was recently published. The Efficacy of Xience/Promus versus Cypher in rEducing Late Loss after stENTing (EXCELLENT) trial will prospectively enroll 1,400 patients. In addition to comparing EES versus SES, using a 2 × 2 factorial design, this study will also address the issue of a 6- versus 12-month duration of dual antiplatelet therapy.[28]

Conclusions

In sum, the results of the SPIRIT family of trials published to date suggest both excellent safety, and improved efficacy of the Xience V EES compared to both the MULTI-LINK VISION bare metal stent and the Taxus PES. Indirect data suggest that the Xience V is comparable to the Cypher but final comments await the planned randomized trial. The RESOLUTE III study comparing the Xience V to the other second-generation DES, Endeavor, is eagerly awaited. Lastly, with rapidly evolving DES technology, second-generation DES including Xience V will need to be compared to stents such as the BioMatrix and Norobi. These third-generation devices combine a bioresorbable polymer with an analogue of sirolimus, Biolimus A9, and preliminary results evaluating the inhibition of neointimal tissue are favorable.

Disclosures

The authors declare no conflicts of interest.

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