One- versus three-month dual antiplatelet therapy in high bleeding risk patients undergoing percutaneous coronary intervention for non-ST-segment elevation acute coronary syndromes

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One- versus three-month DAPT in high bleeding risk patients undergoing PCI for non-ST-segment elevation acute coronary syndromes

Running title: Short DAPT after NSTE-ACS in HBR patients

Davide Cao, MD[a,b]; Pascal Vranckx, MD[c]; Marco Valgimigli, MD, PhD[d]; Samantha Sartori, PhD[a]; Dominick J. Angiolillo, MD, PhD[e]; Sripal Bangalore, MD, MHA[f]; Deepak L. Bhatt, MD, MPH[a]; Yihan Feng, MS[a]; Junbo Ge, MD[g]; James Hermiller, MD[h]; Raj R. Makkar, MD[i]; Franz-Josef Neumann, MD[j]; Shigeru Saito, MD[k]; Hector Picon, MD[l]; Ralph Toelg, MD[m]; Aziz Maksoud, MD[n]; Bassem M. Chehab, MD[o]; James W. Choi, MD[p]; Gianluca Campo, MD[q]; Jose M. De la Torre Hernandez, MD, PhD[r]; Mitchell W. Krucoff, MD[s]; Vijay Kunadian, MD[t]; Gennaro Sardella, MD[u]; Alessandro Spirito; MD[a]; Holger Thiele, MD[v]; Olivier Varenne, MD[w]; Birgit Vogel, MD[a]; Yujie Zhou, MD[x]; Stephan Windecker, MD[y]; Roxana Mehran, MD[a]

Affiliations:

a) Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, New York, NY, USA
b) Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI), Italy
c) Heart Centre Hasselt and University of Hasselt, Hasselt, Belgium
d) Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Lugano and Bern University Hospital, Bern, Switzerland
e) University of Florida College of Medicine-Jacksonville, Jacksonville, FL USA
f) New York University-Langone Medical Center, New York, NY, USA
g) Zhongshan Hospital Fudan University, Shanghai, China
h) St Vincent's Medical Center of Indiana, Indianapolis, IN, USA
i) Cedars-Sinai Medical Center, Los Angeles, CA, USA
j) University Heart Center Freiburg, Bad Krozingen, Germany
k) Shonan Kamakura General Hospital, Kamakura, Japan
l) Redmond Regional Medical Center, Rome, GA, USA
m) Segeberger Kliniken GmbH, Herzzentrum, Bad Segeberg, Germany
n) Kansas Heart Hospital and University of Kansas School of Medicine, Wichita, KS, USA
o) Ascension Via Christi Hospital, Wichita, KS, USA
p) Texas Health Presbyterian Hospital, Dallas, TX
q) Azienda Ospedaliero-Universitaria di Ferrara, Cona (FE), Italy.
r) Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain
s) Duke University Medical Center and Duke Clinical Research Institute, Durham, NC, USA

t) Translational and Clinical Research Institute, Newcastle University and Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom
u) Policlinico Umberto I di Roma, Rome, Italy
v) Heart Center Leipzig at University of Leipzig and Leipzig Heart Institute, Leipzig, Germany
w) Hospital Cochin, Paris, France
x) Beijing AnZhen Hospital, Beijing, China
y) Inselspital, Bern University Hospital, Bern, Switzerland

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Address for correspondence:
Roxana Mehran, MD
Mount Sinai Heart
Icahn School of Medicine at Mount Sinai
One Gustave L. Levy Place, Box 1030
New York, NY,10029
Tel: +1-212-659-9649
Fax: +1-646-537-8547
Email: roxana.mehran@mountsinai.org

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Abstract

Background: A short dual antiplatelet therapy (DAPT) duration has been proposed for patients at high bleeding risk (HBR) undergoing drug-eluting coronary stent (DES) implantation. Whether this strategy is safe and effective after a non-ST-segment elevation acute coronary syndrome (NSTE-ACS) remains uncertain.

Aims: To compare the impact of 1-month versus 3-month DAPT on clinical outcomes after DES implantation among HBR patients with or without NSTE-ACS.

Methods: This is a prespecified analysis from the XIENCE Short DAPT program involving three prospective, international, single-arm studies evaluating the safety and efficacy of 1-month (XIENCE 28 USA and Global) or 3-month (XIENCE 90) DAPT among HBR patients after implantation of a cobalt-chromium everolimus-eluting stent. Ischemic and bleeding outcomes associated with 1- versus 3-month DAPT were assessed according to clinical presentation using propensity-score stratification.

Results: Of 3,364 HBR patients (1,392 on 1-month DAPT and 1,972 on 3-month DAPT), 1164 (34.6%) underwent DES implantation for NSTE-ACS. At 12 months, the risk of the primary endpoint of death or myocardial infarction was similar between 1- and 3-month DAPT in patients with (HR 1.09, 95%CI 0.71-1.65) and without NSTE-ACS (HR 0.88, 95%CI 0.63-1.23; p-interaction=0.34). The key secondary endpoint of BARC (Bleeding Academic Research Consortium) type 2-5 bleeding was consistently reduced in both NSTE-ACS (HR 0.57, 95% CI 0.37-0.88) and stable patients (HR 0.84, 95%CI 0.61-1.15; p-interaction=0.15) with 1-month DAPT.

Conclusions: Among HBR patients undergoing implantation of an everolimus-eluting stent, 1-month compared to 3-month DAPT was associated with similar ischemic risk and reduced bleeding at 1 year, irrespective of clinical presentation.

Key words: high bleeding risk; acute coronary syndrome; NSTE-ACS; short DAPT; everolimus-eluting stent; thrombosis; bleeding

ABBREVIATIONS

ACS: Acute coronary syndromes

BARC: Bleeding Academic Research Consortium

CCS: Chronic coronary syndrome

DAPT: Dual antiplatelet therapy

HBR: High bleeding risk

MI: Myocardial infarction

NSTEMI: Non-ST-segment elevation acute coronary syndromes myocardial infarction

NSTE-ACS: Non-ST-segment elevation acute coronary syndromes

PCI: Percutaneous coronary intervention

STEMI: ST-segment elevation myocardial infarction

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is recommended for up to 12 months after percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS) to prevent recurrent ischemic events.[1, 2] However, DAPT is encumbered by a significant risk of bleeding complications, which are proportional to the duration of treatment and negatively affect patient morbidity and mortality.[3-5] Up to 40% of patients undergoing PCI present with clinical conditions associated with a high bleeding risk (HBR) that make prolonging the duration of DAPT unattractive.[6-8] Among those patients, DAPT shorter than a standard 6-month course has been proposed to mitigate the bleeding risk without compromising antithrombotic protection,[9] but evidence in support of this practice in an ACS setting is scarce.[10-14]

The XIENCE Short DAPT clinical program has previously demonstrated that among HBR patients undergoing PCI with cobalt-chromium everolimus-eluting stents for either acute or chronic coronary syndrome, but without ST-segment elevation myocardial infarction (STEMI), DAPT for 1 or 3 months followed by aspirin monotherapy was noninferior to a historical control of 6- or 12-month DAPT for ischemic outcomes and superior in preventing bleeding.[15-17] Moreover, in the overall study population, the 1-month regimen compared with 3 months was associated with similar ischemic risk and further reduced bleeding events at 1 year.[17] With the present analysis, we aimed to compare the impact of 1-month versus 3-month DAPT on clinical outcomes of HBR patients undergoing PCI according to clinical presentation (i.e., with or without non-ST-segment elevation ACS [NSTE-ACS]).

METHODS

Study Design

This is a pre-specified sub-study within the XIENCE Short DAPT program, which consisted of three prospective, multicenter registries conducted at 101 sites in the US (XIENCE 90; NCT03218787), 58 sites in the US and Canada (XIENCE 28 USA; NCT03815175), and 52 sites in Europe and Asia (XIENCE 28 Global; NCT03355742) from July 2017 to February 2020. The study rationale, design, and principal results have been previously reported.[15-17] In brief, this clinical program explored two different DAPT durations in patients undergoing PCI with a fluoropolymer-based cobalt-chromium everolimus-eluting stent (XIENCE, Abbott). The XIENCE 28 and 90 studies were executed under nearly identical protocols, except for the DAPT duration. It was prespecified that the USA and Global studies of XIENCE 28 were to be pooled together for data analysis. Abbott sponsored the studies. An independent data monitoring committee provided external oversight to ensure public safety. All enrolled patients provided written informed consent.

Study Population

After successful PCI with the XIENCE stent, patients were eligible for inclusion in the study if at least one of the following HBR criteria was met: age ≥75 years, indication for chronic anticoagulant therapy, history of major bleeding within 12 months of the index procedure, history of ischemic or hemorrhagic stroke, renal insufficiency (creatinine ≥2.0 mg/dL) or failure (maintenance dialysis), anemia (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.[15-17] All studies 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 during index PCI. Key exclusion criteria were presentation

with STEMI, implantation of a drug-eluting stent other than a cobalt-chromium everolimus-eluting stent in the previous 12 months, target lesions that were in-stent restenosis or chronic total occlusions, those requiring overlapping stents, located in the left main stem, arterial or venous graft, or lesions containing thrombus (for XIENCE 90 only). After index PCI, all patients received open-label aspirin plus a $P2Y_{12}$ inhibitor, preferably clopidogrel. Eligibility to discontinue DAPT was assessed at 1 month after index PCI in XIENCE 28 and at 3 months in XIENCE 90. Patients who had been adherent to treatment and free from myocardial infarction (MI), repeat coronary revascularization, stroke, or stent thrombosis, discontinued the $P2Y_{12}$ inhibitor and continued aspirin until the end of the study. Follow-up was performed 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. Per study protocol, eligibility to discontinue DAPT was assessed at different time points in the XIENCE 28 and 90 programs. Patients from XIENCE 90 who were event-free and adherent to treatment at 1 month were retrospectively selected to match the XIENCE 28 event-free population.

Clinical endpoints

The primary endpoint was the composite of all-cause death or MI between 1 and 12 months after index PCI. The key secondary endpoint was Bleeding Academic Research Consortium (BARC) type 2 to 5 bleeding.[18] Other secondary endpoints included target lesion failure (a composite of cardiovascular death, target vessel MI, or target lesion revascularization), the individual components of the composite endpoints, stroke, definite or probable stent thrombosis, BARC type 3 to 5 bleeding. All clinical events were adjudicated by an independent event committee.

Statistical analysis

The effects of 1- versus 3-month DAPT on ischemic and bleeding outcomes were evaluated according to clinical presentation (NSTE-ACS vs. chronic coronary syndrome [CCS]) at the time of PCI. Clinical and procedural characteristics of each group are summarized using means and standard deviations for continuous variables or counts and percentages for categorical ones. Chi-square and Student's t-test were used to compare groups, as appropriate. The cumulative incidence rates for both primary and secondary endpoints were calculated with the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) were generated using Cox proportional hazard models. Because treatment arms were not randomized, adjusted risks for all endpoints were estimated using propensity score stratification into quintiles. Propensity scores were derived using a logistic regression model that included the treatment group as the outcome and the selected baseline demographic, clinical, and procedural covariates as the predictors.[16, 17] 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 ten imputed datasets. Heterogeneity of treatment effects by clinical presentation was examined with a subgroup by treatment interaction term.

As all patients in the registries were treated with single antiplatelet therapy (i.e., aspirin) after 3 months of PCI, landmark analyses at 3 months were performed to isolate the effects of actual treatment difference (1-3 months) between the two DAPT arms. In a sensitivity analysis, treatment effects were estimated across the spectrum of NSTE-ACS presentation, including non-ST-segment elevation myocardial infraction (NSTEMI) and unstable angina, with formal interaction testing to assess for effect modification. Another sensitivity analysis was conducted by excluding patients on oral anticoagulation from the comparison between 1- versus 3-month

DAPT. A two-sided P-value of <0.05 was considered statistically significant. All analyses were performed using Stata version 16.0 (StataCorp., College Station, TX, USA).

RESULTS

Population characteristics

A total of 3,652 patients were enrolled in the XIENCE Short DAPT program. Out of 3,364 eligible patients at 1 month (**Figure 1**), 1,164 (34.6%) patients had undergone PCI for NSTE-ACS, and 2,200 (65.4%) for CCS. Among NSTE-ACS patients, 475 received 1-month DAPT and 689 3-month DAPT; in the CCS group, 917 and 1,283 were treated with 1- and 3-month DAPT, respectively (**Figure 1**).

Baseline clinical and procedural characteristics by clinical presentation are reported in **Supplementary Table 1**. NSTE-ACS patients were more likely to be women, Asian or African American, to have a history of MI, anemia, and higher PRECISE-DAPT and PARIS bleeding scores.[19, 20] Radial access, complex lesions, and ticagrelor use at discharge were more frequent among NSTE-ACS patients. Baseline characteristics according to treatment arm by clinical presentation are summarized in **Table 1**, while DAPT use at different time points up to 1 year is reported in **Supplementary Figure 1**.

Ischemic outcomes

As shown in **Supplementary Table 2**, NSTE-ACS patients experienced numerically higher rates of the primary endpoint of all-cause death or MI (9.0% vs 7.4%; p=0.074), primarily driven by an increased risk of MI at 1 year (5.3% vs 2.8%; p<0.001). In the NSTE-ACS cohort, the primary endpoint occurred in 9.6% of patients receiving 1-month DAPT and 8.5% of those on 3-month DAPT. After propensity score stratification, the risk of death or MI was similar between the two

groups (adj. HR 1.09, 95% CI 0.71-1.65) (**Figure 2**). The adjusted risks for the secondary ischemic endpoints were also similar between NSTE-ACS patients on 1- vs. 3-month DAPT, including all-cause death (adj. HR 0.85, 95% CI 0.41-1.37), MI (adj. HR 1.13, 95% CI 0.65-1.96), stroke (adj. HR 0.39, 95% CI 0.12-1.27) and target lesion failure (adj. HR 0.99, 95% CI 0.61-1.59). Consistent treatment effects were observed in CCS patients for the primary endpoint (adj. HR 0.88, 95% CI 0.63-1.24) as well as other secondary endpoints, with no significant interaction between clinical presentation and DAPT duration (p-interaction >0.1 for all) (**Figure 2** and **Table 2**).

Bleeding outcomes

The 1-year incidence of the key secondary endpoint of BARC type 2 to 5 bleeding was similar between NSTE-ACS and CCS patients (10.1% vs 8.9%; p=0.213) (**Supplementary Table 2**). In the NSTE-ACS cohort, BARC 2-5 bleeding occurred in 7.3% of those on 1-month DAPT vs 12.2% on 3-month DAPT, with a significant risk reduction after propensity score stratification (adj. HR 0.57, 95% CI 0.37-0.88) (**Figure 2**). Similar treatment effects on BARC 2-5 bleeding were observed in CCS patients for 1 vs. 3 months of DAPT (adj. HR 0.84, 95% CI 0.61-1.15; p-interaction=0.15). The risk of major BARC 3-5 bleeding did not differ between treatment arms in both NSTE-ACS (adj. HR 0.66, 95% CI 0.36-1.19) and CCS patients (adj. HR 0.80, 95% CI 0.50-1.27; p-interaction=0.63) (**Figure 2** and **Table 2**).

Exploratory analyses

Landmark analyses between 1 and 3 months (**Figure 3**) showed a numerical increase in the risk of death or MI with 1- versus 3-month DAPT among NSTE-ACS (adj. HR 2.05, 95% CI 0.74-5.66) but not CCS patients (adj. HR 0.51, 95% CI 0.25-1.07; p-interaction=0.032). This finding was primarily driven by differences in the risk of MI (p-interaction=0.040) and to a lesser extent

by deaths (p-interaction=0.076). Conversely, between 3 and 12 months when both arms were on aspirin monotherapy, treatment effects on death or MI were consistent between CCS and NSTE-ACS patients (p-interaction=0.726).

Bleeding risk at 3 months was lower with 1- versus 3-month DAPT without evidence of heterogeneity by clinical presentation (p-interaction=0.237 for BARC 2-5, p-interaction=0.429 for BARC 3-5). No significant differences between treatment arms were observed beyond 3 months up to 1 year.

The sensitivity analysis by NSTE-ACS subtypes (**Supplementary Table 3**) suggested treatment effect modification according to presentation for NSTEMI or unstable angina, with a greater benefit of 1-month DAPT in terms of death or MI among patients with unstable angina and CCS (p-interaction=0.02) and a larger risk reduction in BARC 2-5 bleeding among those with NSTEMI (p-interaction<0.001).

In the sensitivity analysis without patients on oral anticoagulation (**Supplementary Table 4**), the risk of the primary and key secondary endpoints with 1- versus 3-month DAPT according to clinical presentation remained consistent with the primary analysis. A significant interaction between clinical presentation and DAPT was observed for MI (p-interaction=0.012), with a lower risk associated with 1-month DAPT in CCS but not NSTE-ACS patients.

DISCUSSION

In a large cohort of HBR patients undergoing successful, non-complex PCI with a cobalt-chromium everolimus-eluting stent, who had been adherent to treatment and free from ischemic events while on DAPT, discontinuation of the $P2Y_{12}$ inhibitor after 1 month compared with 3 months was associated with similar ischemic risk and reduced actionable bleeding events, irrespective of

clinical presentation at the time of PCI. Although NSTE-ACS compared with CCS presentation was associated with a two-fold higher risk of MI at 12-month follow-up, extending DAPT to 3 months did not appear to confer an extra ischemic protection across the spectrum of HBR patients. Conversely, the incidence of BARC type 2-5 bleeding was comparable between NSTE-ACS and CCS patients, with both subgroups deriving consistent benefit from 1-month DAPT.

The XIENCE Short DAPT program was designed to assess the safety and efficacy of two abbreviated DAPT regimens (1 month in XIENCE 28 and 3 months in XIENCE 90) which have previously been shown to be non-inferior to a historical cohort of patients receiving 6 to 12 months of DAPT for the primary endpoint of death or MI.[16] Other stent platforms have proven similar safety with a DAPT duration as short as 3 months but, at variance with our study, failed to include ACS patients.[21] In a more recent analysis from XIENCE Short DAPT involving the overall study population, DAPT for 1 month compared with 3 months was associated with similar ischemic risk and lower bleeding complications at 1-year follow-up.[17] The present substudy extends these observations to HBR patients presenting with NSTE-ACS, in whom bleeding avoidance strategies that do not compromise antithrombotic efficacy are most challenging.

Real-world registries have reported on the prevalence and prognostic impact of HBR conditions in relation to clinical presentation at the time of PCI.[22, 23] Advanced age, oral anticoagulation, and anemia were the most frequent HBR conditions, the latter being more prevalent among NSTE-ACS than CCS patients in our study, together with higher PRECISE-DAPT and PARIS bleeding risk scores. ACS presentation, per se, has previously been found to be an independent predictor of bleeding, with a graded relationship across ACS subtypes: highest risk after a STEMI and lowest in case of unstable angina.[22] Although we observed a similar incidence of BARC 2-5 bleeding among NSTE-ACS and CCS patients (10.1% vs. 8.9%), the sensitivity analysis by

NSTE-ACS subtypes highlighted a numerical trend towards higher bleeding risk in those with a NSTEMI. Given these considerations, the signal of larger bleeding risk reduction with 1- vs 3-month DAPT among NSTEMI patients relative to those with unstable angina or CCS (p-interaction <0.001) is of high clinical relevance and warrants prospective confirmation from dedicated studies.

Overall, our findings are in keeping with those from the MASTER DAPT trial which randomized HBR patients undergoing PCI with a biodegradable-polymer sirolimus-eluting stent between 1-month vs standard (≥3-month) DAPT. In line with the main trial results, the subgroups presenting with and without an acute or recent MI (i.e., within the past 12 months), including STEMI, derived consistent net benefit from 1-month DAPT, with similar cardiovascular events (prior MI: 7.6% vs. 8.7% and non-prior MI: 5.0 vs. 4.5%), and reduced BARC 2, 3, or 5 bleeding (prior MI: 6.2% vs. 9.3% and non-prior MI: 6.7 vs. 9.4%).[11] Notably, the study designs of XIENCE Short DAPT and MASTER DAPT were different with respect to stent platform, ACS subgroup definition, and single antiplatelet regimen post-DAPT (75% of patients in MASTER DAPT received $P2Y_{12}$ inhibitor monotherapy after DAPT discontinuation). Moreover, in our landmark analysis, the effects of 1- vs 3-month DAPT on the risk of death or MI was inconsistent among NSTE-ACS and CCS patients between 1 and 3 months. It is remarkable, however, that this finding was driven by a relatively small number of events and there was no such signal of heterogeneity on the 1-year outcomes. These differences notwithstanding, taken together, both trials provide encouraging data on the safety of 1 compared with ≥3 months of DAPT after PCI, regardless of clinical presentation.

An important caveat of all short DAPT studies relates to the monotherapy regimen based on either aspirin or $P2Y_{12}$ inhibitors following DAPT discontinuation. The XIENCE Short DAPT

protocol required the use of aspirin monotherapy after the initial DAPT course. However, recent evidence supports the superiority of $P2Y_{12}$ inhibitor monotherapy over aspirin for long-term secondary prevention in subjects with established coronary artery disease.[24] This observation may partly explain the heterogeneity in treatment effects seen in our landmark and sensitivity analyses where 1-month DAPT (followed by aspirin for 11 months) was associated with less favorable outcomes among higher risk subgroups, such as those with NSTE-ACS or NSTEMI. In fact, a growing body of evidence suggests a potential role of early aspirin withdrawal followed by potent $P2Y_{12}$ inhibitor monotherapy among those subjects in whom both bleeding and ischemic risks are of concern.[25, 26] Owing to their double-sided risk, HBR-ACS patients may be ideal candidates for such an approach. In the TWILIGHT trial, subjects at high risk for ischemic and bleeding events were randomized to ticagrelor monotherapy or ticagrelor plus aspirin after 3 months of PCI, for an additional 12 months.[27] Surprisingly, the NSTE-ACS subgroup derived the greatest net benefit from this monotherapy regimen.[10] To be enrolled in the trial, however, patients had to be deemed eligible for a long-term DAPT with ticagrelor, which resulted in only 17% of them classified as HBR.[28] Other trials on short DAPT followed by potent $P2Y_{12}$ inhibitor monotherapy have yielded consistent results.[12] However, controversies persist with regard to clopidogrel monotherapy, especially in an ACS setting. In the STOPDAPT-2 ACS trial, which enrolled 4196 patients mostly at low-to-intermediate bleeding risk who underwent PCI for an ACS using the same cobalt-chromium everolimus-eluting stent, 1-month DAPT followed by clopidogrel monotherapy failed to attest noninferiority to 12-month DAPT for the primary endpoint of net clinical benefit, with a numerical increase in cardiovascular events despite less bleeding.[13] Whether a strategy of $P2Y_{12}$ inhibitor monotherapy holds the promise of preserving

ischemic protection while effectively reducing bleeding after only 1 month of DAPT, or even omitting DAPT, among HBR patients is yet to be proven in large scale studies.[29-31]

Limitations

The non-randomized design introduces the risk for residual unmeasured confounding despite efforts to adjust through propensity score stratification using rigorous statistical methodology. The ACS subgroup analysis as well as the comparison between 1 and 3 months DAPT were pre-specified, but the propensity score analysis of the pooled XIENCE 28 and 90 population was not. In XIENCE 90, there was no scheduled follow-up at 1 month, and event-free patients were derived retrospectively to match the corresponding cohort of patients on 1-month DAPT from XIENCE 28. The XIENCE Short DAPT program included only patients undergoing successful PCI of non-complex target-lesion anatomy, with exclusive use of the same cobalt-chromium everolimus-eluting stent platform. Those with STEMI were excluded, and therefore our findings do not apply to patients not meeting the study enrollment criteria and who were not event-free at the predefined time points. Moreover, the HBR criteria used in XIENCE Short DAPT partially differ from that proposed by the Academic Research Consortium consensus, which became available after both XIENCE 28 and 90 started enrolling.[15, 32] Lastly, our findings must be considered hypothesis-generating. As most subgroup analyses, the present study was likely underpowered to detect clinically relevant differences in ischemic and bleeding outcomes, and the wide CIs do conclusively not rule out a potential for harm with either of the two DAPT strategies.

CONCLUSIONS

Among HBR patients undergoing non-complex PCI with an everolimus-eluting stent and enrolled in the XIENCE Short DAPT program, about one in three presented with NSTE-ACS. DAPT for 1 month compared with DAPT for 3 months followed by aspirin monotherapy, was associated with similar 1-year risk of death or MI and lower bleeding risk, irrespective of clinical presentation.

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Figure legends

Figure 1. Study population. DAPT, dual antiplatelet therapy; NSTE-ACS, non-ST-elevation acute coronary syndrome; CCS, chronic coronary syndrome.

Figure 2. Clinical outcomes with 1-month vs 3-month DAPT by clinical presentation. DAPT, dual antiplatelet therapy; NSTE-ACS, non-ST-elevation acute coronary syndrome; CCS, chronic coronary syndrome; MI, myocardial infarction; BARC, Bleeding Academic Research Consortium.

Figure 3. Landmark analysis at 3 months DAPT, dual antiplatelet therapy; NSTE-ACS, non-ST-elevation acute coronary syndrome; CCS, chronic coronary syndrome; MI, myocardial infarction; BARC, Bleeding Academic Research Consortium

Tables

Table 1. Baseline characteristics

	NSTE-ACS (N=1164)			CCS (N=2200)		
	1-month DAPT N= 475 (40.8%)	**3-month DAPT N= 689 (59.2%)**	**p-value**	**1-month DAPT N= 917 (41.7%)**	**3-month DAPT N=1283 (58.3%)**	**p-value**
High bleeding risk criteria						
Age ≥75 years	308 (64.8%)	447 (64.9%)	0.990	641 (69.9%)	845 (65.9%)	0.046
Chronic anticoagulant therapy	201 (42.3%)	280 (40.6%)	0.568	416 (45.4%)	525 (40.9%)	0.036
Anemia	90 (18.9%)	119 (17.3%)	0.464	111 (12.1%)	194 (15.1%)	0.045
History of stroke	54 (11.4%)	86 (12.5%)	0.566	91 (9.9%)	137 (10.7%)	0.573
Renal insufficiency	51 (10.7%)	47 (6.8%)	0.018	65 (7.1%)	110 (8.6%)	0.207
Thrombocytopenia	15 (3.2%)	14 (2.1%)	0.235	16 (1.8%)	24 (1.9%)	0.900
History of major bleeding	19 (4.0%)	25 (3.6%)	0.744	27 (2.9%)	32 (2.5%)	0.517
Number of HBR criteria	1.6±0.7	1.5±0.7	0.074	1.5±0.7	1.5±0.7	0.246
Clinical characteristics						
Age, years	75.6±9.3	74.9±9.4	0.191	76.2±7.8	75.2±9.4	0.010
Female sex	170 (35.8%)	260 (37.7%)	0.499	283 (30.9%)	441 (34.4%)	0.084
Race						
American Indian or Alaskan Native	2 (0.6%)	4 (0.6%)	1.000	0 (0.0%)	7 (0.5%)	0.103
Asian	56 (17.8%)	18 (2.6%)	<.001	70 (10.7%)	27 (2.1%)	<.001
Black or African American	18 (5.7%)	47 (6.8%)	0.516	18 (2.7%)	70 (5.5%)	0.007
Native Hawaiian or Pacific Islander	0 (0.0%)	0 (0.0%)	N.A.	0 (0.0%)	5 (0.4%)	0.174

	NSTE-ACS (N=1164)			CCS (N=2200)		
	1-month DAPT N= 475 (40.8%)	**3-month DAPT N= 689 (59.2%)**	**p-value**	**1-month DAPT N= 917 (41.7%)**	**3-month DAPT N=1283 (58.3%)**	**p-value**
White	238 (75.8%)	597 (86.6%)	<.001	569 (86.6%)	1142 (89.0%)	0.120
Hispanic or Latino ethnicity	55 (12.2%)	18 (2.6%)	<.001	83 (9.6%)	38 (3.0%)	<.001
Hypertension	405 (85.3%)	626 (90.9%)	0.003	774 (84.4%)	1145 (89.2%)	<.001
Dyslipidemia	309 (65.1%)	580 (84.2%)	<.001	630 (68.7%)	1042 (81.2%)	<.001
Diabetes mellitus	179 (37.8%)	282 (40.9%)	0.291	333 (36.6%)	505 (39.4%)	0.186
Chronic kidney disease	232 (50.2%)	277 (40.6%)	0.001	399 (46.0%)	524 (41.1%)	0.026
Prior PCI	120 (25.3%)	231 (33.5%)	0.003	270 (29.4%)	376 (29.3%)	0.944
Prior CABG	37 (7.8%)	77 (11.2%)	0.056	75 (8.2%)	169 (13.2%)	<.001
Prior MI	93 (19.7%)	131 (19.4%)	0.891	134 (14.7%)	186 (14.7%)	0.983
Multivessel disease	184 (38.7%)	321 (46.6%)	0.008	389 (42.4%)	597 (46.5%)	0.056
NSTEMI	245 (51.6%)	141 (20.5%)	<.001	-	-	-
Unstable angina	230 (48.4%)	572 (83.0%)	<.001	-	-	-
PARIS bleeding risk score	6.5±2.3	6.1±2.3	0.001	5.9±2.3	6.0±2.3	0.381
PARIS bleeding risk score [IQR]	6.0 (5.0-8.0)	6.0 (4.0-8.0)	<.001	6.0 (4.0-8.0)	6.0 (4.0-8.0)	0.472
PRECISE-DAPT bleeding risk score	29.4±12.3	26.7±11.6	<.001	26.8±10.6	25.9±11.7	0.101
PRECISE-DAPT bleeding risk score [IQR]	28.0 (22.0-37.0)	26.0 (19.0-33.0)	<.001	26.0 (19.0-32.0)	25.0 (18.0-32.0)	0.058
Procedural characteristics						
Number of lesions treated [IQR]	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.945	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.972
Number of vessels treated [IQR]	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.144	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.408
B2/C lesion	197 (41.5%)	257 (37.3%)	0.151	301 (32.8%)	430 (33.5%)	0.735

	NSTE-ACS (N=1164)			CCS (N=2200)		
	1-month DAPT N= 475 (40.8%)	**3-month DAPT N= 689 (59.2%)**	**p-value**	**1-month DAPT N= 917 (41.7%)**	**3-month DAPT N=1283 (58.3%)**	**p-value**
Bifurcation	51 (10.7%)	57 (8.3%)	0.154	110 (12.0%)	96 (7.5%)	<.001
Radial access	371 (78.1%)	414 (60.1%)	<.001	615 (67.1%)	614 (47.9%)	<.001
Number of stents per subject [IQR]	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.844	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.653
Total stent length, mm	28.6±15.3	26.5±14.5	0.021	26.5±13.9	25.0±13.4	0.013
Pre-procedure RVD, mm	3.0±0.5	3.0±0.5	0.856	3.0±0.5	3.0±0.5	0.190
Pre-procedure % DS	85.0±10.8	84.4±9.9	0.363	81.3±9.9	83.7±9.4	<.001
Antiplatelet therapy at discharge						
Aspirin	424 (89.3%)	644 (93.5%)	0.010	708 (77.2%)	1157 (90.2%)	<.001
Clopidogrel	368 (77.5%)	551 (80.0%)	0.304	836 (91.2%)	1061 (82.7%)	<.001
Prasugrel	4 (0.8%)	19 (2.8%)	0.021	10 (1.1%)	27 (2.1%)	0.068
Ticagrelor	103 (21.7%)	120 (17.4%)	0.069	71 (7.7%)	197 (15.4%)	<.001

Values are n/N (%) or mean ± SD, unless otherwise specified. ACS: acute coronary syndrome, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, MI: myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, RVD: reference vessel diameter, DS: diameter stenosis

Table 2. Primary and secondary outcomes with 1-month vs 3-month DAPT by clinical presentation

Outcomes	ACS (N=1164)				CCS (N=2200)				Interaction p-value‡
	XIENCE 28 1-month DAPT (N= 475)	XIENCE 90 3-month DAPT (N= 689)	Adjusted Hazard ratio† (95% CI)	p-value	XIENCE 28 1-month DAPT (N= 917)	XIENCE 90 3-month DAPT (N=1283)	Adjusted Hazard ratio† (95% CI)	p-value	
	no. of events (%)				no. of events (%)				
All-cause death, or MI	44 (9.6%)	55 (8.5%)	1.09 (0.71 - 1.65)	0.703	59 (7.1%)	90 (7.6%)	0.88 (0.63 - 1.24)	0.479	0.337
All-cause death	20 (4.3%)	30 (4.8%)	0.75 (0.41 - 1.37)	0.352	44 (5.3%)	58 (4.9%)	1.03 (0.68 - 1.55)	0.885	0.803
Cardiovascular death	13 (2.8%)	19 (3.1%)	0.90 (0.43 - 1.90)	0.783	19 (2.3%)	30 (2.6%)	0.84 (0.46 - 1.54)	0.580	0.798
MI	24 (5.5%)	34 (5.2%)	1.13 (0.65 - 1.96)	0.658	16 (1.9%)	39 (3.4%)	0.56 (0.31 - 1.02)	0.059	0.134
Definite or probable ST	0 (0.0%)	3 (0.5%)	N/A	N/A	4 (0.5%)	3 (0.3%)	2.32 (0.50 - 10.81)	0.282	0.992
Stroke	4 (0.9%)	12 (1.9%)	0.39 (0.12 - 1.27)	0.118	7 (1.0%)	21 (1.8%)	0.43 (0.18 - 1.05)	0.064	0.959
Ischemic stroke	3 (0.7%)	10 (1.6%)	0.32 (0.08 - 1.22)	0.095	6 (0.9%)	20 (1.7%)	0.37 (0.14 - 0.95)	0.040	0.964
Target lesion failure	32 (7.3%)	47 (7.5%)	0.99 (0.61 - 1.59)	0.957	37 (4.4%)	54 (4.6%)	0.94 (0.61 - 1.45)	0.775	0.897
Target lesion revascularization	6 (1.4%)	16 (2.6%)	0.56 (0.21 - 1.50)	0.250	12 (1.5%)	10 (0.8%)	1.77 (0.74 - 4.23)	0.198	0.079
Target vessel revascularization	9 (2.3%)	23 (3.7%)	0.56 (0.25 - 1.26)	0.162	20 (2.6%)	23 (1.9%)	1.35 (0.72 - 2.51)	0.347	0.123
BARC 2-5 bleeding	33 (7.3%)	76 (12.2%)	0.57 (0.37 - 0.88)	0.011	70 (8.5%)	108 (9.1%)	0.84 (0.61 - 1.15)	0.270	0.150
BARC 3-5 bleeding	18 (4.0%)	36 (5.6%)	0.66 (0.36 - 1.19)	0.166	31 (3.8%)	50 (4.2%)	0.80 (0.50 - 1.27)	0.341	0.632

DAPT: dual-antiplatelet therapy, ACS: acute coronary syndrome, MI: myocardial infarction, ST: stent thrombosis

† Propensity stratified outcomes according to gender, baseline serum creatinine, anticoagulation therapy, history of stroke, history of major bleeding, baseline platelet, baseline hemoglobin, BMI, hypertension, hypercholesterolemia, prior PCI, prior CABG, prior MI, multi-vessel disease, diabetes, B2/C lesion, total lesion length, mean pre RVD, mean pre DS, bifurcation lesion, number of lesion treated, number of vessel treated, number of stents, total stent length, P2Y12 on discharged, PARIS risk score for major bleeding, PRECISE DAPT risk score for bleeding

‡ P value is obtained from the interaction test between clinical presentation and DAPT treatment.

The percentages mentioned above represent K-M rates at 12 months after index procedure