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Contemporary Incidence and Predictors of Stent Thrombosis and Other Major Adverse Cardiac Events in the Year After XIENCE V Implantation

Results From the 8,061-Patient XIENCE V United States Study

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Objectives The aim of this study was to identify predictors of clinical events after XIENCE V (Abbott Vascular, Santa Clara, California) stenting.

Background The XIENCE V USA (XIENCE V Everolimus Eluting Coronary Stent System [EECSS] USA Post-Approval) study is a prospective, multicenter, Food and Drug Administration-required post-approval study to examine safety and effectiveness in real-world settings. After an initial 5,062 patients, 2,999 more were included as part of the DAPT (Dual Antiplatelet Therapy) trial (total n = 8,061).

Methods One-year clinical events, including stent thrombosis (ST), cardiac death/myocardial infarction (MI), target lesion failure, and target lesion revascularization, were adjudicated according to Academic Research Consortium criteria, with ST and cardiac death/MI as primary and co-primary endpoints. Demographic, clinical, and procedural variables were assessed by multivariable analysis. A time-dependent covariate assessed the association between DAPT usage and ST.

Results Roughly 61% were off-label; 85.6% remained on DAPT without interruption through 1 year. Incidences of definite/probable ST, cardiac death/MI, target lesion failure, and target lesion revascularization were 0.80% (95% confidence interval [CI]: 0.61% to 1.03%), 7.1% (95% CI: 6.51% to 7.68%), 8.9% (95% CI: 8.30% to 9.60%), and 4.3% (95% CI: 3.82% to 4.75%), respectively. Several independent clinical and angiographic predictors were identified for each outcome. Predictors of ST included DAPT interruption ≤30 days (hazard ratio [HR]: 8.63, 95% CI: 2.69 to 27.73, p = 0.0003), renal insufficiency (HR: 3.72, 95% CI: 1.71 to 8.09, p = 0.0009), and total stent length (HR: 1.30, 95% CI: 1.16 to 1.47, p < 0.0001). A DAPT interruption >30 days was not predictive of ST.

Conclusions In this large, real-world population, XIENCE V demonstrated low event rates at 1 year, with several independent predictors. Early DAPT interruption (≤30 days) was the most potent predictor of ST, whereas delayed interruption (>30 days) was not predictive. (XIENCE V Everolimus Eluting Coronary Stent System [EECSS] USA Post-Approval Study; NCT00676520) (J Am Coll Cardiol Intv 2012;5:626–35) © 2012 by the American College of Cardiology Foundation

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The rapid uptake of the initial first-generation drug-eluting stents (DES) in cardiovascular practice was subsequently tempered by a perception of increased incidence of late stent thrombosis (ST), prompting declines in DES use (1–3). Large meta-analyses of the pivotal randomized controlled trials and several "real-world" registries were then evaluated and confirmed an increased incidence of very late ST (4–6). Newer second-generation DES were targeted to maintain (or surpass) the antirestenotic efficacy of first-generation DES while improving their long-term safety, particularly with regard to the incidence of ST. The XIENCE V everolimus-eluting coronary stent system (EECSS) (Abbott Vascular, Santa Clara, California) has potential advantages over first-generation DES, including thinner struts, reduced and biocompatible polymer layer, early yet complete drug elution, and use of a novel sirolimus derivative (7). Its efficacy in reducing in-stent restenosis and major adverse cardiac events (MACE) compared with the paclitaxel-eluting stent was confirmed in multiple randomized controlled trials (8–12). However, performance in a large, complex "real-world" clinical setting, including "off-label" scenarios, remains uncertain, especially with regard to rates of low-frequency safety events, such as ST (13).

Recently, there has been concern that trial results seen outside the United States might not mirror those noted within the United States, for reasons that remain unclear (14). Accordingly, the current study is the largest multicenter prospective evaluation of the XIENCE V EECSS in a complex "real-world" patient population within the United States. One-year major adverse clinical events including both early and late ST and their independent predictors are reported and discussed, with particular attention to the predictive power of clinical and angiographic factors, including premature interruption of dual antiplatelet therapy (DAPT).

Methods

Study design. The XIENCE V USA (IDE G050050) study (XIENCE V Everolimus Eluting Coronary Stent System [EECSS] USA Post-Approval) is a prospective, open-label, multicenter, observational, single-arm trial designed to further inform the safety evaluation of the EECSS during commercial use in real-world settings. A total of 8,061 patients who underwent EECSS implantation were enrolled from 192 sites in the United States. The study had 2 enrollment phases. The first enrollment phase started from July 2008 to December 2008 with 5,062 patients. The second enrollment phase was initiated to support the Food and Drug Administration (FDA) DAPT initiative, which started from August 2009 to February 2010 with 2,999 patients.

All patients who could provide written informed consent and were treated only with EECSS during the index procedure were eligible. There were no additional clinical descriptors or angiographic exclusion criteria for either enrollment phase. 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. Antiplatelet therapy for at least 1 year was recommended in patients who are not at high risk of bleeding per guidelines, but antiplatelet therapy was not otherwise mandated by protocol per se (15,16). There were no protocol required treatments or tests, except that post-procedure cardiac enzyme collections were required during the second enrollment phase per FDA request.

All patients were clinically followed at 14 days, 30 days, and 6 months either by telephone contacts or office visits. The 1-year visit was conducted in office. There was no mandatory angiographic follow-up in this study. Planned follow-up in patients from the first enrollment phase will continue for 5 years from the index procedure and will be reported annually. Eligible patients who were enrolled during the second enrollment phase were randomized to different DAPT arms at 1 year and will be followed up at 15, 24, 30, and 33 months according to the DAPT study (17). The remaining patients from the second enrollment phase will not be followed up any further.

Abbreviations and Acronyms

ARC = Academic Research Consortium
CI = confidence interval
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
EECSS = everolimus-eluting coronary stent system
FDA = Food and Drug Administration
HR = hazard ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
ST = stent thrombosis
TLF = target lesion failure
TLR = target lesion revascularization
WHO = World Health Organization

The primary endpoint was the incidence of Academic Research Consortium (ARC)-defined definite and probable ST. The coprimary endpoint was the composite rate of cardiac death and any ARC-defined myocardial infarction (MI) at 1 year. Other major prospectively identified secondary endpoints included target lesion failure (TLF); the composite rate of cardiac death, any MI attributed to the target vessel, and clinically indicated target lesion revascularization (CI-TLR); major bleeding complications defined by Thrombolysis in Myocardial Infarction grade; and clinical device and procedural success. Clinical device success was defined as achievement of a final in-stent residual diameter stenosis of <50% assessed by online quantitative coronary angiography or visual estimation, using XIENCE V, and without device malfunction. Clinical procedural success was defined as achievement of a final in-stent diameter stenosis <50% by online quantitative coronary angiography or visual estimation—using XIENCE V, 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 health care facility stay. "Off-label" was characterized as patients with any of the following: baseline lesion length >28 mm; reference vessel diameter <2.5 or >4.25 mm; chronic total occlusion; graft lesion; bifurcation with side branch ≥2 mm; ostial; left main; 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.

At the request of the FDA, ARC-defined MI was prospectively adjudicated and reported in this study. For purposes of comparisons with historical data, MI was also adjudicated by World Health Organization (WHO) criteria. Real-world usage of DAPT within the first year was also examined in this study. 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 in the first enrollment phase, and 5% of randomly selected patients in the second enrollment phase. 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. 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. The XIENCE V USA study is registered with ClinicalTrials.gov (NCT00676520).

Statistical analysis. All analyses were performed on prespecified analytical populations on the basis of available data. Patient/angiographic characteristics and event rates were analyzed with descriptive statistics with SAS (version 9.1 or higher; SAS Institute, Cary, North Carolina). The 2 enrollment phases had similar designs, eligibility criteria, endpoint definitions, and adjudication processes and therefore were pooled together. Binary or categorical variables were presented as percentages. Means and standard deviations were presented for continuous variables. The time-to-event curves were displayed by Kaplan-Meier methods.

The DAPT medication usage data were collected on the basis of patient reported history. Interruption of DAPT was defined as cessation of either aspirin or thienopyridine therapy for at least 1 day within the time window, including those who discontinued and did not resume dual therapy.

To identify predictors of ST, cardiac death, ARC-defined MI, TLF, and target lesion revascularization (TLR), a total of 36 variables—including 16 clinical variables, 12 angiographic variables, and 8 procedural variables—were assessed for each of the aforementioned endpoints with multivariable, stepwise, Cox regression analysis with predictor variables entered into the model at the 0.05 significance level. In addition, a time-dependent covariate was used to capture the DAPT interruption pattern to assess any association with subsequent ST occurrence.

Results

Baseline characteristics of study patients. Eight thousand sixty-one patients were prospectively enrolled, and 11,168 lesions were treated, including 61% for "off-label" indications. Clinical device success was 99.8%, and clinical procedural success was 97.3%. Clinical, angiographic, and procedure-specific characteristics are noted in Tables 1 and 2. Average age was 65 years, roughly 70% were male, and nearly 36% were diabetic. Twenty-nine percent of patients presented with unstable angina, and 14.8% presented with acute MI. Restenosis, bifurcation, and ostial disease were each represented in roughly 10% of lesions, and average stent length approached 30 mm/patient (1.6 stents/patient). Approximately 94.2% of patients continued to receive DAPT without any interruption through 30 days, and 85.6% continued to receive DAPT without any interruption through 1 year (Table 3). Approximately 89% of the overall population has completed 1-year follow-up.

Primary, co-primary, and other endpoints. One-year major adverse clinical events are presented in Table 4. The ARC criteria are used for definite/probable ST, whereas both ARC and WHO criteria are presented for MI. Figure 1 depicts time-to-event curves for cardiac death/MI, TLF, ST, and TLR, according to both ARC and WHO criteria. ST occurred in 0.8% at 1 year and was roughly evenly split

Table 1. Patient Demographic Data and Risk Factors (N = 8,061)

Age (yrs)	64.57 ± 10.81
Male	5,612 (69.6%)
All diabetes mellitus	2,860 (35.8%)
Dyslipidemia requiring medication	6,501 (82.9%)
Hypertension requiring medication	6,701 (83.9%)
Current tobacco user	1,707 (22.3%)
Renal insufficiency	841 (10.5%)
Anemia	567 (7.2%)
History of previous MI	2,218 (29.7%)
Stable angina	3,408 (44.6%)
Unstable angina	2,203 (28.9%)
AMI	1,058 (14.8%)
Multi-vessel disease	3,208 (39.8%)
LVEF <30%	203 (3.4%)
Past cardiac intervention*	3,986 (50.7%)
PCI	3,072 (39.1%)
CABG	1,292 (16.4%)

Values are mean ± SD or n (%). *Patient can be counted in more than 1 category.
AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Table 2. Lesion and Procedural Characteristics

Target vessel	
RCA	3,673 (32.9%)
LAD	4,178 (37.4%)
LCX	2,624 (23.5%)
LMCA	182 (1.6%)
Graft	510 (4.6%)
ACC/AHA B2/C lesion	4,628 (49.9%)
Restenosis	980 (8.8%)
Lesion length (mm)	15.9 ± 9.4
RVD (mm)	3.02 ± 0.53
Pre-procedure DS (%)	84.0 ± 10.9
TIMI 0 ≥3 months old	214 (2.0%)
Bifurcation	1,085 (9.7%)
Ostial	1,177 (11.2%)
Lesions treated	1.4 ± 0.7
Direct stenting	4,105 (36.8%)
Post-dilation done	6,235 (55.9%)
Stents/patient	1.6 ± 0.9
Stents/lesion	1.2 ± 0.4
Stent length/patient	29.2 ± 19.1
Stent length/lesion	21.2 ± 11.3

Values are n (%) or mean ± SD. N = 8,061 patients; N = 11,168 lesions.
ACC/AHA = American College of Cardiology/American Heart Association class; DS = diameter stenosis; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery: RVD = reference vessel diameter; TIMI = Thrombolysis in Myocardial Infarction grade.

Table 4. 1-Year Major Clinical Outcomes (N = 8,061)

Death	175 (2.3%)
Cardiac death	99 (1.3%)
MI (ARC)	468 (6.2%)
Q-wave	38 (0.5%)
Non–Q-wave	435 (5.8%)
MI (WHO)	158 (2.1%)
Q-wave	38 (0.5%)
Non–Q-wave	122 (1.6%)
Cardiac death/MI (ARC)	534 (7.1%)
Cardiac death/MI (WHO)	237 (3.1%)
TLF (cardiac death/TVMI [ARC]/CI-TLR)	674 (8.9%)
TLF (cardiac death/TVMI [WHO]/CI-TLR)	479 (6.4%)
TLR	322 (4.3%)
TVR, non-TLR	166 (2.2%)
TIMI major bleeding	192 (2.6%)
ST (ARC definite/probable)	59 (0.80%)
Acute ST (0–24 h)	7 (0.09%)
Subacute ST (>24 h to 30 days)	25 (0.31%)
Late ST (>30 days to 365 days)	27 (0.37%)

Values are n (%).
ARC = Academic Research Consortium; CI = clinically indicated; MI = myocardial infarction; ST = stent thrombosis; TLF = target lesion failure; TLR = target lesion revascularization; TVMI = myocardial infarction attributed to target vessel; TVR = target vessel revascularization; WHO = World Health Organization.

between acute/early (<30 days) and late (>30 to 365 days) time periods. Overall incidence of death was 2.3%, with slightly over one-half being cardiac-related (1.3%). Myocardial infarction occurred in 6.2% by ARC criteria and 2.1% by WHO criteria, with cardiac death/MI rates 7.1% and 3.1%, respectively. The majority of MIs were non-Q-wave. Target lesion failure and TLR rates were low, the latter approximating 4% at 1 year.

Univariate and multivariable predictors. Several clinical, procedural, or lesion-specific univariate predictors of ST, cardiac death/MI (ARC-criteria), TLF (ARC-criteria), and TLR were identified and are presented in Table 5. Strong predictors (hazard ratio [HR]: >2.0) of ST in univariate analysis included DAPT interruption ≤30 days, ejection fraction <30%, renal insufficiency, lesion length ≥22 mm, multi-vessel intervention, in-stent restenosis, multi-stent implanted, type B2/C lesion, prior coronary artery bypass graft surgery, multi-vessel disease, and multi-lesion intervention. Strong predictors (HR: >2.0) of cardiac death/MI included renal insufficiency, graft intervention, multi-vessel intervention, and bailout stent use, whereas graft intervention, previous brachytherapy, and multi-vessel intervention were strong predictors of TLF. Target lesion revascularization was strongly (HR: >2.0) predicted by in-stent restenosis, prior brachytherapy, left main intervention, graft intervention, prior coronary artery bypass graft surgery, prior percutaneous coronary intervention, multi-vessel intervention, multi-lesion intervention, multi-vessel disease, and multi-stent implanted.

Multivariable predictors of all 4 outcomes are presented in Table 6. There were only 3 independent predictors of ST, the strongest being DAPT interruption within 30 days (HR: 8.63, 95% confidence interval [CI]: 2.69 to 27.73, p = 0.0003), followed by renal insufficiency (HR: 3.72, 95% CI: 1.71 to 8.09, p = 0.0009) and total length of stents (HR: 1.30, 95% CI: 1.16 to 1.47, p < 0.0001). Neither diabetes

Table 3. DAPT Usage

	No Interruption Through 30 Days	No Interruption Through 180 Days	No Interruption Through 1 Yr
Aspirin	95.9%	93.4%	91.4%
Thienopyridine	97.4%	94.7%	90.2%
DAPT (aspirin and thienopyridine)	94.2%	90.5%	85.6%

Values are % of patients. Dual antiplatelet therapy (DAPT) interruption was defined as medication not taken for at least 1 day through the time window.

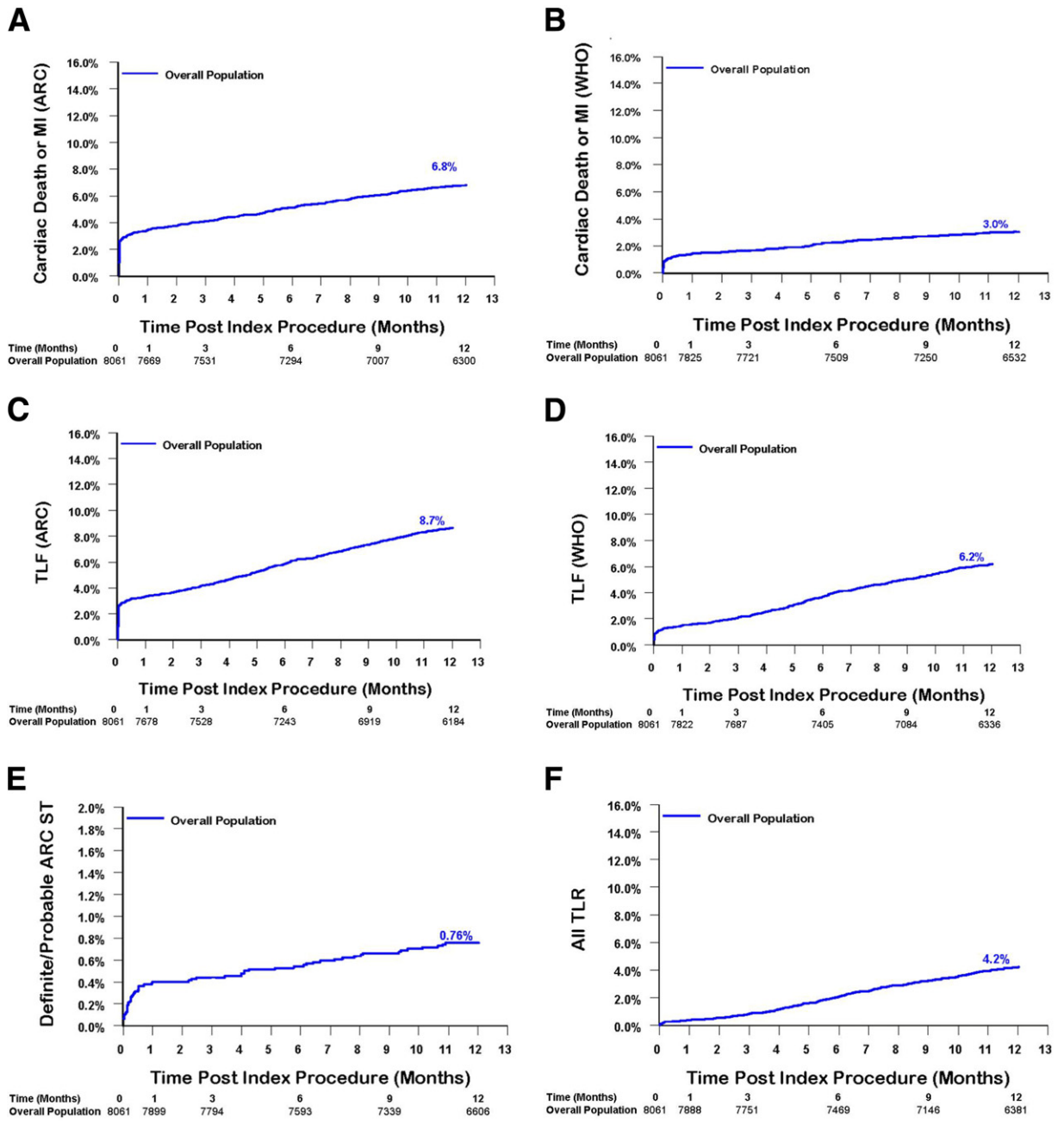

Figure 1. Time-to-Event Curves

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 (TLF) (the composite of cardiac death, ARC-defined MI attributed to target vessel and clinically indicated target lesion revascularization [TLR]); **(D)** TLF (the composite of cardiac death, WHO-defined MI attributed to target vessel and clinically indicated TLR); **(E)** ARC-defined definite and probable stent thrombosis (ST); **(F)** TLR. Event rates shown here were calculated at 365 days with Kaplan-Meier methods.

nor later DAPT interruption (>30 days) was a predictor of ST. In-stent restenosis was the strongest predictor of TLR. Of note, neither lesion length >22 mm nor bifurcation disease predicted TLR, whereas total length of stents independently predicted ST, cardiac death/MI, and TLF. Diabetes, graft intervention, and multi-vessel disease independently predicted TLF and TLR, whereas renal insufficiency was a predictor for ST, cardiac death/MI, and TLF; and ostial disease predicted both TLF and TLR. Female sex predicted cardiac death/MI and therefore also TLF,

Table 5. Univariate Predictors of 1-Year Clinical Outcomes

Variables	ST	CD/MI (ARC)	TLF (ARC)	TLR
Age ≥65 yrs	NS	1.23 (1.03–1.47)	1.20 (1.03–1.41)	NS
Female	NS	1.38 (1.15–1.66)	1.31 (1.11–1.54)	NS
Current smoker	NS	NS	NS	0.68 (0.49–0.93)
Diabetes Rx	NS	1.49 (1.24–1.78)	1.55 (1.32–1.82)	1.67 (1.33–2.10)
HyperteNAion Rx	NS	NS	NS	NS
Hypercholesterolemia Rx	NS	NS	NS	NS
Prior CABG	2.15 (1.09–4.23)	1.53 (1.24–1.90)	1.76 (1.46–2.11)	2.28 (1.77–2.92)
Prior PCI	NS	NS	1.34 (1.14–1.57)	2.21 (1.75–2.80)
CCS III/IV angina	NS	NS	NS	NS
Prior MI	NS	1.43 (1.18–1.74)	1.36 (1.14–1.61)	NS
Brachytherapy	NS	NS	2.19 (1.04–4.61)	3.30 (1.36–8.00)
AMI	NS	1.29 (1.01–1.65)	NS	NS
Renal insufficiency	3.21 (1.66–6.22)	2.16 (1.73–2.70)	1.87 (1.52–2.31)	1.55 (1.13–2.14)
Stroke	NS	1.49 (1.03–2.16)	NS	NS
LVEF <30%	4.67 (1.63–13.43)	1.78 (1.15–2.77)	1.60 (1.06–2.42)	NS
Multi-vessel disease	2.17 (1.20–3.93)	1.64 (1.37–1.96)	1.81 (1.55–2.12)	2.05 (1.63–2.57)
LAD	NS	NS	0.84 (0.72–0.99)	0.78 (0.62–0.99)
Left main vessel	NS	1.83 (1.17–2.86)	1.80 (1.20–2.68)	2.62 (1.60–4.27)
Graft	NS	2.08 (1.55–2.79)	2.24 (1.74–2.89)	2.55 (1.81–3.60)
Heavy calcification	NS	NS	NS	NS
2.5-mm stent	1.98 (1.10–3.57)	NS	1.31 (1.11–1.53)	1.55 (1.24–1.95)
Pre-procedure DS% ≥70%	NS	NS	NS	NS
Pre-procedure TIMI	0.70 (0.53–0.93)	NS	NS	NS
Lesion length ≥22 mm	2.77 (1.50–5.12)	1.68 (1.38–2.04)	1.57 (1.32–1.87)	NS
ISR	2.55 (1.13–5.77)	NS	1.71 (1.35–2.18)	3.38 (2.55–4.49)
Bifurcation	NS	NS	NS	NS
Ostial	NS	1.41 (1.12–1.78)	1.62 (1.33–1.97)	1.83 (1.39–2.41)
B2/C lesion	2.24 (1.07–4.66)	1.52 (1.24–1.86)	1.57 (1.31–1.87)	1.56 (1.20–2.03)
Pre-dilation	NS	NS	NS	NS
Post-dilation	NS	NS	NS	NS
Max balloon pressure	1.08 (1.02–1.15)	1.05 (1.02–1.07)	1.05 (1.03–1.07)	1.05 (1.02–1.09)
Treated lesions, n	2.08 (1.16–3.74)	1.64 (1.37–1.97)	1.85 (1.58–2.17)	2.10 (1.67–2.63)
Treated vessels, n	2.57 (1.31–5.05)	2.01 (1.61–2.50)	2.03 (1.67–2.46)	2.15 (1.63–2.84)
Bailout stent use	NS	2.00 (1.24–3.25)	1.86 (1.19–2.91)	NS
Stents implanted, n	2.45 (1.34–4.48)	1.72 (1.44–2.06)	1.87 (1.59–2.18)	2.01 (1.60–2.53)
Stent length (10 mm)	1.30 (1.18–1.43)	1.16 (1.12–1.21)	1.16 (1.13–1.20)	1.15 (1.09–1.20)
DAPT interruption* ≤30 days	7.32 (2.66–20.14)	NS	NS	NS
DAPT interruption* >30 days	NS	NS	NS	NS

Values are hazard ratio (95% confidence interval) for variables that reached statistical significance ($p < 0.05$). NA indicates not applicable, because those variables were not included in the model. *The DAPT interruption was defined as cessation of either aspirin or thienopyridine for at least 1 day within 1 year from procedure. The timing of interruption was based on when the first interruption occurred for that patient.

CD/MI = cardiac death and myocardial infarction (per ARC); DS = diameter stenosis; ISR = in-stent restenosis; NS = not significant; Rx = requiring medication; ST = stent thrombosis (ARC definite/probable); TLF = target lesion failure (a composite of cardiac death, MI [per ARC] attributed to target vessel and clinically indicated TLR); other abbreviations as in Tables 1 to 4.

whereas use of small diameter stents (2.5 mm) only predicted TLR.

Discussion

The current study represents the largest, prospective single-arm trial of EECSS in "real-world" clinical practice within the United States, extending the results of the original XIENCE V USA study and allowing a more robust and contemporary evaluation of both incidence and predictors of outcome. Characteristic of current practice, one-third presented with unstable angina, roughly 15% presented with acute MI, and a significant percentage of patients had diabetes, renal insufficiency, and high-risk angiographic findings. Approximately 94% continued to receive DAPT without any interruption within 30 days, and 85% continued

Table 6. Multivariate Predictors of 1-Year Clinical Outcomes

	Multivariate Predictors	Hazard Ratio (95% CI)	p Value
ARC definite/probable ST	DAPT interruption* ≤30 days	8.63 (2.69–27.73)	0.0003
	Renal insufficiency	3.72 (1.71–8.09)	0.0009
	Total length of stents (10 mm)	1.30 (1.16–1.47)	<0.0001
Cardiac death and ARC MI (CD/MI)	Renal insufficiency	1.64 (1.22–2.19)	0.0010
	Female	1.46 (1.18–1.82)	0.0006
	Prior MI	1.43 (1.15–1.78)	0.0014
	Multi-vessel intervention	1.40 (1.05–1.85)	0.0214
	Diabetes Rx	1.34 (1.07–1.67)	0.0096
	Total length of stents (10 mm)	1.16 (1.10–1.22)	<0.0001
TLF	Bailout stent usage	1.88 (1.15–3.07)	0.0188
	Target vessel: graft	1.78 (1.28–2.47)	0.0007
	ISR	1.47 (1.12–1.92)	0.0048
	Diabetes Rx	1.46 (1.22–1.76)	<0.0001
	Renal insufficiency	1.46 (1.14–1.86)	0.0026
	Multi-vessel disease	1.41 (1.16–1.70)	0.0004
	Female	1.41 (1.17–1.69)	0.0003
	Prior CABG	1.35 (1.06–1.71)	0.0156
	Ostial lesion	1.26 (1.01–1.58)	0.0398
	Total length of stents (10 mm)	1.14 (1.10–1.19)	<0.0001
TLR	ISR	2.28 (1.63–3.19)	<0.0001
	Prior PCI	1.69 (1.27–2.25)	0.0003
	Prior CABG	1.67 (1.22–2.29)	0.0014
	Diabetes Rx	1.60 (1.23–2.07)	0.0004
	Target vessel: graft	1.60 (1.04–2.47)	0.0309
	Multi-vessel disease	1.52 (1.13–2.03)	0.0054
	Multiple lesions treated	1.50 (1.12–2.01)	0.0070
	Ostial lesion	1.39 (1.03–1.89)	0.0328
	2.5-mm stent	1.36 (1.04–1.77)	0.0241

*The DAPT interruption was defined as cessation of either aspirin or thienopyridine for at least 1 day within 1 year from procedure. The timing of interruption was based on when the first interruption occurred for that patient.

Abbreviations as in Tables 1 to 5.

to receive DAPT without any interruption within 1 year. Despite this complex patient population, very low rates of all major adverse clinical events were noted, including 0.80% ST and roughly 4% TLR rates. Several independent predictors were identified in multivariable analysis. Importantly, only 3 characteristics seem to independently predict ST, with clinical predictors dominating. Of these, early (≤30 days) interruption of DAPT conferred an almost 9-fold increased risk, whereas interruption after 30 days did not seem to elevate risk, reinforcing the importance of exploring shorter durations of DAPT in patients treated with EECSS.

The safety and efficacy of the EECSS has been confirmed in several completed and relatively large randomized controlled trials, including the SPIRIT IV trial (SPIRIT IV Clinical Trial: Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) within the United States and both the COMPARE (A Randomized Controlled Trial of Everolimus-eluting Stents and Paclitaxel-eluting Stents for Coronary Revascularization in Daily Practice: The COMPARE Trial) and RESOLUTE All-Comers (RESOLUTE-III All-comers Trial: A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) trials outside the United States (18–20). Yet, such evaluations might be limited by relatively strict entry criteria, the selection bias inherent to all randomized controlled trials, and relatively low patient enrollment that might not fully characterize rare events, such as ST. As a result, baseline characteristics of these pivotal randomized controlled trials tended to include patients of lower risk than the XIENCE V USA trial. Compared with the SPIRIT IV trial, for example, the XIENCE V USA trial included a numerically higher percentage with diabetes, unstable angina, and previous MI as well as a higher mean reference vessel diameter (reflecting the lack of strict inclusion or exclusion criteria). Dual antiplatelet therapy was used approximately 95% at 1 year in the SPIRIT IV trial, compared with 85% in the XIENCE V

USA trial, whereas usage at 1 year in the Dutch single-center COMPARE trial was 70%. Despite these differences, the per-WHO incidences of cardiac death/MI, TLF, and TLR remained low albeit numerically higher in the XIENCE V USA trial (3.1%, 6.4%, and 4.3%, respectively) compared with the EECSS arm of the SPIRIT IV trial (2.8%, 4.2%, and 2.5%, respectively), and rates of cardiac death/MI and TLR were similar to the EECSS arm of the COMPARE trial (4% and 2%, respectively). The EECSS arm of the RESOLUTE All-Comers trial is perhaps more comparable to the present study, with roughly 65% "off-label" use compared with the 61% "off-label" use of the XIENCE V USA trial (20). Rates of TLF (6.4% vs. 8.3%) and cardiac death/MI (3.1% vs. 5.4%) are numerically lower in the XIENCE V USA trial, with similar rates of TLR (4.3% vs. 3.4%).

These 1-year results are similar to other "real-world" registries of DES, including a 12-month MACE rate of 7.5% (cardiac death/MI 3.0%, TLR 4.5%) in the E-FIVE (World-Wide Registry With The Endeavor Zotarolimus Eluting Coronary Stent) Registry of the zotarolimus-eluting stent (21). In addition, a 12-month MACE rate of 5.8% was noted in the e-Cypher Registry of the sirolimus-eluting stent, and 9-month MACE rates of 8.0% and 7.5% were found for the sirolimus-eluting and paclitaxel-eluting stents, respectively, in the STENT (Strategic Transcatheter Evaluation of New Therapies) Registry, with again similar rates in the REWARDS (Registry Experience at the Washington Hospital Center with Drug-Eluting Stents) Registry (22–25). On the basis of these data, the EECSS seems to perform as well or better at the 1-year mark than any other available DES.

From an ST standpoint, studies of the EECSS to date have indicated a very low <1% rate of ARC-defined definite/probable ST at 1 year, regardless of baseline patient population risk profile (18–20). However, there remains concern that larger patient populations in complex "real-world" patient subsets are required to accurately inform the absolute rate of these low-frequency events in day-to-day practice (13,17). Although the FDA-mandated DAPT Trial—which recently completed enrollment—has included over 20,000 patients, the allowance of all available DES as well as bare-metal stents will ultimately limit its ability to reflect the current incidence of ST for any individual stent. Therefore results from the XIENCE V USA study provide the most robust and practical estimate of ST in routine practice. In this regard, the 0.80% rate of ST through 1 year seen here (and consistent with the 0.7% rate in the EECSS arms of both the COMPARE and RESOLUTE All-Comers trials) is reassuring (19,20). Moreover, this rate is numerically lower than that seen at 1 year with either the first-generation or second-generation zotarolimus-eluting stents (1.1% and 1.6%, respectively) (20,21).

There are limited data on independent predictors of major adverse clinical events with routine use of the EECSS. Pooling data from several randomized controlled trials in almost 7,000 patients comparing the EECSS with the paclitaxel-eluting stent found that insulin-requiring diabetes, hypertension, multi-lesion intervention, prior percutaneous coronary intervention, pre-procedure reference vessel diameter, and LAD location all predicted MACE, with use of the EECSS strongly protective (36% relative risk reduction) (26). However, whether all these factors would remain predictive if the study were limited to the EECSS is unclear. We found that both clinical and angiographic characteristics continue to predict MACE when using a sole-EECSS strategy. Not surprisingly, clinical characteristics such as renal insufficiency, female sex, prior MI, and diabetes dominated as predictors of cardiac death/MI, whereas angiographic features such as in-stent restenosis, graft intervention, multi-vessel disease, multi-lesion intervention, ostial location, and 2.5-mm stent diameter dominated as predictors of TLR. Target lesion failure, being a combination of cardiac death, target vessel MI, and clinically indicated TLR, showed significant confluence of these clinical and angiographic predictors.

The issue of ST has dominated the interventional cardiology landscape for the past 5 years, with newer-generation stents developed with dual goals of both reducing rates of ST at all time points and perhaps providing sufficient safety data to allow earlier discontinuation or interruption of DAPT. In the current study, not only were ST rates low but only 3 independent predictors of ST were noted when using EECSS. Two clinical criteria, namely renal insufficiency and early (≤30 days) interruption of DAPT, emerged as the only clinical predictors, whereas total stent length emerged as the sole angiographic predictor (and a relatively weak one by comparison). Although these have been noted before, the fact that only 3 predictors remain with use of this particular DES, with clinical variables by far dominating, is indeed notable, as is the absence of several previously identified predictors, such as diabetes, reduced ejection fraction, and bifurcation disease (27). Additionally, the current study is the first to suggest that DAPT interruption after 30 days does not increase the incidence of ST within the first post-procedure year when using the EECSS. Although the current study cannot be used to advocate for interruption of DAPT before 1 year (or, if necessary, after 30 days), it might help confirm recent studies of 6-month DAPT, such as the PRODIGY study (PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study), and serve as the basis for further studies of extremely short duration DAPT (28).

Study limitations. The main limitations of the current study are its observational, nonrandomized nature, the lack of mandatory angiographic follow-up, and that there is currently only 1-year follow-up. Comparisons between differ-

ent DES platforms cannot be drawn from the present study and are included herein as hypothesis-generating only. Importantly, because the concern with first-generation DES is primarily related to very late (>1 year) ST, the present paper cannot address this issue. Furthermore, DAPT adherence was assessed on the basis of patient reported history rather than pill counts, and there were a relatively small number of ST events and a large number of predictor variables built into the model. For these reasons, the interpretation of predictors, such as DAPT usage and their relationship with ST, needs to be cautious. However, several mechanisms were incorporated into the prospective XIENCE V USA single-arm trial to improve generalizability. Chief among these are the incorporation of few exclusion criteria, namely inability to give informed consent and use of stents other than the EECSS, rigorous data monitoring and high follow-up rates, independent endpoint adjudication, and other quality-control methods that mirror those found in high-quality randomized controlled trials. In addition, prospectively defined analysis plans, random auditing of source documents in a large percentage of patients, and descriptor and endpoint definitions identical to similar randomized controlled studies were used. Thus, the large patient database in the XIENCE V USA trial provided an accurate evaluation of the actual incidence of major adverse clinical events (including rare events, such as ST) and the identification of multivariable predictors in contemporary, real-world clinical practice with this second-generation DES.

Conclusions

Incidences of all major adverse clinical events are low in the first year after EECSS deployment in a large "real-world" and complex patient population within the United States, despite a low 85% use of DAPT through 1 year, and are predicted generally by clinical and angiographic characteristics, including diabetes, renal insufficiency, multi-vessel disease, graft intervention, ostial disease, and total length of stents. Only 3 characteristics (2 clinical and 1 angiographic) predicted definite/probable ST within the first year, with clinical predictors dominating. Premature interruption of DAPT strongly predicted ST but only when stopped within 30 days of the procedure.

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