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Coronary Artery Disease

Switching from Ticagrelor to Clopidogrel in Asian Patients with ST-Elevated Myocardial Infarction – A Time Dependent Analysis Study

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Background: Ticagrelor is initially prescribed after an ST-elevated myocardial infarction (STEMI) and this may be followed by a switch to clopidogrel. However, studies involving antiplatelet switching have been conflicting and only assessed at a specific switch point. The objective of this study was to investigate switching from ticagrelor to clopidogrel in an Asian population, after accounting for various switch points as in a real-world environment.

Methods: A retrospective cohort of 349 STEMI patients started on ticagrelor and aspirin were followed-up for 1 year after a percutaneous coronary intervention that was performed between June 2014 and November 2016. Patients who switched to clopidogrel were compared with those who remained on ticagrelor. Outcomes measured were major adverse cardiac and cerebrovascular events (MACCEs) and clinically significant bleeding (CSB). Cox regression analysis with switch status as a time-dependent covariate was performed.

Results: The switched group was not associated with MACCEs or CSB [10.0% vs. 13.8%; hazard ratio (HR) = 0.484; 95% confidence interval (CI): 0.196- 1.191; p = 0.114]. There was also no significant difference when MACCEs were analyzed alone (2.3% vs. 7.7%; HR = 0.518; 95% CI: 0.137-1.957; p = 0.332). For CSB, the switched group was less likely to have an event (7.8% vs. 8.5%; HR = 0.298; 95% CI: 0.091-0.982; p = 0.047).

Conclusions: This study showed no significant difference between staying on ticagrelor and switching to clopidogrel. Switching might decrease the incidence of CSB. De-escalation from ticagrelor to clopidogrel could translate to cost savings for Asian patients without compromising safety and efficacy.

Key Words: Acute coronary syndrome • Clopidogrel • Dual antiplatelet • Switching • Ticagrelor

INTRODUCTION

The use of prasugrel or ticagrelor has become the standard of therapy[1] and is recommended over clopidogrel for dual antiplatelet therapy (DAPT) in both the latest European Society of Cardiology (ESC) guidelines[2] and the American Heart Association guidelines[3] for the management of ST elevated myocardial infarction (STEMI) after a percutaneous coronary intervention (PCI). In the PLATO trial, ticagrelor was reported to be more effective than clopidogrel in reducing ischemic recurrence, with a similar risk of bleeding. However, there were concerns over the safety and efficacy of ticagrelor in Asian populations. In the PHILO trial, Asian patients on ticagrelor had an increased risk in both adverse cardiac events and bleeds compared to those on clopidogrel, although this result did not reach statistical significance. In the Taiwan acute coronary syndrome (ACS) Full Spectrum Registry, the use of clopidogrel was asso-

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ciated with decreased mortality and improved cardiovascular outcomes in ACS patients with chronic kidney disease.[6] In addition, ticagrelor is more expensive than clopidogrel, constituting a financial burden for patients. Considering these risks and benefits, it remains unclear whether a strategy of remaining on ticagrelor or switching to clopidogrel is more appropriate for Asian patients with STEMI.

It has been suggested that using ticagrelor as the initial DAPT agent and subsequently de-escalating to clopidogrel might reduce the risk of bleeding. The recent expert consensus by Angiolillo[7] provided recommendations on how to switch between antiplatelets, however it acknowledged that there was a lack of evidence to recommend whether switching or non-switching strategies were preferred. The latest ESC guidelines[2] state that de-escalation may be considered and guided based on bleeding risk and economic factors.

Results from the TOPIC study suggested that switching after 1 month of ticagrelor or prasugrel treatment could reduce the risk of bleeding while not increasing the risk of ischemic complications compared to not switching.[8] Secondary analysis of the PRAGUE-18 trial also showed that economically motivated switching to clopidogrel in low risk patients was associated with lower risks of ischemic and bleeding events.[9] However, these studies were performed in Western populations and may not be generalizable to Asian populations as evidenced by the PLATO and PHILO trials. More importantly, most previous studies have only assessed differences in clinical outcomes at a specific switch point. In a real-life environment, switches can take place at any time during DAPT duration in which these studies would not be able to take into consideration.

Our study therefore aims to fill in the gap in current literature by investigating the effects of switching from ticagrelor to clopidogrel in an Asian population, after accounting for the various switch points in a real-world environment.

METHODS

Study design

This was a single-centre retrospective cohort study. Patients aged 21 and above who were admitted to Khoo Teck Puat Hospital in Singapore between June 2014 and November 2016 for a PCI following STEMI were included in the study. These STEMI patients were loaded with DAPT with ticagrelor and aspirin and maintained on ticagrelor 90 mg twice a day and aspirin 100 mg once a day following the PCI. Some eventually switched to clopidogrel therapy 75 mg once a day at their physician's discretion, and the date of switching was noted. All subjects in whom the $P2Y_{12}$ inhibitor was switched from ticagrelor to clopidogrel were classified as the "switched" group, while subjects who remained on ticagrelor for the full 12 months were classified as the 'ticagrelor only' group.

Patients were recruited into this study if they had received at least 1 year of DAPT. We recorded the outcomes of these patients who received DAPT in their first year of treatment. The exclusion criteria included hypersensitivity to ticagrelor or aspirin, multiple antiplatelet switches, thrombocytopenia, anemia and active cancer. This study was approved by the local Institutional Review Board.

Outcomes

The primary outcome was a composite of an efficacy endpoint [major adverse cardiac and cerebrovascular events (MACCEs)], and a safety endpoint (clinically significant bleeding). Secondary outcomes included MACCEs and clinically significant bleeding (CSB) as individual endpoints.

MACCEs were defined as all-cause mortality, myocardial infarction, target vessel revascularization or ischemic stroke.[10] Myocardial infarction was defined in accordance with the Third Universal Definition of Myocardial Infarction.[1] Ischemic stroke was defined as a focal loss of neurological function caused by an ischemic event, with residual symptoms lasting 24 hours or leading to death.[12] CSB was defined as type 2 bleeding and above according to the Bleeding Academic Research Consortium (BARC) classification.[13]

Electronic medical records and case notes dating from 1 June 2014 to 31 November 2017 were accessed to retrieve data on these outcomes. The study subjects were followed up for 1 year, and all outcomes were adjudicated in a blinded fashion by an independent committee comprising two cardiologists and a gastroenterologist.

Statistical analysis

Baseline characteristics including gender, age, ethnicity, body mass index, comorbidities, smoking, number of stents, type of post STEMI procedure, proton pump inhibitor (PPI) use, baseline platelet count and hemoglobin count were collected. Univariate analysis was conducted between the covariates and the two groups (switched and ticagrelor only groups). Covariates with a p-value of < 0.10 were included into Cox regression models to adjust for potential confounders. Categorical variables were compared using the χ^2-test or Fisher's exact test where appropriate. Continuous variables were compared using the Student's T-test and bootstrapped to account for any potential asymmetric distribution.

Cox regression with switch status as a time-dependent covariate (expressed in weeks) was used to investigate the effect of switching from ticagrelor to clopidogrel on the efficacy and safety of the DAPT. The time-dependent covariate could account for the various times to switching, and take into consideration the duration of ticagrelor therapy which the patient had received before switching to clopidogrel. In other words, the results from the Cox regression analysis would take into account the duration the patients had been on the respective antiplatelet therapy.

In order to picture the effects of the time-dependent switch status, the switched group was classified into blocks of 4 weeks depending on the time of switch. Each block was further differentiated into whether the event had occurred when the patient was on ticagrelor or clopidogrel and visualized in a table, one each for MACCE and CSB events. A patient could have an event with ticagrelor and hence switch to clopidogrel. The time dependent Cox regression analysis and the table could then account for this. This study was done in an exploratory, hypothesis generating manner, and sample size calculation was not done. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0.

RESULTS

A total of 480 patients were identified between June 2014 and November 2016, of whom 349 were eligible for analysis after exclusion (Figure 1). Overall, 88.3% of the study patients were males, with a mean age of 55 years, and 51.9% were of Chinese ethnicity, 26.9% were of Malay ethnicity, and 18.6% were of Indian ethnicity. The mean body mass index was 25.2 kg/m^2. Two hundred and nineteen patients switched to clopidogrel and 130 patients remained on ticagrelor over the 12-month period following the index event. The baseline characteristics are shown in Table 1. The following covariates with p values < 0.10 were entered into the multivariate analysis: gender, presence of chronic kidney disease (CKD), type of PCI procedure done and PPI use.

A total of 40 first encountered events were recorded, including 14 MACCEs and 26 CSB. Two of the patients who presented with MACCEs as the first event subsequently developed CSB while still on DAPT. Conversely, one of the patients with CSB as the first event subsequently died as the second event. The cause of death was cardiac arrest. All three cases were accounted for under the first event only for the composite outcome. The second event was accounted for when analyzing MACCEs and CSB separately. The outcome results are shown in Table 2. In the switched group, there were 22 (10.0%) first encountered events. Within the switched group, 14 events (6.3%) occurred when on ticagrelor and 8 (3.7%) events when on clopidogrel. There were 18 (13.8%) events in the ticagrelor only group. Figure 2 shows the time distribution of the switches after the index event.

Cox regression analysis with switch status as a time-dependent covariate was performed, adjusting for gen-

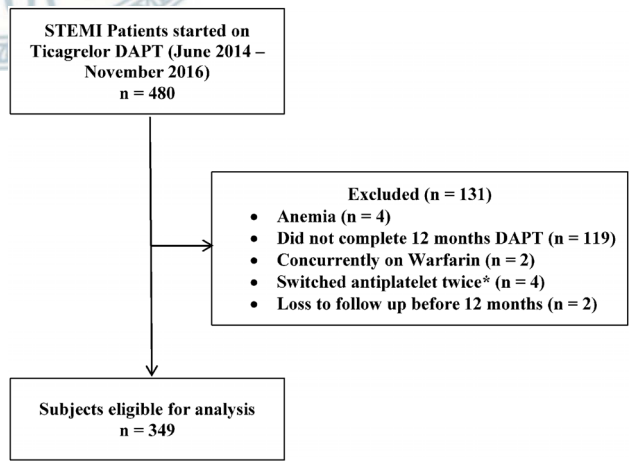

Figure 1. *Study design flowchart. DAPT, dual antiplatelet therapy; STEMI, ST elevation myocardial infarction. * In all 4 patients, DAPT duration at the second switch was still less than 12 months.*

Table 1. Baseline characteristics of study population

	Underwent switching to clopidogrel (n = 219)	Stayed on ticagrelor (n = 130)	p-value
Males	188 (85.8%)	120 (92.3%)	0.070
Age	55.2 ± 9.1	55.1 ± 10.1	0.943
Ethnicity			0.123
Chinese	112 (51.1%)	69 (53.1%)	
Malay	67 (30.6%)	27 (20.8%)	
Indian	36 (16.4%)	29 (22.3%)	
Others	4 (1.8%)	5 (3.8%)	
Body mass index (kg/m^2)	25.5 ± 4.3 (30 missing)	26.0 ± 4.2 (8 missing)	0.306
Hypertension	90 (41.1%)	64 (49.2%)	0.139
Dyslipidemia	189 (86.3%)	115 (88.5%)	0.560
Diabetes mellitus	79 (36.1%)	52 (40.0%)	0.464
Chronic kidney disease	1 (0.5%)	4 (3.1%)	0.066
Smoker	110 (50.2%)	62 (47.7%)	0.647
Number of stents			0.173
0	16 (7.3%)	4 (3.1%)	
1	147 (67.1%)	101 (77.7%)	
2	46 (21.0%)	22 (16.9%)	
3	9 (4.1%)	2 (1.5%)	
4	1 (0.5%)	1 (0.8%)	
Type of procedure			0.013
Thrombectomy	3 (1.4%)	0	
BMS	41 (18.7%)	11 (8.5%)	
DES	157 (71.7%)	114 (87.7%)	
BMS + DES	3 (1.4%)	1 (0.8%)	
POBA/drug-eluting balloon	15 (6.8%)	4 (3.1%)	
Concomitant proton pump inhibitor use	60 (27.4%)	20 (15.4%)	0.010
Baseline platelet count	249.2 ± 57.4	256.9 ± 66.2 (1 missing)	0.212
Baseline hemoglobin count	14.4 ± 1.6	14.5 ± 1.5 (1 missing)	0.319

BMS, bare metal stent; DES, drug-eluting stent; POBA, plain old balloon angioplasty.

Table 2. Study outcomes

	Number of first encountered event	
	Switched to clopidogrel group (n = 219)	Ticagrelor only group (n = 130)
MACCE	5 (2.3%)[#]	9 (6.9%)
Target vessel revascularization	4	4
Myocardial infarction	0	3[†]
All-cause mortality	0	2
Stroke	1	0
Clinical significant bleeds	17 (7.8%)[#]	9 (6.9%)
BARC 2	15	8*
BARC 3	2	1

[#] Details if the events had occurred when on clopidogrel or ticagrelor may be found in Tables 4 & 5.
[†] Two subjects had type 2 bleeds (1 epistaxis and 1 hemoptysis) as a second event subsequently while still on DAPT.
* One subject died from cardiac arrest as a second event subsequently while still on DAPT.
BARC, Bleeding Academic Research Consortium; MACCE, major adverse cardiac and cerebrovascular events.

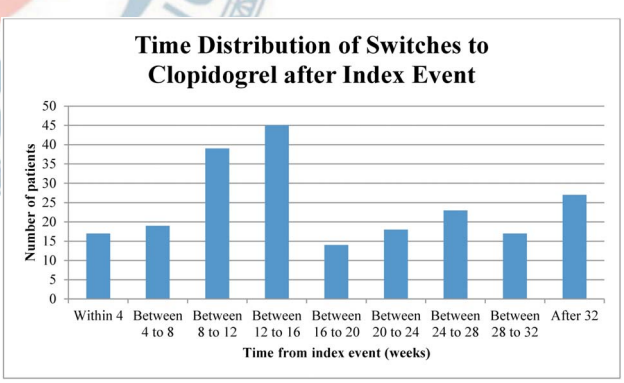

Figure 2. *Time distribution of switches to clopidogrel after index event.*

der, CKD, type of procedure and use of PPI (Table 3). Compared to the ticagrelor only group, the switched group was not significantly associated with MACCE or CSB events [hazard ratio (HR) = 0.484; 95% confidence interval (CI): 0.196-1.191; p = 0.114]. MACCE and CSB events were also analyzed separately, using the same covariates in the model.

Table 3. Results of the Cox regression models using switch status as a time dependent covariate

Outcomes	Switched to clopidogrel group (n = 219)	Ticagrelor only group (n = 130)	HR (95% CI)	p-value
Composite – bleeding + MACCE	22 (10.0%)	18 (13.8%)	0.484 (0.196-1.191)	0.114
Bleeding only	17 (7.8%)	11 (8.5%)	0.298 (0.091-0.982)	0.047
MACCE only	5 (2.3%)	10 (7.7%)	0.518 (0.137-1.957)	0.332

* Adjusted for gender, chronic kidney disease, type of procedure and use of proton pump inhibitors.
CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events.

During the full 12-month study period, a total of 11 CSB events (8.5%) occurred in the ticagrelor only group compared to 17 CSB events (7.8%) in the switched group. Within the switched group, 13 bleeds (5.9%) occurred when on ticagrelor compared to 4 bleeds (1.8%) when on clopidogrel. The switched group was then split into blocks of 4 weeks according to the time of switching as seen in Table 4. Throughout each of the blocks, there were either equal or more patients who had bleeding on ticagrelor compared to clopidogrel. The switched group was 70% less likely to have a CSB event (HR = 0.298; 95% CI: 0.091-0.982; p = 0.047) than the ticagrelor only group.

During the full 12-months study period, a total of 10 MACCE events (7.7%) occurred in the ticagrelor only group compared to five MACCE events (2.3%) in the switched group. Within the switched group, one MACCE (0.5%) occurred when on ticagrelor compared to four MACCEs (1.8%) when on clopidogrel. There was no significant difference between the switched and ticagrelor only groups in terms of MACCE outcomes (HR = 0.518; 95% CI: 0.137-1.957; p = 0.332). While more patients in the switched group had a MACCE when on clopidogrel, there were still fewer events in the switched group compared to the ticagrelor only group. This resulted in a HR of less than 1 for the Cox regression model above, albeit without significance. As above with the CSB events, the switched group was split into blocks of 4 weeks according to the time of switching (Table 5).

DISCUSSION

This study reflects the great variability of practice in the real world. To the best of our knowledge, this is the

Table 4. Clinically significant bleeding outcomes in 4-weekly blocks

Time of switching from index event	Antiplatelet therapy associated with bleeding event	Clinically significant bleeding
Switched within 4 weeks (n = 17)	Ticagrelor	1 (5.9%)
	Clopidogrel	1 (5.9%)
Switched between 4 to 8 weeks (n = 19)	Ticagrelor	1 (5.3%)
	Clopidogrel	1 (5.3%)
Switched between 8 to 12 weeks (n = 39)	Ticagrelor	1 (2.6%)
	Clopidogrel	0
Switched between 12 to 16 weeks (n = 45)	Ticagrelor	4 (8.9%)
	Clopidogrel	1 (2.2%)
Switched between 16 to 20 weeks (n = 14)	Ticagrelor	1 (7.1%)
	Clopidogrel	1 (7.1%)
Switched between 20 to 24 weeks (n = 18)	Ticagrelor	3 (16.7%)
	Clopidogrel	0
Switched between 24 to 28 weeks (n = 23)	Ticagrelor	1 (4.3%)
	Clopidogrel	0
Switched between 28 to 32 weeks (n = 17)	Ticagrelor	1 (5.9%)
	Clopidogrel	0
Switched after 32 weeks (n = 27)	Ticagrelor	0
	Clopidogrel	0
Total of all blocks (n = 219)	Ticagrelor	13 (5.9%)
	Clopidogrel	4 (1.8%)

Table 5. Major adverse cardiac and cerebrovascular events (MACCE) in 4-weekly blocks

Time of switching from index event	Antiplatelet therapy associated with MACCE event	MACCE
Switched within 4 weeks (n = 17)	Ticagrelor	0
	Clopidogrel	0
Switched between 4 to 8 weeks (n = 19)	Ticagrelor	0
	Clopidogrel	0
Switched between 8 to 12 weeks (n = 39)	Ticagrelor	0
	Clopidogrel	2 (5.1%)
Switched between 12 to 16 weeks (n = 45)	Ticagrelor	0
	Clopidogrel	1 (2.2%)
Switched between 16 to 20 weeks (n = 14)	Ticagrelor	0
	Clopidogrel	0
Switched between 20 to 24 weeks (n = 18)	Ticagrelor	0
	Clopidogrel	0
Switched between 24 to 28 weeks (n = 23)	Ticagrelor	0
	Clopidogrel	1 (4.3%)
Switched between 28 to 32 weeks (n = 17)	Ticagrelor	0
	Clopidogrel	0
Switched after 32 weeks (n = 27)	Ticagrelor	1 (3.7%)
	Clopidogrel	0
Total of all blocks (n = 219)	Ticagrelor	1 (0.5%)
	Clopidogrel	4 (1.8%)

first study to examine and control for a variety of switch points as a primary objective. After accounting for the various switch points, switch status as a time-dependent covariate was not significantly associated with the composite outcome of MACCEs or CSB (HR = 0.484; 95% CI: 0.196-1.191; p = 0.114). After separating the outcomes from the composite outcome, switch status was not significantly associated with MAACE outcomes (HR = 0.518; 95% CI: 0.137-1.957; p = 0.332), but was significantly associated with lower rates of CSB outcomes (HR = 0.298; 95% CI: 0.091-0.982; p = 0.047). This was evident in Table 4, in which there were more bleeding events with ticagrelor compared to clopidogrel at any of the switch points. However, the outcomes regarding MACCE were not as obvious. While the switched group had a lower event rate (2.3%) than the ticagrelor only group (7.7%), most of the MACCE events (80%) in the switched group occurred on clopidogrel. This contributed to its non-significant result. It must be noted that subgroup analysis of the composite outcome was not powered to detect differences.

Reduced costs and concerns over increased bleeding risks with the more potent ticagrelor remain the most common reasons for switching to clopidogrel.[14] Other side effects such as dyspnea are also a potential reason for switching away from ticagrelor.[15,16] The recently published 2018 expert consensus on the management of adverse effects of DAPT in Asian patients stressed the importance of completing a 12-month regimen but did not recommend switching of antiplatelets, with the exception of persistent, severe dyspnea caused by ticagrelor.[17] The ESC guidelines suggested that de-escalation may be considered, but they also refrained from providing a detailed recommendation on the matter.[2] This may be due to the paucity of studies assessing the clinical efficacy and safety of switching to clopidogrel, and the conflicting results of these studies. The SCOPE registry showed that de-escalation of antiplatelets early after a PCI (within 3 months) in patients with ACS was associated with an increased risk of ischemic events (OR = 5.3; 95% CI: 2.1-18.2; p = 0.04) with no differences in bleeding.[18] However, the TOPIC trial showed that switching at 1 month had no significant difference on ischemic outcomes, but that it reduced bleeding complications (HR = 0.30; 95% CI: 0.18-0.50; p < 0.01).[8] The TOPIC trial is currently the only randomized trial that involved switching from ticagrelor to clopidogrel. The results of the present study along with those of TOPIC[8] and PRAGUE-18[9] trials add to the growing body of evidence that supports the

de-escalation to clopidogrel. However, it must be noted that none of the above studies were sufficiently powered for outcomes.

All three Cox regression models yielded a HR of less than 1, showing that switching to clopidogrel resulted in lower rates of MACCEs and CSB in an Asian population. This result is mirrored by the PHILO trial conducted on Asian patients,[5] in which 801 patients were randomized to receive either DAPT with ticagrelor or clopidogrel. At 12 months, major bleeding had occurred in 10.3% and 6.8% of the patients receiving ticagrelor and clopidogrel, respectively (HR = 1.54; 95% CI: 0.94-2.53). In addition, the primary efficacy endpoint occurred in 9.0% and 6.3% of the patients receiving ticagrelor and clopidogrel, respectively (HR = 1.47; 95% CI: 0.88-2.44). More research is warranted to investigate the efficacy and safety of ticagrelor in Asian patients.

De-escalation to monotherapy with ticagrelor after 1-3 months of DAPT might theoretically reduce bleeding while still maintaining anti-ischemic effects. This was investigated by both the GLOBAL LEADERS and TWILIGHT studies. While TWILIGHT is still ongoing,[19] GLOBAL LEADERS showed no difference between the two treatment arms.[20] Based on current evidence and the cost of ticagrelor, monotherapy with ticagrelor remains questionable. Switching to clopidogrel and subsequently staying on aspirin only remains the most reasonable de-escalation method to date.

There is a growing interest in personalized methods to de-escalation. The TROPICAL-ACS trial compared standard therapy with prasugrel for 12 months with a de-escalation regimen guided by platelet function testing.[21] The personalized de-escalation arm was shown to be non-inferior to standard therapy at the 1 year mark. The ongoing POPular Genetics trial uses CYP2C19 genotyping instead to guide the choice of antiplatelet.[22] Efficacy, safety and cost effectiveness outcomes will be measured at 1 year. As more research and funding are invested into personalized medicine, such laboratory testing could become more common.

Our study has several limitations. First, being a retrospective study, we were unable to accurately ascertain the reason for switching antiplatelets due to a lack of documentation. However, we were able to determine that most cases of switching from ticagrelor to clopidogrel were not at the time of review when the physician had documented the bleeding event. Thus, it was likely that switching was carried out because of financial concerns and personal preferences, although the physicians would also insist on continuing ticagrelor if the lesion was complex or high risk. Regardless, selection bias of the intervention is likely as the risk of ischemia and the severity of the coronary lesions were not easily quantifiable and not accounted for in our study. However, an observational study design would be needed to provide a variety of switch points as in a real-world environment instead of a single switch point to which a randomized trial would be limited.

Second, the present study was likely not powered to detect differences in the different outcomes between the ticagrelor only and switched groups. While the switched group had a lower MACCE rate (2.3%) than the ticagrelor only group (7.7%), most of the MACCE events (80%) in the switched group occurred on clopidogrel. A larger study should be carried out with a larger group of patients with higher ischemic risk, such as patients with multivessel disease. However our method of time-dependent Cox regression accounted for the time to switching, with adjustments for clinically important predictors such as gender, presence of CKD, type of procedure and use of PPI serving the purpose of a descriptive study. This method was sufficient to generate a hypothesis.

CONCLUSIONS

The present study showed no significant difference between staying on ticagrelor and switching to clopidogrel in terms of clinical efficacy. In addition, switching to clopidogrel might decrease the incidence of CSB. Given that ticagrelor is more expensive than clopidogrel, it would appear logical to use a shorter duration of ticagrelor as this could translate to substantial cost savings for Asian patients without compromising safety and efficacy. Selection bias of the switching group was possible given the observational nature of the present study. Larger prospective randomized controlled trials could be commissioned to further evaluate the impact of switching in Asian patients, in particular, patients with substantial vessel disease burden and high bleeding risks.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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