Clinical Impact of Dual Antiplatelet Therapy Use in Patients Following Everolimus-eluting Stent Implantation: Insights from the SEEDS Study

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Abstract

Background: Studies have suggested that use of prolonged dual antiplatelet therapy (DAPT) following new generation drug-eluting stent implantation may increase costs and potential bleeding events. This study aimed to investigate the association of DAPT status with clinical safety in patients undergoing everolimus-eluting stent (EES) implantation in the SEEDS study (A Registry to Evaluate Safety and Effectiveness of Everolimus Drug-eluting Stent for Coronary Revascularization) at 2-year follow-up.

Methods: The SEEDS study is a prospective, multicenter study, where patients ($n = 1900$) with small vessel, long lesion, or multi-vessel diseases underwent EES implantation. Detailed DAPT status was collected at baseline, 6-month, 1- and 2-year. DAPT interruption was defined as any interruption of aspirin and/or clopidogrel more than 14 days. The net adverse clinical events (NACE, a composite endpoint of all-cause death, all myocardial infarction (MI), stroke, definite/probable stent thrombosis (ST), and major bleeding (Bleeding Academic Research Consortium II-V)) were investigated according to the DAPT status at 2-year follow-up.

Results: DAPT was used in 97.8% of patients at 6 months, 69.5% at 12 months and 35.4% at 2 years. It was observed that the incidence of NACE was low (8.1%) at 2 years follow-up, especially its components of all-cause death (0.9%), stroke (1.1%), and definite/probable ST (0.7%). DAPT was not an independent predictor of composite endpoint of all-cause death/MI/stroke (hazard ratio [*HR*]: 0.693, 95% confidence interval [*CI*]: 0.096–4.980, *P* = 0.715) and NACE (*HR*: 1.041, 95% *CI*: 0.145–7.454, *P* = 0.968). Of 73 patients who had DAPT interruption, no patient had ST at 12-month, and only 1 patient experienced ST between 1- and 2-year (1.4%). There was a high frequency of major bleeding events (53/65, 82.5%) occurred in patients receiving DAPT treatment.

Conclusions: Prolonged DAPT use was not associated with improved clinical safety. The study emphasized that duration of DAPT needs to be shortened in Chinese patients following EES implantation (ClinicalTrials.gov identifier: NCT 01157455).

Key words: Bleeding; Dual Antiplatelet Therapy; Everolimus-eluting Stent; Net Adverse Clinical Events; Stent Thrombosis

INTRODUCTION

Drug-eluting stents (DESs) delivering antiproliferative drugs have significantly reduced the incidence of restenosis and the need for revascularization compared with bare metal stents,[1,2] but increased risk of stent thrombosis (ST) necessitated dual antiplatelet therapy (DAPT),

especially in first generation DES.[3,4] New generation DES with biocompatible or biodegradable polymers has significantly improved clinical safety and efficacy.[5-7] Although 6 months DAPT use for patients who underwent new generation DES implantation has been recommended in recent guidelines,[8] the optimal duration of DAPT use has not been fully defined.

The results observed in 4896 patients from the pooled RESOLUTE clinical program indicated DAPT interruption

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between 1 and 12 months were associated with low rates of ST and adverse cardiac outcomes.[9] Recently, it has been reported in some randomized trials that short duration of DAPT appears acceptable, without any concern of clinical safety.[10,11] Early vascular healing from optical coherence tomography studies in a new generation DES may provide an essential explanation for short duration of DAPT.[12] To date, but no study has investigated the use of DAPT in patients with complex lesions and its relationship with ST and net adverse clinical events (NACE) at 2-year follow-up after everolimus-eluting stent (EES). We therefore aimed to examine the DAPT status in patients with small vessel, long lesion, and multi-vessel diseases undergoing EES implantation and its association with clinical outcomes in the prospective SEEDS study (A Registry to Evaluate Safety and Effectiveness of Everolimus Drug-eluting Stent for Coronary Revascularization).

METHODS

Study design

The SEEDS study was a prospective, multicenter trial including 1900 patients who underwent percutaneous coronary intervention (PCI) with cobalt-chromium alloyed EES. Study design of the SEEDS registry has been previously described (ClinicalTrials.gov identifier: NCT 01157455).[13] Briefly, patients aged 18–75 years with symptomatic ischemic heart disease with small vessel (reference diameter <2.75 mm) or long lesion (length >25 mm) or multi-vessel (>2 target vessels). Major exclusion criteria included acute myocardial infarction (MI) within 1 week, congenital heart disease, severe valve dysfunction, severe heart failure, low left ventricular ejection fraction (<30%), renal dysfunction (serum creatinine >0.02 g/L), bleeding disorder contraindicating antiplatelet and/or anticoagulant therapy, hypersensitivity or allergy to drugs and devices related to PCI procedure. All patients signed the written informed consents.

Procedure was performed according to the local clinical practice with standard techniques. Patient received a dose of 300 mg aspirin within 24 h and 300 mg clopidogrel 6 h or 75 mg/d at least 3 days before the procedure. After procedure, DAPT (aspirin, 100 mg/d indefinitely and clopidogrel 75 mg/d for at least 12 months) was recommended.

Dual antiplatelet therapy status, clinical endpoints, and definitions

Detailed DAPT status was collected at baseline, 6 months, 1- and 2-year follow-up. Study endpoint was the impact of DAPT on a composite endpoint (NACE, including all-cause death, all MI, stroke, definite/probable ST, and major bleeding [Bleeding Academic Research Consortium (BARC) II-V]). Definitions of clinical outcomes (MI, ST, etc.) in the SEEDS study have been described previously.[13] Bleeding complications were classified as BARC criteria.[14] An independent clinical research organization (CCRF, Beijing, China) was responsible for all data collection, source document verification for all reported events, and on-site monitoring. A Clinical Events Committee independently adjudicated all clinical events.

Dual antiplatelet therapy interruption was defined as any interruption of aspirin and/or clopidogrel more than 14 days. All ST and major bleeding (BARC II-V) were classified into "on DAPT" or "off DAPT" group according to the DAPT interruption at the time of the event occurred.

Statistical analysis

Categorical variables were reported as counts and percentages, and differences were assessed using the χ^2-test or the Fisher's exact test. Continuous variables were presented as mean ± standard deviation (SD) and were compared using Student's t-test or the Mann-Whitney test. Time-to-event variables were presented as Kaplan-Meier curves. Hazard ratios (HRs) with 95% confidence interval (CI) were calculated with multivariable cox regression using DAPT status as a time-dependent covariate. All analyses were conducted using SPSS 21.0 (IBM Corp., New York, USA). A $P < 0.05$ was considered to be statistically significant.

RESULTS

Dual antiplatelet therapy status in the a registry to evaluate safety and effectiveness of everolimus drug-eluting stent for coronary revascularization study

The percentage of DAPT use in all patients ($n = 1900$) at each follow-up time point was shown in Figure 1. DAPT was used in 97.8% of patients at 6 months, and 69.5% at 12 months. At 2-year follow-up, there were still 35.4% of patients receiving DAPT treatment. Patient characteristics according to DAPT status (DAPT or non-DAPT at 2 years) were shown in Tables 1 and 2.

Clinical outcomes

The incidence of composite endpoint of all-cause death/MI/stroke was 5.3%, and target vessel failure (TVF, a composite endpoint of cardiac death, target vessel MI, and ischemia-driven target vessel revascularization) was 6.8% at 2-year follow-up [Figure 2]. It is observed that the incidence of NACE was low (8.1%), and its components of all-cause death (0.9%), stroke (1.1%), and definite/probable ST (0.7%). Predictors of NACE included age ≥65 years (HR: 1.726, 95% CI: 1.228–2.426, $P = 0.002$), residual SYNergy between PCI with TAXus and cardiac surgery score (HR: 1.398, 95% CI: 1.131–1.729, $P = 0.002$).

Cumulative effect of dual antiplatelet therapy use on net adverse clinical event

Adjusted cox regression analysis using DAPT as a time-dependent covariate showed that DAPT was not associated with significantly reduced risk of NACE at 1 months (HR: 0.505, 95% CI: 0.070–3.649, $P = 0.498$), 6 months (HR: 0.707, 95% CI: 0.098–5.083, $P = 0.731$), 1 year (HR: 0.875, 95% CI: 0.122–6.269, $P = 0.894$), and 2 years follow-up (HR: 1.041, 95% CI: 0.145–7.454, $P = 0.968$)

[Figure 3a]. Similar results were found in composite endpoint of all-cause death/MI/stroke at 1 months (*HR*: 0.454, 95% *CI*: 0.063–3.285, *P* = 0.434), 6 months (*HR*: 0.548, 95% *CI*: 0.076–3.952, *P* = 0.551), 1 year (*HR*: 0.606, 95% *CI*: 0.084–4.367, *P* = 0.619), and 2 years follow-up (*HR*: 0.693, 95% *CI*: 0.096–4.980, *P* = 0.715) [Figure 3b].

Dual antiplatelet therapy interruption, stent thrombosis, and bleeding

Dual antiplatelet therapy interruption was mainly attributed to clinical, patient-related, completed script causes. There was 14 definite/probable ST (in 13 patients) occurred during 2 years follow-up. Of 73 patients who had DAPT interruption, no patient had ST at 12-month, and only 1 patient experienced ST between 1- and 2-year (1.4%) [Figure 4a]. There was a high frequency of major bleeding events (53/65, 82.5%) occurred in patients receiving DAPT treatment [Figure 4b].

Table 1: Baseline characteristics according to DAPT status at 2-year follow-up

Characteristics	DAPT group (*n* = 621)	Non-DAPT group (*n* = 1214)	*P*
Age (mean ± SD, years)	59.8 ± 9.5	59.6 ± 9.5	0.651
Male, *n* (%)	466 (75.0)	890 (73.3)	0.425
Diabetes, *n* (%)	185 (29.8)	321 (26.4)	0.109
Hypertension, *n* (%)	404 (65.1)	780 (64.3)	0.905
Hypercholesterolemia, *n* (%)	203 (32.7)	432 (35.6)	0.455
Current smoker, *n* (%)	265 (42.7)	498 (41.0)	0.611
Family history of CAD, *n* (%)	85 (13.7)	145 (11.9)	0.521
Peripheral vascular disease, *n* (%)	7 (1.1)	22 (1.8)	0.527
Prior MI, *n* (%)	153 (24.6)	309 (25.5)	0.092
Previous CABG, *n* (%)	12 (1.9)	15 (1.2)	0.385
Previous PCI, *n* (%)	62 (10.0)	92 (7.6)	0.187
Angina pectoris, *n* (%)			0.004
Stable angina	21 (3.4)	89 (7.3)	
Unstable angina	544 (87.6)	1004 (82.7)	
Silent ischemia	24 (3.9)	61 (5.0)	
LVEF (mean ± SD, %)	61.5 ± 9.0	60.8 ± 8.3	0.112

CABG: Coronary artery bypass graft; CAD: Coronary artery disease; DAPT: Dual antiplatelet therapy; MI: Myocardial infarction; LVEF: Left ventricular ejection fraction; PCI: Percutaneous coronary intervention; SD: Standard deviation.

DISCUSSION

This *post-hoc* analysis of a prospectively collected registry has shown a lack of association between DAPT utilization and clinical safety endpoints in patients with small vessel, long lesion, and multi-vessel diseases undergoing EES implantation. DAPT interruption rarely occurred in these patients and did not increase the risk of ST.

Patients with coronary artery disease are now extensively treated by PCI with a new generation DES. Meta-analyses and randomized trials have shown that current DES with biocompatible (EES, etc.) or biodegradable polymers offer better safety outcomes.[6] The "all-comers" COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial) trial showed EES was associated with a significant reduction in definite/probable ST compared with paclitaxel-eluting stent (0.6% vs. 2.5%, *P* < 0.001) at 2 years follow-up.[15] Recently, a large registry study found that EES had a lower risk of very late ST (2.0%) than sirolimus-eluting stent (2.8%, *P* = 0.05) and paclitaxel-eluting stent (4.0%, *P* < 0.001).[16] A pooled analysis from the SPIRIT II, III, IV, and COMPARE trials also showed that EES significantly reduced composite endpoint of cardiac death/MI/ischemia-driven target lesion revascularization compared with the old generation DES.[6] In this analysis, we demonstrated a consistent low risk of ST, TVF, and NACE in patients following EES implantation at 2-year follow-up.

Optimal duration of DAPT use after EES implantation, however, is unknown. The randomized SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trial testing the noninferiority of 6 vs. 12 months DAPT in patients undergoing PCI with a new generation DES reported that no differences on clinical outcomes were observed between the two groups.[17] Interestingly, 33.8% of patients in the 6-month group maintained DAPT treatment at 12 months follow-up. This protocol violation may be potentially due to the concerns from both physicians and patients on ST after DES implantation. Recently, consensus document on DAPT
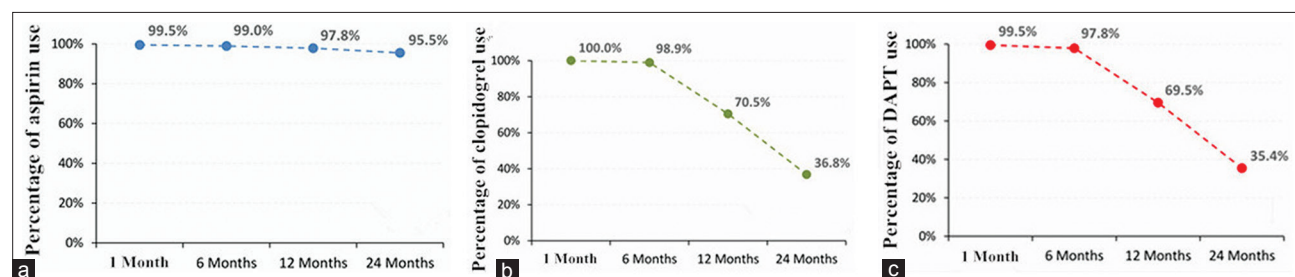

Figure 1: The use of dual antiplatelet therapy (DAPT) in the SEEDS study. DAPT was used in the majority of patients at 1 month and 6 months (a, b, c). Two-third of patients was taking DAPT at 12 months, and one-third of patients at 24 months (c). The reduced proportion of DAPT use at each time point was mostly due to complete script of clopidogrel.

Table 2: Lesion characteristics and procedural results according to DAPT status at 2-year follow-up

Items	DAPT group (n = 621)	Non-DAPT group (n = 1214)	P
Target lesion assessment			
Target lesion number (n)	1808	920	
Target lesion location, n (%)			0.265
LM	16 (1.8)	43 (2.4)	
LAD	407 (44.9)	854 (47.9)	
LCX	251 (27.7)	452 (25.4)	
RCA	232 (25.6)	433 (24.3)	
ACC/AHA lesion classification, n (%)			0.030
A	16 (1.8)	31 (1.7)	
B1	149 (16.5)	362 (20.3)	
B2	316 (34.9)	647 (36.3)	
C	425 (46.9)	742 (41.6)	
Lesion characteristics, n (%)			
Lesion types			0.099
Small vessel	104 (16.8)	247 (20.4)	
Long lesion	281 (45.3)	497 (40.9)	
Multi-vessel	236 (38.0)	470 (38.7)	
Total occlusion	86 (9.5)	149 (8.4)	0.327
Bifurcation lesion	248 (27.4)	476 (26.7)	0.715
Thrombus-containing lesion	5 (0.6)	10 (0.6)	0.976
TIMI flow preprocedural			0.152
0	87 (9.6)	151 (8.5)	
1	14 (1.6)	13 (0.7)	
2	27 (3.0)	49 (2.8)	
3	778 (85.9)	1569 (88.1)	
Preprocedural QCA			
Reference vessel diameter (mean ± SD, mm)	2.66 ± 0.48	2.64 ± 0.47	0.178
Lesion length (mean ± SD, mm)	19.95 ± 12.67	18.59 ± 11.98	0.009
Diameter stenosis (mean ± SD, %)	69.84 ± 15.79	69.38 ± 15.45	0.468
Minimal luminal diameter (mean ± SD, mm)	0.81 ± 0.46	0.81 ± 0.45	0.758
Procedural results			
Predilatation, n (%)	749 (80.9)	1527 (83.0)	0.172
Stent per patient (mean ± SD)	2.1 ± 1.1	2.1 ± 1.1	0.576
Stent per lesion (mean ± SD)	1.4 ± 0.6	1.4 ± 0.6	0.091
Stent diameter (mean ± SD, mm)	2.91 ± 0.44	2.89 ± 0.43	0.179
Postdilation, n (%)	418 (45.1)	706 (38.4)	<0.001
Postprocedural QCA			
Reference vessel diameter (mean ± SD, mm)	2.66 ± 0.45	2.62 ± 0.45	0.065
Diameter stenosis (mean ± SD, %)			
In-stent	8.84 ± 6.12	9.07 ± 6.06	0.354
In-segment	13.28 ± 8.41	13.39 ± 8.23	0.753
Minimal luminal diameter (mean ± SD, mm)			
In-stent	2.48 ± 0.41	2.45 ± 0.42	0.046
In-segment	2.30 ± 0.44	2.27 ± 0.44	0.056
Acute gain (mean ± SD, mm)			
In-stent	1.67 ± 0.50	1.64 ± 0.47	0.056
In-segment	1.49 ± 0.53	1.46 ± 0.51	0.066
SYNTAX scores (mean ± SD)			
Preprocedural	10.73 ± 7.20	10.99 ± 7.27	0.480
Postprocedural	1.94 ± 3.74	2.27 ± 4.01	0.095

Contd...

DAPT: Dual antiplatelet therapy; LAD: Left anterior descending artery; LCX: Left circumflex; LM: Left main; QCA: Quantitative coronary angiography; RCA: Right coronary artery; AHA: American Heart Association; ACC: American College of Cardiology; SD: Standard deviation.

in East Asian patients with acute coronary syndrome (ACS) or undergoing PCI reported that the Chinese recommendations for DAPT in patients with ACS were generally similar to those of the American College of Cardiology/American Heart Association,[18] as there was a lack of data existed to assess the efficacy and safety of DAPT for ACS or PCI. In our study, we for the first time presented the distribution of DAPT use in Chinese patients with small vessel, long lesion, and multi-vessel disease undergoing new generation DES implantation. It was observed that more than 30% of Chinese patients either subjectively or passively prolonged DAPT use after PCI, even though whether longer DAPT use had a beneficial effect after EES implantation was unknown.

Dual antiplatelet therapy use was not associated with improved clinical safety in patients with EES treatment in this analysis. The results were performed using DAPT as a time-dependent covariate after adjusting other predictors of NACE and the composite endpoint of all-cause death/MI/stroke. Meta-analyses have indicated short-term DAPT use is associated with a reduced risk of bleeding but preserved antithrombotic efficacy.[19] It is recognized from optical coherence tomography imaging studies that early endothelialization and low incidence of malapposition were seen in new generation DESs.[12,20] Therefore, more investigations of early vascular healing might provide important information for understanding the low risk of ST with short-term DAPT use after new generation DES implantation. Our study did not show any statistically beneficial effect of DAPT utilization, which could be explained by the fact that the greatest risk of ST is within the first 30 days.

Dual antiplatelet therapy interruption frequently occurred after PCI, which could be due to medical/dental/surgical procedure, another clinical indication, etc. In a large pooled population of patients treated with a resolute zotarolimus-eluting stent, there was no ST event reported among 752 patients with a longer than 14 days DAPT interruption.[9] It has also been seen in EES that no significant difference in 2-year ST rates according to early DAPT discontinuation. In the current analysis, out of 14 ST occurred in all patients, only 1 ST was possibly related
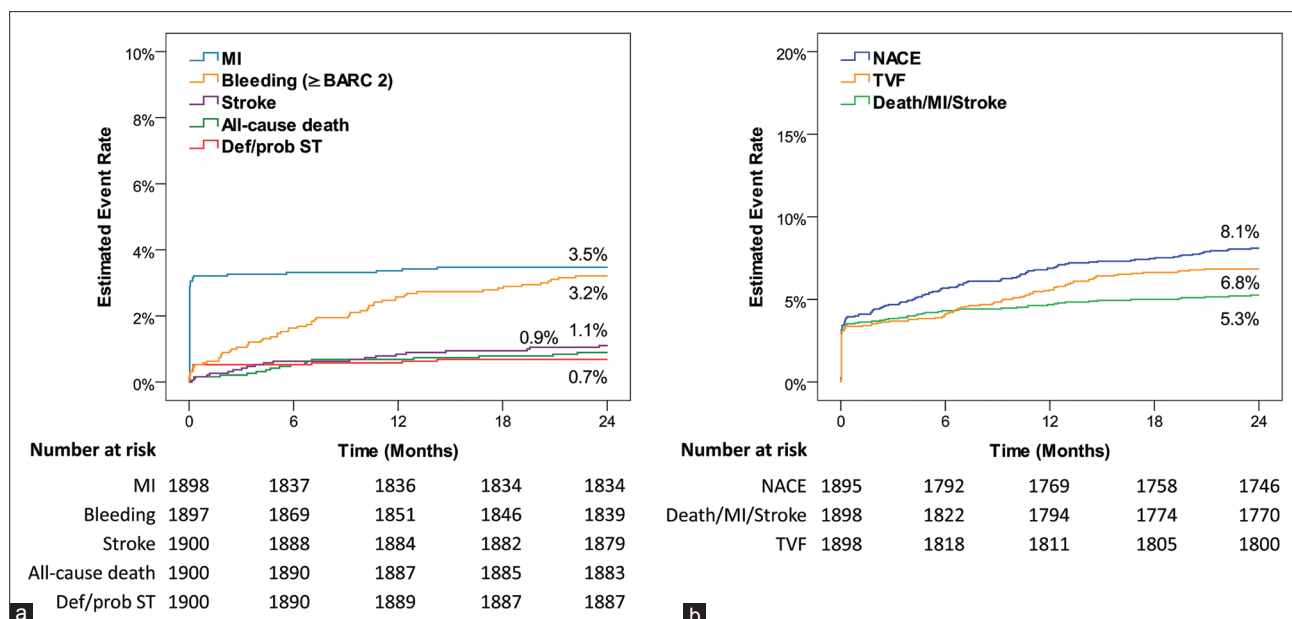
Figure 2: Clinical outcomes of patients treated with EES at 2-year follow-up. Clinical outcomes were presented with Kaplan–Meier curves in patient with small vessel, long lesion, and multi-vessel disease undergoing EES implantation at 2-year follow-up (a, b). Def/prob: Definite/probable; EES: Everolimus-eluting stent; MI: Myocardial infarction; NACE: Net adverse clinical event; ST: Stent thrombosis; TVF: Target vessel failure.
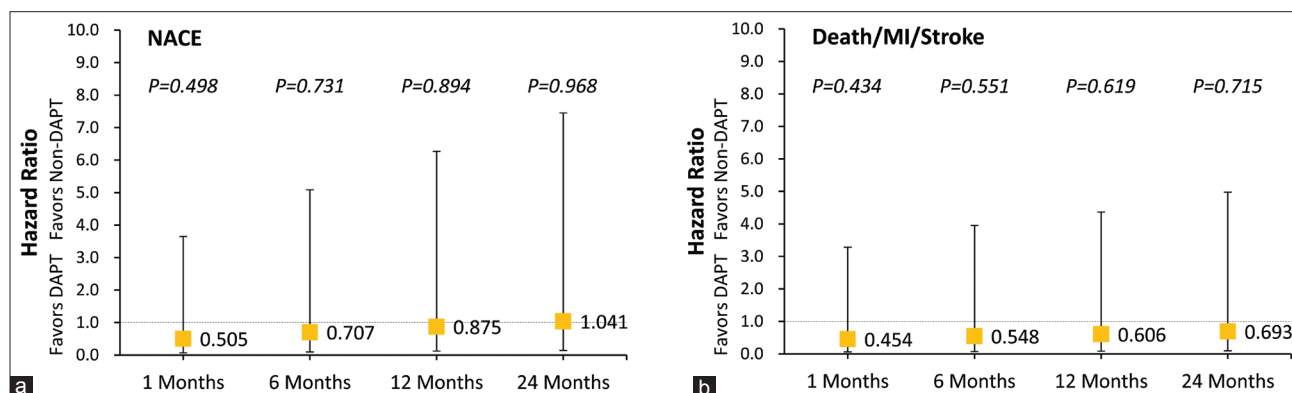

Figure 3: Cumulative effect of DAPT on clinical safety endpoints. Adjusted cox regression analyses using DAPT as a time-dependent covariate showed that the use of DAPT was not associated with significantly reduced risk of NACE (a) and composite endpoint of all-cause death/MI/stroke; (b) Cumulative effect analyses revealed a reduced beneficial effect of DAPT use on clinical safety at follow-up. DAPT: Dual antiplatelet therapy; MI: Myocardial infarction; NACE: Net adverse clinical event.
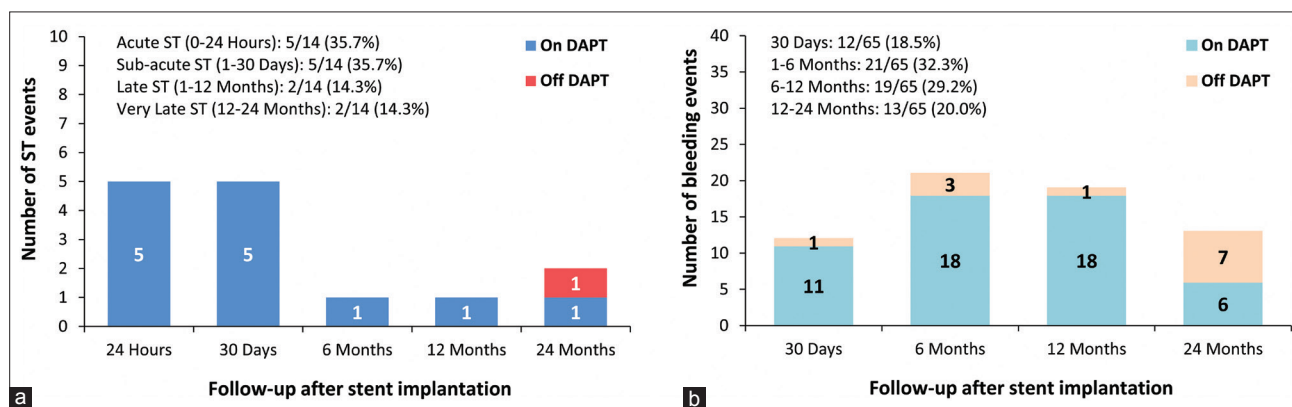

Figure 4: (a) Status of DAPT at the time of ST and major bleeding events. No patient who had DAPT interruption experienced ST at 12 months, and only one patient between 1- and 2-year; (b) There was a high frequency of major bleeding events occurred in patients receiving DAPT treatment. DAPT: Dual antiplatelet therapy; ST: Stent thrombosis.

to DAPT interruption, consistent with previous reports. Although these observational studies has revealed that lack of association between ST and DAPT interruption in patients treated with new generation DES, DAPT interruption at early follow-up should be avoided and randomized clinical trials are warranted to provide more robust evidence on DAPT duration after PCI.

According to the recent evidence on DAPT use after new generation DES implantation, together with this *post-hoc* analysis from Chinese population of patients undergoing EES implantation, Chinese guideline on DAPT use needs to be updated urgently to facilitate physicians and patients use DAPT appropriately. The beneficial effect of DAPT use should not be overestimated, especially when patients received new generation DES. Optimal duration of DAPT use in patients treated with Chinese local DES should be investigated in future randomized trials.

Our study had several limitations. It is a nonrandomized registry; therefore, potential bias and unmeasured confounders may have influenced the outcomes. Second, the NACE was not prespecified clinical endpoint prospectively; however, to assess the clinical impact of DAPT in patients treated with EES, we believe that NACE was one of the most suitable composite adverse events. Third, the results may be only applicable for Asian population of patients with CAD, as a higher level of platelet reactivity during clopidogrel treatment in East Asian patients than white patients was verified.[21] Given these limitations, our *post-hoc* analysis is truly exploratory to provide the clinical insight and warrants randomized trials to assess the clinical safety and optimal duration of DAPT use in patients treated with a new generation DES.

In conclusion, dual antiplatelet therapy was not associated with improved clinical safety in patients with small vessel, long lesion, and multi-vessel disease undergoing EES implantation. Moreover, it seems that lack of relationship between DAPT interruption and ST in this type of patients treated with EES. Larger, powered randomized trials are warranted to investigate optimal duration of DAPT in the contemporary DES era.

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