

## CHINA INTERNATIONAL SYMPOSIUM (CIT)

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# Dual Antiplatelet Therapy Over 6 Months Increases the Risk of Bleeding after Biodegradable Polymer-Coated Sirolimus Eluting Stents Implantation: Insights from the CREATE Study

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**Background:** The optimal duration of dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation remains controversial. The primary aim of our study was to evaluate the impact of optimal DAPT duration on bleeding events between 6 and 12 months after biodegradable polymer-coated DES implantation. The secondary aim is to determine the predictors and prognostic implications of bleeding.

**Methods:** This study is a post hoc analysis of the Multi-Center Registry of EXCEL Biodegradable Polymer Drug Eluting Stents (CREATE) study population. A total of 2,040 patients surviving at 6 months were studied, including 1,639 (80.3%) who had received 6-month DAPT and 401 (19.7%) who had received DAPT greater than 6 months. Bleeding events were defined according to the bleeding academic research consortium (BARC) definitions as described previously and were classified as major/minor (BARC 2–5) and minimal (BARC 1). A left censored method with a landmark at 6 months was used to determine the incidence, predictors, and impact of bleeding on clinical prognosis between 6 and 12 months.

**Results:** At 1-year follow-up, patients who received prolonged DAPT longer than 6 months had a significantly higher incidence of overall (3.0% vs. 5.5%,  $P = 0.021$ ) and major/minor bleeding (1.1% vs. 2.5%,  $P = 0.050$ ) compared to the patients who received 6-month DAPT. Multivariate analysis showed that being elderly (OR = 1.882, 95% CI: 1.109–3.193,  $P = 0.019$ ), having diabetes (OR = 1.735, 95% CI: 1.020–2.952,  $P = 0.042$ ), having a history of coronary artery disease (OR = 2.163, 95% CI: 1.097–4.266,  $P = 0.026$ ), and duration of DAPT longer than 6 months (OR = 1.814, 95% CI: 1.064–3.091,  $P = 0.029$ ) were independent predictors of bleeding. Patients with bleeding events had a significantly higher incidence of cardiac death, myocardial infarction, target lesion revascularization, and stent thrombosis.

**Conclusions:** Prolonged DAPT (greater than 6 months) after biodegradable polymer-coated DES increases the risk of bleeding, and is associated with adverse cardiac events at 1-year follow-up. (*J Intervent Cardiol* 2014;27:119–126)

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## Introduction

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Dual antiplatelet therapy (DAPT) with aspirin and a P2Y<sub>12</sub> receptor antagonist has played a pivotal role in reducing the risk of recurrent thrombotic events in high-risk settings, such as patients with acute coronary syndromes (ACS) and/or undergoing percutaneous coronary intervention (PCI).<sup>1–3</sup> Prolonged (at least 12 months) DAPT is recommended especially for patients treated with drug-eluting stents (DES). This is due to the increased risk of thrombotic occlusion of the

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DES following early discontinuation of DAPT.<sup>4-8</sup> However, in balancing the bleeding versus thrombotic risks, the optimal duration of DAPT following DES implantation remains controversial.<sup>9-14</sup> Furthermore, prior literature has underscored the association of postprocedural bleeding events with adverse clinical outcomes in patients with ACS and/or undergoing PCI.<sup>15-18</sup> Recent data suggest that the new-generation DES with biodegradable polymer may be effective in reducing the risk of late stent thrombosis, as compared with durable polymer DES. As absorbable polymer may promote vascular healing, these novel devices may permit a shortened duration of DAPT. We had previously reported that 6-month DAPT is feasible and as effective as extended DAPT (>6 months) after biodegradable polymer-coated sirolimus stent (EXCEL<sup>TM</sup>, JW Medical System, Weihai, China) implantation in real-world settings.<sup>19,20</sup> However, the effect of such a regimen on bleeding has not been elucidated and reported. The aim of our study was to evaluate the impact of different DAPT durations on bleeding events between 6 and 12 months after EXCEL stent implantation and to identify the predictors and prognostic implications of bleeding.

## Method

**Study Population.** This study is a post hoc analysis of the Multicenter Registry of EXCEL Biodegradable Polymer Drug Eluting Stent (CREATE) Study.<sup>19,20</sup> The CREATE Study is a post-marketing surveillance study that enrolled 2,077 real-world patients at 59 medical centers from 4 countries. All lesions were exclusively treated with the EXCEL stent. Patients were excluded if they had device or procedural failure,  $\geq 1$  stent (other than the protocol stent), contraindications to DAPT, functional status greater than New York Heart Association Class III, or planned surgery in the near future. A 6-month DAPT regimen (aspirin 100–300 mg per day for 30 days followed by 100 mg per day indefinitely; clopidogrel 75 mg per day for 6 months) was recommended but not mandatory. Prasugrel and ticagrelor were not available at the time of the study, so no new platelet inhibitors were used. The Ethics Committee in all participating centers approved the study protocol, and a signed, informed consent was obtained from every enrolled patient. The study is registered in the National Institutes of Health website as identifier NCT00331578.

**Device Description.** The Excel stent is a sirolimus-eluting stent coated with a biodegradable polylactic acid (PLA) polymer. The platform is a laser-cut, 316L stainless steel, open-cell design with strut thickness of 0.0047 in. The PLA coating is mixed with sirolimus (C<sub>51</sub>H<sub>79</sub>NO<sub>13</sub>, molecular weight 914.2) (North China Pharmaceutical Group Corporation, Shijiazhuang, China) and coated onto the abluminal surfaces to a thickness of 10–15  $\mu$ m. The coating has been shown in animal studies to completely degrade into carbon dioxide and water within 6–9 months (based on communications with JW Medical System, October, 2007). There is no adhesive surface between the polymer and the stent struts. Total sirolimus dosage varies from 195 to 376  $\mu$ g per stent according to the stent length.

**Data Collection and Adjudication.** Clinical data were prospectively collected on case-report forms and submitted to a data coordination center (located at Shenyang Northern Hospital). Independent study monitors performed audit checks for at least 15% of patients in each center. All adverse clinical events were reviewed and adjudicated by an independent Clinical Events Committee.<sup>19</sup>

**Definitions.** This study focused on the incidence, predictors, and prognostic implications of bleeding events between 6 and 12 months after the index procedure. Bleeding complications were defined according to the Bleeding Academic Research Consortium (BARC).<sup>21,22</sup> We classified bleeding complications as major/minor (BARC type 2–5) and minimal (BARC type 1). All deaths were considered to be cardiac unless a noncardiac origin could be clearly established by clinical and/or pathological study. Myocardial infarction (MI) was defined as detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least 1 of the following: (1) symptoms of ischemia; (2) electrocardiogram (ECG) changes indicative of new ischemia (new ST-T changes or new left bundle branch block); (3) development of pathological Q waves in the ECG; (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. The PCI-related MI was defined by patients with normal baseline troponin values, but showed increases in biomarkers greater than 3 times of 99th percentile upper range limit after the index PCI. We defined target lesion revascularization (TLR) as any repeat intervention inside the stent that had been implanted during the

index procedure or within the 5 mm proximal or distal to the stent. Stent thrombosis (ST) was classified as definite, probable, and possible according to definitions proposed by the Academic Research Consortium (ARC).<sup>22</sup>

**Statistical Analysis.** Comparisons between continuous variable data, expressed as mean ± SD, were performed with the *t*-test, while the chi-square or the Fisher’s exact test was used for categorical data, expressed as percentages. The last observation carried forward method of imputation for missing observations was the prospectively defined statistical method. Cumulative incidence of events was calculated according to the Kaplan–Meier method. Survival curves were constructed with Kaplan–Meier estimates and compared by log-rank tests. Multivariate predictor analyses were performed with a binary logistic regression model. All available variables considered potentially relevant were included: age, gender, smoking history, hypertension, diabetes mellitus, hyperlipidemia, heart failure, previous history of MI, family history, and duration of DAPT. A “landmark survival analysis,” with a landmark set at 6 months, was performed to determine the impact of bleeding events between 6 and 12 months on clinical outcomes. Results are presented as odds ratio (OR) with 95% confidence interval (CI). Statistical analyses were performed with the SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA). A 2-side P value of <0.05 was considered statistically significant.

## Results

The baseline clinical and procedural characteristics were previously reported in the CREATE Study.<sup>19–20</sup> A total of 2,040 patients with 6-month bleeding-free survival after PCI were included in this analysis. Of those patients, 1,639 (80.3%) received 6-month DAPT and 401 (19.7%) received extended DAPT >6 months. The reasons for continuing DAPT beyond 6 months are as follows: (1) some patients underwent a second PCI procedure due to TLR; (2) some patients were not willing to stop DAPT at 6 months; (3) some patients followed local referral physicians’ advice to continue clopidogrel. DAPT >6 months was associated with increased bleeding events (3.0% vs. 5.5%, *P* = 0.021) and major/minor bleeding (1.1% vs. 2.5%, *P* = 0.050) between 6 and 12 months (Table 1).

**Predictors of Bleeding Events.** Baseline characteristics of patients with and without bleeding between

**Table 1.** Bleeding Events between 6 and 12 Months for Patients with Different DAPT Durations

Bleeding Events (6–12 Months)	DAPT		P-Values
	≤6 Months (n = 1,639)	>6 Months (n = 401)	
All bleeding events	49 (3.0)	22 (5.5)	0.021
Minimal	31 (1.9)	12 (3.0)	0.170
Major/minor	18 (1.1)	10 (2.5)	0.050

6 and 12 months are shown in Table 2. Patients with bleeding events had longer durations of DAPT and were more likely to be female or elderly. Those who experienced a bleeding event were also more likely to have diabetes, family history of coronary artery disease (CAD), and prior stroke. Multivariate analysis showed that age >65 years (OR = 1.882, 95% CI: 1.109–3.193, *P* = 0.019), diabetes mellitus (OR = 1.735, 95% CI: 1.020–2.952, *P* = 0.042), family history of CAD (OR = 2.163, 95% CI: 1.097–4.266, *P* = 0.026), and DAPT >6 months (OR = 1.814, 95% CI: 1.064–3.091, *P* = 0.029) were independent predictors of bleeding (Fig. 1). There was no difference in the percentage of patients taking proton pump inhibitors or anticoagulants in the 2 groups. The sites of bleeding and their incidence are listed in Table 3.

**Bleeding-related Adverse Events.** Case-based analysis showed that a total of 17 patients (23.9%) with bleeding suffered from major adverse cardiac events between 6 and 12 months, including 5 cardiac deaths, 1 MI, and 11 TLRs. Of those patients, 8 had TLRs before bleeding. The other 9 patients had events after bleeding, which were therefore defined as bleeding-related event. All those 9 patients had DAPT at the time of bleeding and clopidogrel was discontinued thereafter. Details of these events are listed in Table 3. Even taking into account the 8 nonbleeding related TLRs, patients who had any bleeding event between 6 and 12 months had a significantly higher incidence of all events, which included all-cause death, cardiac death, nonfatal MI, TLR, and ST at follow-up (Table 4). Survival curves demonstrated that bleeding events were predictive of significantly worse event-free survival rates (Fig. 2).

## Discussion

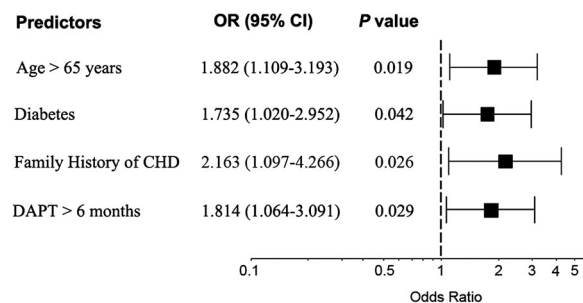
This is a post hoc analysis of the multicenter registry of the CREATE study. The main findings are as

**Table 2.** Univariate Analysis of Predictors of Bleeding between 6 and 12 Months

Predictors	Any Bleeding between 6 and 12 Months		P-Values
	Yes (n = 71)	No (n = 1,969)	
Female gender	27 (38.0)	517 (26.3)	0.039
Age, years	63.6 ± 11.7	60.6 ± 11.1	0.027
Smoking history	36 (50.7)	986 (50.1)	1.000
Diabetes mellitus	23 (32.4)	404 (20.5)	0.025
Hypertension	39 (54.9)	1,099 (55.8)	0.904
Hyperlipidemia	20 (28.2)	596 (30.3)	0.793
Family history of CHD	11 (16.2)	151 (8.4)	0.043
Prior stroke	19 (26.8)	328 (16.7)	0.035
Prior MI	6 (8.6)	239 (12.3)	0.456
Heart failure	6 (8.5)	183 (9.3)	1.000
PCI indications			0.889
Silent ischemia	4 (5.7)	77 (3.8)	
Stable angina	4 (5.7)	127 (6.3)	
Unstable angina	37 (52.9)	1,068 (53.2)	
Recent MI (24 hours to 30 days)	14 (20.0)	360 (17.9)	
Acute MI within 24 hours	11 (15.7)	375 (18.7)	
Multivessel stenting	24 (33.8)	532 (27.0)	0.222
Stent no. per patient	2.00 ± 1.23	1.79 ± 1.12	0.128
Number of target vessels	1.59 ± 0.79	1.48 ± 0.76	0.208
Mean RVD, mm	3.01 ± 0.47	2.99 ± 0.50	0.751
Mean lesion length, mm	26.42 ± 15.25	26.96 ± 12.96	0.734
Duration of DAPT, days	217.4 ± 67.0	200.0 ± 50.7	0.005
Medications			
Anticoagulant agents	6 (8.5)	157 (8.0)	0.884
Proton pump inhibitors	58 (81.7)	1,592 (80.9)	0.860

CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; RVD, reference vessel diameter; DAPT, dual antiplatelet therapy.

follows: (1) prolonged DAPT increased the risk of bleeding; (2) higher risk of bleeding could be predicted by female gender, older age, diabetes, family history of CAD, prior stroke, and longer duration of DAPT; (3) bleeding events occurring between 6 and 12 months



**Figure 1.** Independent predictors of bleeding between 6 and 12 months. CHD, coronary heart disease; DAPT, dual antiplatelet therapy; OR: odds ratio; CI: confidence interval.

were associated with a significant increase in MACEs at 1-year follow-up.

**Literature Review.** The advent of DES has dramatically reduced the rate of in-stent restenosis and repeat interventions. However, due to the delayed healing on the endovascular wall, the use of prolonged DAPT, ideally up to 12 months, has been strongly recommended.<sup>18</sup> This prolonged DAPT, coupled with the development of more potent antiplatelet agents, prompted safety concerns of bleeding complications.<sup>23</sup> DAPT has been previously associated with increased risk of bleeding with a hazard ratio of 19.8.<sup>24</sup> However, safety data from real-world patients are limited, as most analyses are derived from randomized trials with stringent inclusion criteria, which may not reflect the true scope of problem. Moreover, most published studies address the incidence of bleeding during the acute phase of ACS, often reflecting the in-hospital utilization of powerful antithrombotic regimens, as

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**Table 3.** Time of Bleeding, DAPT Discontinuation and Adverse Events in the 9 Patients with Bleeding-Related Events

ID	Bleeding Classification	Bleeding Time (Days)	Time of DAPT Discontinuation (Days)	Adverse Events	Events Time (Days)
3	Major/minor (GI bleeding)	196	197	TLR	307
348	Major/minor (GI bleeding)	219	219	Sudden death/ST	312
923	Minimal (Gum bleeding)	222	223	TLR	351
975	Major/minor (GI bleeding)	239	239	Died of HF	351
1,276	Major/minor (GI bleeding)	263	263	Died of VA	329
1,461	Major/minor (ICH)	247	247	Died of ICH	247
1,749	Major/minor (GI bleeding)	206	206	Sudden death/ST	227
1,780	Major/minor (GI bleeding)	224	225	MI	291
2,056	Minimal (Gum bleeding)	236	236	TLR	299

DAPT, dual antiplatelet therapy; TLR, target lesion revascularization; ST stent thrombosis; VA, ventricular arrhythmias; ICH, intracerebral hemorrhage; MI, myocardial infarction.

opposed to the long-term risk related to prolonged DAPT. In a recent pooled analysis of the ACUITY and HORIZONS-AMI trials, non-CABG-related major bleeding occurred within 30 days of randomization in 520 (3.8%) of the 13,819 ACUITY patients and in 224 (6.2%) of the 3,602 HORIZONS-AMI patients.<sup>18</sup> Data from the OASIS-Registry, OASIS-2, and CURE trials reported a 6-month major bleeding rate of 2%.<sup>25</sup> Moreover, DES with biodegradable polymer have been associated a lower risk of too late stent thrombosis occurring >1 year after implantation. However, in that study, there was no difference in stent thrombosis at 1 year, while DAPT use was variable between 6 and 12 months.<sup>26</sup>

**Bleeding Rate.** Consistent with the results of previous studies, our study demonstrated that over 3.5% of patients experienced a bleeding event in the 12 months following DES implantation, with 2.1% experiencing major bleeding. Of note, the present population, although derived from a “real-world” scenario, may have a lower bleeding risk profile, as all patients were selected for DES implantation. The suggestion to patient for DES implantation often implies a careful prior stratification of patients for bleeding risk. Moreover, 10% of the patients in this study had stable coronary artery disease, a subpopulation associated with a lower risk of bleeding complications.

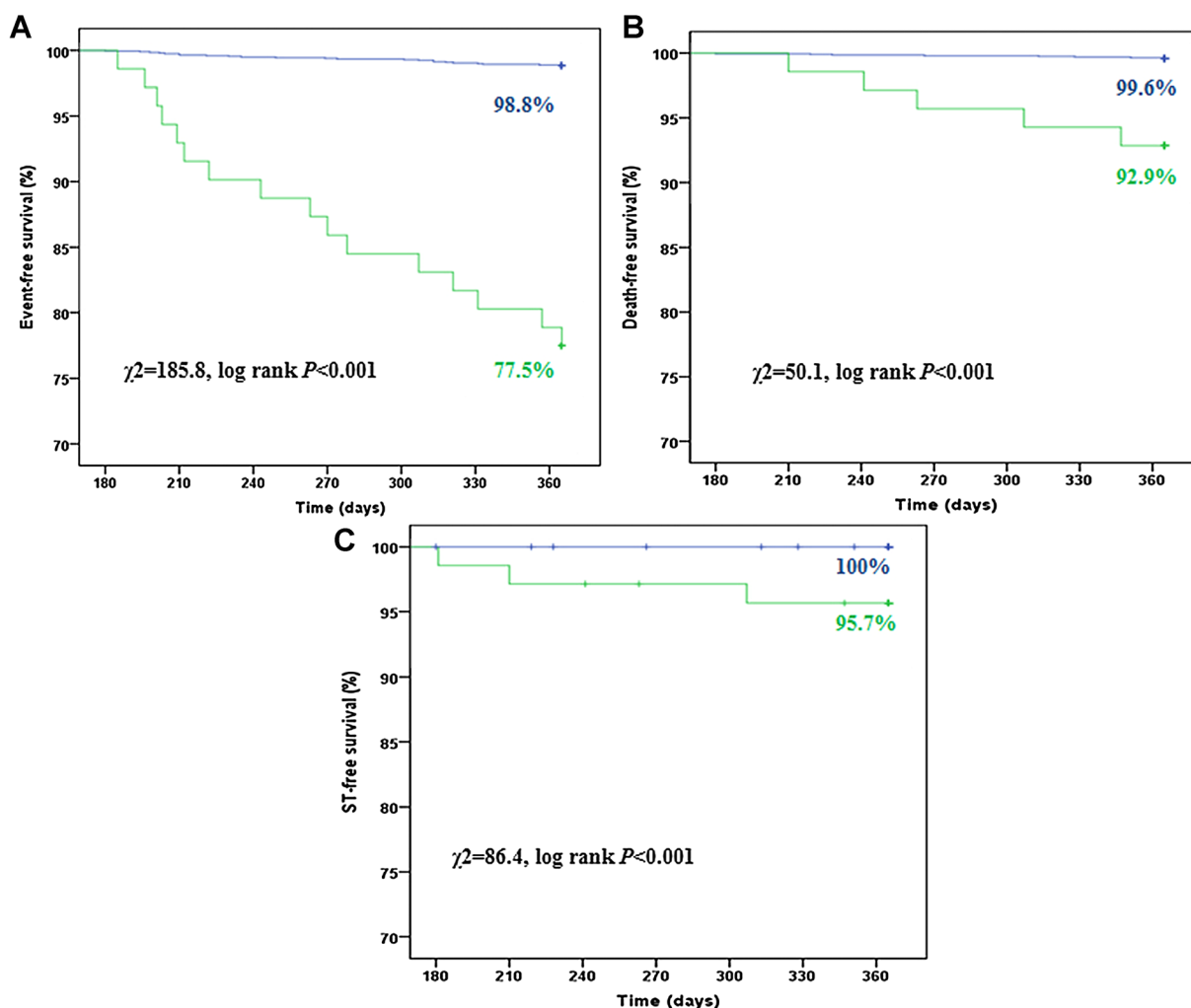
**Predictors of Bleeding.** Large-scale registry and clinical trial data have consistently identified elderly patients, women, and patients with impaired renal function, ACS, diabetes, and/or baseline anemia to be at increased risk for bleeding.<sup>15,26,27</sup> In our study, bleeding can be predicted by female gender, older age, diabetes, family history of CAD, prior stroke, and

prolonged duration of DAPT. To balance thrombotic prevention and bleeding risk, prediction of bleeding complications as well as thrombotic events would be crucial. Diabetes has been shown to be an independent predictor of stent thrombosis.<sup>7</sup>

Like other previous studies, our study has also shown diabetes to be a predictor of bleeding. The encouraging news from our study could be a potentially shorter duration of DAPT (6 months) after DES with biodegradable polymer resulting in a lower incidence of subsequent bleeding events without a higher incidence of stent thrombosis. Diener et al.<sup>14</sup> showed that DAPT in patients with recent history of stroke is associated with a higher risk of major bleeding especially, intracranial hemorrhage, with the risk increasing consistently beyond the first 3 months of DAPT. With prior stroke being a predictor of increased bleeding events beyond 6 months of DAPT in our study, patients with prior stroke who need a DES could potentially benefit from 6-month-only DAPT, which could reduce risk of major bleeding subsequently.

Regrettably, most research of prediction models for bleeding events have been confined to the short term.<sup>18,28–30</sup> Moreover, some risk factors of bleeding such as ACS, diabetes mellitus, and renal insufficiency<sup>31,32</sup> were, at the same time, reported as risk factors of ST.<sup>33,34</sup> This observation is reflective of the common paradox in clinical practice whereby, for a specific therapy, there is often concurrence of maximal benefit and maximal risk in the same population.

**Stent Thrombosis after Bleeding.** Major bleeding is the Achilles heel of prolonged DAPT. Aside from the obvious hemorrhagic sequelae, bleeding has been associated with MI, stroke, ST, and death, in patients with ACS and in those undergoing PCI<sup>35–40</sup> in both



**Figure 2.** Kaplan–Meier curves of survival free from all events (A), all-cause death (B) and any ST (C) stratified by bleeding events between 6 and 12 months (green line: with bleeding; blue line: without bleeding).

**Table 4.** The Relationship between Bleeding and Clinical Outcomes

Parameters	Any Bleeding between 6 and 12 Months		P-Values
	Yes (n = 71)	No (n = 1,969)	
All events between 6 and 12 months	17 (23.9)	23 (1.2)	<0.001
All-cause death	5 (7.0)	8 (0.4)	<0.001
Cardiac death	5 (7.0)	0 (0.0)	<0.001
Non-fatal MI	1 (1.4)	0 (0.0)	0.035
TLR	11 (15.5)	15 (0.7)	0.023
Stent thrombosis	3 (4.2)	0 (0.0)	0.001

MI, myocardial infarction; TLR, target lesion revascularization.

short- and long-term antithrombotic settings.<sup>16,41</sup> There is a seemingly paradoxical association between bleeding and thrombotic/ischemic risk. One possible explanation for this observation may be the obligatory withdrawal of crucial antithrombotic medications, mainly P2Y12 inhibitors during acute bleeding. In our study, case-based analysis of the bleeding events occurring between 6 and 12 months showed that all 9 bleeding-related events happened after discontinuation of DAPT. This observation questions the appearance of ST after routine discontinuation of P2Y12 inhibitor versus the abrupt stopping of P2 Y12 inhibitors in a patient with increasing thrombotic tendency during acute bleed. Thus, balancing the anti-ischemic benefits

against the bleeding risk of antiplatelet agents and interventions is of paramount importance in assessing new therapies and in managing patients. One of the speculative solutions to reduce the length of required DAPT is to use a stent with biodegradable polymer because biodegradable polymer produces better endothelialization and tissue coverage to the stent struts, as in the Optical Coherence Tomographic substudy on the Limus-Eluted from a Durable versus Erodable Stent Coating (LEADERS) Trial.<sup>42</sup>

In conclusion, current guidelines regarding the duration of DAPT may not be reflective of the latest stent technologies, such as biodegradable polymers and possibly the second-generation DES such as everolimus and Zotarolimus durable polymer stents. Current data suggest that 6-month DAPT may be safe for some lower-risk patients, while ACS or high-risk patients might require a longer duration of DAPT, up to 12 months. The significance of other risk factors in balancing ST and bleeding risks remains to be determined. With developing technology, newer DES like EXCEL may permit shorter DAPT duration, as compared with the first-generation DES. So there is a need for further study in a randomized fashion with longer follow-up.

**Limitations.** This study has several limitations shared by most nonrandomized trials. Follow-up information, including BARC-defined bleeding events and DAPT adherence rates, was based on patient self-reports. The number of events was small, due to the low frequency of the adverse events. Patients at a higher risk of bleeding could have been excluded from this study. The risk of bleeding with aspirin and clopidogrel would undoubtedly be higher in unselected patients. Furthermore, the causal effect of bleeding on MACE is not clear as it may be related to comorbidities not addressed by the statistical analysis. Finally, despite multivariable adjustment of important confounders in all of the models, there remains the possibility of unmeasured confounders. The results of this study should not be generalized to patients unlike those enrolled.

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