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Duration of Dual Antiplatelet Therapy for Patients at High Bleeding Risk Undergoing PCI

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ABSTRACT

BACKGROUND The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) among patients at high bleeding risk (HBR) is unknown.

OBJECTIVES The purpose of this analysis was to compare 1 vs 3 months of DAPT in HBR patients undergoing drug-eluting stent implantation.

METHODS The XIENCE Short DAPT program comprised 3 prospective, multicenter, single-arm studies of HBR patients treated with a short DAPT course followed by aspirin monotherapy after PCI with a cobalt-chromium everolimus-eluting stent. In this exploratory analysis, patients who received 1-month DAPT (XIENCE 28 USA and 28 Global) were compared with those on 3-month DAPT (XIENCE 90) using propensity score stratification. Ischemic and bleeding outcomes were assessed between 1 and 12 months after index PCI.

RESULTS A total of 3,652 patients were enrolled and 1,392 patients after 1-month DAPT and 1,972 patients after 3-month DAPT were eligible for the analyses. The primary endpoint of all-cause mortality or myocardial infarction was similar between the 2 groups (7.3% vs 7.5%; difference −0.2%; 95% CI: −2.2% to 1.7%; $P = 0.41$). The key secondary endpoint of BARC (Bleeding Academic Research Consortium) type 2-5 bleeding was lower with 1-month DAPT compared with 3-month DAPT (7.6% vs 10.0%; difference −2.5%; 95% CI: −4.6% to −0.3%; $P = 0.012$). Major BARC type 3-5 bleeding did not differ at 12 months (3.6% vs 4.7%; difference −1.1%; 95% CI: −2.6% to 0.4%; $P = 0.082$), but was lower with 1-month DAPT at 90 days (1.0% vs 2.1%; $P = 0.015$).

CONCLUSIONS Among HBR patients undergoing PCI, 1 month of DAPT, compared with 3 months of DAPT, was associated with similar ischemic outcomes and lower bleeding risk. (XIENCE 90 Study; NCT03218787; XIENCE 28 USA Study; NCT03815175; XIENCE 28 Global Study; NCT03355742) (J Am Coll Cardiol 2021;78:2060–2072) © 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-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Dual antiplatelet therapy (DAPT) is recommended for the prevention of thrombotic events after coronary stent implantation (1). However, DAPT also increases the risk of bleeding complications, which have shown a prognostic impact comparable to that of thrombotic events (2,3). Therefore, providing optimal antithrombotic protection without increase in bleeding-related harm is key in the management of DAPT following percutaneous coronary intervention (PCI).

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More than 1 in 3 patients undergoing PCI exhibits clinical and comorbid conditions linked to an increased hemorrhagic risk (4,5), which may potentially offset the protective effects of DAPT against ischemic events. Contemporary improvements in stent design and technology have led to a significant reduction in the rate of thrombotic complications compared with older-generation devices (6-9), thus providing a rationale to the use of abbreviated DAPT regimens among patients at high bleeding risk (HBR). Previous trials have indeed demonstrated a benefit associated with the use of new-generation drug-eluting stents over bare-metal stent in HBR patients receiving a 1-month course of DAPT (10-12). However, there is a lack of comparative data on the safety and efficacy of different DAPT durations among HBR patients, which is reflected in the low level of evidence supporting guideline recommendations on short DAPT regimens (13,14).

The XIENCE Short DAPT studies have recently demonstrated that, among HBR patients undergoing successful PCI with cobalt-chromium everolimus-eluting stents, a DAPT regimen of 1 or 3 months was noninferior to a 6- or 12-month DAPT historical control with respect to ischemic outcomes and was associated with less major bleeding and a low incidence of stent thrombosis (15). In the present study, we sought to appraise the comparative ischemic and bleeding outcomes among HBR patients who received 1- or 3-month DAPT regimens after successful PCI with cobalt-chromium everolimus-eluting stents.

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

DAPT = dual antiplatelet therapy

HBR = high bleeding risk

MI = myocardial infarction

PCI = percutaneous coronary intervention

METHODS

STUDY DESIGN. The XIENCE Short DAPT program rationale, design, and principal results have been reported previously (15,16). In brief, XIENCE Short DAPT is a clinical program including 3 prospective, multicenter, single-arm studies conducted at 101 sites in the United States (XIENCE 90; NCT03218787), 58 sites in the United States and Canada (XIENCE 28 USA; NCT03815175), and 52 sites in Europe and Asia (XIENCE 28 Global; NCT03355742) (Supplemental Tables 1 to 3). It was prespecified that the USA and Global studies of XIENCE 28 were to be pooled together for data analysis. Abbott sponsored the studies. The principal investigators with members of the executive and steering committees and the sponsor designed the protocol. National regulatory agencies and institutional review boards or ethics committees of participating sites approved the study protocol. An independent data monitoring committee provided external oversight to ensure public safety. All enrolled patients provided written informed consent.

STUDY POPULATION. Patients undergoing successful PCI exclusively with a fluoropolymer-based cobalt-chromium everolimus-eluting stent (XIENCE, Abbott) were eligible for inclusion if they fulfilled at least 1 of the following HBR criteria: age ≥75 years, chronic anticoagulant therapy, history of major bleeding in the previous 12 months, history of ischemic or hemorrhagic stroke, renal insufficiency (creatinine ≥2.0 mg/dL or maintenance dialysis), anemia (hemoglobin <11 g/dL), and systemic conditions associated with an increased risk of bleeding including hematological disorders such as thrombocytopenia (platelet count <100,000/mm^3) or coagulation disorder. The study allowed for the treatment

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of up to 3 target lesions with a maximum of 2 target lesions per epicardial vessel and of bifurcation lesions without 2-stent techniques during index PCI. Key exclusion criteria included presentation with ST-segment elevation myocardial infarction (MI), 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 XIENCE 28 and 90 studies were developed under nearly identical protocols (Supplemental Table 4), except for the mandated DAPT duration (16). All patients received open-label aspirin 75 to 100 mg plus a $P2Y_{12}$ inhibitor, preferably clopidogrel 75 mg, after the index PCI. For those on oral anticoagulants, dual therapy with a $P2Y_{12}$ inhibitor could be considered at the investigator discretion. Eligibility to discontinue DAPT was assessed at 1 month in XIENCE 28 and at 3 months in XIENCE 90. Patients who had been adherent to treatment and free from MI, repeat coronary revascularization, stroke, or stent thrombosis discontinued the $P2Y_{12}$ inhibitor and continued aspirin until the end of the study. Follow-up occurred in-person or via telephone at 1, 3, 6, and 12 months after index PCI in XIENCE 28, and at 3, 6, and 12 months in XIENCE 90.

ENDPOINTS. The primary endpoint of the study was the composite of all-cause death or MI between 1 and 12 months after index procedure. MI was defined according to a modified Academic Research Consortium definition (17). The key secondary endpoint was Bleeding Academic Research Consortium (BARC) type 2-5 bleeding (18). Other secondary endpoints included the individual components of the primary endpoint, definite or probable stent thrombosis, stroke, cardiovascular death, target lesion failure (composite of cardiovascular death, target vessel MI, or clinically indicated target lesion revascularization), and BARC type 3-5 bleeding. The primary and secondary endpoints definitions are provided in Supplemental Tables 5 and 6. All clinical events were adjudicated by an independent external committee.

STATISTICAL ANALYSIS. This analysis was designed to compare clinical outcomes of HBR patients enrolled in XIENCE 28 who received 1 month of DAPT with those from XIENCE 90 who received 3-month DAPT. Given that eligibility to discontinue DAPT was assessed at different time points in the 2 studies, patients from XIENCE 90 who were event-free and adherent to treatment at 1 month were derived to match the corresponding cohort of patients on 1-month DAPT from XIENCE 28.

A descriptive comparison of outcome data between patients receiving 1-month DAPT (XIENCE 28) vs 3-month DAPT (XIENCE 90) was prespecified in the statistical analysis plan. Because treatment arms were not randomized, all endpoints were analyzed using propensity score stratification into quintiles, consistently with the main study design (16). Propensity scores (patients' estimated probability of receiving 1- or 3-month DAPT) were derived using a logistic regression model that included the study group as the outcome and the baseline demographic, clinical, and procedural covariates as the predictors. The list of variables included in the propensity score model is reported in Supplemental Table 7.

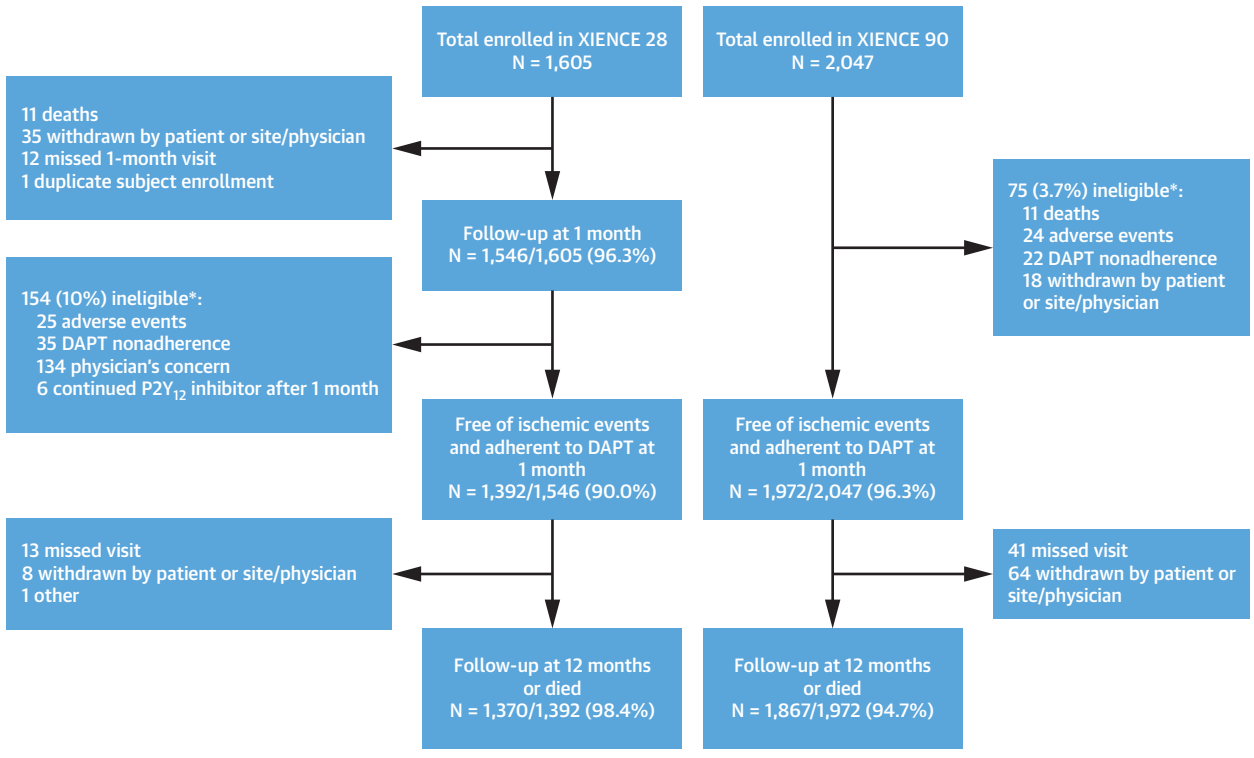
The Markov Chain Monte Carlo multiple imputation method was used to handle missing data in the propensity score building. The Rubin's combination rule was used to integrate the final analysis with each of the 10 imputed data sets. All endpoints were tested for superiority with the Farrington-Manning method and a 1-sided alpha of 0.025. The stratification weight was based on the total sample size in each stratum relative to the overall sample size for both arms. Heterogeneity of treatment effects was assessed across prespecified subgroups using a generic version of the meta-analysis where each subgroup contributes a normalized treatment effect and its standard error. A landmark analysis at 3 months was performed to discriminate between events occurring in the period of actual treatment difference between the 2 DAPT groups (1-3 months) and thereafter (3-12 months). All statistical analyses were performed with the R software, version 3.6.2 (R Foundation for Statistical Computing), or the SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENT CHARACTERISTICS. A total of 3,652 patients were enrolled in the XIENCE Short DAPT program from July 19, 2017, to February 7, 2020. Of 1,605 patients who were included in XIENCE 28, 1,392 (90.0%) were free of ischemic events and adherent to treatment at 1 month, and 98.4% had complete follow-up at 12 months. The corresponding rates among the 2,047 patients enrolled in XIENCE 90 were 1,972 (96.3%) at 1 month, with 94.7% completing 12-month follow-up. Hence, the final study cohort comprised 3,364 patients, 1,392 (41.4%) of whom were in the 1-month DAPT group and 1,972 (58.6%) in the 3-month DAPT group (**Figure 1**).

Baseline clinical and procedural characteristics are reported in **Table 1**. The mean number of HBR criteria per patient was 1.5 ± 0.7 in both treatment groups. The distribution of HBR criteria was similar between the 2

FIGURE 1 Study Flowchart



The analysis population includes patients who were free from myocardial infarction, repeat coronary revascularization, stroke, or stent thrombosis and adherent to DAPT (ie, without interruption of either aspirin and/or $P2Y_{12}$ inhibitor for more than 7 consecutive days) within 1 month after index PCI. In XIENCE 90, there was no scheduled follow-up at 1 month, and eligible patients were derived retrospectively. *Reasons for ineligibility are not mutually exclusive. DAPT = dual antiplatelet therapy.

groups, with age ≥75 years being the most common criterion (68.2% and 65.5%), followed by chronic anticoagulant therapy (44.3% and 40.8%) and anemia (14.4% and 15.9%). Approximately 1 in 3 patients was female (32.5% and 35.5%), 37.0% and 39.9% had diabetes, and 47.4% and 41.0% had chronic kidney disease among those on 1- and 3-month DAPT, respectively. Non–ST-segment elevation acute coronary syndrome was the indication for index PCI in 34.1% and 34.9% of the patients, whereas clopidogrel was the most commonly prescribed $P2Y_{12}$ inhibitor (86.5% and 81.7%) in both treatment groups.

In the 1-month DAPT group, 3.1% of the patients were on DAPT at 45 days, 2.9% at 180 days, and 3.9% at 365 days. The corresponding rates in the 3-month DAPT group were 85.1% at 45 days, 14.5% at 180 days, and 12.8% at 365 days (**Figure 2**).

ISCHEMIC OUTCOMES. From 1 to 12 months after index PCI, a total of 103 (7.5%) primary endpoint events occurred in patients on 1-month DAPT compared with 145 (7.6%) in the 3-month DAPT group. After propensity score stratification into quintiles, the mean rate of death or MI was 7.3% in patients who discontinued DAPT at 1 month and 7.5% in those who discontinued DAPT at 3 months (difference −0.2%; 95% CI: −2.2% to 1.7%; $P = 0.41$) (**Figure 3A**). There were no significant differences in the individual propensity score stratified mean rates of all-cause death (4.5% vs 4.6%; $P = 0.45$) or MI (3.0% vs 3.8%; $P = 0.12$), nor in other secondary ischemic endpoints, including definite or probable stent thrombosis (0.3% vs 0.3%; $P = 0.41$), cardiovascular death (2.3% vs 2.6%; $P = 0.36$), and target lesion failure (5.1% vs 5.3%; $P = 0.42$). Stroke occurred less frequently in patients receiving 1-month DAPT (0.9% vs 1.9%; $P = 0.016$) (**Table 2**). The treatment effect of 1-month vs 3-month DAPT on the primary endpoint was consistent across prespecified subgroups (Supplemental Figure 1), except for a borderline significant heterogeneity by diabetic status ($I^2 = 74\%$; $P = 0.048$).

TABLE 1 Baseline Characteristics

	1-Month DAPT (n = 1,392)	3-Month DAPT (n = 1,972)
High bleeding risk criteria		
Age ≥75 y	950/1,392 (68.2)	1,292/1,972 (65.5)
Chronic anticoagulant therapy	617/1,392 (44.3)	805/1,972 (40.8)
Anemia[a]	201/1,392 (14.4)	313/1,972 (15.9)
History of stroke	145/1,392 (10.4)	223/1,972 (11.3)
Renal insufficiency[b]	116/1,392 (8.3)	157/1,972 (8.0)
Thrombocytopenia[c]	55/1,392 (4.0)	60/1,972 (3.0)
History of major bleeding	46/1,392 (3.3)	57/1,972 (2.9)
Number of HBR criteria	1.5 ± 0.7	1.5 ± 0.7
Clinical characteristics		
Age, y	76.0 ± 8.4	75.1 ± 9.4
Female	453/1,392 (32.5)	701/1,972 (35.5)
Race		
American Indian or Alaskan native	2/1,392 (0.1)	11/1,972 (0.6)
Asian	126/1,392 (9.1)	45/1,972 (2.3)
Black or African American	36/1,392 (2.6)	117/1,972 (5.9)
Native Hawaiian or Pacific Islander	0/1,392 (0.0)	5/1,972 (0.3)
White	807/1,392 (58.0)	1,739/1,972 (88.2)
Hispanic or Latino ethnicity	138/1,392 (9.9)	56/1,972 (2.8)
Hypertension	1,179/1,392 (84.7)	1,771/1,972 (89.8)
Dyslipidemia	939/1,392 (67.5)	1,622/1,972 (82.3)
Diabetes mellitus	512/1,382 (37.0)	787/1,970 (39.9)
Chronic kidney disease[d]	631/1,330 (47.4)	801/1,956 (41.0)
Prior PCI	390/1,392 (28.0)	607/1,972 (30.8)
Prior CABG	112/1,392 (8.0)	246/1,972 (12.5)
Prior MI	227/1,382 (16.4)	317/1,942 (16.3)
Multivessel disease	573/1,392 (41.2)	918/1,972 (46.6)
Clinical presentation		
Chronic coronary syndrome	917/1,392 (65.9)	1,283/1,972 (65.1)
Acute coronary syndrome	475/1,392 (34.1)	689/1,972 (34.9)
NSTEMI	245/1,392 (17.6)	141/1,972 (7.2)
Unstable angina	230/1,392 (16.5)	572/1,972 (29.0)
PARIS bleeding risk score		
Mean ± SD	6.1 ± 2.3	6.0 ± 2.3
Median (IQR)	6.0 (4.0-8.0)	6.0 (4.0-8.0)
PRECISE-DAPT bleeding risk score		
Mean ± SD	27.7 ± 11.3	26.2 ± 11.7
Median (IQR)	27.0 (20.0-34.0)	26.0 (19.0-32.0)

Continued on the next page

BLEEDING OUTCOMES. A total of 103 (7.7%) secondary endpoint events were reported in patients on 1-month DAPT and 184 (10.0%) in those on 3-month DAPT. The propensity score stratified mean rate of BARC type 2-5 bleeding was lower in patients who discontinued DAPT at 1 month compared with those who discontinued DAPT at 3 months (7.6% vs 10.0%; $P = 0.012$) (**Figure 4A**). The rates of BARC type 3-5 bleeding did not significantly differ between patients on 1-month compared with 3-month DAPT (3.6% vs 4.7%; $P = 0.082$) (**Table 2**). The subgroup analyses showed no evidence of heterogeneity of the treatment effects on the bleeding endpoints (Supplemental Figures 2 and 3).

LANDMARK ANALYSIS. The results of the landmark analysis at 90 days are summarized in **Table 3**. The propensity score stratified mean rates of the primary ischemic endpoint were similar among patients on 1- and 3-month DAPT between 31 and 90 days (1.5% vs 1.8%; $P = 0.26$) and from 91 to 365 days (6.1% vs 6.1%; $P = 0.49$) (**Figure 3B**). Conversely, the key secondary bleeding endpoint was significantly lower in patients receiving 1-month DAPT before 90 days (2.7% vs 4.4%; $P = 0.009$), but not thereafter (5.2% vs 6.3%; $P = 0.12$) (**Figure 4B**). A similar pattern was observed for BARC type 3-5 bleeding, which was reduced before 90 days (1.0% vs 2.1%; $P = 0.015$), but not thereafter (2.9% vs 2.8%; $P = 0.44$).

DISCUSSION

This study assessed the safety and efficacy of discontinuing DAPT at 1 month compared with DAPT prolongation for an additional 2 months in HBR patients undergoing PCI with a cobalt-chromium everolimus-eluting stent. Among subjects who had been adherent to treatment and free from ischemic events during the first month post-PCI, 1-month DAPT followed by aspirin monotherapy was associated with similar ischemic outcomes and reduced bleeding compared with 3 months of DAPT. Landmark analyses between 1 and 3 months did not show an excess in ischemic events with 1-month DAPT, whereas not only BARC type 2-5 but also BARC type 3-5 was reduced with 1- vs 3-month DAPT (**Central Illustration**).

HBR patients represent an increasingly prevalent subgroup among those undergoing PCI in daily practice (4,5). This partly reflects the technical advancements and improved pharmacological strategies that allowed expanding the indication to PCI to frailer and more vulnerable cohorts. Notwithstanding, the evidence informing on the optimal management of HBR patients after PCI remains scarce. To date, randomized trials have only investigated the performance of different intracoronary devices, including drug-eluting stents or drug-coated balloons, compared with bare-metal stents or other drug-eluting stents among HBR patients receiving 1-month DAPT (10-12,19,20). Yet, none of these trials reported on the benefits and risks associated with such ultra-short antiplatelet regimen compared with a standard DAPT duration. The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) study randomized subjects at high risk for both bleeding and ischemic events to ticagrelor monotherapy vs ticagrelor plus aspirin after 3 months of DAPT (21). However, the trial enrolled only patients

who were deemed eligible to a long-term DAPT with ticagrelor, thereby limiting the inclusion of those with predominant HBR features. Similarly, the GLOBAL LEADERS trial did not formally exclude HBR patients, but mandated 1-month DAPT with ticagrelor followed by ticagrelor monotherapy for 23 months or 12-month DAPT followed by aspirin monotherapy, which greatly limited the generalizability to other $P2Y_{12}$ inhibitors as well as the number of HBR patients (22-24). Moreover, in both prior studies, patients with indication to oral anticoagulation were excluded. Additional studies investigating DAPT regimens of 1 or 3 months followed by either aspirin or $P2Y_{12}$ inhibitor monotherapy included relatively low-risk patients, and therefore, their findings may not apply to higher-risk cohorts (25-29).

The XIENCE Short DAPT program was specifically designed to evaluate the safety of a DAPT duration as short as 1 or 3 months among HBR patients receiving an everolimus-eluting stent (16). The principal study findings demonstrated that DAPT for 1 month (XIENCE 28) or 3 months (XIENCE 90) followed by aspirin monotherapy was noninferior to a historical cohort of patients receiving a standard DAPT of up to 12 months for ischemic events, and was associated with a low incidence of stent thrombosis and a reduced risk of major bleeding (15). Despite raising awareness on the need of safe bleeding-avoidance strategies in HBR patients, there remains uncertainty as to which is the optimal DAPT duration and how early the $P2Y_{12}$ inhibitor can be safely withdrawn. The acute phase after PCI is indeed the most vulnerable for thrombotic events, with a risk that gradually attenuates over time. Conversely, the risk for nonperiprocedural bleeding is sustained and proportional to the duration and intensity of antithrombotic therapy (30). Therefore, the widespread use of biocompatible and low-thrombogenic stent platforms along with improved PCI optimization techniques may have enabled shorten the duration of DAPT to prevent bleeding without compromising patient safety.

The present study was the first to demonstrate the bleeding-related benefits and absence of ischemic harm associated with a DAPT duration of 1 month as compared with 3 months among HBR patients. Although treatment arms were not randomized, both XIENCE 90 and 28 studies were developed with almost identical protocols, as shown by the very similar prevalence and distribution of HBR criteria. Blanking the period between index PCI and 1 month further minimized the impact of periprocedural imbalances, such as that of arterial access site on bleeding complications. Finally, the potential for remaining confounding was addressed using a propensity score stratified adjustment.

In XIENCE 90, eligibility to discontinue DAPT was originally assessed at 3 months after PCI. Conversely, in the present study, patients from XIENCE 90 were included in the 3-month DAPT group if free from ischemic events and adherent to treatment at 1 month, as was done in XIENCE 28. Although the derivation of the 1-month event-free cohort in XIENCE 90 was necessary for the purpose of the analysis, it resulted in lower rates of adherence to 3-month DAPT compared with 1-month DAPT. This imbalance might have contributed to the outcome differences between the 2 groups, especially with respect to bleeding. However, the results of the landmark analysis are concordant with the timing of DAPT interruption as highlighted by the significant bleeding risk reduction observed in the period of actual treatment difference (1-3 months) and not thereafter (3-12 months). Moreover, the rates of the primary ischemic endpoint were largely comparable between 1-month and 3-month DAPT during the overall follow-up as well as at 90 days.

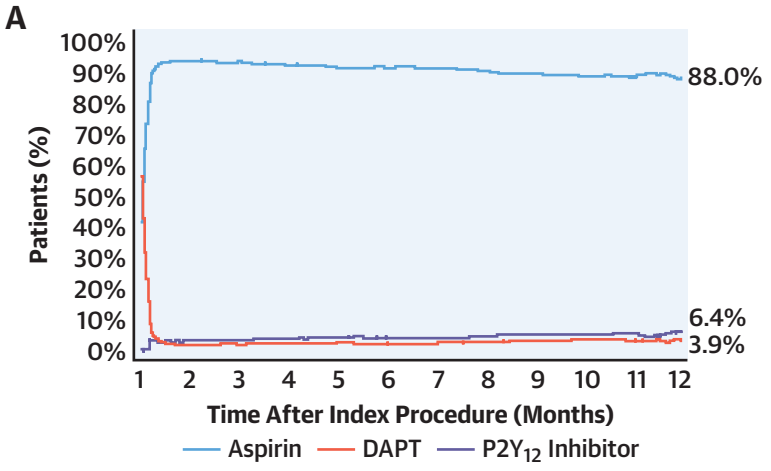
TABLE 1 Continued

	1-Month DAPT (n = 1,392)	3-Month DAPT (n = 1,972)
Procedural characteristics		
Number of lesions treated	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Number of vessels treated	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Target lesion location		
Left anterior descending	719/1,392 (51.7)	959/1,972 (48.6)
Left circumflex	382/1,392 (27.4)	553/1,972 (28.0)
Right coronary artery	456/1,392 (32.8)	662/1,972 (33.6)
B2/C lesion	498/1,392 (35.8)	687/1,972 (34.8)
Bifurcation	161/1,392 (11.6)	153/1,972 (7.8)
Radial access	986/1,392 (70.8)	1,028/1,972 (52.1)
Number of stents per subject	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Total stent length, mm	27.2 ± 14.4	25.6 ± 13.8
Preprocedure RVD, mm	3.00 ± 0.48	2.98 ± 0.47
Preprocedure % DS	82.5 ± 10.3	83.9 ± 9.6
Antiplatelet therapy at discharge		
Aspirin	1,132/1,392 (81.3)	1,801/1,972 (91.3)
Clopidogrel	1,204/1,392 (86.5)	1,612/1,972 (81.7)
Prasugrel	14/1,392 (1.0)	46/1,972 (2.3)
Ticagrelor	174/1,392 (12.5)	317/1,972 (16.1)

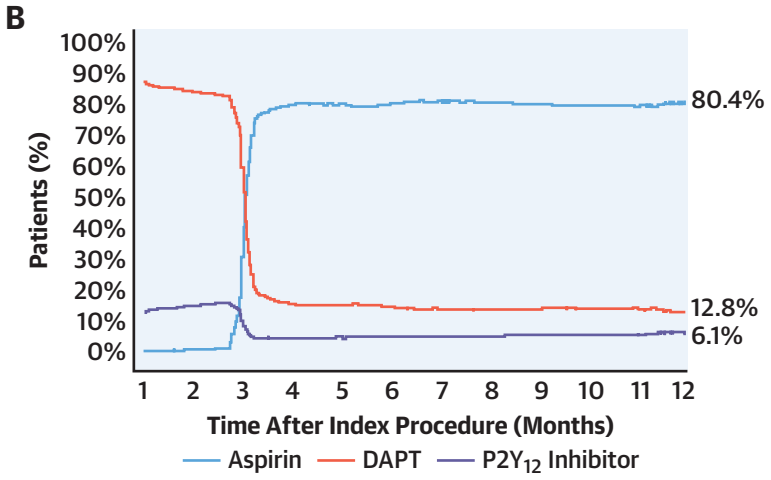
Values are n/N (%), mean ± SD, or median (interquartile range [IQR]). [a]Anemia defined as hemoglobin <11 g/dL. [b]Renal insufficiency defined as creatinine ≥2 mg/dL or maintenance dialysis. [c]This category includes any systemic conditions associated with an increased bleeding risk (eg, hematological 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). [d]Chronic kidney disease defined as an estimated glomerular filtration rate <60 mL/min.

CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; DS = diameter stenosis; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PARIS = Patterns of Non-Adherence to Dual Anti-Platelet Regimen in Stented Patients; PCI = percutaneous coronary intervention; RVD = reference vessel diameter.

FIGURE 2 Antiplatelet Medication Use



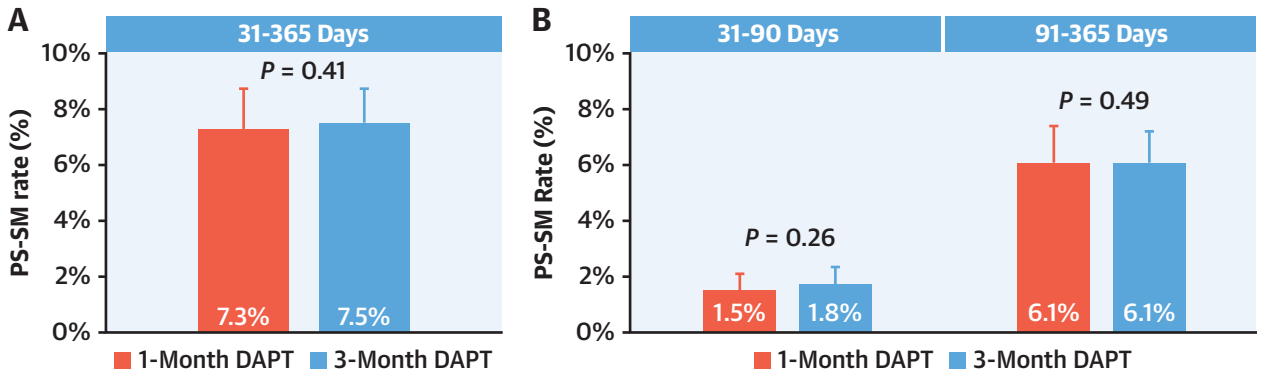
	30 Days	45 Days	90 Days	180 Days	365 Days
Aspirin	28.4%	93.2%	93.3%	91.6%	88.0%
$P2Y_{12}$ Inhibitor	1.0%	3.4%	3.8%	4.8%	6.4%
DAPT	69.7%	3.1%	2.6%	2.9%	3.9%



	30 Days	45 Days	90 Days	180 Days	365 Days
Aspirin	0.3%	0.7%	17.6%	79.9%	80.4%
$P2Y_{12}$ Inhibitor	12.0%	14.1%	12.2%	5.1%	6.1%
DAPT	87.6%	85.1%	70.0%	14.5%	12.8%

Rates of adherence to antiplatelet therapy in patients on 1-month DAPT **(A)** and 3-month DAPT **(B)**. The aspirin group includes patients on aspirin only or aspirin plus oral anticoagulant. The DAPT group includes patients on DAPT only or DAPT plus oral anticoagulant. The $P2Y_{12}$ inhibitor group includes patients on $P2Y_{12}$ inhibitor only or $P2Y_{12}$ inhibitor plus oral anticoagulant. No patients were censored. DAPT = dual antiplatelet therapy.

FIGURE 3 Primary Ischemic Endpoint



Propensity score stratified mean (PS-SM) rates of all-cause death or myocardial infarction from 1 to 12 months post-PCI in patients receiving 1-month DAPT vs 3-month DAPT **(A)**, and landmark analysis at 90 days **(B)**. *P* value is from superiority test with a 1-sided alpha of 0.025. Error bars are SEM. DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention.

A number of studies have evaluated the benefits of early DAPT de-escalation strategies achieved by lowering the dose or the potency of the $P2Y_{12}$ inhibitor (31-34). Other approaches that have recently been investigated involve early aspirin withdrawal followed by potent $P2Y_{12}$ inhibitor monotherapy (35). These studies altogether offer effective and potentially safe alternatives to a standard DAPT regimen in HBR patients, especially in the context of acute coronary syndromes. However, important gaps remain in the management of those undergoing elective procedures, which are partly filled by the results of the present study, where two-thirds of patients underwent index PCI for chronic coronary syndrome. Further and more conclusive evidence is expected from the MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen), which randomized more than 4,300 HBR patients to an abbreviated vs standard DAPT regimen across all the spectrum of coronary artery disease presentations (36).

STUDY LIMITATIONS. Although a comparison of clinical outcomes between patients on 1-month vs 3-month DAPT was prespecified, the propensity score stratified analysis was not. Therefore, the present analysis should be seen as post hoc and its results as hypothesis-generating. The nonrandomized design entails an inevitable risk for residual unmeasured confounding, which may have contributed to the

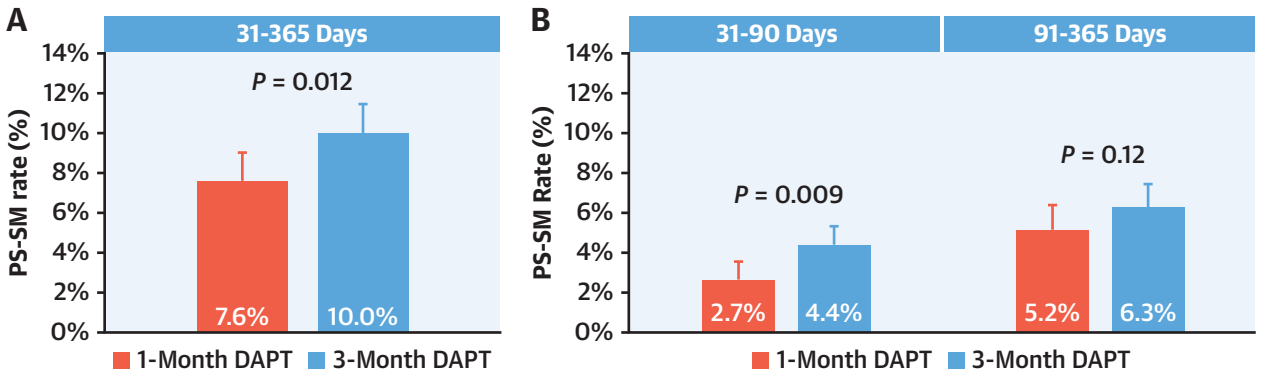
TABLE 2 Outcomes Between 1 and 12 Months After PCI

	1-Month DAPT (n = 1,392)	3-Month DAPT (n = 1,972)		
	PS-SM Rate, %	PS-SM Rate, %	PS-SM Difference, % (95% CI)	*P* Value
All-cause death or MI	7.3	7.5	−0.23 (−2.16 to 1.69)	0.41
All-cause death	4.5	4.6	−0.09 (−1.62 to 1.44)	0.45
Cardiovascular death	2.3	2.6	−0.21 (−1.35 to 0.92)	0.36
MI	3.0	3.8	−0.79 (−2.14 to 0.55)	0.12
Definite or probable ST	0.3	0.3	0.05 (−0.37 to 0.47)	0.41
Stroke	0.9	1.9	−0.96 (−1.83 to −0.09)	0.016
Ischemic stroke	0.7	1.7	−1.01 (−1.83 to −0.20)	0.008
Target lesion failure	5.1	5.3	−0.17 (−1.79 to 1.45)	0.42
BARC 2-5 bleeding	7.6	10.0	−2.46 (−4.59 to −0.33)	0.012
BARC 3-5 bleeding	3.6	4.7	−1.07 (−2.57 to 0.43)	0.082

Event rates are expressed as propensity score stratified mean (PS-SM) rates across quintiles in patients discontinuing DAPT at 1 and 3 months. Target lesion failure is a composite of cardiovascular death, target vessel MI, or clinically indicated target lesion revascularization.

BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; ST = stent thrombosis.

FIGURE 4 Key Secondary Bleeding Endpoint



PS-SM rates of Bleeding Academic Research Consortium (BARC) type 2-5 from 1 to 12 months post-PCI in patients receiving 1-month DAPT vs 3-month DAPT **(A)**, and landmark analysis at 90 days **(B)**. *P* value is from superiority test with a 1-sided alpha of 0.025. Error bars are SEM. Abbreviations as in Figure 3.

difference in stroke rates. Nonetheless, this risk excess was more evident after 3 months of PCI when both treatment groups discontinued DAPT, and a play of chance cannot be excluded. The derivation of the 1-month event-free cohort in XIENCE 90 resulted in poorer adherence to the antiplatelet regimen among patients on 3-month DAPT compared with those on 1-month DAPT. The findings of this study may not apply to patients who do not meet the XIENCE Short DAPT program inclusion and exclusion criteria, such

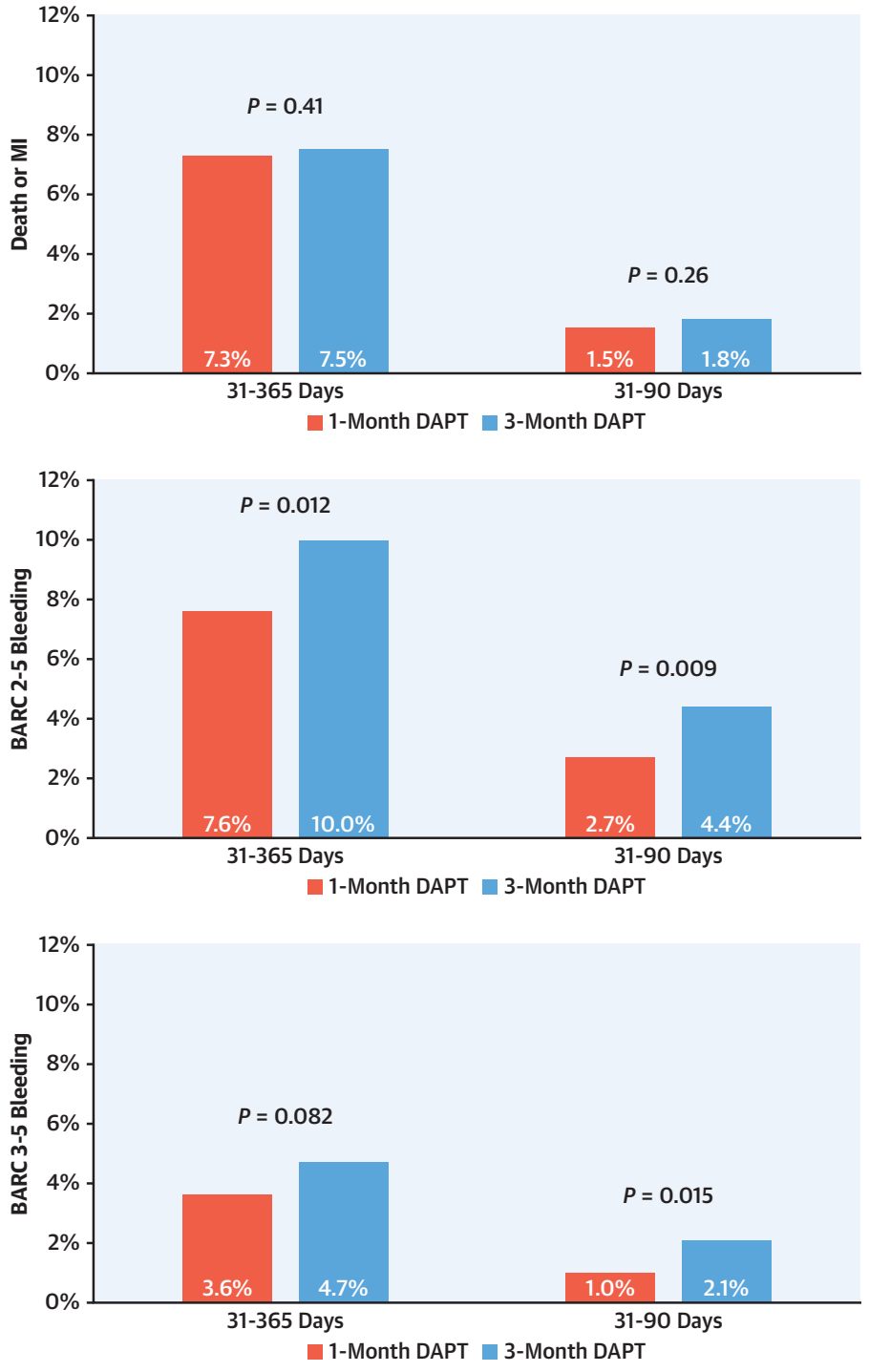
TABLE 3 Landmark Analysis at 90 Days

	1-Month DAPT (n = 1,392)	3-Month DAPT (n = 1,972)		
	PS-SM Rate, %	PS-SM Rate, %	PS-SM Difference, % (95% CI)	*P* Value
From 31 to 90 days				
All-cause death or MI	1.5	1.8	−0.31 (−1.23 to 0.61)	0.26
All-cause death	0.6	0.9	−0.36 (−1.01 to 0.28)	0.13
Cardiovascular death	0.4	0.5	−0.17 (−0.66 to 0.31)	0.24
MI	0.9	0.8	0.06 (−0.60 to 0.71)	0.43
Definite or probable ST	0.2	0.1	N/A	N/A
Stroke	0.2	0.4	−0.20 (−0.61 to 0.22)	0.18
Ischemic stroke	0.2	0.3	−0.16 (−0.55 to 0.24)	0.22
Target lesion failure	1.2	1.1	0.08 (−0.68 to 0.84)	0.42
BARC 2-5 bleeding	2.7	4.4	−1.66 (−3.04 to −0.28)	0.009
BARC 3-5 bleeding	1.0	2.1	−1.05 (−1.99 to −0.10)	0.015
From 91 to 365 days				
All-cause death or MI	6.1	6.1	0.03 (−1.73 to 1.79)	0.49
All-cause death	3.9	3.6	0.29 (−1.11 to 1.69)	0.34
Cardiovascular death	2.0	2.0	−0.03 (−1.07 to 1.00)	0.48
MI	2.3	3.2	−0.89 (−2.11 to 0.32)	0.074
Definite or probable ST	0.2	0.2	N/A	N/A
Stroke	0.8	1.4	−0.69 (−1.46 to 0.07)	0.038
Ischemic stroke	0.6	1.4	−0.79 (−1.51 to −0.07)	0.015
Target lesion failure	4.1	4.4	−0.22 (−1.70 to 1.27)	0.39
BARC 2-5 bleeding	5.2	6.3	−1.05 (−2.78 to 0.68)	0.12
BARC 3-5 bleeding	2.9	2.8	0.10 (−1.12 to 1.32)	0.44

Event rates are expressed as propensity score stratified mean (PS-SM) rate across quintiles in patients discontinuing DAPT at 1 and 3 months. Target lesion failure is a composite of cardiovascular death, target vessel MI, or clinically indicated target lesion revascularization.

N/A = not applicable; other abbreviations as in Table 2.

CENTRAL ILLUSTRATION **1 vs 3 Months of Dual Antiplatelet Therapy in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention**



Valgimigli, M. et al. J Am Coll Cardiol. 2021;78(21):2060–2072.

Propensity score stratified mean rates of **(top)** death or MI, **(middle)** Bleeding Academic Research Consortium type 2-5 bleeding, and **(bottom)** Bleeding Academic Research Consortium type 3-5 bleeding from 1 to 12 months and from 1 to 3 months post-PCI in patients receiving 1-month dual antiplatelet therapy (n = 1,392) vs 3-month dual antiplatelet therapy (n = 1,972) after cobalt-chromium everolimus-eluting stent implantation. *P* value is from superiority test with a 1-sided alpha of 0.025. BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; MI = myocardial infarction.

as those with ST-segment elevation MI or requiring complex PCI. Last, the HBR criteria used in the XIENCE Short DAPT program were defined before the Academic Research Consortium definition of HBR became available.

CONCLUSIONS

Among HBR patients undergoing PCI with a cobalt-chromium everolimus-eluting stent, a DAPT regimen of 1 month compared with DAPT for 3 months was associated with similar ischemic events and lower bleeding risk.

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The study was sponsored by Abbott. Dr Valgimigli has received grants and personal fees from Terumo; has received personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi-Sankyo, Bayer, CoreFLOW, Idorsia Pharmaceuticals Ltd, Universität Basel Department Klinische Forschung, and Vifor; and has received personal fees from Bristol Myers Squibb SA, Biotronik, Boston Scientific, Medtronic, Vesalio, Novartis, Chiesi, and PhaseBio, outside of the submitted work. Dr Angiolillo has received consulting fees or honoraria from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company; has received payments for participation in review activities from CeloNova and St Jude Medical, outside the present work; and his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Janssen, Matsutani Chemical Industry Co, Merck, Novartis, Osprey Medical, Renal Guard Solutions, and Scott R. MacKenzie Foundation. Dr Bangalore has received grants from Abbott Vascular; and has received personal fees from Abbott Vascular, Biotronik, Amgen, and Pfizer. 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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: For patients at high risk of bleeding, discontinuation of DAPT at 1 month after PCI with drug-eluting stents is a safe and effective strategy to avoid bleeding.

TRANSLATIONAL OUTLOOK: Future trials in patients at high risk of bleeding should compare the bleeding and ischemic outcomes of monotherapy with either aspirin or a $P2Y_{12}$ inhibitor following 1 month of DAPT post-PCI.

REFERENCES

1. Cao D, Chandiramani R, Chiarito M, Claessen BE, Mehran R. Evolution of antithrombotic therapy in patients undergoing percutaneous coronary intervention: a 40-year journey. *Eur Heart J*. 2021;42:339–351.

2. Mehran R, Pocock SJ, Stone GW, et al. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. *Eur Heart J*. 2009;30:1457–1466.

3. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J*. 2017;38:804–810.

4. Cao D, Mehran R, Dangas G, et al. Validation of the academic research consortium high bleeding risk definition in contemporary PCI patients. *J Am Coll Cardiol*. 2020;75:2711–2722.

5. Corpataux N, Spirito A, Gragnano F, et al. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. *Eur Heart J*. 2020;41:3743–3749.

6. Sabate M, Cequier A, Iñiguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet*. 2012;380:1482–1490.

7. Bhatt DL. EXAMINATION of new drug-eluting stents—top of the class! *Lancet*. 2012;380:1453–1455.

8. Valgimigli M, Sabaté M, Kaiser C, et al. Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis. *BMJ*. 2014;349:g6427.

9. Piccolo R, Bonaa KH, Efthimiou O, et al. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet*. 2019;393:2503–2510.

10. Ariotti S, Adamo M, Costa F, et al. Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention? A pre-specified analysis from the ZEUS trial. *J Am Coll Cardiol Intv*. 2016;9:426–436.

11. Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med*. 2015;373:2038–2047.

12. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet*. 2018;391:41–50.

13. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1082–1115.

14. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39:213–260.

15. Mehran R, Cao D, Angiolillo DJ, et al. 3- or 1-month DAPT in patients at high bleeding risk undergoing everolimus-eluting stent implantation. *J Am Coll Cardiol Intv*. 2021;14:1870–1883.

16. Valgimigli M, Cao D, Makkar RR, et al. Design and rationale of the XIENCE short DAPT clinical program: an assessment of the safety of 3-month and 1-month DAPT in patients at high bleeding risk undergoing PCI with an everolimus-eluting stent. *Am Heart J*. 2021;231:147–156.

17. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351.

18. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747.

19. Windecker S, Latib A, Kedhi E, et al. Polymer-based or polymer-free stents in patients at high bleeding risk. *N Engl J Med*. 2020;382:1208–1218.

20. Rissanen TT, Uskela S, Eränen J, et al. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. *Lancet*. 2019;394:230–239.

21. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032–2042.

22. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392:940–949.

23. Franzone A, McFadden E, Leonardi S, et al. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. *J Am Coll Cardiol*. 2019;74:2223–2234.

24. Gragnano F, Heg D, Franzone A, et al. PRECISE-DAPT score for bleeding risk prediction in patients on dual or single antiplatelet regimens: insights from the GLOBAL LEADERS and GLASSY. *Eur Heart J Cardiovasc Pharmacother*. Published online September 17, 2020. https://doi.org/10.1093/ehjcvp/pvaa106

25. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol*. 2012;60:1340–1348.

26. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE Randomized trial. *JAMA*. 2013;310:2510–2522.

27. De Luca G, Damen SA, Camaro C, et al. Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention*. 2019;15:e990–e998.

28. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414–2427.

29. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE Randomized Clinical Trial. *JAMA*. 2019;321:2428–2437.

30. Rodriguez F, Harrington RA. Management of antithrombotic therapy after acute coronary syndromes. *N Engl J Med*. 2021;384:452–460.

31. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet*. 2017;390:1747–1757.

32. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y(12) inhibitors in primary PCI. *N Engl J Med*. 2019;381:1621–1631.

33. Kim HS, Kang J, Hwang D, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet*. 2020;396:1079–1089.

34. Koo BK, Kang J, Park KW, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet*. 2021;397(10293):2487–2496.

35. Valgimigli M, Mehran R, Franzone A, et al. Ticagrelor monotherapy versus dual-antiplatelet therapy after PCI: an individual patient-level meta-analysis. *J Am Coll Cardiol Intv*. 2021;14:444–456.

36. Frigoli E, Smits P, Vranckx P, et al. Design and rationale of the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen (MASTER DAPT) Study. *Am Heart J*. 2019;209:97–105.

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

APPENDIX For supplemental tables and figures, please see the online version of this paper.