JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 4, NO. 12, 2011

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2011.08.010

A New Era of Prospective Real-World Safety Evaluation

Primary Report of XIENCE V USA (XIENCE V Everolimus Eluting Coronary Stent System Condition-of-Approval Post-Market Study)

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Objectives The XIENCE V USA (XIENCE V Everolimus Eluting Coronary Stent System Condition-of-Approval Post-Market study) sought to: 1) evaluate the safety of everolimus-eluting coronary stent systems (EECSS) in a contemporary cohort of real-world subjects; and 2) prospectively test the quality of event reporting with analysis of matched patients from the randomized SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) trial.

Background Randomized trials have demonstrated the safety and efficacy of EECSS in selected "standard-risk" patients.

Methods The XIENCE V USA trial was a prospective, multicenter, single-arm study in unselected patients. The primary endpoint was Academic Research Consortium (ARC)-defined definite and probable stent thrombosis (ST); the co-primary endpoint was the composite of cardiac death and myocardial infarction at 1 year. Secondary analyses included: 1) stratification by standard-risk and extended-risk cohorts; and 2) late ST after dual antiplatelet therapy interruption.

Results Of 5,054 participants (1,875 standard-risk; 3,179 extended-risk), 4,958 (98.1%) reached 1-year follow-up. The rate of ARC-defined definite and probable ST was 0.84% (95% confidence interval [CI]: 0.60% to 1.14%) in the overall population and 0.33% (95% CI: 0.12% to 10.72%) and 1.14% (95% CI: 0.80% to 11.58%) in the standard-risk and extended-risk cohorts, respectively. No late ST was observed after dual antiplatelet therapy interruption in either cohort after 6 months. The composite rate of cardiac death and ARC-defined myocardial infarction was 6.5% (95% CI: 5.79% to 17.17%) in the overall population, 3.8% (95% CI: 2.98% to 14.78%) in the standard-risk cohort, and 8.0% (95% CI: 7.09% to 19.02%) in the extended-risk cohort.

Conclusions This study comprehensively reports ST rates for EECSS in a contemporary real-world population. The absence of ST after dual antiplatelet therapy interruption beyond 6 months in standard-risk and high-risk patients is notable. Consistent safety outcomes between matched standard-risk cohorts from the XIENCE V USA study and the SPIRIT IV randomized trial suggest that this study affords a reliable benchmark for understanding the safety of EECSS in the context of real-world clinical practice. (XIENCE V Everolimus Eluting Coronary Stent System [EECSS] USA Post-Approval Study; NCT00676520) (J Am Coll Cardiol Intv 2011;4:1298–309) © 2011 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) have proven to be highly effective at reducing restenosis rates in patients undergoing percutaneous coronary intervention (PCI). However, concerns have been raised as to whether these permanent cardiac implants might inhibit local vascular healing, resulting in rare but catastrophic complications, such as stent thrombosis (ST), myocardial infarction (MI), and death (1). Randomized clinical trials provide statistically robust comparisons of new DES with control devices and are the preferred study design for pre-approval evaluations. Logistical constraints on the size of such studies and the frequent use of prescriptive eligibility criteria might leave questions about the statistical certainty and generalizability of randomized study findings pertaining to rare safety issues in real-world practice. To address this issue, the U.S. Food and Drug Administration (FDA) has added large, rigorous, prospective, single-arm condition-of-approval studies to further inform the safety profiles of new DES platforms. The XIENCE V USA (XIENCE V Everolimus Eluting Coronary Stent System Condition-of-Approval Post-Market) study of everolimus-eluting coronary stent systems (EECSS) is the first such DES Condition-of-approval study to report its findings.

In the randomized SPIRIT II to IV trials (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions), the use of EECSS in highly selected or "standard-risk" patients showed reductions in late loss, target lesion revascularization, and major adverse cardiac events as well as significant reduction in ST when compared with paclitaxel-eluting stents (2–7). The XIENCE V USA study was prospectively designed as a rigorous, single-arm, condition-of-approval study to further inform the safety data available on this EECSS platform, including the generalizability of those data to a real-world mix of patients. To support comparisons and reliability assessments, the XIENCE V USA study adopted the definitions of patient descriptors, coronary anatomy, and clinical outcomes used in the SPIRIT studies.

Methods

Study design and patients. The XIENCE V USA study (IDE G050050) is a prospective, open-label, multicenter, observational, single-arm study designed to further inform the safety evaluation of EECSS during commercial use in real-world settings. Everolimus-eluting stents received FDA approval on July 2, 2008; study enrollment lasted from July 7, 2008 to December 8, 2008. With the interactive voice or Web response enrollment service (Covance, Princeton, New Jersey), 5,054 patients were consecutively enrolled from 162 sites in 37 states across the United States.

Consecutive patients who could provide written informed consent and were treated only with EECSS were included, on the basis of the FDA requirement to report safety specific to EECSS. There were no protocol exclusions on the basis of clinical descriptors or angiographic criteria. Use of non-everolimus-eluting stents was determined by the implanting clinician, and those patients were not included in the study population. For the purposes of this study, 3 patient populations were prospectively identified: 1) the overall population, including all patients enrolled; 2) the "standard-risk" ("on label") cohort characterized by eligibility criteria from the SPIRIT IV study (7); and 3) the "extended-risk" ("off label") cohort characterized by the SPIRIT IV exclusion criteria, specifically defined as patients with any of the following: baseline lesion length >28 mm; reference vessel diameter <2.5 mm or >4.25 mm; chronic total occlusion; graft lesion; bifurcation with side branch ≥2 mm; ostial, left main, in-stent restenosis; more than 2 lesions stented in the same vessel; more than 2 vessels treated; acute MI; renal insufficiency; ejection fraction <30%; or staged procedure. This stratification was intended: 1) to provide a quality assessment of data collection and reporting in this study (by examining the consistency outcomes of standard-risk patients with those from the SPIRIT IV trial); and 2) to provide safety data informative of general, real-world clinical practice, in particular data on adverse event rates in larger numbers of complex patients not represented in pre-approval randomized studies.

Abbreviations and Acronyms

ARC = Academic Research Consortium
CI = confidence interval
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
EECSS = everolimus-eluting coronary stent systems(s)
FDA = U.S. Food and Drug Administration
MI = myocardial infarction
PCI = percutaneous coronary intervention
ST = stent thrombosis
TLR = target lesion revascularization
WHO = World Health Organization

The study complied with the Declaration of Helsinki for investigation in human beings and was approved by the institutional review board at each study center.

Outcome and data management. The primary endpoint was the incidence of Academic Research Consortium (ARC)-defined definite and probable ST (8). The co-primary endpoint was the composite rate of cardiac death and any ARC-defined MI at 1 year. Other major prospectively identified secondary endpoints included the ARC-defined,

by Abbott Vascular (Santa Clara, California). Dr. Krucoff received research grants from and does moderate consulting for Abbott Vascular. Ms. Jonnavithula and Drs. Rutledge, Mao, Simonton, Wang, Wilburn, Zhao, and Sudhir are employees of Abbott Vascular and hold stock in the company. Dr. Lombardi is a consultant for, received honoraria, and is on the advisory board of Abbott Vascular. Dr. Sharma received consulting fees for Speaking Bureau for Abbott, Boston Scientific, The Medicines Co., and Eli Lilly. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 11, 2011; revised manuscript received July 26, 2011; accepted August 4, 2011.

patient-oriented endpoint (the composite rate of all death, any MI, and any repeat revascularization); target lesion failure (the composite rate of cardiac death, any MI attributed to the target vessel, and clinically indicated target lesion revascularization [TLR]); and major bleeding complications defined by Thrombolysis in Myocardial Infarction grade. Clinical device success was defined as achievement of a final in-stent residual diameter stenosis of <50% assessed by online quantitative angiography or visual estimation, with EECSS and without a device malfunction. Clinical procedure success was defined as achievement of a final in-stent diameter stenosis of <50% by online QCA or visual estimation with EECSS, with or without any adjunctive devices, and without the occurrence of cardiac death, target vessel MI (Q-wave and non–Q-wave MI), or repeat revascularization of the target lesion during the healthcare facility stay. All endpoint definitions were identical to those used in the SPIRIT IV trial, as has previously been published (7), except for clinical device success, clinical procedure success, bleeding, and MI. At the request of the FDA, ARC-defined MI was prospectively adjudicated and reported in this study. For purposes of comparisons, MI was also adjudicated by World Health Organization (WHO) criteria (9,10) used in the SPIRIT IV trial. Finally, use of dual anti-platelet therapy (DAPT) and its association with subsequent late ST were examined through protocol telephone or office visit contacts at 14, 30, and 180 days; 1 year; and then annually up to 5 years.

Patients were clinically followed either by telephone contacts or office visits. There was no mandatory angiographic follow-up in this study, consistent with the SPIRIT IV study design (the most contemporary of the series of SPIRIT randomized trials). Planned follow-up in all patients will continue for 5 years from the index procedure and will be reported annually.

All clinical endpoint events—including ST, death, MI, revascularization, and major bleeding—were adjudicated by an independent clinical events committee at the Cardiovascular Research Foundation (New York, New York). The data and safety monitoring board (Axio, Seattle, Washington) reviewed cumulative study safety data on a regular basis to ensure public safety.

The study monitoring plan included up to 30% of randomly selected patients with 100% source document verification. All site-reported adjudicable endpoint events were reviewed and source-verified. In addition, sites with low rates of reported events received additional training and monitoring visits to confirm rigorous event reporting.

Study device. As previously described (6), the EECSS is designed so that everolimus is released from a thin (7.8 μm), nonadhesive, durable, biocompatible fluoropolymer that has been coated onto a low-profile (81-μm-thin strut), flexible, cobalt-chromium stent. The EECSS used in this study ranged from 2.5 to 4.0 mm in diameter and from 8 to 28 mm in length.

Procedures. Treatment strategy was determined by the individual investigator. Stent implantation was performed according to the standard practice of each site. Periprocedural pharmacotherapy was also determined by site-based clinical practice and, staged procedures were permitted. Recommendations for antiplatelet therapy included provision of professional society guidelines (11–13) to all investigators, but antiplatelet therapy was not otherwise mandated by protocol per se. These guideline recommendations include DAPT for at least 1 year in all patients not at high risk of bleeding.

Statistical analysis. All analyses were performed on prespecified analytical populations on the basis of available data. Binary or categorical variables were presented as percentages. Mean ± SD were presented for continuous variables. Baseline demographic and lesion characteristics, procedural variables, and clinical outcomes were first reported for the overall population and then for the standard-risk and extended-risk patient subgroups. Baseline lesion characteristics, assessed by the visual estimation of each physician, were compared between the standard-risk and extended-risk cohorts with a 2-sample t test for continuous variables and the Fisher exact test for categorical variables. Statistical comparisons of clinical outcomes were performed between the standard-risk cohort and the comparable SPIRIT IV EECSS arm, with a 2-sample t test for continuous variables and the Fisher exact test for binary variables.

The time-to-event curves were displayed by Kaplan-Meier methods, and the comparison between the standard-risk cohort and the SPIRIT IV EECSS arm was performed with the log-rank test. Unless otherwise specified, a 2-sided p value of <0.05 was considered statistically significant. In the SPIRIT IV trial, adjudicated MI was only available with the WHO definition. Therefore, the statistical comparisons between the standard-risk cohort and the SPIRIT IV trial were only performed on MI data with the WHO definition.

Patients with DAPT usage at 1 year were defined as those who took both aspirin and a thienopyridine for at least 1 day during the 1-year visit window (365 ± 42 days). Interruption of DAPT was identified as cessation of either aspirin or thienopyridine therapy for at least 1 day within 1 year from the stent implantation, including those who discontinued and did not resume dual therapy before the end of the 1-year evaluation.

Subsequent late ST rates were summarized for patients with any type of interruption that occurred before and after 6 months as well as for patients without interruptions.

Role of funding source. The XIENCE V USA study was a condition-of-approval post-market study whose operational expenses were funded by the sponsor. The sponsor, principal investigator, and co-principal investigators actively col-

laborated with the FDA to design, conduct, and analyze the study.

Results

Baseline characteristics of study patients. A total of 5,054 patients with 7,075 lesions treated during the index procedure were enrolled in the study. Of the total population, 1,875 (37.1%) were standard-risk or "on label" patients and 3,179 (62.9%) were extended-risk or "off label" patients, a complex population not studied previously in randomized SPIRIT trials. Clinical, angiographic, and procedural characteristics of the overall population as well as the standard-risk and extended-risk cohorts are shown in Tables 1 and 2. The extended-risk population was older; had more severe comorbidities and more complex lesion characteristics; and had a higher incidence of diabetes, history of MI, multivessel disease, previous cardiac intervention, B2/C lesions, and longer lesions. They also received, on average, more stents per lesion and more stents per patient.

Procedural success. Clinical device success was 99.9% in the overall population, 100.0% in the standard-risk cohort, and 99.8% in the extended-risk cohort. Clinical procedural success was 98.0% in the overall population and 98.8% in the standard-risk cohort. The procedure success rate was lower (97.5%) in the more complex, extended-risk patients compared with the standard-risk group (p = 0.0011).

ST. At 1 year, the ARC-defined definite and probable ST rate was 0.84% (95% confidence interval [CI]: 0.60% to 1.14%) in the overall population, 0.33% (95% CI: 0.12% to 0.72%) in the standard-risk cohort, and 1.12% (95% CI: 0.80% to 1.58%) in the extended-risk population (Table 3). The ST rate of the standard-risk cohort was comparable to that reported in the matched population of the EECSS arm of the SPIRIT IV trial (0.33% vs. 0.29%, p = 1.0). Kaplan-Meier curves of the timing of ST events over the first year and 30-day landmark analysis are shown in Figure 1.

Cardiac death and MI. The event rate for the co-primary endpoint of the composite of cardiac death and ARC-defined MI at 1 year was 6.5% (95% CI: 5.79% to 7.17%) in the overall population, 3.8% (95% CI: 2.98% to 4.78%) in the standard-risk cohort, and 8.0% (95% CI: 7.09% to 9.02%) in the extended-risk cohort. This composite endpoint was driven primarily by non–Q-wave MI (4.4%, 2.7%, and 5.4% in the overall, standard-risk, and extended-risk cohorts, respectively). Kaplan-Meier curves of cardiac death and ARC-defined MI are shown in Figure 2.

The composite of cardiac death and WHO-defined MI (used in the SPIRIT IV study) was 3.3% (95% CI: 2.86% to 3.89%) in the overall population, 1.9% (95% CI: 1.33% to 2.64%) in the standard-risk cohort, and 4.2% (95% CI: 3.52% to 4.96%) in the extended-risk cohort. Cardiac death and MI rates with the WHO definition were comparable between the XIENCE V USA standard-risk cohort and

Table 1. Patient Demographic Data and Risk Factors

	Overall (n = 5,054)	Standard-Risk (n = 1,875)	Extended-Risk (n = 3,179)	p Value*
Age (yrs)	64.74 ± 11.06	64.34 ± 10.95	64.97 ± 11.12	0.05
Male	3,478 (68.8%)	1,246 (66.5%)	2,232 (70.2%)	0.01
All diabetes mellitus	1,779 (35.6%)	574 (30.9%)	1,205 (38.4%)	<0.0001
Dyslipidemia requiring medication	4,122 (84.2%)	1,512 (83.0%)	2,610 (84.9%)	0.07
Hypertension requiring medication	4,286 (85.8%)	1,577 (84.9%)	2,709 (86.4%)	0.15
Current tobacco user or former tobacco user (quit ≤1 month ago)	1,087 (22.8%)	409 (23.0%)	678 (22.6%)	0.75
Renal insufficiency	557 (11.1%)	0 (0.0%)	557 (17.6%)	.
Anemia	406 (8.3%)	98 (5.4%)	308 (10.0%)	<0.0001
History of previous MI	1,409 (30.8%)	432 (24.8%)	977 (34.5%)	<0.0001
Stable angina	2,478 (53.5%)	1,021 (58.5%)	1,457 (50.5%)	<0.0001
Unstable angina	1,421 (30.7%)	430 (24.7%)	991 (34.4%)	<0.0001
AMI	673 (16.0%)	0 (0.0%)	673 (25.0%)	.
Multivessel disease	2,061 (40.8%)	578 (30.8%)	1,483 (46.6%)	<0.0001
LVEF <30%	131 (3.4%)	0 (0.0%)	131 (5.3%)	.
Past cardiac intervention†	2,495 (51.2%)	799 (44.1%)	1,696 (55.4%)	<0.0001
PCI	1,950 (40.0%)	660 (36.4%)	1,290 (42.2%)	<0.0001
CABG	755 (15.5%)	158 (8.7%)	597 (19.5%)	<0.0001

Values are n (%) or mean ± SD. *Standard- versus extended-risk. †Patient can be counted in more than 1 category.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

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Table 2. Lesion and Procedural Characteristics

	Overall (n = 5,054) (7,075 Lesions)	Standard-Risk (n = 1,875) (2,316 Lesions)	Extended-Risk (n = 3,179) (4,759 Lesions)	p Value*
Target vessel				
RCA	2,329 (32.9%)	736 (31.8%)	1,593 (33.5%)	0.15
LAD	2,629 (37.2%)	986 (42.6%)	1,643 (34.5%)	<0.0001
LCX	1,663 (23.5%)	594 (25.6%)	1,069 (22.5%)	0.003
LMCA	113 (1.6%)	0 (0.0%)	113 (2.4%)	.
Graft	339 (4.8%)	0 (0.0%)	339 (7.1%)	.
ACC/AHA lesion class				
A	1,094 (18.7%)	548 (27.4%)	546 (14.2%)	<0.0001
B1	1,874 (32.0%)	739 (37.0%)	1,135 (29.4%)	<0.0001
B2	1,470 (25.1%)	450 (22.5%)	1,020 (26.5%)	0.0009
C	1,415 (24.2%)	261 (13.1%)	1,154 (29.9%)	<0.0001
Restenosis	670 (9.5%)	0 (0.0%)	670 (14.1%)	.
Lesion length (mm)	16.0 ± 9.8	14.2 ± 5.9	17.0 ± 11.2	<0.0001
≥20 mm	1,942 (29.2%)	521 (22.5%)	1,421 (32.8%)	<0.0001
RVD (mm)	3.02 ± 0.52	3.00 ± 0.44	3.03 ± 0.56	0.004
Pre-procedure DS (%)	83.8 ± 11.0	82.4 ± 10.4	84.5 ± 11.3	<0.0001
Post-procedure DS (%)	0.89 ± 3.56	0.86 ± 3.19	0.90 ± 3.73	0.67
Chronic total occlusion	167 (2.5%)	0 (0.0%)	167 (3.7%)	.
Bifurcation	634 (9.0%)	40 (1.7%)	594 (12.5%)	<0.0001
Ostial	789 (11.9%)	0 (0.0%)	789 (17.7%)	.
Lesions treated	1.4 ± 0.7	1.2 ± 0.5	1.5 ± 0.8	<0.0001
Direct stenting	2,735 (38.7%)	1,028 (44.4%)	1,707 (35.9%)	<0.0001
Post-dilation done	3,785 (53.6%)	1,088 (47.0%)	2,697 (56.8%)	<0.0001
Stents/patient	1.6 ± 0.9	1.3 ± 0.5	1.8 ± 1.0	<0.0001
Stents/lesion	1.2 ± 0.5	1.1 ± 0.2	1.2 ± 0.5	<0.0001
Stent length/patient	29.6 ± 19.8	22.8 ± 11.6	33.5 ± 22.3	<0.0001
Stent length/lesion	21.2 ± 11.7	18.6 ± 6.8	22.5 ± 13.3	<0.0001
Loading dose received	2,837 (56.2%)	1,055 (56.4%)	1,782 (56.1%)	0.86

Values are n (%) or mean ± SD. *Standard- versus extended-risk.
ACC/AHA = American College of Cardiology/American Heart Association; DS = diameter stenosis; LAD = left anterior descending coronary artery; LCX = left circumflex artery; LMCA = left main coronary artery; RCA = right coronary artery; RVD = reference vessel diameter.

the SPIRIT IV EECSS arm (1.9% vs. 2.2%, respectively, p = 0.52).

Other pre-specified secondary endpoints. Target lesion failure rate at 1 year (the primary effectiveness endpoint for the SPIRIT IV trial) with the WHO definition for MI was 6.7% (95% CI: 5.98% to 7.39%) in the overall population, 3.5% (95% CI: 2.74% to 4.48%) in the standard-risk cohort, and 8.5% (95% CI: 7.54% to 9.53%) in the extended-risk cohort. The event rate in the XIENCE V USA standard-risk cohort was comparable with the EECSS arm in the SPIRIT IV trial (3.5% vs. 4.2%, respectively, p = 0.30). The additional prospective secondary endpoints for the overall, standard risk, and extended-risk cohorts as well as for the EECSS arm of the SPIRIT IV trial are shown in Table 4. As can be seen, 1-year standard-risk cohort death and cardiac death rates were slightly higher for the XIENCE V USA study compared with the SPIRIT IV trial, which could be attributed to real-world, community-based clinical practice. The other endpoints were comparable between the 2 trials, suggesting freedom from reporting bias. Key anatomic and clinical subgroups of the extended-risk population and their clinical outcomes are detailed in Table 5.

Antiplatelet therapy. At 1 year, 79.4% of patients remained on DAPT (Table 6). Among patients who discontinued DAPT, most had either temporarily interrupted (n = 209 of 696 [30.0%]) or permanently discontinued (n = 354 of 696 [50.9%]) their therapy (Table 7). The 2 most common reasons for temporary interruption of DAPT were invasive surgical procedure (40.7%) and adverse event (34.4%). The 2 most common reasons for permanent discontinuation of DAPT were adverse event (22.3%) and invasive surgical procedure (11.0%). The timing of dual therapy interruption and its relationship with subsequent late ST (Fig. 3) showed that DAPT interruption after 6 months was not associated with late ST in standard- or extended-risk patients. In the standard-risk cohort there was no late ST after dual therapy interruption at any time after implantation.

Table 3. ARC-Defined Stent Thrombosis

Stent Thrombosis	Overall (n = 5,054)	Standard-Risk (n = 1,875)	Extended-Risk (n = 3,179)	SPIRIT IV EECSS (n = 2,458)	p Value*
Acute (0–24 h)					
Definite	2 (0.04%)	1 (0.05%)	1 (0.03%)	4 (0.16%)	0.40
Probable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Possible	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Definite/probable	2 (0.04%)	1 (0.05%)	1 (0.03%)	4 (0.16%)	0.40
Definite/probable/possible	2 (0.04%)	1 (0.05%)	1 (0.03%)	4 (0.16%)	0.40
Sub-acute (>24 h–30 days)					
Definite	9 (0.18%)	1 (0.05%)	8 (0.25%)	0 (0.0%)	—
Probable	11 (0.22%)	2 (0.11%)	9 (0.29%)	0 (0.0%)	—
Possible	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Definite/probable	20 (0.40%)	3 (0.16%)	17 (0.54%)	0 (0.0%)	—
Definite/probable/possible	20 (0.40%)	3 (0.16%)	17 (0.54%)	0 (0.0%)	—
Early (0–30 days)					
Definite	11 (0.22%)	2 (0.11%)	9 (0.29%)	4 (0.16%)	0.70
Probable	11 (0.22%)	2 (0.11%)	9 (0.29%)	0 (0.0%)	—
Possible	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Definite/probable	22 (0.44%)	4 (0.21%)	18 (0.57%)	4 (0.16%)	0.73
Definite/probable/possible	22 (0.44%)	4 (0.21%)	18 (0.57%)	4 (0.16%)	0.73
Late (31–365 days)					
Definite	14 (0.29%)	0 (0.0%)	14 (0.46%)	2 (0.08%)	—
Probable	5 (0.10%)	2 (0.11%)	3 (0.10%)	1 (0.04%)	0.58
Possible	35 (0.72%)	12 (0.66%)	23 (0.75%)	8 (0.33%)	0.17
Definite/probable	19 (0.39%)	2 (0.11%)	17 (0.56%)	3 (0.13%)	1.00
Definite/probable/possible	54 (1.11%)	14 (0.77%)	40 (1.31%)	11 (0.46%)	0.23
Event rate at 1 yr (0–365 days)					
Definite	25 (0.51%)	2 (0.11%)	23 (0.75%)	6 (0.25%)	0.48
Probable	16 (0.33%)	4 (0.22%)	12 (0.39%)	1 (0.04%)	0.17
Possible	35 (0.72%)	12 (0.66%)	23 (0.75%)	8 (0.33%)	0.17
Definite/probable	41 (0.84%)	6 (0.33%)	35 (1.14%)	7 (0.29%)	1.00
Definite/probable/possible	75 (1.53%)	18 (0.99%)	57 (1.86%)	15 (0.63%)	0.22

Values are n (%). *Standard-risk versus the SPIRIT IV trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions).

ARC = Academic Research Consortium; EECSS = everolimus-eluting coronary stent systems.

Discussion

Historically, pivotal U.S. DES studies have randomized fewer than 2,000 patients, exposing one-half to investigational stents. These studies have been underpowered for rare safety events, reporting wide CIs for ST, death, and MI. In addition, higher-risk patients have been excluded from these studies. Meta-analytic approaches to defining rare outcomes with DES have previously expressed concerns about interpretability of comparisons between RCT and observational studies (14). To support both the need for expeditious medical device innovation and better definition of residual safety issues in the transition to real-world practice, new approaches to post-approval studies to bridge the pre- and post-approval continuum have emerged.

The XIENCE V USA study was a prospective, open-label, multicenter, observational, single-arm, condition-of-approval study designed to provide additional data on the safety of the EECSS and its generalizability to real-world clinical practice. Data from more than 5,000 patients treated exclusively with this stent help narrow CIs regarding rare safety events, such as ARC-defined definite and probable ST, cardiac death, and MI.

The capability to further inform clinical outcomes in a real-world population with post-approval studies beyond those from selected patients in randomized pre-approval studies is most fundamentally dependent on the use of common definitions and nomenclature across trials. The involvement of the FDA in such efforts to build pragmatic consensus reference points and encourage their use for new device evaluations enhances interpretability of data across studies (8). This construct allows a quality assessment of the reliability of this post-approval study by comparing event rates with those reported in the more rigorous randomized

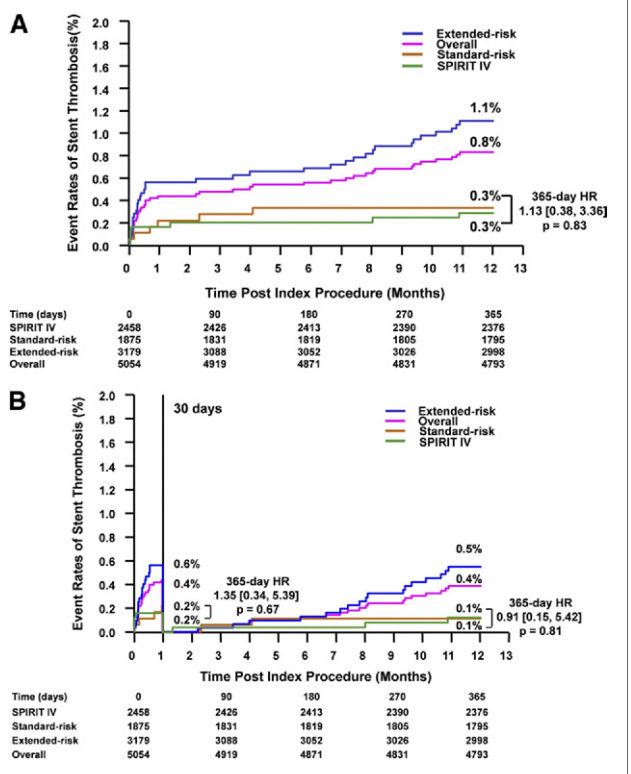

Figure 1. Stent Thrombosis at 1 Year and 30-Day Landmark

Time-event-curves for 1-year Academic Research Consortium-defined definite and probable stent thrombosis **(A)** and 30-day landmark analysis **(B)**. The event rates shown here were calculated through 365 days with the Kaplan-Meier method. The hazard ratio (HR) and p value comparing the standard-risk cohort and the SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) everolimus-eluting coronary stent systems arm were calculated at 30 and 365 days with log-rank test.

SPIRIT trial. Consistency in this comparison, as was seen between the XIENCE V USA standard-risk cohort and the matched SPIRIT IV EECSS arm, are encouraging in that the event rates reported in the overall and extended-risk populations are likely to reflect a reliable benchmark for expectations with regard to device performance and safety in real-world use. The use of this approach across pre- and post-approval studies, reflected in the results reported here, represents a novel approach to further advance the public health by providing better safety information, while still encouraging innovation, new device approvals, and the advance of medicine.

In this study, the incidence of ARC-defined definite and probable ST was 0.84% in the overall population, with 0.44% occurring early (0 to 30 days) and 0.39% occurring late (31 to 365 days). The likelihood that these results provide a reliable benchmark for overall safety and performance in clinical practice is suggested by: 1) the comparability of the findings from the standard-risk cohort to those seen in the randomized EECSS group from the SPIRIT IV trial (0.33% vs. 0.29%, respectively; p = 1.0); and 2) the consistency of these findings relative to other "all-comers" reports from outside of the United States. Although ad hoc comparisons across trials with different design require caution, the ST rate in the XIENCE V USA study was consistent with those reported in all-comers patient populations treated with EECSS from both the COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) (0.7%) (15) and RESOLUTE (Randomized, Two-arm, Non-inferiority Study Comparing Endeavor-Resolute Stent) (0.7%) trials (16). Rates comparable to these 2 randomized studies of "all comer" complex patients is also encouraging in that the data quality and reliability of event reporting in the XIENCE V USA study is independent of patient cohort complexity per se. The 1-year ST rate in the XIENCE V USA study also compares favorably with other real-world, all-comer DES registries, such as: e-SELECT: 0.98% (17); ARRIVE: 1.8% (18); and E-Five: 1.1% (19).

Another important area of new information provided by this post-approval study relates to the real-world use of DAPT and the safety of the EECSS with interruption or termination of DAPT. Unlike the SPIRIT IV trial, in which DAPT was required by protocol for at least 12 months (7), antiplatelet therapy was not mandated by protocol in the XIENCE V USA study. Rather, all study investigators were provided with copies of the American College of Cardiology/American Heart Association/Society for Cardiac Angiography and Interventions/FDA recommendations for dual therapy and encouraged to use them on a discretionary basis. Under these circumstances, only 79.4% of the population remained on both aspirin and thienopyridine (primarily clopidogrel) therapy at the end of 1 year.

Despite this lower use of dual therapy out to 12 months compared with protocol-driven use in previous randomized trials (7), the ARC-defined definite/probable ST rates at 1 year were highly comparable. In the XIENCE V USA study, there were 696 patients in whom dual therapy was interrupted in some fashion, from interruption of at least 1 agent (aspirin or thienopyridine) for at least 1 day to complete discontinuation at any time during the 1-year time frame. Because discontinuation of DAPT has been shown in previous reports with other DES platforms to pose one of the most significant risks as a causal factor in ST (18,20), it was encouraging to see no late ST events in standard-risk patients after any interruption of dual therapy and no late ST events in extended-risk patients with interruption of dual therapy after 6 months.

The XIENCE V USA study was designed at a time of transition, particularly among regulatory authorities, to the use of ARC definitions (8). Although the ARC definitions of ST were commonly used in pre-approval studies, the WHO definition of MI was more commonly used in such studies including the SPIRIT IV trial. For the XIENCE V

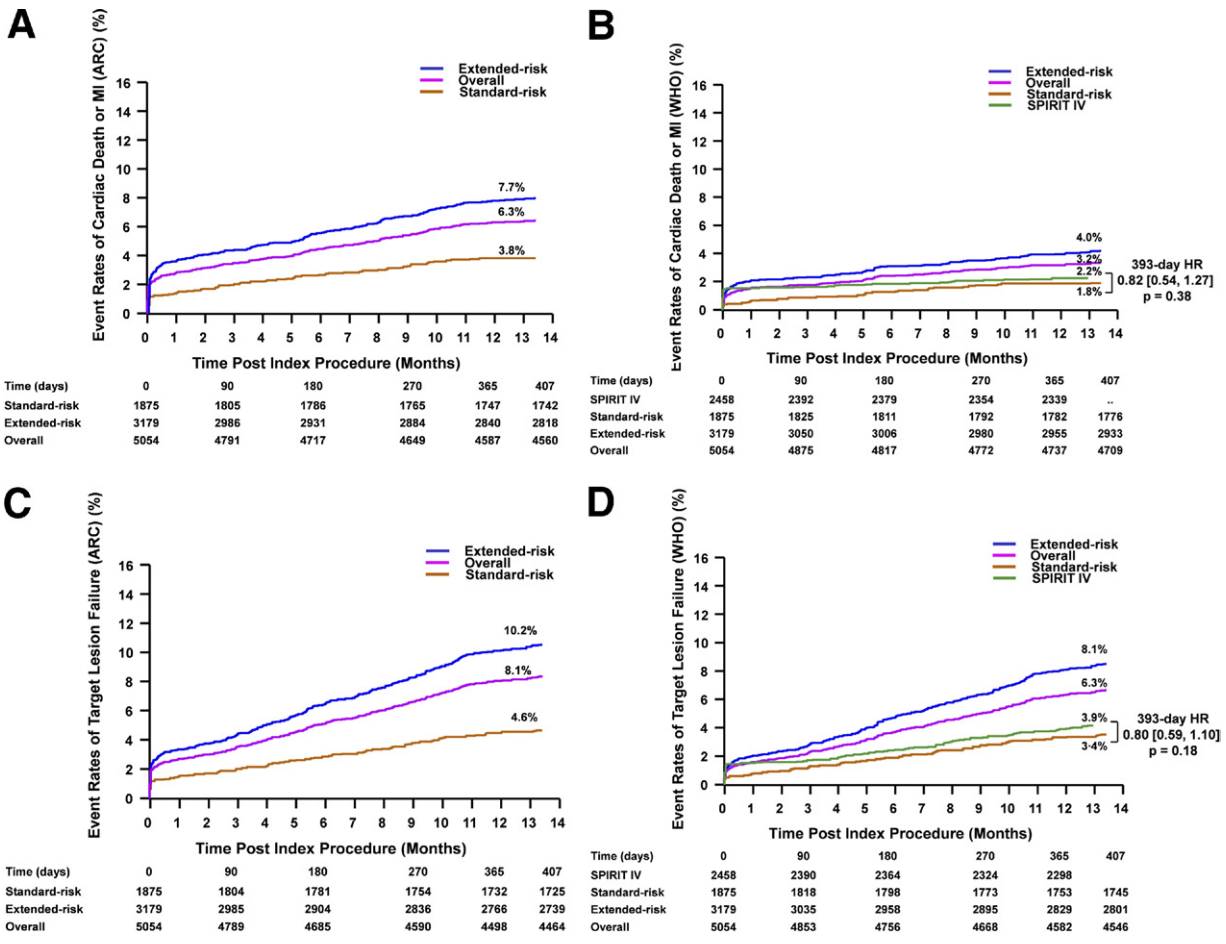

Figure 2. Cardiac Death/MI and Target Lesion Failure at 1 Year

Time-to-event curves for: **(A)** cardiac death and Academic Research Consortium (ARC)-defined myocardial infarction (MI); **(B)** cardiac death and World Health Organization (WHO)-defined MI; **(C)** target lesion failure (the composite of cardiac death, ARC-defined MI attributed to target vessel and clinically indicated target lesion revascularization); **(D)** target lesion failure (the composite of cardiac death, WHO-defined MI attributed to target vessel and clinically indicated target lesion revascularization). Event rates shown here were calculated at 365 days with Kaplan-Meier methods. Hazard ratio (HR) and p value comparing the standard-risk cohort and the SPIRIT IV everolimus-eluting coronary stent systems arm were calculated at 393 days with the log-rank test.

USA study, WHO definitions of MI were thus included to understand the historically benchmarked risk level to be expected in real-world practice. However, because the FDA moved its emphasis to the ARC definition for MI at the time of this study, both the historical WHO (for comparisons with previously reported trials) and ARC definitions (for regulatory compliance) were prospectively included in the statistical analysis plan of XIENCE V USA. The inclusion of troponin (a more sensitive marker than creatine kinase) in the ARC definition but not the WHO definition resulted in rates of MI that were approximately 2.5 times higher than with the ARC definition. This difference was also reflected in the composite co-primary endpoint of cardiac death and MI, depending on whether ARC or WHO criteria were used, because the MI component was the main driver of the composite. The difference between these 2 MI definitions has previously been observed in the RESOLUTE trial (16) and will be an important feature in future studies as well.

Approximately 63% of patients in this study comprised the extended-risk or "off label" cohort. Although statistical comparisons were not performed, adverse event rates were numerically higher in this cohort compared with the standard-risk cohort. This difference is consistent with findings reported in the ARRIVE 1 (21) and E-Five (19) post-approval DES registries, in which the expanded-use or extended-use cohorts had higher event rates compared with the simple-use or standard-use cohorts (ARC-defined definite/probable ST: 2.6% vs. 1.4% in ARRIVE 1 and 1.4% vs. 0.4% in E-Five, respectively; cardiac death: 1.3% vs. 0.8% in ARRIVE 1 and 2.0% vs. 0.9% in E-Five, respectively; MI: 1.9% vs. 1.6% in ARRIVE 1 and 1.9% vs. 0.7%

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Table 4. 1-Year Major Clinical Outcomes

	Overall (n = 5,054)	Standard-Risk (n = 1,827)	Extended-Risk (n = 3,227)	SPIRIT IV EECSS (n = 2,458)	p Value*
Death	131 (2.6%)	34 (1.8%)	97 (3.1%)	25 (1.0%)	0.03
Cardiac death	80 (1.6%)	17 (0.9%)	63 (2.0%)	10 (0.4%)	0.05
MI (ARC)	268 (5.4%)	59 (3.2%)	209 (6.7%)	—	—
Q-wave	31 (0.6%)	5 (0.3%)	26 (0.8%)	—	—
Non–Q-wave	242 (4.9%)	54 (2.9%)	188 (6.0%)	—	—
MI (WHO)	102 (2.1%)	20 (1.1%)	82 (2.6%)	45 (1.9%)	0.04
Q-wave	31 (0.6%)	5 (0.3%)	26 (0.8%)	3 (0.1%)	0.30
Non–Q-wave	73 (1.5%)	15 (0.8%)	58 (1.9%)	42 (1.7%)	0.01
Cardiac death/MI (ARC)	320 (6.5%)	70 (3.8%)	250 (8.0%)	—	—
Cardiac death/MI (WHO)	166 (3.3%)	35 (1.9%)	131 (4.2%)	54 (2.2%)	0.52
TLF (cardiac death/TVMI [ARC]/CI-TLR)	416 (8.4%)	86 (4.7%)	330 (10.6%)	—	—
TLF (cardiac death/TVMI [WHO]/CI-TLR)	330 (6.7%)	65 (3.5%)	2,653 (8.5%)	101 (4.2%)	0.30
All death/MI (ARC)/ revascularization)	682 (13.8%)	184 (10.0%)	498 (16.0%)	—	—
All death/MI (WHO)/ revascularization)	598 (12.1%)	161 (8.8%)	437 (14.0%)	218 (9.0%)	0.79
TLR	221 (4.5%)	41 (2.2%)	180 (5.8%)	66 (2.7%)	0.32
TVR, non-TLR	109 (2.2%)	40 (2.2%)	69 (2.2%)	57 (2.4%)	0.76
TIMI major bleeding	123 (2.5%)	37 (2.0%)	86 (2.8%)	—	—

Values are n (%). *Standard-risk versus the SPIRIT IV trial.

CI = clinically indicated; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; TLF = target lesion failure; TLR = target lesion revascularization; TVMI = myocardial infarction attributed to target vessel; TVR = target vessel revascularization; WHO = World Health Organization; other abbreviations as in Table 3.

in E-Five, respectively). In the recently reported COMPARE study of all-comer patients randomized to EECSS versus paclitaxel-eluting stents (Taxus Liberté, Boston Scientific, Natick, Massachusetts) (15), overall ST and the composite of cardiac death and MI at 1 year for the 2 arms were 0.7% versus 3% and 4% versus 6%, respectively, consistent with those observed in XIENCE V USA. Consistent overall results were also demonstrated from the RESOLUTE all-comers randomized trial by low rates of ST (0.7% vs. 1.6%) and the composite of cardiac death and target-vessel MI (5.4% vs. 5.4%) in the EECSS versus zotarolimus-eluting stent arm (16). Rates specific to standard-risk and extended-risk cohorts comparable to the XIENCE V USA study were not reported in these all-comer trials. One-year clinical outcomes were also reported for the subgroups within the extended-risk cohort. However, estimates of low-frequency events are limited by small sample sizes of certain subgroups and should be interpreted

Table 5. Extended-Risk Subgroup 1-Year Clinical Outcomes

	ST*	CD/MI (ARC)	CD/MI (WHO)	TLF† (ARC)	TLF† (WHO)	MI (ARC)	MI (WHO)	TLR	TVR, Non-TLR
Lesion length >28 mm (n = 384)	1.62%	9.4%	5.3%	11.8%	8.8%	8.8%	3.7%	5.3%	1.6%
RVD <2.5 mm (n = 183)	0.00%	5.5%	1.6%	8.2%	4.4%	4.9%	1.1%	3.3%	1.6%
RVD >4.25 mm (n = 59)	1.79%	3.6%	1.8%	8.9%	8.9%	1.8%	0.0%	7.1%	3.6%
CTO (n = 130)	0.80%	3.1%	0.8%	7.1%	4.7%	2.4%	0.0%	3.9%	0.8%
Graft (n = 270)	1.53%	13.3%	7.4%	18.9%	16.7%	11.5%	5.6%	11.5%	1.9%
Bifurcation with side branch ≥2 mm (n = 403)	1.80%	7.7%	4.6%	9.9%	8.2%	6.4%	3.1%	5.4%	4.3%
Ostial (n = 688)	1.21%	8.6%	4.6%	12.3%	10.4%	7.6%	3.4%	7.1%	2.4%
Left main (n = 110)	0.95%	13.9%	4.6%	19.4%	18.5%	11.1%	1.9%	14.8%	1.9%
ISR (n = 387)	1.60%	8.1%	3.4%	16.0%	14.2%	7.3%	2.4%	12.6%	3.9%
>2 lesions in same vessel (n = 135)	0.77%	11.2%	6.7%	13.4%	9.7%	9.0%	4.5%	3.7%	2.2%
>2 vessels treated (n = 659)	1.72%	9.9%	4.6%	13.1%	9.7%	9.0%	3.2%	7.4%	4.5%
AMI (n = 673)	1.10%	9.1%	4.2%	9.1%	7.0%	7.4%	2.4%	4.1%	1.5%
Renal insufficiency (n = 518)	2.22%	13.1%	7.2%	14.9%	11.4%	10.0%	3.3%	5.7%	2.0%
EF <30% (n = 123)	2.59%	14.3%	10.1%	16.0%	12.6%	10.9%	5.0%	5.9%	3.4%
With staged procedure (n = 257)	1.20%	10.9%	5.4%	10.9%	9.3%	8.9%	3.5%	6.6%	1.6%

*ARC-defined definite and probable. †TLF = cardiac death, MI attributed to target vessel and clinically indicated TLR.

CD = cardiac death; CTO = chronic total occlusion; EF = ejection fraction; ISR = in-stent restenosis; other abbreviations as in Tables 2 and 4.

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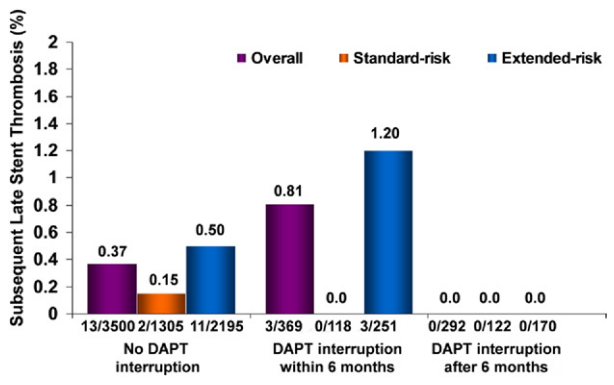

Figure 3. Stent Thrombosis and Interruption of DAPT

Late stent thrombosis rates (30 to 365 days, Academic Research Consortium-defined definite and probable) in patients without dual antiplatelet therapy (DAPT) interruption and with DAPT interruption within or after 6 months.

most important limitation of even the most rigorously performed single-arm condition-of-approval studies. Despite this limitation, it is noteworthy that the consistency of EECSS compared with paclitaxel-eluting stents in the SPIRIT (4,6,7) and COMPARE (15) trials is encouraging with regard to both the safety and effectiveness of its novel "second-generation" DES design features.

Conclusions

Rigorously conducted, single-arm, post-market condition-of-approval studies with prospective statistical analysis plans potentially serve both a regulatory and public health role by further informing pre-approval randomized evaluations with regard to residual safety issues, such as rare safety events and generalizability to the real-world practice of medicine. Such information from the post-market setting is critical to help balance safety concerns with the ability to encourage new device innovation. The XIENCE V USA study was designed scientifically, statistically, and with quality control measures to fulfill this intent. Comparability of event rates between both standard-risk patients and the EECSS arm of the SPIRIT IV trial and the overall population and the EECSS arm of COMPARE suggest that quality control measures, event reporting, and adjudication provide reasonable and reliable estimates on the safety of this novel DES platform. The absence of late ST events in standard-risk patients with any DAPT interruption and in extended-risk patients with DAPT interruption after 6 months is also encouraging. However, definitive confirmation of such enhanced safety relative to other DES would require a randomized clinical trial.

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Key Words: drug-eluting stent(s) ■ dual-antiplatelet therapy ■ everolimus ■ percutaneous coronary intervention ■ real-world ■ stent ■ stent thrombosis.