Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Ischemic Heart Disease

Ticagrelor vs. Clopidogrel in Japanese, Korean and Taiwanese Patients With Acute Coronary Syndrome

– Randomized, Double-Blind, Phase III PHILO Study –

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Background: Few data on the relative efficacy and safety of new $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor in Japanese, Taiwanese and South Korean patients with acute coronary syndromes (ACS) exist.

Methods and Results: The multicenter, double-blind, randomized PHILO trial compared the safety and efficacy of ticagrelor vs. clopidogrel in 801 patients with ACS (Japanese, n=721; Taiwanese, n=35; South Korean, n=44; unknown ethnicity, n=1). All were planned to undergo percutaneous coronary intervention and randomized within 24 h of symptom onset. Primary safety and efficacy endpoints were time to first occurrence of any major bleeding event and to any event from the composite of myocardial infarction, stroke or death from vascular causes, respectively. At 12 months, overall major bleeding occurred in 10.3% of ticagrelor-treated patients and in 6.8% of clopidogrel-treated patients (hazard ratio (HR), 1.54; 95% confidence interval (CI): 0.94–2.53); the composite primary efficacy endpoint occurred in 9.0% and in 6.3% of ticagrelor- and clopidogrel-treated patients, respectively (HR, 1.47; 95% CI: 0.88–2.44). For both analyses, the difference between groups was not statistically significant.

Conclusions: In ACS patients from Japan, Taiwan and South Korea, event rates of primary safety and efficacy endpoints were higher, albeit not significantly, in ticagrelor-treated patients compared with clopidogrel-treated patients. This observation could be explained by the small sample size, imbalance in clinical characteristics and low number of events in the PHILO population. (*Circ J* 2015; **79:** 2452–2460)

Key Words: Acute coronary syndrome; Clopidogrel; East Asia; Japan; Ticagrelor

In the early 21st century, the annual incidence of acute myocardial infarction (MI) in Japan was reported to be approximately 25% of the incidence in the USA,[1] but registry data indicate that the incidence in Japan has steadily increased between 1979 and 2008.[1] In patients with acute coronary syndrome (ACS), the incidence of ST-segment elevation MI (STEMI) was higher in patients from the Japanese PACIFIC registry[2] than in those from the global GRACE registry.[3] The vast majority (93.5%) of ACS patients in Japan undergo percutaneous coronary intervention (PCI) with angiography or stent implantation,[2] while data from the global registries GRACE and CRUSADE report a lower rate of PCI (50–60%).[3,4] Antiplatelet therapy is used in >90% of ACS patients, both in Japan and worldwide.[2,3,5]

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Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor antagonist is the established standard of care in ACS patients[6] (unstable angina/non ST-segment elevation MI [NSTEMI],[7,8] and STEMI[9]), especially in those undergoing PCI.[10] Given that evidence-based clinical guidelines for Asian countries often rely on data obtained elsewhere,[11] current clinical practice does not differ largely from that in other regions of the world regarding antiplatelet therapy in ACS patients, except for the lower dose of prasugrel in Japan.[2,3,12,13]

With regard to the use of clopidogrel, poor drug metabolism is more common in Asian populations compared with other international regions, due to the prevalence of CYP2C19 loss-

Received March 4, 2015; revised manuscript received August 12, 2015; accepted August 17, 2015; released online September 16, 2015
Time for primary review: 20 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-15-0112

of-function alleles in these patients.[14] The overall rate of thrombotic complications (eg, stent thrombosis), however, is generally lower in patients from Asia than in patients from the USA and Europe,[15,16] suggesting that regional differences in thrombogenesis may also influence the altered response of clopidogrel to the onset of thrombotic events in Asian patients.[13]

Ticagrelor is the first of a new class of adenosine diphosphate (ADP) receptor antagonists, which does not require metabolic activation[17] and has a unique mode of action that encompasses inhibition of both $P2Y_{12}$ and equilibrative nucleoside transporter 1 (ENT1).[18–20] ENT1 inhibition increases adenosine plasma concentration in ACS patients,[19] which augments the antiplatelet effect[20] and may contribute to other cardioprotective effects such as vasodilation and increases in coronary blood flow.[21] The global Phase III PLATO trial demonstrated that ticagrelor significantly reduced the composite of MI, stroke and death from vascular causes, without increasing overall major bleeding, compared with clopidogrel in patients with ACS.[17] Ticagrelor, however, was associated with a higher rate of major bleeding not related to coronary artery bypass grafting (CABG) compared with clopidogrel.[17] The Asian/Australian subgroup of the PLATO population represented 6% of patients overall,[17] but did not include any patients from Japan. The current Phase III study (PHILO) was designed to investigate the efficacy, safety and tolerability of ticagrelor vs. clopidogrel in Japanese and East Asian patients with ACS. The ticagrelor dose chosen for PHILO was selected on the basis that it was previously shown to provide superior inhibition of platelet aggregation relative to clopidogrel in Asian patients with chronic stable coronary artery disease (CAD).[22]

Methods

PHILO, which was designed to mirror PLATO, was a multicenter, randomized, double-blind, double-dummy, parallel-group, non-event-driven study conducted in Japan and East Asian countries (NCT01294462; study code: D5130C00027). Unlike PLATO, PHILO was not statistically powered to detect treatment differences between groups. Instead, PHILO was designed to explore the consistency of the effects of ticagrelor in PLATO patients with patients from Japan, South Korea and Taiwan, because PLATO did not include any patients from Japan and few from South Korea or Taiwan.

An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data (**Methods** in **Supplementary File 1**). The sponsor coordinated the data management. Statistical analysis was performed by the sponsor, and confirmed by a third party (Uppsala Clinical Research Centre, Uppsala, Sweden), both of whom had full access to the final study data. If there was a difference between the analysis by the sponsor and the third party, the result calculated by the third party was used. The study was designed in accordance with the Declaration of Helsinki and was consistent with the International Committee on Harmonization, Good Clinical Practice and applicable regulatory requirements, and the AstraZeneca bioethics policy. The protocol was approved by the appropriate national and institutional regulatory authorities and ethics committees, and all participants provided written informed consent.

Patients

Patients were eligible if they were hospitalized for ST- or non-ST-segment elevation ACS with onset of symptoms during the previous 24 h (cardiac ischemic symptoms of ≥10 min duration at rest) and if PCI was planned. Inclusion and exclusion criteria were similar to those for PLATO,[17] with major exclusion criteria being any contraindication against the use of clopidogrel; active bleeding or a history of bleeding; fibrinolytic therapy within 24 h before randomization; need for oral anticoagulation therapy; increased risk of bradycardia; and concomitant therapy with a strong CYP3A inhibitor or inducer. The aim was to recruit approximately 800 patients from Japan and East Asian countries.

Study Treatment

Patients were randomly assigned 1:1 to receive ticagrelor or clopidogrel, administered in a double-blind, double-dummy fashion. Randomization was performed using a central interactive web response or voice system. Directly after randomization, patients received either oral ticagrelor tablets (or matching placebo), or oral clopidogrel capsules (or matching placebo). In the ticagrelor group, patients received an initial loading dose of 180 mg, followed by 90 mg twice daily (b.i.d.) and once-daily (o.d.) placebo tablets. In the active clopidogrel group, patients who were clopidogrel naïve received an initial loading dose of 300 mg clopidogrel or matching placebo, then 75 mg o.d. and placebo capsules b.i.d. thereafter. Patients in the clopidogrel group who had already received a loading dose or who were already taking maintenance doses of clopidogrel or ticlopidine for ≥5 days prior to randomization were given clopidogrel 75 mg o.d. plus placebo capsules b.i.d. The ticagrelor dose was chosen based on a dose-guiding pharmacodynamic (PD) study in Asian patients,[22] and the clopidogrel dose was based on international guideline recommendations for Japanese clinical practice.[8,12] In patients undergoing CABG, the blinded study drug (eg, active drug or placebo) was withheld for 5 days in the clopidogrel group and for 24–72 h in the ticagrelor group – consistent with the protocol of PLATO. All patients received acetylsalicylic acid (aspirin) at a dose of 75–100 mg once daily (a loading dose of up to 330 mg was permitted) unless aspirin was contraindicated or poorly tolerated. In contrast, higher doses of aspirin were used in PLATO (160–500 mg loading dose, 75–325 mg daily maintenance dose).

Outpatient visits were scheduled at 1, 3, 6, 9 and 12 months, with a safety follow-up visit 1 month after the end of treatment. The randomized treatment was scheduled for at least 6 months and up to 12 months, consistent with the PLATO study.[17]

Endpoints and Study Aims

The study had 2 primary co-objectives: (1) assessment of the short- and long-term safety and tolerability (especially bleeding) of ticagrelor vs. clopidogrel, administered on a background of low-dose aspirin; and (2) evaluation of the effect of ticagrelor vs. clopidogrel in the prevention of vascular events. Efficacy and safety endpoints were defined as in the PLATO study.[17] Major life-threatening bleeding was defined as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring vasopressors or surgery, decline in hemoglobin ≥5.0 g/dl, or the need for transfusion of at least 4 units of whole blood or packed red blood cells.[17] Bleeding that required medical intervention but did not meet the criteria for major bleeding was defined as minor, and bleeding that did not require intervention was defined as minimal (**Methods** in **Supplementary File 1**). Peri-procedural MI were defined as elevation of creatine kinase-myocardial band ≥300% that of laboratory specified upper normal limits (with or without development of pathological Q-waves on electrocardiogram [ECG]), with no symptoms required.

The primary efficacy variable in PHILO was the same as in PLATO, which was time to first occurrence of MI, stroke or death from vascular causes.[17] During the analysis, however, it became clear that 62% of primary endpoint events during follow-up were associated with peri-procedural MI, in contrast to spontaneous MI. Although there is evidence to suggest that infarct size is predictive of subsequent cardiovascular (CV) death,[23] the majority of peri-procedural MI are small and are not associated with CV death. A post-hoc analysis was therefore undertaken using the composite endpoint of spontaneous MI, stroke, or CV death. Secondary efficacy endpoints were the individual components of the primary composite endpoint variable, all-cause mortality, and any of the following events: vascular death, MI (including silent MI on ECG), stroke, recurrent cardiac ischemia, transient ischemic attack (TIA), or other arterial thrombotic events.

Vital signs were assessed at each study visit; ECG recordings were undertaken at baseline, month 1 and at the end of treatment; blood samples were taken for hematology and biochemistry assessments at months 1, 3, 6 and at the end of treatment. A subgroup of 101 Japanese patients also underwent 24-h Holter ECG recording at visit 1 and visit 2.

Pharmacokinetic (PK) and PD Evaluation

A substudy of PK and PD parameters was undertaken. PK data were collected from all patients and PD data were collected only from Japanese patients who provided written informed consent (**Methods** in **Supplementary File 1**).

Statistical Analysis

A sample size of 800 patients (730 from Japan, 30 from South Korea and 40 from Taiwan) was expected, based on recruitment estimates from 110 investigational centers. Efficacy analyses were undertaken on the full analysis set (FAS), which consisted of all patients randomized to treatment (equivalent to the intention-to-treat population). Safety data were analyzed for all patients who took at least 1 dose of study medication (equivalent to the on-treatment population). For primary efficacy and safety endpoints, treatment groups were compared using the Cox proportional hazards model with a factor for treatment group, and censored at the last available assessment for those who did not report an endpoint event. All patients who discontinued the study drug but who did not withdraw were followed up for study endpoints. The risk of an event in the ticagrelor group relative to the clopidogrel group is presented as hazard ratios (HR) with 2-sided 95% confidence intervals (CI). The contribution of each component of the composite efficacy endpoint to the overall treatment effect was examined. The occurrence of the primary efficacy endpoint in selected subgroups (based on baseline patient demographic and clinical characteristics) was examined if there were at least 15 events in each subgroup. Data on the secondary composite endpoints and all-cause mortality were analyzed in a similar manner to the primary efficacy endpoint, but descriptive analysis only was undertaken on the individual components of secondary endpoints. All statistical analysis was re-analyzed by an independent third party (Uppsala Clinical Research Centre) to ensure accuracy of results.

Although the study was underpowered to detect a treatment difference between groups, a justification of the sample size (360 Japanese and 40 non-Japanese patients per arm) is given here. Based on the PLATO data,[17] and assuming an annual dropout rate of 6.24%, with a 9-month recruitment period, 6-month minimum treatment period, and 12-month maximum treatment period, the expected proportion of patients with major bleeding events would be 9.5% and 9.2%, respectively for ticagrelor and clopidogrel. In this scenario, the 2-sided 95% CI for the difference in incidence of major bleeding events would be approximately ±4.3%, and an increase of approximately ≥4.6% compared with clopidogrel could be excluded. Assuming a primary efficacy event rate among Japanese patients of approximately 6%,[11] and the HR observed in PLATO,[17] it was expected that approximately 15 primary events would be seen with ticagrelor and 18 events with clopidogrel. In this case, the upper boundary of the 95% CI for the HR of ticagrelor to clopidogrel would be approximately 1.67, allowing exclusion of the possibility that ticagrelor would be associated with a 67% increase in the risk of the composite primary endpoint event relative to clopidogrel.

Results

Patients

We recruited 817 patients from East Asian countries; 801 patients were randomized to ticagrelor or clopidogrel and comprised the FAS (723 patients were recruited at Japanese sites). Sixteen patients were not randomized because of incorrect enrolment (n=15) or withdrawn consent (n=1). Patient disposition is shown in **Figure**. Of the 801 patients randomized to treatment, 767 received study drug and comprised the safety analysis set: 387 in the ticagrelor group and 380 in the clopidogrel group. Thirty-four patients did not take the study drug because of unwillingness (n=9), occurrence of adverse event (n=1) or for other undefined reasons (n=24). Overall, 141 patients (35.2%) prematurely discontinued ticagrelor and 126 (31.5%) prematurely discontinued clopidogrel during the study. The most common reasons for discontinuation were adverse events (ticagrelor, n=38; clopidogrel, n=40) and for other undefined reasons (ticagrelor, n=60; clopidogrel, n=44).

Patients were aged 34–93 years (mean, 67 years), and included 612 men (76.5%). ACS diagnosis was STEMI in 415 patients (51.8%), unstable angina or NSTEMI in 368 (46.0%), and other in 17 (2.1%). The 2 randomized groups were mostly balanced with regard to baseline characteristics (**Table 1**), although some exceptions were noted. The proportion of patients aged ≥75 years was higher in the ticagrelor group than in the clopidogrel group. The prevalence of conventional coronary risk factors (hypertension, diabetes and dyslipidemia) was higher in the ticagrelor group compared with the clopidogrel group. A higher number of patients in the clopidogrel group had a history of TIA (2.8% vs. 1.5%), but fewer had a history of CABG (0.3% vs. 1.2%), compared with the ticagrelor group. Relative to the clopidogrel group, a higher proportion of ticagrelor-treated patients had positive troponin I levels (77.1% vs. 74.5%) and ST depression ≥1 mm (46.9% vs. 38.3%) during the index event.

Overall, non-study medications and procedures were generally similar between groups (**Table 2**). Consistent with the current management of ACS patients in Japan, most patients (84.6%) underwent PCI while on treatment. Mean exposure to study drug was similar in the 2 groups: 200 days for ticagrelor and 210 days for clopidogrel.

Safety Endpoints

The primary safety endpoint of PLATO-defined total major bleeding occurred in 40 patients (10.3%) in the ticagrelor group vs. 26 patients (6.8%) in the clopidogrel group (HR, 1.54; 95% CI: 0.94–2.53; **Table 3**). A higher rate of major bleeding with ticagrelor was seen in all categories of bleeding (CABG-related, non-CABG-related and coronary procedural), except non-coronary procedural bleeding, but none of the between-

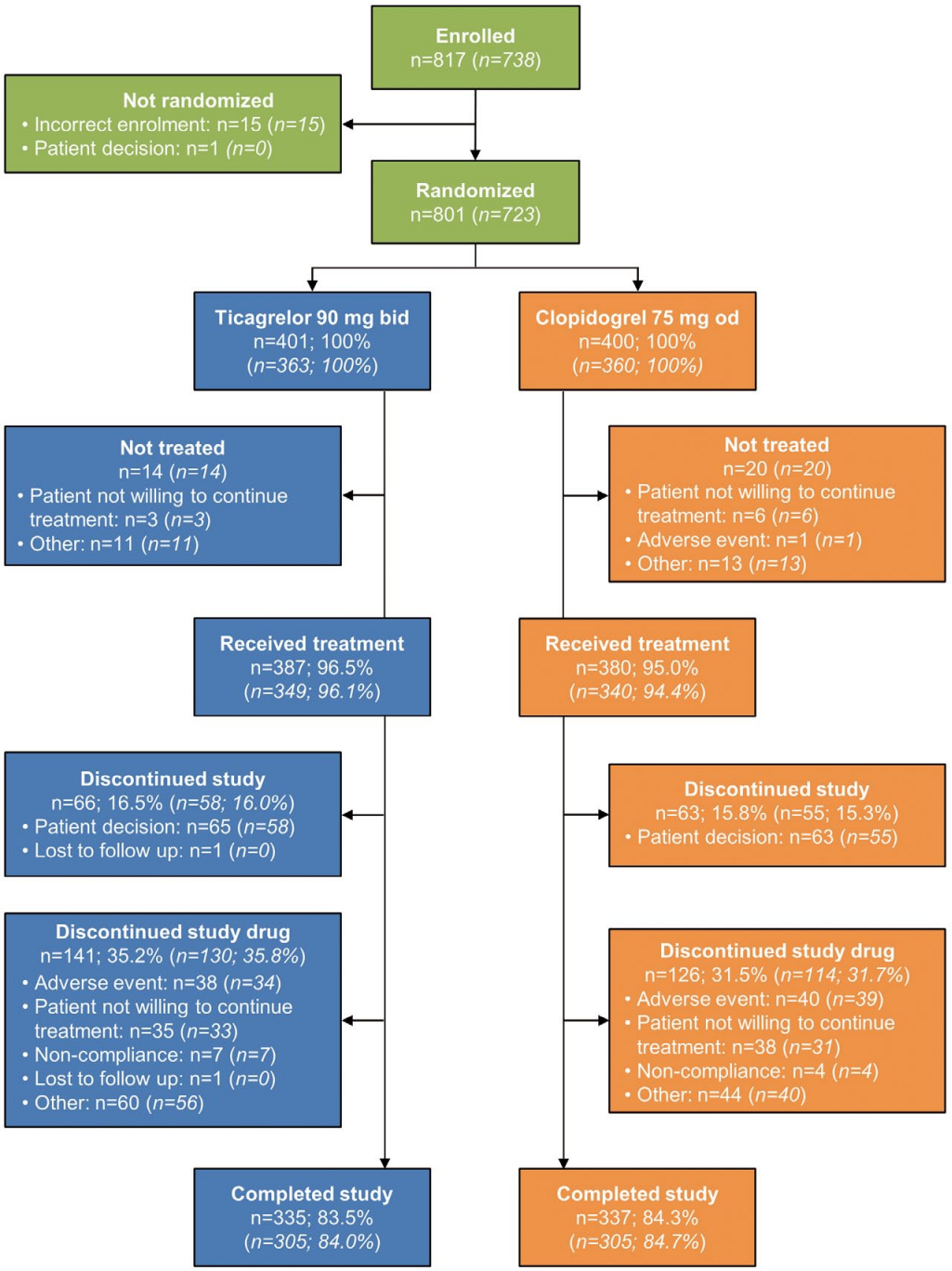

Figure. Patient disposition. Non-italic, whole PHILO study population; (*italic*), subgroup of Japanese patients. b.i.d., twice daily; o.d., once daily.

group differences were statistically significant. In patients recruited from Japan, 34 ticagrelor-treated patients (9.7%) and 24 clopidogrel-treated patients (7.1%) experienced major bleeding (HR, 1.41; 95% CI: 0.83–2.38).

Overall, the rates of non-bleeding adverse events were similar in the 2 groups, and consistent with the established safety profiles of ticagrelor and clopidogrel (**Table 3**). Dyspnea occurred in 22 ticagrelor recipients (5.7%) vs. 9 clopidogrel recipients (2.4%), and bradycardia occurred in 11 (2.8%) and 8 (2.1%) patients, respectively.

A serious adverse event occurred in 88 patients in the ticagrelor group (22.7%), compared with 107 patients in the clopidogrel group (28.2%). Fewer patients taking ticagrelor discontinued treatment because of a serious adverse event (22; 5.7%) compared with the clopidogrel group (33; 8.7%).

Table 1. Demographics and Baseline Characteristics (Full Analysis Set)

	Ticagrelor 90 mg b.i.d. (n=401)†	Clopidogrel 75 mg o.d. (n=400)
Age (years)	67±12	66±11
Age ≥75 years	109 (27.2)	98 (24.5)
Female	95 (23.7)	93 (23.3)
Body weight (kg)	63 [35–104]	62 [36–109]
Body weight <60 kg	154 (38.4)	152 (38.0)
BMI (kg/m²)	23.7 [15.6–43.4]	23.6 [14.2–38.6]
Race		
Asian	401 (100)	400 (100)
Ethnic group		
Chinese	16 (4.0)	19 (4.8)
Japanese	361 (90.0)	360 (90.0)
Korean	23 (5.7)	21 (5.3)
Unknown†	1 (0.3)	0
CV risk factor		
Habitual smoker	151 (37.7)	157 (39.3)
CAD	46 (11.5)	43 (10.8)
Hypertension	305 (76.1)	290 (72.5)
Dyslipidemia	314 (78.3)	289 (72.3)
Type 1 DM	0	1 (0.3)
Type 2 DM	154 (38.4)	123 (30.8)
Family history of CAD	67 (16.7)	59 (14.8)
Other medical and surgical history		
MI	33 (8.2)	31 (7.8)
PCI	45 (11.2)	42 (10.5)
Angina pectoris	102 (25.4)	110 (27.5)
Congestive heart failure	30 (7.5)	28 (7.0)
Non-hemorrhagic stroke	27 (6.7)	28 (7.0)
Peripheral arterial disease	13 (3.2)	14 (3.5)
TIA	6 (1.5)	11 (2.8)
CABG	5 (1.2)	1 (0.3)
Chronic renal disease	18 (4.5)	20 (5.0)
Peptic ulcer disease	37 (9.2)	37 (9.3)
Gastrointestinal bleeding	6 (1.5)	7 (1.8)
Asthma	12 (3.0)	14 (3.5)
History of dyspnea	32 (8.0)	41 (10.3)
COPD	7 (1.7)	10 (2.5)
Gout	23 (5.7)	19 (4.8)
ECG changes at study entry		
Persistent ST-segment elevation	218 (54.4)	225 (56.3)
ST-segment depression	188 (46.9)	153 (38.3)
T-wave inversion	142 (35.4)	126 (31.5)
Positive troponin I test at study entry	309 (77.1)	298 (74.5)
ACS diagnosis of index event		
ST-elevation MI	205 (51.1)	210 (52.5)
Non-ST-elevation MI	66 (16.5)	74 (18.5)
Unstable angina	119 (29.7)	109 (27.3)
Other	10 (2.5)	7 (1.8)
Killip classification		
I	349 (87.0)	351 (87.8)
II	40 (10.0)	35 (8.8)
III	8 (2.0)	10 (2.5)
IV	2 (0.5)	4 (1.0)

Data given as mean±SD, median [range] or n (%). †Ethnicity was not determined because patient withdrew from study. ACS, acute coronary syndrome; b.i.d., twice daily; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DM, diabetes mellitus; ECG, electrocardiogram; MI, myocardial infarction; o.d., once daily; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Table 2. Randomized Treatments and Procedures (Full Analysis Set)†

	Ticagrelor 90 mg b.i.d. (n=401)	Clopidogrel 75 mg o.d. (n=400)
Duration of exposure (days)		
Mean ± SD	200±134	210±131
Median (range)	236 (1–377)	244 (1–385)
Duration of exposure >30 days	289/387 (74.7)	301/380 (79.2)
Patients >80% compliant with study medication‡	389 (97.0)	388 (97.0)
Other medication taken from index event to randomization		
Organic nitrates	344 (85.8)	353 (88.3)
β-blocker		
Selective	28 (7.0)	30 (7.5)
Non-selective	8 (2.0)	11 (2.8)
Other	4 (1.0)	3 (0.8)
ACE inhibitor	67 (16.7)	64 (16.0)
Angiotensin receptor blocker	102 (25.4)	95 (23.8)
Cholesterol-lowering drug (statin)	215 (53.6)	205 (51.3)
Calcium channel blocker	117 (29.2)	109 (27.3)
Proton pump inhibitor	167 (41.6)	175 (43.8)
Coronary procedures during study treatment		
Coronary angiography	385 (96.0)	378 (95.4)
PCI	340 (84.8)	338 (84.5)
CABG	9 (2.2)	3 (0.8)
Other cardiac surgery	0	1 (0.3)

Data given as n (%) unless specified otherwise. †Except for duration of exposure, which used the safety analysis set. ‡Assessed on pill count during each study visit: patients who took their medication for >80% of the days between each visit were regarded as compliant. ACE, angiotensin-converting enzyme. Other abbreviations as in Table 1.

Efficacy Endpoints

The primary efficacy endpoint (composite of MI, stroke and CV death) occurred in 36 patients (9.0%) in the ticagrelor group vs. 25 patients (6.3%) in the clopidogrel group (HR, 1.47; 95% CI: 0.88–2.44; Table 4). In the Japanese cohort, the primary efficacy endpoint occurred in 34 patients in the ticagrelor group (9.4%) vs. 24 patients (6.7%) in the clopidogrel group (HR, 1.44; 95% CI: 0.85–2.43).

A similar rate of events for the primary efficacy endpoint in both treatment groups was also seen in the subgroup post-hoc analysis (Table S1), which was carried out using the modified composite endpoint of CV death, spontaneous MI or stroke. Overall, the post-hoc modified composite endpoint occurred in 18 patients (4.5%) in the ticagrelor group vs. 13 patients (3.3%) in the clopidogrel group (HR, 1.39; 95% CI: 0.68–2.85; Table 4). Among Japanese patients, the modified composite endpoint occurred in 16 patients (4.4%) in the ticagrelor group vs. 12 patients (3.3%) in the clopidogrel group (HR, 1.34; 95% CI: 0.63–2.83). No statistically significant between-group differences were seen for any of the composite primary or secondary efficacy endpoints, or for any of the individual secondary efficacy endpoints (Table 4).

PK and PD Results

Results of the PK and PD analysis are described in Supplementary File 1.

Discussion

The design of this study was similar to that of the large-scale PLATO study, with the important distinction that PHILO recruited only patients with planned PCI treatment, whereas PLATO recruited patients with planned invasive or non-invasive (ie, medically managed) treatment. PHILO was conducted in Japan, Taiwan and South Korea, given that PLATO did not include patients from Japan, and few from Taiwan and South Korea. In PHILO, patients received a 90 mg b.i.d. dose of ticagrelor, given that the PLATO Asian/Australian subpopulation had similar efficacy and safety profiles for this dose compared with the overall PLATO population.[17] In PHILO, there were no statistically significant differences in safety or efficacy profiles between the 2 treatment groups.

PHILO was not powered to be a confirmatory study, but rather to explore consistency of effect in patients from PLATO, compared with patients from a specific region of East Asia. Lower event rates of primary and secondary efficacy endpoints were noted in ticagrelor-treated patients in PHILO (primary endpoint, 9.0%; CV death, 2.2%; all-cause mortality, 2.5%) compared with the corresponding treatment arm in PLATO (Kaplan-Meier: primary endpoint, 9.8%; CV death, 4.0%; all-cause mortality, 4.5%).[17] The same was true for clopidogrel-treated patients (PHILO: primary endpoint, 6.3%; CV death, 1.8%; all-cause mortality, 1.8%; PLATO: primary endpoint, 11.7%; CV death, 5.1%; all-cause mortality, 5.9%). Compared with patients from other geographical regions, the lower CV event rate in East Asian patients with ACS (the majority of whom were recruited from Japan) was consistent with comparable registry data.[2,24] The higher rate of stroke in PHILO (2.2% with ticagrelor and 1.5% with clopidogrel) relative to PLATO (1.5 and 1.3%, respectively)[17] suggests that East Asian patients could be more prone to cerebrovascular disease than CAD.[25] It should be noted, however, that the between-treatment HR for stroke rate in PHILO (1.50) falls within the 95% CI of the between-group HR for stroke rate in PLATO (0.91–1.52).[17] Furthermore, given that patients recruited to the PHILO study were generally older than

Table 3. Adverse Events for All Patients

	Ticagrelor 90 mg b.i.d.	Clopidogrel 75 mg o.d.	HR for ticagrelor (95% CI)
Major bleeding (PLATO-defined)	40 (10.3)	26 (6.8)	1.54 (0.94–2.53)
CABG-related	8 (2.1)	5 (1.3)	1.57 (0.51–4.81)
Non-CABG-related	32 (8.3)	22 (5.8)	1.45 (0.84–2.50)
Coronary procedural	14 (3.6)	11 (2.9)	1.25 (0.57–2.77)
Non-coronary procedural	2 (0.5)	3 (0.8)	0.66 (0.11–3.93)
Minor bleeding (PLATO-defined)	59 (15.2)	35 (9.2)	1.75 (1.15–2.67)
CABG-related	0	1 (0.3)	
Non-CABG-related	59 (15.2)	34 (8.9)	1.81 (1.18–2.76)
Coronary procedural	31 (8.0)	22 (5.8)	1.43 (0.82–2.48)
Non-coronary procedural	10 (2.6)	4 (1.1)	2.51 (0.79–8.01)
Composite of major and minor bleeding	92 (23.8)	56 (14.7)	1.72 (1.23–2.40)
CABG-related	8 (2.1)	5 (1.3)	1.57 (0.51–4.81)
Non-CABG-related	85 (22.0)	52 (13.7)	1.71 (1.20–2.41)
Coronary procedural	44 (11.4)	31 (8.2)	1.44 (0.91–2.29)
Non-coronary procedural	12 (3.1)	7 (1.8)	1.72 (0.68–4.36)
Any adverse event (excluding bleeding)	327 (84.5)	337 (88.7)	
Mild	321 (82.9)	322 (84.7)	
Moderate	67 (17.3)	83 (21.8)	
Severe	30 (7.8)	38 (10.0)	
Dyspnea	22 (5.7)	9 (2.4)	
Bradycardia	11 (2.8)	8 (2.1)	
Ventricular extrasystoles	7 (1.8)	6 (1.6)	
Ventricular pauses ≥3 s on Holter monitoring	0	1 (1.9)	
Increase in serum creatinine >30% (on treatment)	75 (19.4)	60 (15.8)	
Increase in serum uric acid from baseline to end of treatment (μmol/L)	34±87	9±80	
Any uric acid adverse event†	26 (6.7)	20 (5.3)	

Data given as mean±SD or n (%). †Includes hyperuricemia, blood uric acid increase, gout, blood urine present, calculus ureteric, joint swelling. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Table 4. Primary and Secondary Efficacy Endpoints

	Ticagrelor 90 mg b.i.d. (n=401)	Clopidogrel 75 mg o.d. (n=400)	HR (95% CI)
Primary			
Composite of CV death/MI (excluding silent MI)/stroke	36 (9.0)	25 (6.3)	1.47 (0.88–2.44)
Post-hoc			
Composite of CV death/spontaneous MI/stroke	18 (4.5)	13 (3.3)	1.39 (0.68–2.85)
Secondary			
Composite of all-cause mortality/MI (excluding silent MI)/stroke	37 (9.2)	25 (6.3)	1.51 (0.91–2.50)
Composite of CV death/total MI/stroke/RI (including SRI)/TIA/Other ATE	38 (9.5)	32 (8.0)	1.20 (0.75–1.93)
MI (excluding silent MI)	24 (6.0)	15 (3.8)	1.63 (0.85–3.11)
Peri-procedural MI	18	12	–
Spontaneous MI	6	3	–
CV death	9 (2.2)	7 (1.8)	1.28 (0.48–3.45)
Stroke	9 (2.2)	6 (1.5)	1.50 (0.54–4.23)
All-cause mortality	10 (2.5)	7 (1.8)	1.42 (0.54–3.74)

Data given as n (%). ATE, arterial thromboembolic event; RI, recurrent cardiac ischemia; SRI, serious recurrent ischemia. Other abbreviations as in Tables 1,3.

patients recruited to PLATO,[17] the higher rate of stroke in PHILO may be explained, in part, by differences in patient characteristics between the 2 populations.

Notably, the PHILO study was not designed to detect a treatment difference between groups in the primary outcome. The overall population (n=801) and number of endpoint events that occurred during the PHILO study (n=61) was small, but higher than expected based on pre-trial calculations. The rate of CV events in the PHILO ticagrelor group was generally consistent with the findings of PLATO (where sig-

nificant interaction was shown among regions), whereas the CV event rate for clopidogrel was lower in PHILO (6.3%) vs. PLATO (11.7%).[17] In PHILO, differences between groups such as the relatively higher prevalence of classical risk factors and greater number of patients positive for troponin I or with persistent ST segment depression during the index hospitalization in the ticagrelor arm, may potentially explain the higher CV event rate reported for ticagrelor compared with clopidogrel.

Regarding safety, it is notable that patients recruited in PHILO were generally smaller than PLATO patients: the median body weight of patients in PHILO was 62–63 kg vs. 80 kg in PLATO, and the median body mass index of patients in PHILO was 24 kg/m^2 vs. 27 kg/m^2 in PLATO.[17] This could cause higher exposure of potent antiplatelet agents in the PHILO patient population, potentially resulting in an increased risk of bleeding compared with clopidogrel. The results of the present PK substudy, however, were consistent with previous PK studies in Asian and Caucasian populations.[22,26,27] Furthermore, the rate of major bleeding in the ticagrelor arm of PHILO, 10.3%, was similar to that (11.6%) reported for the ticagrelor arm of PLATO. The rate of major bleeding events in the clopidogrel arm of PHILO (6.8%) was markedly lower than that for the clopidogrel arm of PLATO (11.2%), and lower than anticipated based on pre-trial calculations.[17] Arguably, the lower rate of serious bleeding events in the clopidogrel arm of PHILO could be explained by the high prevalence of the CYP2C19 loss-of-function allele in Asian compared with Caucasian patients.[28] CV event rates in the clopidogrel arm of PHILO, however, were not higher than that of PLATO. Equally, there is clear evidence that patients who have a major bleeding event in the acute phase of ACS are at higher risk of ischemic events in the following months compared with patients who do not have a major bleeding event.[29,30] In the ticagrelor arm of PHILO, the higher rate of the efficacy endpoint could be explained by the higher rate of major bleeding in these patients compared with clopidogrel recipients.

The majority of patients who participated in PHILO were recruited from Japan. The type of medical care offered in Japan may contribute to some of the specific patient characteristics reported in PHILO, with the differences relative to the PLATO population being consistent with previously published clinical data obtained from Japan and other regions of the world.[2,24,31–35] Patients recruited in PHILO were less likely to be treated by β-blockers (10% in PHILO vs. 90% in PLATO), angiotensin-converting enzyme inhibitors (16% in PHILO vs. 76% in PLATO) or cholesterol-lowering drugs (52% in PHILO vs. 89% in PLATO). The use of nitrates, angiotensin receptor blockers, calcium channel blockers and proton pump inhibitors, however, was similar between the 2 populations. There was a substantial difference between PHILO and PLATO patients with regards to PCI use (85% PHILO vs. 65% PLATO) and CABG (1% PHILO vs. 10% PLATO). In the subgroup of PLATO patients in whom an invasive strategy was planned, the primary composite endpoint occurred in 9.0% of ticagrelor recipients,[36] which is identical to the primary endpoint rate in the ticagrelor arm of PHILO. Furthermore, the all-cause mortality rate in the intended-for-invasive-treatment cohort of ticagrelor recipients was 3.9% in PLATO,[36] and 2.5% in PHILO. Medically managed ACS patients tend to have a high-risk profile on presentation,[27] so the PHILO population may represent a cohort of lower-risk patients than the overall PLATO population. Certainly, the PHILO population contained a lower proportion of patients with a history of previous MI (8.0% vs. 20.5% in PLATO), CABG (0.7% in PHILO vs. 6.0% in PLATO), and peripheral arterial disease (3.4% in PHILO vs. 6.1% in PLATO). Conversely, the PHILO population contained a higher proportion of patients aged ≥75 years (25.8% vs. 15.5% in PLATO), with hypertension (74.3% vs. 65.4% in PLATO), dyslipidemia (75.3% vs. 46.7% in PLATO), or diabetes (34.7% vs. 25.0% in PLATO).

The high rate of invasive management in the PHILO study may have contributed to the high rate of procedural MI during follow-up. The study definition of procedural MI in both PLATO and PHILO required only cardiac enzyme elevation, not symptoms or ECG changes. Using this definition, approximately 20% of MI in PLATO were procedural[37] compared with 83% in Japanese PHILO patients. We performed a post-hoc analysis using a modified primary composite endpoint to include only spontaneous MI (to allow comparison with the results of PLATO, in which only a small number of MI were procedural). The clinically relevant endpoint of spontaneous MI was low in PHILO: 18 patients in the ticagrelor arm vs. 13 patients in the clopidogrel arm (HR, 1.39; 95% CI: 0.68–2.85). The low event rate after ACS in Japan is consistent with recently published registry data.[2]

The present PD substudy of the PHILO population showed that ticagrelor is a more potent inhibitor of ADP-induced platelet aggregation than clopidogrel. The fact that this did not translate into a significant difference in outcomes between the treatment groups is likely a result of the factors described here.

Conclusions

In this study, East Asian patients with ACS undergoing PCI who received ticagrelor had a non-significantly higher rate of major bleeding events and more, albeit not significantly, major CV events (CV death, MI or stroke), compared with clopidogrel. This may be explained by the small sample size, imbalance in baseline demographics and clinical characteristics, and the generally low number of events in the PHILO population.

Acknowledgments

Medical writing support was provided by Jackie Phillipson and Lisa Michel (Zoetic Science) and funded by AstraZeneca. The authors would like to thank Professor Lars Berglund (Uppsala Clinical Research Centre) for his contribution to the independent data re-analysis.

Conflicts of Interest

The manuscript was drafted by the chair (S.G.) of the executive committee, which consisted of academic authors. The sponsor reviewed the manuscript before submission, but the authors made the final decision regarding content. S.G. has received remuneration fees (eg, lecture fees) from AstraZeneca, Bayer and Sanofi-Aventis, and has received research funding from Sanofi-Aventis; H.E. is a full-time employee of AstraZeneca; S.-J.P., T.K. and C.-H.H. declare no conflicts of interest.

Funding Source

This study was funded by AstraZeneca.

References

1. Takii T, Yasuda S, Takahashi J, Ito K, Shiba N, Shirato K, et al. Trends in acute myocardial infarction incidence and mortality over 30 years in Japan: Report from the MIYAGI-AMI Registry Study. *Circ J* 2010; **74:** 93–100.
2. Daida H, Miyauchi K, Ogawa H, Yokoi H, Matsumoto M, Kitakaze M, et al. Management and two-year long-term clinical outcome of acute coronary syndrome in Japan: Prevention of atherothrombotic incidents following ischemic coronary attack (PACIFIC) registry. *Circ J* 2013; **77:** 934–943.
3. Fox KA, Goodman SG, Klein W, Brieger D, Steg PG, Dabbous O, et al. Management of acute coronary syndromes. Variations in practice and outcome; Findings from the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2002; **23:** 1177–1189.

4. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: Results from the CRUSADE Quality Improvement Initiative. *JAMA* 2004; **292:** 2096–2104.
5. Nakatani D, Sakata Y, Suna S, Usami M, Matsumoto S, Shimizu M, et al. Incidence, predictors, and subsequent mortality risk of recurrent myocardial infarction in patients following discharge for acute myocardial infarction. *Circ J* 2013; **77:** 439–446.
6. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345:** 494–502.
7. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32:** 2999–3054.
8. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; **130:** e344–e426, doi:10.1161/CIR.0000000000000134.
9. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **127:** e362–e425, doi:10.1161/CIR.0b013e3182742cf6.
10. Goto S, Tomita A. New antithrombotics for secondary prevention of acute coronary syndrome. *Clin Cardiol* 2014; **37:** 178–187.
11. Ogawa H, Kojima S. Clinical evidence for Japanese population based on prospective studies: Linking clinical trials and clinical practice. *J Cardiol* 2009; **54:** 171–182.
12. Goto S, Toda E. Antiplatelet therapy after coronary intervention in Asia and Japan: The Asian perspective of antiplatelet intervention. *Hamostaseologie* 2009; **29:** 321–325.
13. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol* 2014; **11:** 597–606.
14. Liang ZY, Han YL, Zhang XL, Li Y, Yan CH, Kang J. The impact of gene polymorphism and high on-treatment platelet reactivity on clinical follow-up: Outcomes in patients with acute coronary syndrome after drug-eluting stent implantation. *EuroIntervention* 2013; **9:** 316–327.
15. Kimura T, Morimoto T, Nakagawa Y, Tamura T, Kadota K, Yasumoto H, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. *Circulation* 2009; **119:** 987–995.
16. Park DW, Yun SC, Lee SW, Kim YH, Lee CW, Hong MK, et al. Stent thrombosis, clinical events, and influence of prolonged clopidogrel use after placement of drug-eluting stent data from an observational cohort study of drug-eluting versus bare-metal stents. *JACC Cardiovasc Interv* 2008; **1:** 494–503.
17. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361:** 1045–1057.
18. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: Evidence and potential clinical relevance. *J Am Coll Cardiol* 2014; **63:** 2503–2509.
19. Bonello L, Laine M, Kipson N, Mancini J, Helal O, Fromonot J, et al. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. *J Am Coll Cardiol* 2014; **63:** 872–877.
20. Armstrong D, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJ. Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equilibrative nucleoside transporter 1. *J Cardiovasc Pharmacol Ther* 2014; **19:** 209–219.
21. Wittfeldt A, Emanuelsson H, Brandrup-Wognsen G, van Giezen JJ, Jonasson J, Nylander S, et al. Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans. *J Am Coll Cardiol* 2013; **61:** 723–727.
22. Hiasa Y, Teng R, Emanuelsson H. Pharmacodynamics, pharmacokinetics and safety of ticagrelor in Asian patients with stable coronary artery disease. *Cardiovasc Interv Ther* 2014; **29:** 324–333.
23. Novack V, Pencina M, Cohen DJ, Kleiman NS, Yen CH, Saucedo JF, et al. Troponin criteria for myocardial infarction after percutaneous coronary intervention. *Arch Intern Med* 2012; **172:** 502–508.
24. Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG, et al. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol* 2004; **93:** 288–293.
25. Goto S. Cardiovascular risk factors in patients at high risk of atherothrombosis: What can be learned from registries? *Thromb Haemost* 2008; **100:** 611–613.
26. Li H, Butler K, Yang L, Yang Z, Teng R. Pharmacokinetics and tolerability of single and multiple doses of ticagrelor in healthy Chinese subjects: An open-label, sequential, two-cohort, single-centre study. *Clin Drug Invest* 2012; **32:** 87–97.
27. James SK, Roe MT, Cannon CP, Cornel JH, Horrow J, Husted S, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: Substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. *BMJ* 2011; **342:** d3527.
28. Ozawa S, Soyama A, Saeki M, Fukushima-Uesaka H, Itoda M, Koyano S, et al. Ethnic differences in genetic polymorphisms of CYP2D6, CYP2C19, CYP3AS and MDR1/ABCB1. *Drug Metab Pharmacokinet* 2004; **19:** 83–95.
29. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006; **114:** 774–782.
30. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: An analysis from the ACUITY trial. *J Am Coll Cardiol* 2007; **49:** 1362–1368.
31. O'Donoghue ML, Bhatt DL, Wiviott SD, Goodman SG, Fitzgerald DJ, Angiolillo DJ, et al. Safety and tolerability of atopaxar in the treatment of patients with acute coronary syndromes: The lessons from antagonizing the cellular effects of thrombin-acute coronary syndromes trial. *Circulation* 2011; **123:** 1843–1853.
32. Goto S, Ogawa H, Takeuchi M, Flather MD, Bhatt DL; J-LANCELOT (Japanese-Lesson from Antagonizing the Cellular Effect of Thrombin) Investigators. Double-blind, placebo-controlled phase II studies of the protease-activated receptor 1 antagonist E5555 (atopaxar) in Japanese patients with acute coronary syndrome or high-risk coronary artery disease. *Eur Heart J* 2010; **31:** 2601–2613.
33. Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med* 2012; **366:** 20–33.
34. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011; **365:** 699–708.
35. Ogawa H, Goto S, Matsuzaki M, Hiro S, Shima D; APPRAISE-J investigators. Randomized, double-blind trial to evaluate the safety of apixaban with antiplatelet therapy after acute coronary syndrome in Japanese patients (APPRAISE-J). *Circ J* 2013; **77:** 2341–2348.
36. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): A randomised double-blind study. *Lancet* 2010; **375:** 283–293.
37. Mahaffey KW, Held C, Wojdyla DM, James SK, Katus HA, Husted S, et al. Ticagrelor effects on myocardial infarction and the impact of event adjudication in the PLATO (PLATelet inhibition and patient Outcomes) trial. *J Am Coll Cardiol* 2014; **63:** 1493–1499.

Supplementary Files

Supplementary File 1

Data and Safety Monitoring Board (DSMB) and Clinical Endpoint Committee (CEC)

Methods

Results

Table S1. Modified composite endpoint (CV death/spontaneous MI/stroke) in subgroups with ≥15 events per treatment group

Table S2. Mean platelet aggregation (final extent) by optical aggregometry in Japanese patients

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-15-0112