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3- or 1-Month DAPT in Patients at High Bleeding Risk Undergoing Everolimus-Eluting Stent Implantation

Roxana Mehran, MD,[a] Davide Cao, MD,[a] Dominick J. Angiolillo, MD, PhD,[b] Sripal Bangalore, MD, MHA,[c] Deepak L. Bhatt, MD, MPH,[d] Junbo Ge, MD,[e] James Hermiller, MD,[f] Raj R. Makkar, MD,[g] Franz-Josef Neumann, MD,[h] Shigeru Saito, MD,[i] Hector Picon, MD,[j] Ralph Toelg, MD,[k] Aziz Maksoud, MD,[l] Bassem M. Chehab, MD,[m] Jose M. De la Torre Hernandez, MD, PhD,[n] Vijay Kunadian, MD,[o] Gennaro Sardella, MD,[p] Holger Thiele, MD,[q] Olivier Varenne, MD,[r] Pascal Vranckx, MD,[s] Stephan Windecker, MD,[t] Yujie Zhou, MD,[u] Mitchell W. Krucoff, MD,[v] Karine Ruster, PhD,[w] Jin Wang, PhD,[w] Marco Valgimigli, MD, PhD,[x] on behalf of the XIENCE 90 and XIENCE 28 Investigators

ABSTRACT

OBJECTIVES The aim of this study was to evaluate 2 abbreviated dual-antiplatelet therapy (DAPT) regimens in patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI).

BACKGROUND Current-generation drug-eluting stents are preferred over bare-metal stents for HBR patients, but their optimal DAPT management remains unknown.

METHODS The XIENCE Short DAPT program included 3 prospective, multicenter, single-arm studies enrolling HBR patients who underwent successful PCI with a cobalt-chromium everolimus-eluting stent. After 1 month (XIENCE 28 USA and XIENCE 28 Global) or 3 months (XIENCE 90) of DAPT, event-free patients discontinued the $P2Y_{12}$ inhibitor. The postmarketing approval XIENCE V USA study was used as historical control in a propensity score–stratified analysis.

RESULTS A total of 3,652 patients were enrolled. The propensity-adjusted rate of the primary endpoint of all-cause mortality or myocardial infarction was 5.4% among 1,693 patients on 3-month DAPT versus 5.4% in the 12-month DAPT historical control ($P_{\text{noninferiority}} = 0.0063$) and 3.5% among 1,392 patients on 1-month DAPT versus 4.3% in the 6-month DAPT historical control ($P_{\text{noninferiority}} = 0.0005$). Bleeding Academic Research Consortium (BARC) types 2 to 5 bleeding was not significantly lower with 3- or 1-month DAPT, while BARC types 3 to 5 bleeding was reduced in both experimental groups. The rate of definite or probable stent thrombosis was 0.2% in XIENCE 90 ($P < 0.0001$ for the performance goal of 1.2%) and 0.3% in XIENCE 28.

CONCLUSIONS Among HBR patients undergoing PCI with cobalt-chromium everolimus-eluting stents, DAPT for 1 or 3 months was noninferior to 6 or 12 months of DAPT for ischemic outcomes and may be associated with less major bleeding and a low incidence of stent thrombosis. (J Am Coll Cardiol Intv 2021;14:1870–1883) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]Icahn School of Medicine at Mount Sinai, New York, New York, USA; [b]University of Florida College of Medicine-Jacksonville, Jacksonville, Florida, USA; [c]New York University Langone Medical Center, New York, New York, USA; [d]Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, Massachusetts, USA; [e]Zhongshan Hospital Fudan University, Shanghai, China; [f]St. Vincent's Medical Center of Indiana, Indianapolis, Indiana, USA; [g]Cedars-Sinai Medical Center, Los Angeles, California, USA; [h]University Heart Center Freiburg, Bad Krozingen, Germany; [i]Shonan Kamakura General Hospital, Kamakura, Japan; [j]Redmond Regional Medical Center, Rome, Georgia, USA; [k]Segeberger Kliniken, Herzzentrum, Bad Segeberg, Germany; [l]Kansas Heart Hospital and University of Kansas School of Medicine, Wichita, Kansas, USA; [m]Ascension Via Christi Hospital, Wichita, Kansas, USA; [n]Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain; [o]Translational and Clinical Research Institute, Newcastle University and Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; [p]Policlinico Umberto I di Roma, Rome, Italy; [q]Heart Center Leipzig at University of Leipzig and Leipzig Heart Institute, Leipzig, Germany; [r]Hospital Cochin, Paris, France; [s]Heart Centre Hasselt and University of Hasselt, Hasselt, Belgium; [t]Bern University Hospital, Bern, Switzerland; [u]Beijing AnZhen Hospital, Beijing, China; [v]Duke University Medical Center and Duke Clinical Research Institute, Durham, North Carolina, USA; [w]Abbott, Santa Clara, California, USA; and [x]Cardiocentro Ticino, Lugano and Bern University Hospital, Bern, Switzerland.
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Dual-antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is generally indicated for 6 to 12 months to prevent ischemic events, including stent thrombosis, after percutaneous coronary intervention (PCI) (1,2). However, DAPT is also associated with an increased risk in bleeding, which is proportional to the duration and intensity of treatment (3). Bleeding complications affect patient morbidity and mortality (4-7), and as many as 40% of patients undergoing PCI have high bleeding risk (HBR) conditions that make prolonging the duration of DAPT clinically unattractive (8). Shortening the duration of DAPT by discontinuing $P2Y_{12}$-inhibiting therapy has therefore been proposed among such patients, but data evaluating their optimal DAPT management remain scarce.

The XIENCE everolimus-eluting stent (Abbott) is a thin-strut (81 μm) cobalt-chromium alloy platform coated with a durable-fluorinated polymer for controlled drug elution. Preclinical studies have shown that this cobalt-chromium everolimus-eluting stent is associated with reduced thrombogenicity compared with other devices, and several clinical trials have shown a lower risk for stent thrombosis and major cardiovascular events (9-11). The XIENCE Short DAPT clinical program was designed to test the hypothesis that HBR patients undergoing successful PCI with the XIENCE stent who are adherent to a DAPT regimen of 1 or 3 months have similar cardiovascular ischemic and lower bleeding risk compared with a DAPT duration of 6 or 12 months.

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METHODS

STUDY DESIGN. The XIENCE Short DAPT program was sponsored by Abbott and comprised 3 prospective, multicenter, single-arm studies, the design of which has been previously reported (12). The XIENCE 90 (A Safety Evaluation of 3-month DAPT After XIENCE Implantation for HBR Patients) study (NCT03218787) was conducted at 101 sites in the United States, the XIENCE 28 USA study (NCT03815175) was conducted at 58 sites in the United States and Canada, and the XIENCE 28 Global study (NCT03355742) was conducted at 52 sites in Europe and Asia (Supplemental Tables S1 to S3). The 2 XIENCE 28 studies were conducted separately, but their datasets were subsequently pooled together as prespecified in the statistical analysis plan. Details on the trial organization and enrolling sites are provided in the Supplemental Appendix. The principal investigators with members of the executive and steering committees and the sponsor designed the protocol. Study principal investigators, site principal investigators, and the sponsor were responsible for the study conduct and the integrity of data analysis. An independent data and safety monitoring board provided external oversight to ensure the safety of study participants.

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

DAPT = dual-antiplatelet therapy

HBR = high bleeding risk

PCI = percutaneous coronary intervention

PARTICIPANTS. HBR patients undergoing successful PCI exclusively with a fluoropolymer-based cobalt-chromium everolimus-eluting stent (XIENCE) in whom, in the opinion of the treating physician, the risk for major bleeding associated with a prolonged DAPT regimen outweighed the benefit were eligible for enrollment. Patients had to meet at least 1 of the following HBR criteria: age ≥75 years, indication for long-term anticoagulant therapy, history of major bleeding in the previous 12 months, history of ischemic or hemorrhagic stroke, renal insufficiency defined as creatinine ≥2.0 mg/dL or maintenance dialysis, anemia with hemoglobin <11 g/dL, and systemic conditions associated with an increased risk for bleeding, including hematologic disorders such as thrombocytopenia (platelet count <100,000/mm^3) and coagulation disorders. The study allowed treatment of up to 3 target lesions, with a maximum of 2 target lesions per epicardial vessel, and of bifurcation lesions without 2-stent techniques. Key exclusion criteria included presentation with ST-segment elevation myocardial infarction, implantation of a drug-eluting stent other than a cobalt-chromium everolimus-eluting stent in the previous 12 months, and target lesion treated with overlapping stents. The full list of inclusion and exclusion criteria is reported in Supplemental Table S4. The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board at each site. All enrolled patients provided written informed consent.

PROCEDURES. The index PCI was performed according to local standard of care, except for the uniform

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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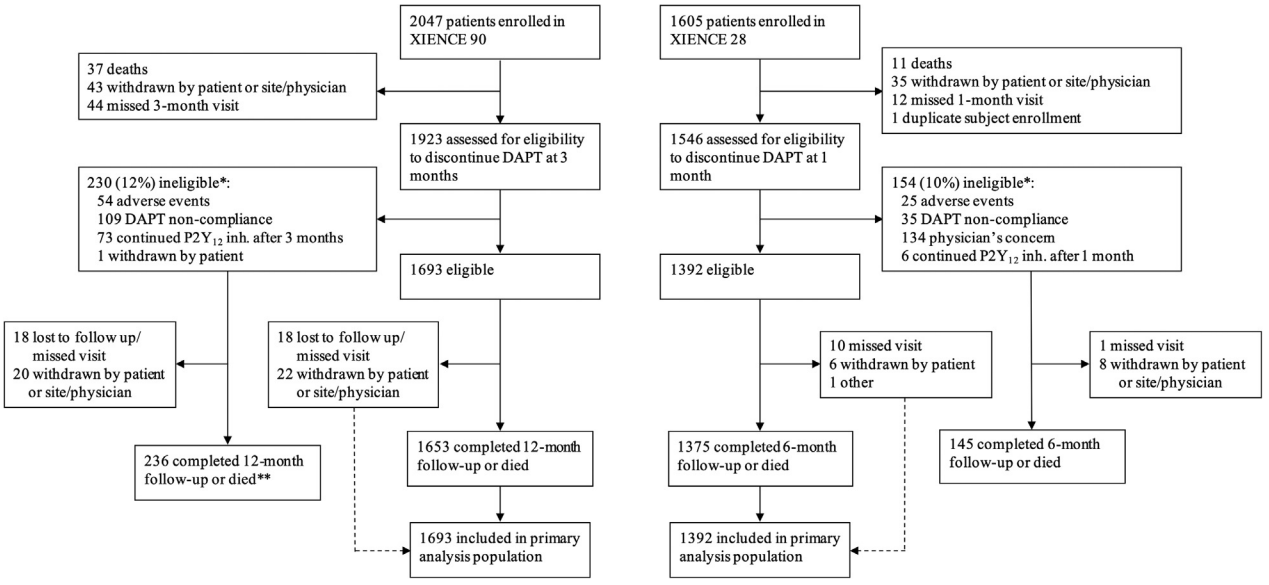
FIGURE 1 Study Design



Patients were eligible to discontinue dual-antiplatelet therapy (DAPT) at 1 or 3 month if they had been adherent to treatment (ie, without interruption of either aspirin and/or $P2Y_{12}$ inhibitor (inh.) for more than 7 consecutive d) and free from myocardial infarction, repeat coronary revascularization, stroke, or stent thrombosis. *Reasons for ineligibility to discontinue DAPT at 1 or 3 months are not mutually exclusive. **Patients who missed the 3-months visit but completed the 12-months visit were included in the ineligible group.

implantation of cobalt-chromium everolimus-eluting stents. After the procedure, all patients received open-label aspirin 75 to 100 mg plus a $P2Y_{12}$ inhibitor. There were no restrictions on the choice of the $P2Y_{12}$ inhibitor, but clopidogrel was recommended. For those on long-term anticoagulant agents, dual therapy consisting of an oral anticoagulant agent and a $P2Y_{12}$ inhibitor, preferably clopidogrel, could be considered per investigator's discretion. Eligibility to discontinue DAPT was assessed at 3 months in XIENCE 90 and at 1 month in XIENCE 28. Patients who had been adherent to treatment and free from myocardial infarction, repeat coronary revascularization, stroke, or stent thrombosis discontinued the $P2Y_{12}$ inhibitor and continued aspirin until the end of the study. Clinical follow-up, including medication adherence assessment, was performed via office visits or telephone contacts at 3, 6, and 12 months after the index procedure in XIENCE 90 and at 1, 3, 6, and 12 months in XIENCE 28.

ENDPOINTS. The primary endpoint was the composite of all-cause death or myocardial infarction, as defined by a modified Academic Research Consortium definition (13). The powered key secondary endpoint was Bleeding Academic Research Consortium (BARC) types 2 to 5 bleeding (14). Definite or probable stent thrombosis was a powered key secondary endpoint in XIENCE 90 but not in XIENCE 28. The time window for the assessment of the primary and secondary endpoints was between 3 and 12 months after the index procedure in XIENCE 90, and between 1 and 6 months in XIENCE 28. Other secondary endpoints with endpoint definitions are provided in the Supplemental Tables S5 and S6. All endpoint events were adjudicated by an independent clinical events committee.

STATISTICAL ANALYSIS. To evaluate the safety and effectiveness of a DAPT duration of 1 and 3 months compared with a standard regimen of up to 12 months, individual patient-level data from the prospective, multicenter, postmarketing approval XIENCE V USA (XIENCE V® Everolimus Eluting Coronary Stent System USA Post-Approval Study) study (NCT00676520) were used as a historical control in a propensity score-stratified analysis. Among the 8,061 patients enrolled in XIENCE V USA, the reported DAPT use was 90.5% and 85.6% at 6 and 12 months, respectively, after PCI (15). The historical control group comprised only those patients fulfilling the eligibility criteria of the XIENCE Short DAPT

program and who were adherent to treatment and free from ischemic events at the time points defined previously.

The primary endpoint was assessed for the noninferiority of a short DAPT regimen to the historical control. For XIENCE 90, we assumed an event rate of 6.1% between 3 and 12 months in both arms, with noninferiority declared if the upper limit of the 1-sided 97.5% confidence interval of the propensity score-stratified difference was <2.8%. We estimated that 2,000 patients were required in XIENCE 90 to achieve 87% power after allowing an attrition rate of 15%. In XIENCE 28 (combining the global and US studies), the rate of the primary endpoint was assumed to be 4.3% between 1 and 6 months. Considering an attrition rate of 10%, with a 2.5% noninferiority margin and a 1-sided alpha level of 0.025, about 1,600 patients were required to achieve 90% power (12).

The key secondary endpoint of BARC type 2 to 5 bleeding was tested for the superiority of a short DAPT regimen over the historical control. We estimated the event rate in the historical control group to be 6.0% between 3 and 12 months and 4.6% between 1 and 6 months. The sample sizes of XIENCE 90 and XIENCE 28 provided each study with at least 90% power to detect a 50% reduction in bleeding rates with 3-month DAPT and 1-month DAPT, respectively, using a 1-sided alpha level of 0.025 (12). Finally, in XIENCE 90, the key secondary endpoint of definite or probable stent thrombosis was evaluated against a prespecified performance goal of 1.2%. An assumed 0.5% rate of stent thrombosis between 3 and 12 months in 2,000 patients receiving 3-month DAPT provided 85% power using the exact test with a 1-sided alpha level of 0.025 (12).

The primary and key secondary endpoint analyses were stratified by propensity score categorized into quintiles. The propensity score of each individual was calculated using a logistic regression model that included the study group as the outcome and the baseline demographic, clinical, and procedural covariates as the predictors. Stratification on the propensity score involves dividing subjects into mutually exclusive strata wherein the distribution of measured covariates is approximately similar. Treatment effects are estimated within each stratum and then pooled together to derive the average treatment effect taking into account the weight of each stratum (16). Unlike other propensity score methods, stratification allows retaining data from all study participants into the final analysis. The stratified noninferiority and superiority tests were performed using the Farrington-Manning method (17), with the weight for each stratum determined by the total number of patients in a stratum versus the total number of patients for the intended analysis. The Markov-chain Monte Carlo multiple imputation method was applied to handle missing data in propensity score building. With 10 duplicates of the imputed propensity score datasets, Rubin's combination rule was used to consolidate the final analysis. The design and modeling of the propensity score for XIENCE 90 and XIENCE 28 were developed separately by an independent statistician blinded to outcome data and then used by the sponsor for the final endpoint analyses. To assess the heterogeneity of treatment effects across prespecified subgroups, a generic version of the meta-analysis was implemented. Each subgroup contributes a normalized treatment effect and its standard error by going through a similar process as the primary endpoint analysis via the Farrington-Manning method and Rubin's combination rule. Statistical analyses were performed with R version 3.6.2 (R Foundation for Statistical Computing) or SAS version 9.4 (SAS Institute).

RESULTS

PATIENT CHARACTERISTICS. Between July 19, 2017, and August 9, 2019, a total of 2,047 patients were enrolled in XIENCE 90. The primary analysis population included 1,693 patients (82.7%) who discontinued DAPT at 3 months after PCI. Of those, 97.6% were followed up until death or their last 12-month visit. In XIENCE 28 (USA and Global studies pooled), a total of 1,605 patients were enrolled between February 9, 2018, and February 7, 2020; 1,392 (86.7%) discontinued DAPT at 1 month; and 98.8% had complete follow-up at 6 months (Supplemental Figure S1). The reasons for exclusion of enrolled patients from the primary analysis population are detailed in **Figure 1**, and their baseline characteristics and clinical outcomes are provided in the Supplemental Appendix (Supplemental Tables S7 to S16, S20, and S24).

Table 1 shows the distribution of the inclusion criteria for HBR and the clinical and procedural characteristics of patients in the experimental and historical control groups. An age of at least 75 years was the most common HBR criterion in both XIENCE 90 and XIENCE 28 (66.5% and 68.2%, respectively), followed by long-term anticoagulant therapy

TABLE 1 Baseline Characteristics

	XIENCE 90		XIENCE 28	
	3-Month DAPT (n = 1,693)	12-Month DAPT (n = 1,280)	1-Month DAPT (n = 1,392)	6-Month DAPT (n = 1,411)
HBR criteria				
Age ≥75 y	1,125/1,693 (66.5)	708/1,280 (55.3)	950/1,392 (68.2)	775/1,411 (54.9)
Chronic anticoagulant therapy	705/1,693 (41.6)	160/1,280 (12.5)	617/1,392 (44.3)	184/1,411 (13.0)
Anemia*	254/1,693 (15.0)	209/1,280 (16.3)	201/1,392 (14.4)	229/1,411 (16.2)
History of stroke	181/1,693 (10.7)	155/1,280 (12.1)	145/1,392 (10.4)	176/1,411 (12.5)
Renal insufficiency†	131/1,693 (7.7)	383/1,280 (29.9)	116/1,392 (8.3)	420/1,411 (29.8)
Thrombocytopenia‡	48/1,693 (2.8)	20/1,280 (1.6)	55/1,392 (4.0)	25/1,411 (1.8)
History of major bleeding	49/1,693 (2.9)	34/1,280 (2.7)	46/1,392 (3.3)	37/1,411 (2.6)
Number of HBR criteria	1.5 ± 0.7	1.3 ± 0.6	1.5 ± 0.7	1.3 ± 0.6
Clinical characteristics				
Age, y	75.25 ± 9.29	72.70 ± 10.26	75.97 ± 8.37	72.56 ± 10.42
Female	596/1,693 (35.2)	524/1,280 (40.9)	453/1,392 (32.5)	576/1,411 (40.8)
Race				
American Indian or Alaskan Native	11/1,693 (0.6)	9/1,280 (0.7)	2/1,392 (0.1)	11/1,411 (0.8)
Asian	37/1,693 (2.2)	17/1,280 (1.3)	126/1,392 (9.1)	19/1,411 (1.3)
Black or African American	96/1,693 (5.7)	110/1,280 (8.6)	36/1,392 (2.6)	115/1,411 (8.2)
Native Hawaiian or Pacific Islander	5/1,693 (0.3)	4/1,280 (0.3)	0/1,392 (0.0)	4/1,411 (0.3)
White	1,496/1,693 (88.4)	1,101/1,280 (86.0)	807/1,392 (58.0)	1,224/1,411 (86.7)
Hispanic or Latino ethnicity	45/1,689 (2.7)	41/1,280 (3.2)	138/1,392 (9.9)	42/1,411 (3.0)
Hypertension	1,516/1,693 (89.5)	1,167/1,272 (91.7)	1,179/1,392 (84.7)	1,283/1,402 (91.5)
Dyslipidemia	1,401/1,693 (82.8)	1,140/1,257 (90.7)	939/1,392 (67.5)	1,254/1,383 (90.7)
Diabetes mellitus	663/1,692 (39.2)	546/1,273 (42.9)	512/1,382 (37.0)	594/1,404 (42.3)
Chronic kidney disease§	677/1,682 (40.2)	532/1,202 (44.3)	631/1,330 (47.4)	584/1,327 (44.0)
Prior PCI	520/1,693 (30.7)	477/1,230 (38.8)	390/1,392 (28.0)	514/1,355 (37.9)
Prior CABG	205/1,693 (12.1)	174/1,230 (14.1)	112/1,392 (8.0)	201/1,355 (14.8)
Prior MI	264/1,669 (15.8)	353/1,174 (30.1)	227/1,382 (16.4)	393/1,295 (30.3)
Multivessel disease	779/1,693 (46.0)	473/1,280 (37.0)	573/1,393 (41.2)	535/1,411 (37.9)
Clinical presentation				
Chronic coronary syndrome	1,105/1,693 (65.3)	790/1,195 (66.1)	917/1,392 (65.9)	846/1,318 (64.2)
Acute coronary syndrome	588/1,693 (34.7)	405/1,195 (33.9)	475/1,392 (34.1)	472/1,318 (35.8)
NSTEMI	120/1,693 (7.1)	113/1,089 (10.4)	245/1,392 (17.6)	138/1,195 (11.5)
Unstable angina	486/1,693 (28.7)	257/1,190 (21.6)	230/1,392 (16.5)	287/1,311 (21.9)
PARIS bleeding risk score				
Mean ± SD	6.0 ± 2.3	5.2 ± 2.2	6.1 ± 2.3	5.2 ± 2.2
Median (IQR)	6.0 (4.0–8.0)	5.0 (3.0–6.0)	6.0 (4.0–8.0)	5.0 (3.0–7.0)
PRECISE-DAPT bleeding risk score				
Mean ± SD	26.1 ± 11.5	25.4 ± 10.9	27.7 ± 11.3	25.3 ± 10.9
Median (IQR)	25.0 (19.0–32.0)	26.0 (18.0–32.0)	27.0 (20.0–34.0)	25.0 (18.0–32.0)

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(41.6% and 44.3%) and anemia (15.0% and 14.4%). The mean number of HBR criteria per patients was 1.5 ± 0.7 in both studies. Overall, 34.7% of patients in XIENCE 90 and 34.1% in XIENCE 28 underwent PCI for a non-ST-segment elevation acute coronary syndrome.

Among patients who were eligible to discontinue DAPT at 3 months, 13.2% were on DAPT at 100 days, 9.1% at 180 days, and 8.7% at 365 days. Corresponding rates among those eligible to discontinue DAPT at 1 month were 2.9% at 45 days, 2.2% at 90 days, and 2.6% at 180 days (**Figure 2**). The use of antiplatelet therapy in the historical control group of XIENCE 90 and 28 is detailed in Supplemental Figures S2 and S3.

ISCHEMIC OUTCOMES. After propensity score stratification into quintiles, the mean rate of death or myocardial infarction between 3 and 12 months was 5.4% in patients who discontinued DAPT at 3 months and 5.4% in those who continued DAPT up to 12 months, with a 1-sided upper 97.5% confidence limit for the propensity-stratified difference of 2.2%, which met the prespecified criterion of 2.8% for noninferiority ($P = 0.0063$) (**Figure 3A**). Discontinuing DAPT at 3 months resulted in a rate of definite or probable stent thrombosis between 3 and 12 months of 0.2%, with the 1-sided upper 97.5% confidence limit (0.63%) being lower than the performance goal of 1.2% ($P < 0.0001$) (**Figure 4A**).

The propensity score–stratified mean rate of death or myocardial infarction was 3.5% in patients who discontinued DAPT at 1 month and 4.3% in those who continued DAPT up to 6 months, with a 1-sided upper

TABLE 1 Continued

	XIENCE 90		XIENCE 28	
	3-Month DAPT (n = 1,693)	12-Month DAPT (n = 1,280)	1-Month DAPT (n = 1,392)	6-Month DAPT (n = 1,411)
Procedural characteristics				
Number of lesions treated				
Mean ± SD	1.2 ± 0.5	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.5
Median (IQR)	1.0 (1.0–1.0)	1.0 (1.0–2.0)	1.0 (1.0–1.0)	1.0 (1.0–2.0)
Number of vessels treated				
Mean ± SD	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3
Median (IQR)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Target lesion location				
Left anterior descending coronary artery	814/1,693 (48.1)	612/1,279 (47.8)	719/1,392 (51.7)	661/1,411 (46.8)
Left circumflex coronary artery	479/1,693 (28.3)	372/1,280 (29.1)	382/1,392 (27.4)	416/1,411 (29.5)
Right coronary artery	578/1,693 (34.1)	441/1,279 (34.5)	456/1,392 (32.8)	490/1,411 (34.7)
Type B2/C lesion	573/1,693 (33.8)	542/1,104 (49.1)	498/1,392 (35.8)	614/1,216 (50.5)
Bifurcation	129/1,693 (7.6)	127/1,278 (9.9)	161/1,392 (11.6)	139/1,408 (9.9)
Radial access	883/1,693 (52.2)	51/1,280 (4.0)	986/1,392 (70.8)	56/1,411 (4.0)
Number of stents per subject	1.3 ± 0.5	1.4 ± 0.7	1.2 ± 0.5	1.4 ± 0.7
Total stent length, mm	25.5 ± 13.8	25.0 ± 13.7	27.2 ± 14.4	25.0 ± 13.6
Preprocedural RVD, mm	3.00 ± 0.47	2.98 ± 0.42	3.00 ± 0.48	2.99 ± 0.42
Preprocedural %DS	83.8 ± 9.7	82.9 ± 9.8	82.5 ± 10.3	83.35 ± 9.94
Antiplatelet therapy at discharge				
Aspirin	1,544/1,693 (91.2)	1,262/1,277 (98.8)	1,132/1,392 (81.3)	1,392/1,411 (98.7)
Clopidogrel	1,384/1,693 (81.7)	1,252/1,277 (98.0)	1,204/1,392 (86.5)	1,381/1,408 (98.1)
Prasugrel	38/1,693 (2.2)	16/382 (4.2)	14/1,392 (1.0)	17/412 (4.1)
Ticagrelor	274/1,693 (16.2)	NA	174/1,392 (12.5)	NA

Values are n/N (%) or mean ± SD, unless otherwise specified. *Anemia was defined as hemoglobin <11 g/dL. †Renal insufficiency was defined as creatinine ≥2 mg/dL or maintenance dialysis. ‡This category includes any systemic conditions associated with an increased bleeding risk (eg, hematologic disorders, including a history of or current thrombocytopenia defined as a platelet count <100,000/mm^3, or any known coagulation disorder associated with increased bleeding risk). §Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min.

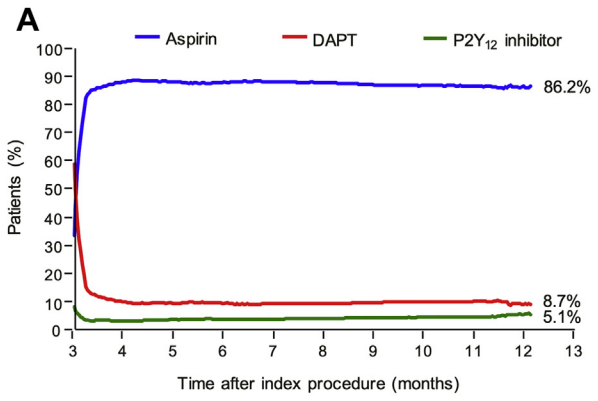
CABG = coronary artery bypass grafting; DAPT = dual-antiplatelet therapy; HBR = high bleeding risk; IQR = interquartile range; MI = myocardial infarction; NA = not available. NSTEMI = non-ST-segment elevation myocardial infarction; PARIS = Patterns of Non-Adherence to Dual Anti-Platelet Regimen in Stented Patients; PCI = percutaneous coronary intervention; %DS = percentage diameter stenosis; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; RVD = reference vessel diameter.

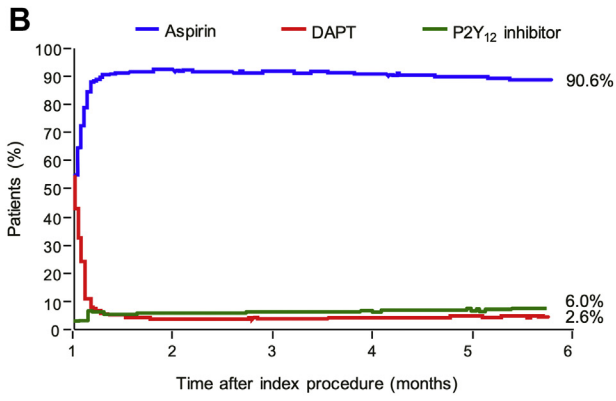
97.5% confidence limit for the propensity-stratified difference of 1.1%, which met the noninferiority criterion of 2.5% ($P = 0.0005$) (Figure 3B). There were 4 instances of definite or probable stent thrombosis between 1 and 6 months among patients discontinuing DAPT at 1 month as well as among those continuing DAPT up to 6 months (0.3% of patients in both groups) (Figure 4B).

BLEEDING OUTCOMES. The propensity score quintile mean percentage of patients with BARC types 2 to 5 bleeding was not significantly lower with 3-month DAPT compared with the 12-month DAPT historical control (5.1% vs 7.0%; $P = 0.069$). Likewise, BARC types 2 to 5 bleeding did not differ between 1-month DAPT and the 6-month DAPT historical control (4.9% vs 5.9%; $P = 0.19$). The stratified mean rate of BARC types 3 to 5 bleeding was lower in the group that discontinued DAPT at 3 months (2.2% vs 6.3%; $P < 0.0001$) and in the group that discontinued DAPT at 1 month (2.2% vs 4.5%; $P = 0.016$) compared with their historical controls (Figure 5).

ADDITIONAL ANALYSES. The unadjusted rates of primary and secondary ischemic and bleeding endpoints are provided in Supplemental Tables S17 to S24. Prespecified subgroup analyses (Supplemental Figures S4 to S9) showed no considerable heterogeneity for the treatment effects of 1- or 3-month DAPT on the primary ischemic endpoint (I^2 <75% and heterogeneity P value >0.10 for all subgroups). There was a signal of effect modification for 3-month DAPT on the key secondary bleeding endpoint according to age and clinical presentation, with a reduced benefit among patients <65 years of age ($I^2 = 80\%$; $P = 0.024$) or presenting with acute coronary syndromes ($I^2 = 64\%$; $P = 0.097$). The landmark analyses for the period between index PCI and the follow-up assessment of eligibility to discontinue DAPT among all enrolled patients are reported in Supplemental Tables S18 and S22.

FIGURE 2 Use of Antiplatelet Therapy During Follow-Up





	91 days	100 days	180 days	365 days
Aspirin	33.4%	83.9%	87.5%	86.2%
DAPT	58.4%	13.2%	9.1%	8.7%
$P2Y_{12}$ inhibitor	8.2%	2.9%	3.4%	5.1%

	30 days	45 days	90 days	180 days
Aspirin	28.5%	92.6%	92.9%	90.6%
DAPT	68.9%	2.9%	2.2%	2.6%
$P2Y_{12}$ inhibitor	1.0%	4.2%	4.5%	6.0%

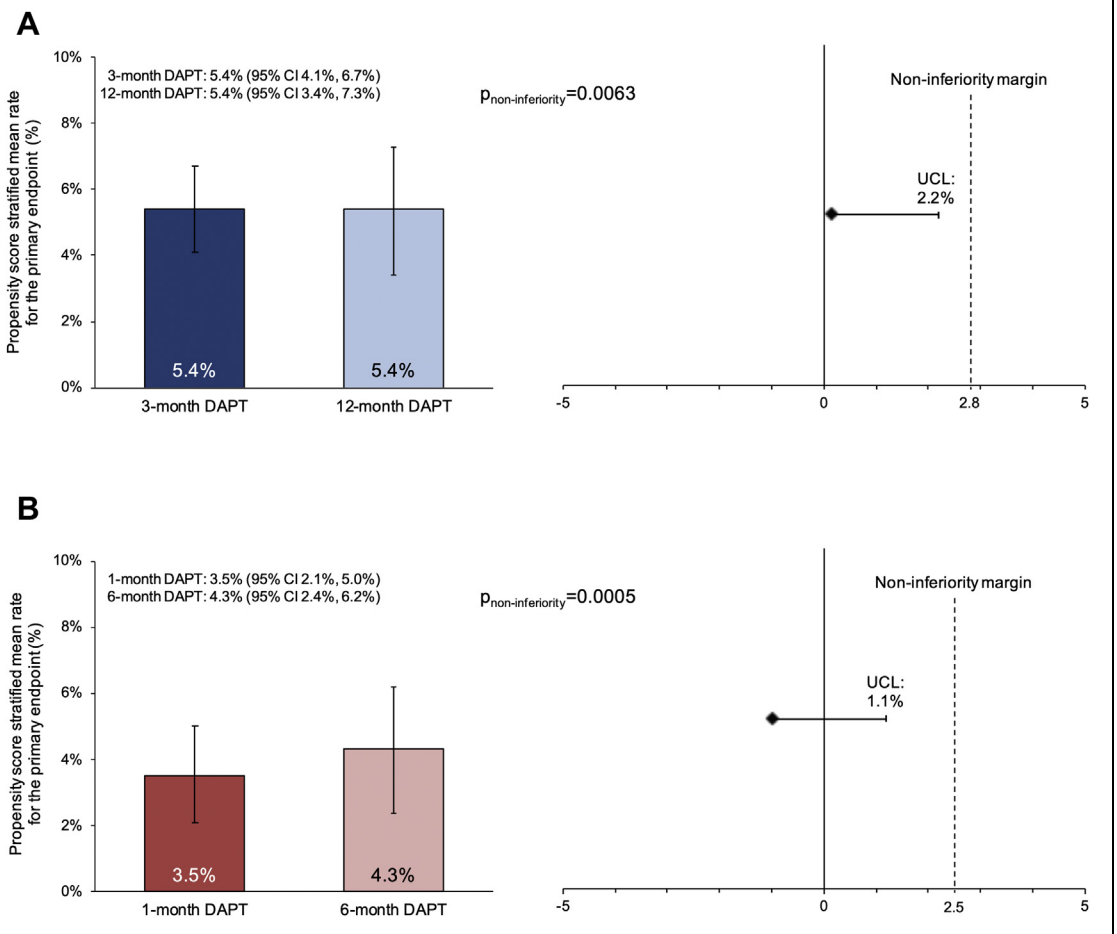
Antiplatelet therapy use in **(A)** XIENCE 90 and **(B)** XIENCE 28. The aspirin group includes patients on aspirin only or aspirin plus an oral anticoagulant agent. The dual-antiplatelet therapy (DAPT) group includes patients on DAPT only or DAPT plus an oral anticoagulant agent. The $P2Y_{12}$ inhibitor group includes patients on a $P2Y_{12}$ inhibitor only or a $P2Y_{12}$ inhibitor plus an oral anticoagulant agent. No patients were censored.

DISCUSSION

The XIENCE Short DAPT program was designed to assess the safety and efficacy of 2 abbreviated DAPT regimens in a large cohort of HBR patients who underwent successful PCI with a cobalt-chromium everolimus-eluting stent. Among patients who had been adherent to treatment and free from ischemic events while on DAPT, the discontinuation of the $P2Y_{12}$ inhibitor after 1 or 3 months of DAPT was noninferior to DAPT prolongation up to 6 or 12 months with respect to the composite of all-cause mortality or myocardial infarction in a propensity score-stratified analysis and was associated with low rates of stent thrombosis. Although a DAPT duration of 1 or 3 months resulted in a meaningful reduction in bleeding complications, statistical significance was achieved only for BARC types 3 to 5 bleeding. Importantly, XIENCE V USA did not mandate the collection of less severe bleeding corresponding to BARC type 2, which may have led to underreporting of these events and the subsequent low rates observed in our historical control compared with other similar studies (18,19). Conversely, the propensity score-stratified analysis for BARC types 3 to 5 bleeding, although post hoc, is likely to provide more reliable treatment effect estimates on a clinically relevant bleeding endpoint. In aggregate, these results suggest that among HBR patients who underwent PCI with a cobalt-chromium everolimus-eluting stent, a short course of DAPT for 1 or 3 months provides similar ischemic risk and may be associated with lower occurrences of major bleeding (**Central Illustration**).

Two previous studies showed that discontinuing the $P2Y_{12}$ inhibitor after 3 months of DAPT in patients undergoing PCI with a zotarolimus-eluting stent was noninferior to a standard regimen of 12 months with respect to a composite endpoint of cardiovascular and bleeding events (20,21). Contrary to our study, however, both excluded HBR patients, as shown by the very low incidence of major bleeding (<1% per year) and the absence of a significant bleeding-related benefit with the experimental arm. Furthermore, aggregate outcomes from these 2 studies suggested an increased risk for myocardial infarction or stent thrombosis with DAPT for 3 months after an acute coronary syndrome (3), with similar findings reported in another study of patients undergoing PCI with a sirolimus-eluting stent (22). More recently, a single-arm study suggested that HBR patients receiving 3-month DAPT after placement of a bioabsorbable-

FIGURE 3 **Propensity Score-Stratified Rates for the Primary Endpoint of All-Cause Mortality or Myocardial Infarction**



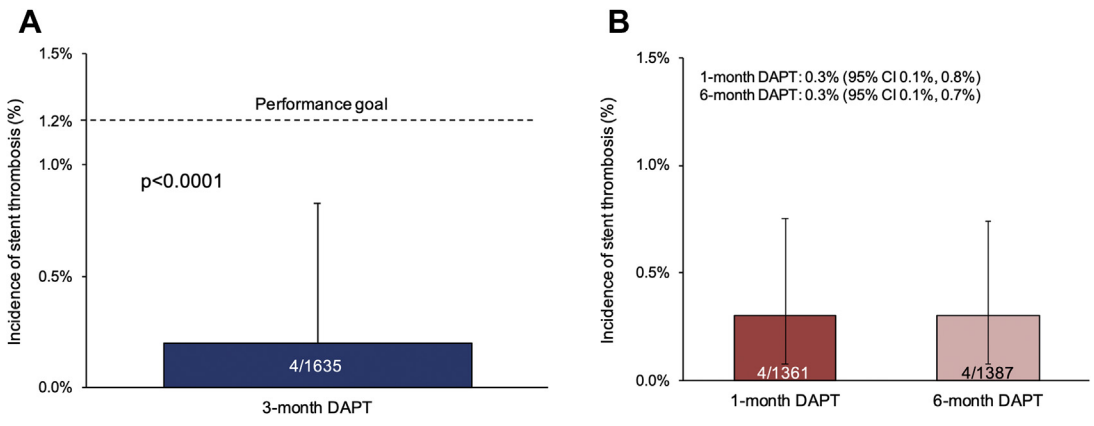
On the **left**, rates of the primary endpoint expressed as propensity score-stratified mean across quintiles in patients discontinuing dual-antiplatelet therapy (DAPT) at 3 months **(A)** or at 1 month **(B)** after index procedure and in their respective historical controls. **Error bars** indicate the 95% CI of the mean. On the **right**, the propensity score-stratified difference between the test and the control group, with the upper limit of the 1-sided 97.5% CI **(error bar)** evaluated for noninferiority to the prespecified margin **(dotted line)** using the stratified Farrington-Manning method. UCL = 1-sided upper 97.5% confidence limit.

polymer everolimus-eluting stent had noninferior ischemic outcomes compared with a 12-month DAPT historical control but failed to show a reduction in bleeding risk (23).

The evidence on the effects of discontinuing the $P2Y_{12}$ inhibitor after 1 month of DAPT is more limited. To date, such a strategy has been used only as background therapy in trials comparing different stent platforms, thus failing to provide any comparative data on the overall safety and risks of this approach (18,19,24,25). The present study is the first specifically aimed at evaluating the treatment effects of 2 different short DAPT regimens in HBR patients.

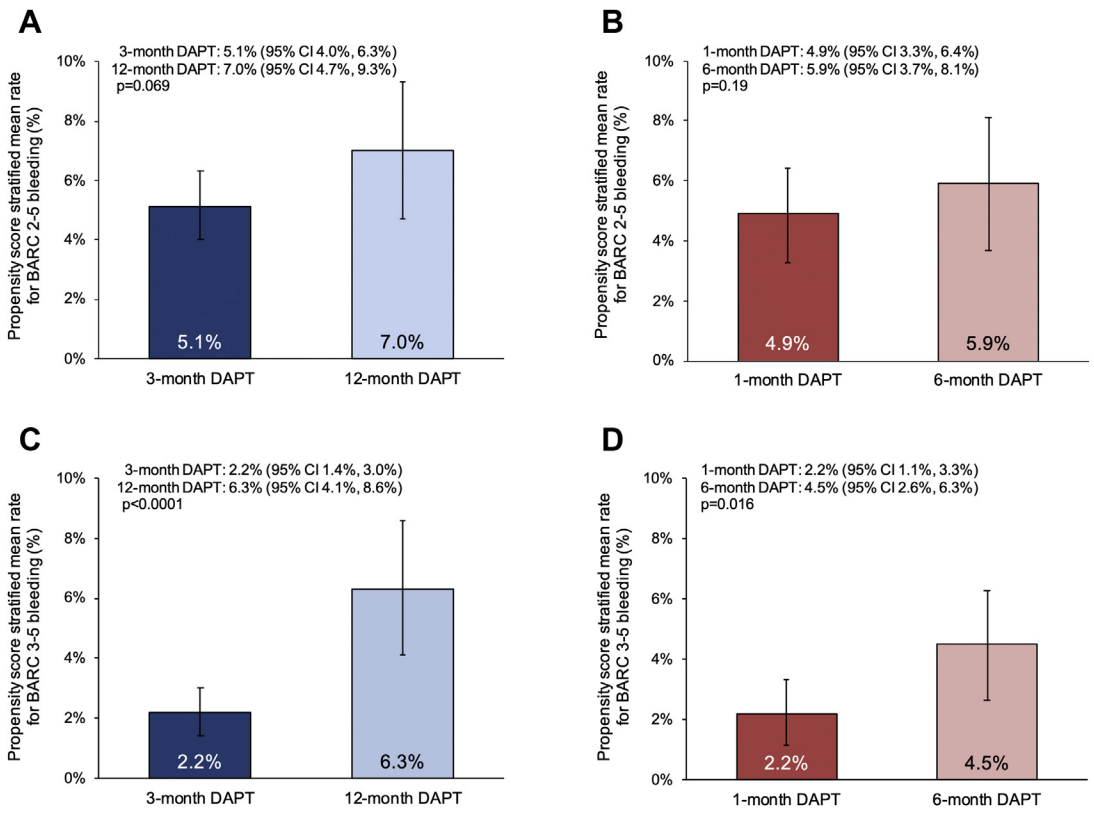
There are several risk scores and consensus-based definitions developed to assist clinicians in identifying patients at high risk for bleeding after PCI (26-28). However, commonly encountered conditions such as advanced age, long-term oral anticoagulation, anemia, and chronic kidney disease, among others, are all contemplated by the available risk assessment tools and, accordingly, were considered as inclusion criteria in our study. Furthermore, a risk for BARC type 3 or 5 bleeding of at least 4% at 1 year after PCI has been proposed as a threshold to objectively recognize HBR patients (28). In keeping with this, we observed an incidence of BARC types 3 to 5 bleeding of 6.4% between index PCI and 12 months among all patients enrolled in XIENCE 90 and of 4.6% at 6 months among those enrolled in XIENCE 28, thereby confirming the HBR nature of our study

FIGURE 4 Incidence of Stent Thrombosis



(A) Rate of definite or probable stent thrombosis in patients discontinuing dual-antiplatelet therapy (DAPT) at 3 month evaluated against a pre-specified performance goal of 1.2% **(dotted line)** using the exact test. **(B)** Rates of definite or probable stent thrombosis in patients discontinuing DAPT at 1 month and in the 6-month DAPT historical control. **Error bars** indicate the 95% CI of the mean.

FIGURE 5 Propensity Score-Stratified Rates for Bleeding



Propensity score–stratified mean rates for Bleeding Academic Research Consortium (BARC) types 2 to 5 bleeding **(A,B)** and BARC types 3 to 5 bleeding **(C,D)** in patients discontinuing DAPT at 3 month **(A to C)** or at 1 month **(B to D)** after index procedure and in their respective historical controls. **Error bars** indicate the 95% CI of the mean. Superiority tested with the stratified Farrington-Manning method using a 1-sided significance level of 0.025. Abbreviations as in Figure 4.

population. Given the nonrandomized design of the XIENCE Short DAPT program, however, the prevalence of specific bleeding risk criteria was not evenly distributed between treatment arms but was accounted for with propensity score stratification. The higher proportion of long-term anticoagulant therapy in the group receiving DAPT for 1 or 3 months as opposed to the higher proportion of renal failure observed in the historical control group might partly be explained by a selection bias favoring the enrollment of patients with a perceived higher risk for bleeding, such as those on concomitant oral anticoagulant therapy, in studies mandating a short DAPT regimen. Such tendencies have also been observed in other trials among HBR patients, wherein the distribution of bleeding risk factors substantially overlap with that reported in our study (18,19).

Current European and American guidelines provide cautious recommendations on the use DAPT regimens of 3 months or less after drug-eluting stent implantation, acknowledging the limited available evidence, derived mostly from trials on low-risk populations (1,2,29). Our findings build on this prior evidence by demonstrating that discontinuing DAPT as early as 1 or 3 months after PCI with a new-generation everolimus-eluting stent is a safe approach and may be considered in HBR patients undergoing noncomplex procedures. Of note, prior studies investigating other drug-eluting stent platforms reported non-negligible rates of stent thrombosis with 1 month of DAPT (18,19). Such findings were attributed partly to the enhanced thrombotic risk associated with HBR conditions, which render the overall risk profile of these patients particularly elevated. It was therefore reassuring that stent thrombosis was rare (<1%) in both XIENCE 28 and XIENCE 90, even after including events occurring in the early post-PCI phase before discontinuing the $P2Y_{12}$ inhibitor. Corroborating these findings, 2 Japanese studies showed very few instances of definite or probable stent thrombosis among lower risk patients undergoing PCI with the same cobalt-chromium everolimus-eluting stent system, with no events reported among those receiving 3 months of DAPT followed by aspirin (30) and only 4 events (0.27%) among those receiving 1 month of DAPT followed by clopidogrel monotherapy (31). Whether these findings apply to other contemporary drug-eluting stents remains unclear (32). Future investigations should explore the effects of monotherapy with a $P2Y_{12}$ inhibitor compared with aspirin after a short course of DAPT among patients with HBR undergoing PCI (33).

STUDY LIMITATIONS. The nonrandomized design introduces the risk for residual unmeasured confounding despite multivariable adjustment through propensity score using rigorous statistical methodology. However, the inclusion of an active control receiving a conventional DAPT regimen of 6 to 12 months would have contrasted with current recommendations for HBR patients. A nonrandomized study design was also justified by the large amount of historical data on patients treated with the XIENCE stent followed by 12 months of DAPT. The use of real-world data as a historical control in the context of well-designed clinical trials is considered an acceptable means to generate evidence, also for regulatory purposes. The findings of our study may not be generalizable to patients who do not meet the XIENCE Short DAPT program inclusion and exclusion criteria. Of note, patients with ST-segment elevation myocardial infarction or requiring complex interventions, such as overlapping stents or a 2-stent bifurcation technique, were excluded. In XIENCE 90, a lower than anticipated rate of the primary endpoint of death or myocardial infarction may have biased the results toward the null. The bleeding-related benefit observed with a DAPT regimen was demonstrated only after the exclusion of BARC type 2 events from the bleeding endpoint. Nonetheless, the rates of BARC types 3 to 5 bleeding were only slightly lower than what was anticipated for the key secondary (BARC types 2-5) bleeding endpoint, for which the study was powered. Last, the HBR criteria used in the XIENCE Short DAPT program were defined before the Academic Research Consortium definition of HBR became available (28).

CONCLUSIONS

Among HBR patients undergoing PCI with a cobalt-chromium everolimus-eluting stent, a DAPT regimen of 1 or 3 months compared with DAPT for 6 or 12 months resulted in noninferior ischemic outcomes and a low incidence of stent thrombosis and may be associated with lower major bleeding occurrences.

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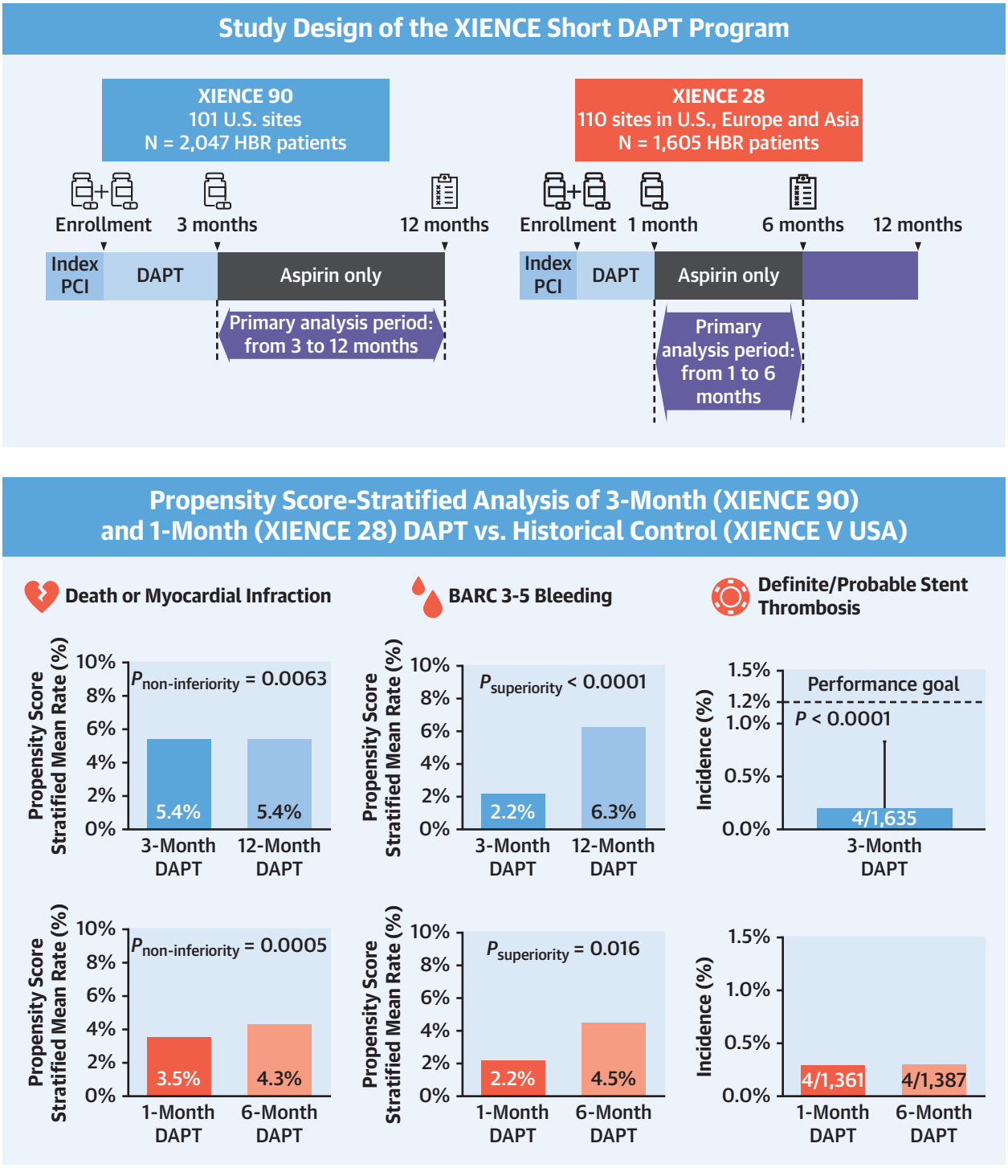
CENTRAL ILLUSTRATION 3-or 1-Month DAPT in HBR Patients Undergoing PCI



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Bayer, Beth Israel Deaconess, CardiaWave, CeloNova, Chiesi, Concept Medical, DSI, Duke University, Idorsia Pharmaceuticals, Medtronic, Novartis, and Philips; holds equity (<1%) in Applied Therapeutics, Elixir Medical, STEL, and CONTROLRAD (spouse); and is a scientific advisory board member for the American Medical Association and Biosensors (spouse). 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CENTRAL ILLUSTRATION Continued

(Top) The XIENCE Short DAPT program included 3 prospective, multicenter, single-arm studies enrolling patients at high bleeding risk who underwent successful percutaneous coronary intervention with a cobalt-chromium everolimus-eluting stent. After 1 month (XIENCE 28 USA and XIENCE 28 Global) or 3 month (XIENCE 90) of dual-antiplatelet therapy (DAPT), patients who had been adherent to treatment and free from ischemic events discontinued the $P2Y_{12}$ inhibitor and continued with aspirin monotherapy. The postmarketing approval XIENCE V USA study was used as a historical control in a propensity score–stratified analysis. Endpoints were assessed between 3 and 12 month in XIENCE 90 and 1 to 6 month in XIENCE 28 after the index procedure. **(Bottom)** In XIENCE 90, 3-month DAPT (n = 1,693) was noninferior to the 12-month DAPT historical control (n = 1,280) for the primary endpoint of death or myocardial infarction (1-sided upper 97.5% confidence limit for the propensity-stratified difference: 2.2%; $P = 0.0063$ for the noninferiority margin of 2.8%) and superior for Bleeding Academic Research Consortium (BARC) types 3 to 5 bleeding. Four patients (0.2%) had definite or probable stent thrombosis (1-sided upper 97.5% confidence limit: 0.63%; $P < 0.0001$ for the performance goal of 1.2%). In XIENCE 28, 1-month DAPT (n = 1,392) was noninferior to the 6-month DAPT historical control (n = 1,411) for the primary endpoint of death or myocardial infarction (1-sided upper 97.5% confidence limit for the propensity-stratified difference: 1.1%; $P = 0.0005$ for the noninferiority margin of 2.5%) and superior for BARC types 3 to 5 bleeding. The rate of stent thrombosis in XIENCE 28 was 0.3%.

Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, V-Wave, and Xeltis (but has not received personal payments from pharmaceutical companies or device manufacturers); is a member of the steering or executive committee groups of several investigator-initiated trials that receive funding from industry without impact on his personal remuneration; and is an unpaid member of the Pfizer Research Award selection committee in Switzerland. Dr Krucoff has received grants and/or personal fees from Abbott Vascular, Biosensors, Boston Scientific, CeloNova, Medtronic, OrbusNeich, and Terumo. Dr Valgimigli has received grants and personal fees from Terumo and has received personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi-Sankyo, Bayer, CoreFLOW, Idorsia Pharmaceuticals, Universität Basel Department Klinische Forschung, Vifor, Bristol Myers Squibb, Biotronik, Boston Scientific, Medtronic, Vesalio, Novartis, Chiesi, and PhaseBio, outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Roxana Mehran, The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, New York 10029, USA. E-mail: roxana.mehran@mountsinai.org.

PERSPECTIVES

WHAT IS KNOWN? New-generation drug-eluting stents have been shown superior to bare-metal stents for HBR patients undergoing PCI followed by a short course of DAPT. To date, however, there is no evidence directly comparing different DAPT durations in HBR patients, and their optimal management remains unclear.

WHAT IS NEW? Results from the XIENCE 28 and XIENCE 90 studies support the role of an abbreviated DAPT regimen of 1 or 3 months as an effective and potentially safe bleeding-avoidance strategy after PCI with a cobalt-chromium everolimus-eluting stent.

WHAT IS NEXT? Future investigations should explore the effects of monotherapy with a $P2Y_{12}$ inhibitor compared with aspirin after a short DAPT course among HBR patients undergoing PCI.

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KEY WORDS bleeding, everolimus-eluting stent, high bleeding risk, percutaneous coronary intervention, short DAPT, thrombosis

APPENDIX For the Short DAPT program organization as well as supplemental tables and figures, please see the online version of this paper.

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