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*Coronary Artery Disease*

# Safety and Cumulative Incidence of Major Cardiovascular Events with Ticagrelor in Taiwanese Patients with Non-ST-Segment Elevation Myocardial Infarction: A 12-Month, Prospective, Phase IV, Multicenter, Single-Arm Study

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***Background:*** Ticagrelor, an oral, direct-acting, and reversible $P2Y_{12}$ receptor antagonist, inhibits platelet activation and aggregation. This phase IV, single-arm study analyzed the safety and tolerability of ticagrelor in Taiwanese patients with non-ST-segment elevation myocardial infarction (NSTEMI) during 1 year of follow-up.

***Methods:*** Patients aged ≥ 20 years with an index event of NSTEMI received ticagrelor (180 mg loading and 90 mg doses twice daily thereafter) plus low-dose aspirin (100 mg/day) for up to 1 year. Safety was evaluated according to adverse events (AEs), serious AEs (SAEs), and PLATO-defined bleeding events. The cumulative incidence of major cardiovascular (CV) events including CV death, myocardial infarction, and stroke was also evaluated.

***Results:*** The safety population included 108 patients across 13 centers in Taiwan. During treatment, 32 (29.6%) patients had ≥ one PLATO-defined bleeding event. Major bleeding events occurred in seven (6.5%) patients with a Kaplan-Meier (KM) estimated event risk [95% confidence interval (CI)] of 7.1% (3.4%-14.4%), including life-threatening bleeding [four (3.7%) patients] and other major bleeding [three (2.8%) patients]. No PLATO-defined fatal bleeding was observed. SAEs were reported in 23 (21.3%) patients. Six (5.6%) patients experienced major CV events during the 1-year follow-up period, with a KM-estimated event risk (95% CI) of 5.6% (2.6%-12.0%).

***Conclusions:*** Ticagrelor for up to 1 year was associated with a low rate of major bleeding events and a low incidence of major CV events in Taiwanese patients with NSTEMI. The overall safety of ticagrelor was in accordance with the known safety profile of ticagrelor.

**Key Words:** Cardiovascular events • Non-ST-segment elevation myocardial infarction • $P2Y_{12}$ inhibition • Safety • Taiwan • Ticagrelor

## INTRODUCTION

Cardiovascular (CV) diseases are the leading cause of death globally.[1] Acute coronary syndrome (ACS), which includes unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI),[2] has a high morbidity and mortality rate and results in an elevated economic burden.[3,4] Moreover, the incidence of NSTEMI has increased compared with STEMI in the past decade in the Asia-Pacific region.[5] The number of patients ad-

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mitted for NSTEMI in Taiwan increased by 300% between 1997 and 2011, with higher in-hospital mortality than patients with STEMI.[6] Adherence to recommended treatment guidelines in patients with NSTEMI and control of major risk factors may improve patient outcomes.[7,8]

The benefit of dual antiplatelet therapy (DAPT) following ACS has been previously established with clopidogrel in several studies.[9-11] Ticagrelor, is an oral, direct-acting, and reversible $P2Y_{12}$ receptor antagonist,[12] that inhibits platelet activation and aggregation by antagonizing the binding of adenosine diphosphate to $P2Y_{12}$ receptors.[13] The PLATO study undertaken in 18,624 patients with ACS showed that ticagrelor was superior to clopidogrel (in addition to aspirin) in reducing the rate of deaths from CV events, myocardial infarction (MI), and stroke at 12 months, with no significant increase in the rate of major bleeding events.[14] In a retrospective analysis of the PLATO study, the efficacy and safety of ticagrelor versus clopidogrel in Asian patients (n = 1,106) were similar to those of non-Asian patients (n = 17,515);[15] however, the Taiwanese cohort was small.

The PHILO[16] clinical trial compared the safety and efficacy of ticagrelor versus clopidogrel (in addition to aspirin) in patients with ACS (Japanese, n = 721; Taiwanese, n = 35; South Korean, n = 44; unknown ethnicity, n = 1). All patients were planned to undergo percutaneous coronary interventions (PCIs) and were randomized within 24 hours of symptom onset. The primary safety (any major bleeding) and efficacy (MI, stroke, or death from vascular causes) endpoint event rates were numerically higher with ticagrelor, albeit not significantly higher. This observation could be explained by the small sample size, imbalance in clinical characteristics, and low number of events in the PHILO population. Using propensity score matched cohorts, a large retrospective registry study compared clinical outcomes in Taiwanese patients with acute myocardial infarction (AMI) receiving DAPT with ticagrelor versus clopidogrel.[17] The authors concluded that in Taiwanese patients with AMI, treatment with ticagrelor compared to clopidogrel seemed to reduce the rate of death from any cause, AMI or stroke without an increase in the rate of major bleeding during 18 months of follow-up. The authors pointed out that these results were different to observations in Japan and Korea and called for more dedicated research on potent $P2Y_{12}$ inhibitors in East Asian patients.[17]

Several guidelines, including those of the Taiwan Society of Cardiology,[18] recommend ticagrelor as first-line treatment to reduce the rate of thrombotic events (CV death, MI, or stroke) in patients with ACS in combination with low-dose aspirin.[19,20]

Ticagrelor was approved by the Taiwan Food and Drug Administration (TFDA) in 2012.[21] In accordance with the TFDA requirements for post-authorization monitoring of drugs, a post-approval study was mandated to describe the safety and tolerability of ticagrelor in Taiwanese patients with NSTEMI.[22] The present study describes the safety and tolerability of ticagrelor in Taiwanese patients with NSTEMI in a real-world setting during a 1-year follow-up period and adds to the knowledge of potent $P2Y_{12}$ inhibitor treatment in Taiwanese patients.

## METHODS

### Study design

This was a multicenter, open-label, single-arm, phase IV study (NCT02406248) conducted at 13 study centers in Taiwan to evaluate the safety of ticagrelor and to describe the incidence of major CV events with ticagrelor in patients with NSTEMI during a 1-year follow-up period. Patients were enrolled following an index NSTEMI event. Eligible patients received ticagrelor [180 mg loading dose followed by 90 mg twice daily (BID)] plus a low maintenance dose of aspirin [100 mg once daily (QD)] for 12 months.

The study conformed to the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice Guidelines, and followed applicable regulatory requirements, including AstraZeneca's global policy on bioethics.[23] The local Institutional Review Boards or Independent Ethics Committees of the participating centers approved the final protocol and amendments. All eligible patients provided written informed consent prior to study participation.

### Patients

Eligible patients were ethnic Taiwanese men or women aged ≥ 20 years with an index ACS event of NSTEMI. Qualifying events met the following criteria: hospitalization for chest pain, potential ACS documented by car-

diac ischemic symptoms of ≥ 10 minutes duration at rest, and positive biomarker evidence for myocardial necrosis with either (1) troponin T or troponin I > laboratory upper limit of normal (ULN) on ≥ one occasion in association with the index clinical event (i.e., any elevated troponin level), or (2) creatinine kinase-muscle/brain (MB), preferably creatinine kinase-MB mass, > laboratory ULN on ≥ one occasion in association with the index clinical event.

Major exclusion criteria were patients with STEMI, defined by persistent ST-segment elevation ≥ 1 mm (0.1 mV) in ≥ two contiguous leads or new/presumed new left bundle-branch block, any contraindications to ticagrelor or aspirin (hypersensitivity, active bleeding, gastrointestinal bleed, etc. within the past 6 months), moderate or severe liver disease, history of intracranial bleeding or major surgery within 30 days, ongoing prasugrel treatment or fibrinolytic therapy in the 24 hours prior to enrollment or planned fibrinolytic treatment following enrollment or an increased risk of bradycardia events, planned urgent coronary artery bypass grafting (CABG) within 7 days from enrollment, and the use of non-selective, non-steroidal anti-inflammatory drugs or oral anticoagulation therapy within 30 days of enrollment that could not be stopped. Concomitant therapy with strong cytochrome P450 3A (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, were prohibited. Women who were pregnant or breastfeeding, or women of childbearing potential who did not use contraceptives were excluded from the study.

**Intervention**

Patients received a loading dose of ticagrelor 180 mg orally, followed by a maintenance dose of 90 mg BID. A loading dose of ticagrelor was given regardless of whether the patient had received the previous loading dose of clopidogrel or had ongoing clopidogrel treatment prior to the index event. All patients took concomitant aspirin, at a planned dose of 100 mg QD, from enrollment through the end of the treatment period (12 months).

**Safety analysis**

Patients returned to the clinic at 6 weeks and 3, 6, 9, and 12 months (each ± 1 week) after the start of the study drug for assessments of adverse events (AEs) and concomitant medication. AEs and serious AEs (SAEs), including bleeding, were recorded by the local investigators according to the standard classifications used in clinical studies. AEs were classified according to the terminology of the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1[24] and presented per system organ classes [SOCs; which are grouped by etiology (e.g. infections and infestations), manifestation site (e.g. gastrointestinal disorders), purpose (e.g. surgical and medical procedures), and issues pertaining to products or social circumstances], and by preferred term [PT; which is a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic]. Bleeding events were classified by the investigator according to PLATO definitions (Online Supplementary Material). Laboratory assessments were conducted at any visit at the discretion of the investigator. For safety analysis, patients were censored at 7 days after their last dose of ticagrelor. Patients who withdrew from the study were included up to the date of their study termination.

**Efficacy analysis**

The cumulative incidence of major CV events (including CV death, MI, or stroke) during the 1-year follow-up period was analyzed. Endpoints were assessed by the investigators; there was no central adjudication of endpoint events in the study. Deaths were classified as being CV- or non-CV-related. MI was diagnosed on the basis of elevation of myocardial necrosis biomarkers, typical of acute MI, with at least one of the following: (1) recurrent cardiac ischemic symptoms ≥ 20 minutes at rest; (2) development of new pathological Q waves on electrocardiography (ECG); (3) new or presumed new ECG changes indicative of ischemia in two or more contiguous leads (ST-segment elevation, ST-segment depression or T-wave inversion). Stroke was defined as a neurological deficit caused by an ischemic or hemorrhagic central nervous system event with residual symptoms at least 24 hours after onset or leading to death. Stroke was further sub-classified as ischemic, hemorrhagic, and unknown. Patients who did not have any event in the primary composite efficacy endpoint were censored at the time of study closure or at the time of last available information, if earlier.

### Sample size calculation and statistical analyses

This was a post-authorization study to investigate the safety profile of ticagrelor further as required by the TFDA. If the fatal/life-threatening bleeding rate was 5%, then approximately 100 patients would allow for the description of the safety profile estimated with a precision of ± 4.3% [95% confidence interval (CI)]. Safety data were summarized descriptively in terms of the frequency and percentage of patients in each category for AEs, SAEs, and PLATO-defined bleeding events. The safety population included all patients who received ≥ one dose of ticagrelor and for whom any post-dose data were available.

The primary analysis was presented with Kaplan-Meier (KM) percentage estimate and 95% CI for the safety and efficacy endpoints. A KM plot of the time to first major CV event, in addition to the presentation of KM estimates at each scheduled time point, was provided. All summaries were performed on the safety population unless otherwise stated. The estimated compliance rate was calculated as the estimated number of drugs taken divided by the number of drugs dispensed. Statistical analyses were performed using SAS version 9.4.

## RESULTS

### Study patients and treatment

A total of 113 patients with NSTEMI were recruited across 13 study centers in Taiwan. The study was conducted between April 23, 2015 (first patient enrolled) and February 09, 2017 (last visit of the last patient enrolled) (Figure 1). Of these patients, 108 (95.6%) received ticagrelor treatment and constituted the safety population, of whom, 79 (73.1%) completed 1 year of ticagrelor treatment. Twenty-nine (26.9%) patients discontinued treatment prematurely (Figure 2). Almost all patients completed the study (91.7%), while nine (8.3%) patients (safety population) withdrew from the study [seven (6.5%) patients due to death and two (1.9%) patients due to patient decision]. Of the seven deaths, five patients died while on study treatment and two died more than 7 days after the last ticagrelor dose.

Table 1 shows the baseline characteristics of the safety population. All patients were ethnic Taiwanese (Asians) with a mean age, medical and surgical history commonly seen in an ACS population. Overall, 17 (15.7%) patients reported a history of PCI and three (2.8%) patients reported a history of CABG. Table 2 lists the con-

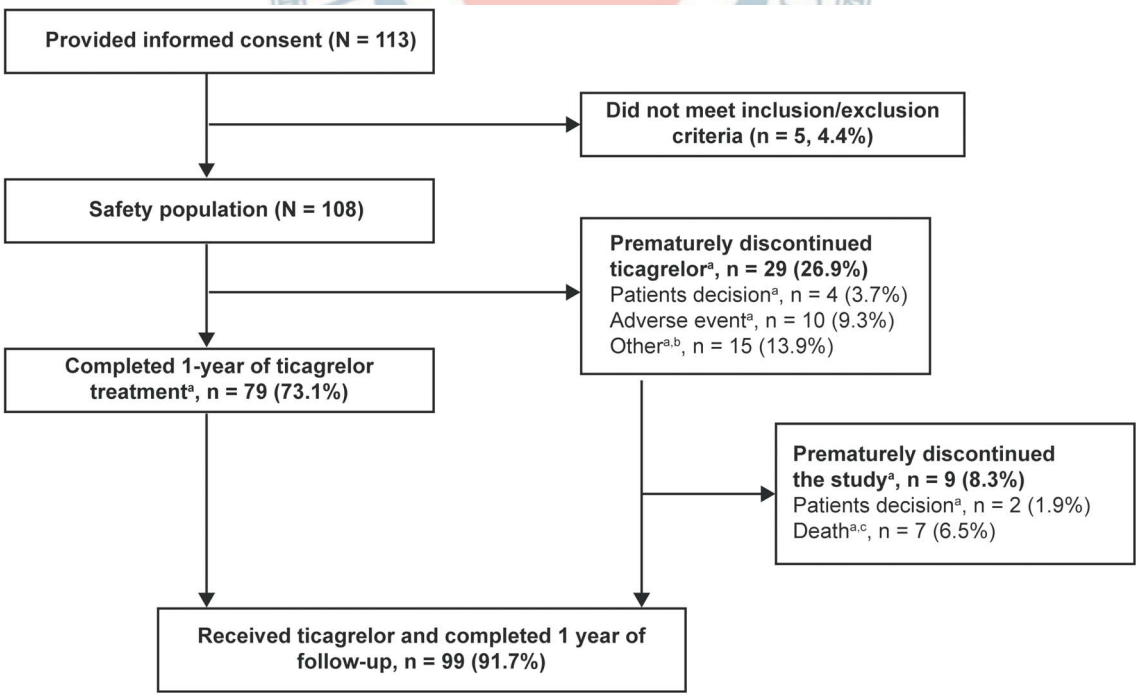


***Figure 1.*** *Patient disposition.* [a] *The percentages were calculated from number of patients who received treatment.* [b] *Included patients who died while on study drug (three patients).* [c] *Included all deaths regardless of time of death.*

comitant medications taken by the patients (safety population) during the study period.

The median compliance rate of ticagrelor was 94.1%, and the median duration of ticagrelor exposure was 356 days (range: 1-369 days). Table 3 shows the percentages of patients with a duration of ticagrelor exposure < 6, 6-9, and > 9-12 months. Twenty-six (24.1%) patients had an interruption in ticagrelor treatment; most patients [20 (18.5%) patients] had only one interruption.

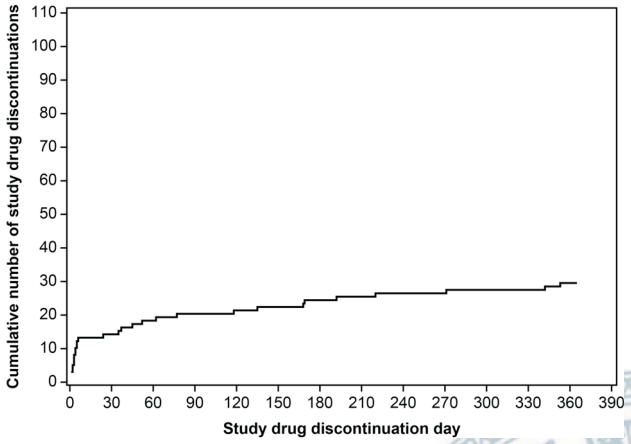


***Figure 2.*** *Cumulative incidence of study drug discontinuation over time.*

**Table 1.** Patient baseline characteristics (safety population)

| Characteristic | Ticagrelor (N = 108) |
|---|---|
| Age, mean (SD), years | 61.7 (12.1) |
| Sex, n (%) | |
| Male | 86 (79.6) |
| Female | 22 (20.4) |
| Race, n (%) | |
| Asian | 108 (100) |
| Hemoglobin, mean (SD), g/dL | 13.9 (1.69) |
| SBP, mean (SD), mmHg | 129.6 (20.3) |
| DBP, mean (SD), mmHg | 75.4 (13.4) |
| Pulse rate, mean (SD), beats/min | 79.1 (16.8) |
| Creatinine, mean (SD), mg/dL | 1.03 (0.38) |
| Medical history*, n (%) | |
| Hypertension | 71 (65.7) |
| Dyslipidemia | 54 (50.0) |
| Type 2 diabetes mellitus | 36 (33.3) |
| Myocardial infarction | 18 (16.7) |
| Angina pectoris | 15 (13.9) |
| Ischemic stroke | 4 (3.7) |
| Chronic obstructive pulmonary disease | 3 (2.8) |
| Asthma | 1 (0.9) |
| Percutaneous coronary intervention | 17 (15.7) |
| Surgical history#, n (%) | |
| Coronary artery bypass grafting | 3 (2.8) |

DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

* Specific relevant medical history conditions of interest.

# Specific relevant surgical history conditions of interest.

## Safety

*AEs and SAEs*

Of the safety population, 80 (74.1%) patients reported ≥ one AE during study treatment (Table 4). The most frequently reported AEs were within the SOCs of respiratory, thoracic and mediastinal disorders [29 (26.9%) patients] and gastrointestinal disorders [27 (25.0%) patients]. Dyspnea, cough, and ecchymosis were the most common AEs reported by 10 (9.3%) patients each by PT.

AEs that led to discontinuation of ticagrelor were reported for 10 (9.3%) patients, of which 4.6% were causally related to ticagrelor use as assessed by the investigator. The most common AE related to study treatment leading to ticagrelor discontinuation was dyspnea [two (1.9%) patients]. Most patients (49.1%) reported AEs that were mild in intensity during study treatment (Table 5).

**Table 2.** Concomitant medications during study

| Medication text | Number (%) of patients (N = 108) |
|---|---|
| Acetylsalicylic acid | 105 (97.2) |
| Statins | 92 (85.2) |
| ARB/ACE-inhibitors | 76 (70.4) |
| Beta-blockers | 75 (69.4) |
| Heparin/low molecular weight heparin | 68 (63.0) |
| Other antithrombotic agents | 4 (3.7) |

Includes concomitant medications administered during treatment with study drug, except for concomitant medications administered the first and last day of treatment with study drug.

Based on ATC codes: C10AA (Statins), C09A/C09C (ARB/ACE-inhibitors), C07 (Beta-blockers), B01AB (Heparin/low molecular weight heparin), B01AX (Other antithrombotic agents).

ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers.

**Table 3.** Duration of ticagrelor exposure

| Total treatment duration | Number (%) of patients (N = 108) |
|---|---|
| < 6 months | 24 (22.2) |
| 6-9 months | 2 (1.9) |
| > 9 months | 82 (75.9) |

**Table 4.** Overall most common adverse events occurring by system organ class and preferred term (frequency of > two patients in the safety population)

| System organ class/preferred term | Number (%) of patients* (N = 108) |
|---|---|
| Patients with any AE | 80 (74.1) |
| Infections and infestations | 20 (18.5) |
| Nasopharyngitis | 4 (3.7) |
| Pneumonia | 4 (3.7) |
| Urinary tract infection | 6 (5.6) |
| Cardiac disorders | 15 (13.9) |
| Angina pectoris | 8 (7.4) |
| Cardiogenic shock | 3 (2.8) |
| Vascular disorders | 8 (7.4) |
| Hematoma | 5 (4.6) |
| Respiratory, thoracic and mediastinal disorders | 29 (26.9) |
| Cough | 10 (9.3) |
| Dyspnea | 10 (9.3) |
| Epistaxis | 3 (2.8) |
| Pleural effusion | 3 (2.8) |
| Productive cough | 4 (3.7) |
| Gastrointestinal disorders | 27 (25.0) |
| Abdominal distension | 3 (2.8) |
| Constipation | 4 (3.7) |
| Diarrhea | 6 (5.6) |
| Vomiting | 3 (2.8) |
| Ear and labyrinth disorders | 3 (2.8) |
| Vertigo | 3 (2.8) |
| Skin and subcutaneous tissue disorders | 19 (17.6) |
| Ecchymosis | 10 (9.3) |
| Pruritis | 4 (3.7) |
| Rash | 3 (2.8) |
| Metabolism and nutrition disorders | 22 (20.4) |
| Hypokalemia | 8 (7.4) |
| Hyperuricemia | 6 (5.6) |
| Psychiatric disorders | 8 (7.4) |
| Dizziness | 5 (4.6) |
| Insomnia | 5 (4.6) |
| Nervous system disorders | 11 (10.2) |
| General disorders and administration site conditions | 15 (13.9) |
| Contusion | 7 (6.5) |
| Injury, poisoning and procedural complications | 15 (13.9) |
| Pyrexia | 7 (6.5) |

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class.
* Number (%) of patients with AEs, sorted by international order for SOC and descending frequency for PT. AEs were coded using MedDRA version 19.1. A patient could have ≥ one AE by PT reported under a given SOC. AEs with an onset date on or after the date of the first dose of ticagrelor and up to and including 7 days following the date of the last dose of ticagrelor were included.

**Table 5.** Overview of adverse events (safety population)

| Characteristic | Number (%) of patients (N = 108) |
|---|---|
| Any AE* | 80 (74.1) |
| Mild | 53 (49.1) |
| Moderate | 14 (13.0) |
| Severe | 13 (12.0) |
| Any SAE* | 23 (21.3) |
| Mild | 8 (7.4) |
| Moderate | 4 (3.7) |
| Severe | 11 (10.2) |
| Deaths due to SAEs[#] | 5 (4.6) |
| Any AE leading to ticagrelor discontinuation | 10 (9.3) |
| SAE | 4 (3.7) |
| Any AE causally related to ticagrelor | 16 (14.8) |
| SAE | 1 (0.9) |

AE, adverse event; SAE, serious adverse event.
Number (%) of patients with AEs, sorted by international order for system organ class and descending frequency for preferred term in severe, moderate, mild intensity. Maximum AE intensity is used.
Mild AE, awareness of sign or symptom, but easily tolerated; Moderate AE, discomfort sufficient to cause interference with normal activities; Severe AE, incapacitating, with inability to perform normal activities
* Patients with multiple events in the same category were counted only once in the most severe category. [#] Patients with events in more than one category were counted once in each of those categories.

Overall, 23 (21.3%) patients experienced ≥ one SAE during the study (Table 5). Cardiac disorders were the most common SAEs (6.5%) by SOC and pneumonia was the most frequently reported SAE by PT (3.7%) (Online Supplementary Material). Four (3.7%) patients reported SAEs that led to discontinuation of ticagrelor. Five (4.6%) patients had an SAE with an outcome of death. An SAE of pericardial effusion was considered to be related to ticagrelor use [one (0.9%) patient]. A total of 21 (19.4%) patients experienced SAEs other than bleeding during the 1-year follow-up period. None of these SAEs were related to ticagrelor use as assessed by the investigator.

All-cause mortality was reported in seven (6.5%) patients during the treatment period. Of these, four were CV deaths and three were non-CV deaths.

*PLATO-defined bleeding events*

A total of 32 (29.6%) patients reported PLATO-de-

fined bleeding events (composite of major, minor, and minimal) within 12 months after the first exposure to ticagrelor. PLATO-defined major bleeding events were reported in seven (6.5%) patients with a KM-estimated event rate (95% CI) of 7.1% (3.4%-14.4%), and were reported within 6 months after the first ticagrelor dose (Figure 3). The subset of PLATO-defined life-threatening bleeding events were reported in four patients (Table 6). No PLATO-defined fatal bleeding events were reported during the study. Other major bleeding events were reported in three (2.8%) patients (Table 6).

*CV events*

In the safety population, six (5.6%) patients experienced major CV events during the 1-year follow-up period, with a KM-estimated event rate (95% CI) of 5.6% (2.6%-12.0%). All of these patients reported the events within 6 months after the first dose of ticagrelor (Table 7).

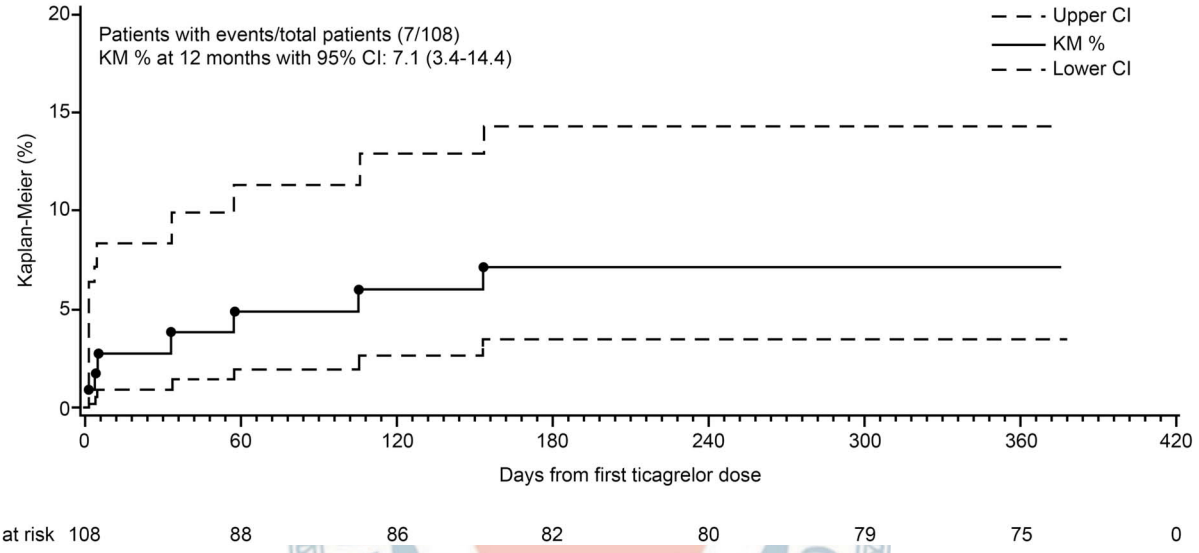


***Figure 3.*** *Kaplan-Meier plot of the cumulative percentage of patients with PLATO-defined major bleeding (safety population). Includes events with an onset date on or after the date of first dose of ticagrelor and up to and including 7 days following the date of last dose of ticagrelor. 95% CI is calculated using log (-log) transformation. CI, confidence interval; KM, Kaplan-Meier.*

**Table 6.** PLATO-defined bleeding events by severity (safety population)

| Bleeding severity | Ticagrelor (N = 108) | |
|---|---|---|
| | Patients with bleeding, n (%) | KM-estimated 12-month event rate (95% CI), % |
| Total major bleeding | 7 (6.5) | 7.1 (3.4-14.4) |
| Life-threatening/fatal | 4 (3.7) | 4.0 (1.5-10.3) |
| Fatal | 0 (0.0) | NA |
| Life-threatening | 4 (3.7) | 4.0 (1.5-10.3) |
| Intracranial hemorrhage | 2 (1.9) | |
| Pericardial hemorrhage | 1 (0.9) | |
| Cardiac catheter/PCI access site | 1 (0.9) | |
| Major, other | 3 (2.8) | 3.2 (1.0-9.7) |
| Gastrointestinal | 2 (1.9) | |
| Cardiac catheter/PCI access site | 1 (0.9) | |
| Composite of major and minor bleeding | 20 (18.5) | 20.2 (13.5-29.6) |
| Minor | 15 (13.9) | 15.6 (9.6-24.6) |
| Composite of major, minor, and minimal bleeding | 32 (29.6) | 31.9 (23.7-42.1) |
| Minimal | 14 (13.0) | 13.8 (8.4-22.3) |

CI, confidence interval; KM, Kaplan-Meier; NA, not applicable; PCI, percutaneous coronary intervention; PLATO, study of PLATelet inhibition and patient Outcomes.

**Table 7.** Major cardiovascular events (safety population)

| CV events | Ticagrelor (N = 108) | |
|---|---|---|
| | Patients with events, n (%) | KM-estimated 12-month event rate (95% CI), % |
| Major CV events (including CV death, MI, or stroke) | 6 (5.6) | 5.6 (2.6-12.0) |
| CV death | 4 (3.7) | 3.8 (1.4-9.7) |
| MI | 2 (1.9) | 1.9 (0.5-7.4) |
| NSTEMI | 2 (1.9) | 1.9 (0.5-7.4) |
| Stroke | 2 (1.9) | 1.9 (0.5-7.3) |
| Ischemic | 2 (1.9) | 1.9 (0.5-7.3) |

CI, confidence interval; CV, cardiovascular; KM, Kaplan-Meier; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction.
95% CI is calculated using log (-log) transformation.
Patient could have been counted in more than one CV event category.

## DISCUSSION

This was a 1-year, open-label study of ticagrelor treatment in Taiwanese patients with NSTEMI in a real-world setting that described the safety and tolerability of ticagrelor and was aligned with the Taiwanese prescribing information for ticagrelor.[25]

The number of hospitalizations for NSTEMI in Taiwan increased from 2,150 cases per year in 1997 to 8,603 cases in 2011.[6] Several cardiology guidelines recommend ticagrelor as part of the first-line management of patients with ACS to reduce the risk of recurrent CV events.[18-20] The safety of ticagrelor has been evaluated in major studies; however, these studies have included small numbers of Taiwanese patients.[14-16] Therefore, post-approval study was mandated by the TFDA to describe the safety and tolerability of ticagrelor in Taiwanese patients with NSTEMI. The present study demonstrated that under real-world conditions, ticagrelor 90 mg BID with low-dose aspirin (100 mg QD) for up to 1 year was associated with a low incidence of major bleeding events, major CV events, and SAEs in a cohort of Taiwanese patients with NSTEMI. The planned (365 days) and reported (356 days; range: 1-369 days) mean durations of ticagrelor exposure in this study were aligned with the prescribing information of ticagrelor and international recommendations,[22,25-27] with a high study completion rate (91.7%).

The incidence of the composite of CV death/MI/stroke was numerically lower (5.6%) in this study compared with the overall PLATO study (9.8%),[14] the PHILO study (9.0%),[16] and a subgroup analysis of patients with NSTEMI in the PLATO study (10.0%).[17] The incidence of PLATO-defined major bleeding events was numerically lower than that reported in the PLATO study (6.5% versus 11.6%)[14] and compared to the PHILO study[16] (10.3%). No PLATO-defined fatal bleeding events were observed. Planned CABG patients were excluded in this study, whereas the PLATO study included CABG patients.[14] Moreover, only patients with NSTEMI were recruited in the current study, whereas the PLATO study recruited patients with ACS (including unstable angina, NSTEMI, and STEMI)[14] and the PHILO study included only patients with ACS planned to undergo PCI. The low incidence of CV and bleeding events in the present study could be attributed to an imbalance in the sample due to the size of the population studied, making it difficult to draw firm, risk-related inferences. However, the overall interpretation is that the observed CV event rate and PLATO major bleeding event rate were comparable with previous data on ticagrelor.[14,15] Previous real-world registry data on Taiwanese patients with AMI found that ticagrelor offered better anti-ischemic protection than clopidogrel in a propensity matched cohort, without an increase in the rate of major bleeding.[17] This observation should be interpreted with caution as this was a non-randomized, retrospective, cohort study only including patients who had survived 30 days post-MI.

In this study of Taiwanese patients with NSTEMI, the most frequently reported SAEs were cardiac disorders, reported in seven (6.5%) patients according to SOC, and pneumonia, reported in four (3.7%) patients according

to PT. The rate of dyspnea (9.3%) in this study was similar to that in the PLATO study (13.8%)[14] and the subgroup of Asian patients in the PLATO study (11.6%).[15] Ticagrelor treatment has been shown to be associated with increased circulating plasma adenosine levels as it inhibits the cellular uptake of adenosine. This effect might contribute partially to the sensation of dyspnea in ticagrelor-treated patients; however, further studies are required to better understand the extent of this effect. Ticagrelor-induced dyspnea is usually of mild intensity, resolves quickly, and does not affect the patient's routine activities.[28] Ticagrelor also does not influence the patient's cardiac and pulmonary function, and patients should be evaluated for related comorbidities according to an Expert Consensus statement.[29] The AEs reported in the present study were consistent with the current ticagrelor prescribing information.[25]

Overall, this prospective, real-world study followed the standard practice and aligned with the ticagrelor label in Taiwan. However, there are a few study limitations. This was a single-arm, non-randomized study designed with no control arm, thereby limiting direct comparisons with other treatments. Baseline data on body weight, smoking history, body mass index, and height were not collected. Neither was data on details of previous PCI procedures (e.g. type of and number of stents) recorded and performance of coronary revascularizations during the study. The sample size of this study was small and included only patients with NSTEMI. However, the design was appropriate for describing the safety of ticagrelor in an ethnic Taiwanese population experiencing an NSTEMI event, as the included study population had a broad diversity with respect to age and was representative of the Taiwanese population.

## CONCLUSIONS

This real-world study provides further safety data on the use of ticagrelor for up to 1 year in Taiwanese patients with NSTEMI, and found low rates of dyspnea and PLATO-defined bleeding events. No fatal bleeding events were observed during the study. The results further show that ticagrelor is well tolerated in such patients, which is consistent with the known safety profile of ticagrelor.

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## CONFLICT OF INTEREST

GYM and CPL declare no conflicts of interest. WR and JW are current employees of AstraZeneca.

## ETHICAL APPROVAL

The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice Guidelines, and followed applicable regulatory requirements, including AstraZeneca's global policy on bioethics and human biological samples. The TFDA approved the final version of the informed consent form, clinical study pro-

tocol and amendments. Written informed consent was obtained from all patients.

## REFERENCES


1. WHO. Cardiovascular diseases (CVDs): Fact Sheet. 2017; https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed August 1, 2019.
2. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-69.
3. Vedanthan R, Seligman B, Fuster V. Global perspective on acute coronary syndrome: a burden on the young and poor. *Circ Res* 2014;114:1959-75.
4. Chan MY, Du X, Eccleston D, et al. Acute coronary syndrome in the Asia-Pacific region. *Int J Cardiol* 2016;202:861-9.
5. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. *Ann Transl Med* 2016;4:256.
6. Yin WH, Lu TH, Chen KC, et al. The temporal trends of incidence, treatment, and in-hospital mortality of acute myocardial infarction over 15 years in a Taiwanese population. *Int J Cardiol* 2016; 209:103-13.
7. Shah BR, O'Brien EC, Roe MT, et al. The association of in-hospital guideline adherence and longitudinal postdischarge mortality in older patients with non-ST-segment elevation myocardial infarction. *Am Heart J* 2015;170:273-80.e1.
8. Cheng CI, Chen CP, Kuan PL, et al. The causes and outcomes of inadequate implementation of existing guidelines for antiplatelet treatment in patients with acute coronary syndrome: the experience from Taiwan Acute Coronary Syndrome Descriptive Registry (T-ACCORD Registry). *Clin Cardiol* 2010;33:E40-8.
9. Budaj A, Yusuf S, Mehta SR, et al. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. *Circulation* 2002;106:1622-6.
10. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607-21.
11. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179-89.
12. Husted S, van Giezen JJ. Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist. *Cardiovasc Ther* 2009;27:259-74.
13. Van Giezen JJ, Nilsson L, Berntsson P, et al. Ticagrelor binds to human P2Y(12) independently from ADP but antagonizes ADP-induced receptor signaling and platelet aggregation. *J Thromb Haemost* 2009;7:1556-65.
14. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
15. Kang HJ, Clare RM, Gao R, et al. Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: a retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Am Heart J* 2015;169:899-905.
16. Goto S, Huang CH, Park SJ, et al. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome – randomized, double-blind, phase III PHILO study. *Circ J* 2015;79:2452-60.
17. Lee CH, Cheng CL, Kao Yang YH, et al. Cardiovascular and bleeding risks in acute myocardial infarction newly treated with ticagrelor vs. clopidogrel in Taiwan. *Circ J* 2018;82:747-56.
18. Li YH, Wang YC, Wang YC, et al. 2018 Guidelines of the Taiwan Society of Cardiology, Taiwan Society of Emergency Medicine and Taiwan Society of Cardiovascular Interventions for the management of non ST-segment elevation acute coronary syndrome. *J Formos Med Assoc* 2018;117:766-90.
19. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Thorac Cardiovasc Surg* 2016;152:1243-75.
20. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119-77.
21. Taiwan Food and Drug Administration Assessment Report. 2012; https://www.fda.gov.tw/TC/searchin.aspx?q=ticagrelor. Accessed August 1, 2019.
22. A Multicenter, Single Arm, Open Label, Phase IV Study to Evaluate Safety and to Describe the Cumulative Incidence of Major Cardiovascular Events of Ticagrelor in Taiwanese Patients with Non ST-segment Elevation Myocardial Infarction. Brilinta Taiwan Post Approval Safety Study. 2018; https://ichgcp.net/clinical-trials-registry/NCT02406248. Accessed August 1, 2019.
23. AstraZeneca global policy-bioethics. 2016; https://www.astrazeneca.com/content/dam/az/our-company/Documents/Bioethics%20policy%207.0.pdf. Accessed August 1, 2019.
24. MedDRA Introductory Guide Version 19.1. 2016; https://www.meddra.org/sites/default/files/guidance/file/intguide_19_1_english.pdf. Accessed August 1, 2019.
25. BRILINTA® prescribing information. 2016; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf. August 1, 2019.
26. Chen IC, Lee CH, Fang CC, et al. Efficacy and safety of ticagrelor versus clopidogrel in acute coronary syndrome in Taiwan: a multicenter retrospective pilot study. *J Chin Med Assoc* 2016;79: 521-30.
27. Lindholm D, Varenhorst C, Cannon CP, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syn-

drome with or without revascularization: results from the PLATO trial. *Eur Heart J* 2014;35:2083-93.
28. Storey RF, Becker RC, Harrington RA, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. *Eur Heart J* 2011;32:2945-53.
29. Li YH, Fang CY, Hsieh IC, et al. 2018 expert consensus on the management of adverse effects of antiplatelet therapy for acute coronary syndrome in Taiwan. *Acta Cardiol Sin* 2018;34: 201-10.



## ONLINE SUPPLEMENTARY MATERIAL

**Supplementary Table 1.** PLATO definitions of bleeding events[14]

| Category | Definition |
|---|---|
| Major fatal/ life-threatening | Fatal, intracranial, or intrapericardial bleeding with cardiac tamponade, hypovolemic shock, or severe hypotension due to bleeding and requiring pressors or surgery; a decrease in Hb of ≥ 5.0 g/dL; or the need for transfusion of ≥ 4 units of RBCs. |
| Other major | Bleeding that led to significant disability (e.g., intraocular bleeding with permanent vision loss), bleeding associated with a drop in Hb of 3.0 - < 5.0 g/dL, or need for transfusion of 2-3 units of RBCs. |
| Minor | Any bleeding requiring medical intervention but not meeting the criteria for major bleeding. |
| Minimal | Bleeding events not requiring treatment (e.g., bruising, bleeding gums, and oozing from injection sites). |

Hb, hemoglobin; PLATO, study of PLATelet inhibition and patient Outcomes; RBC, red blood cell.

**Supplementary Table 2.** Serious adverse events, by SOC and PT (Safety population)

| SOC/PT | Number (%) of patients* (N = 108) |
|---|---|
| Patients with any SAE | 23 (21.3) |
| Infections and infestations | 4 (3.7) |
| Pneumonia | 4 (3.7) |
| Sepsis | 1 (0.9) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 1 (0.9) |
| Hepatocellular carcinoma | 1 (0.9) |
| Nervous system disorders | 1 (0.9) |
| Hemorrhagic transformation stroke[#] | 1 (0.9) |
| Eye disorders | 1 (0.9) |
| Glaucoma | 1 (0.9) |
| Ear and labyrinth disorders | 1 (0.9) |
| Vertigo | 1 (0.9) |
| Cardiac disorders | 7 (6.5) |
| Angina pectoris | 2 (1.9) |
| Acute coronary syndrome | 1 (0.9) |
| Acute myocardial infarction | 1 (0.9) |
| Cardiogenic shock | 1 (0.9) |
| Coronary artery disease | 1 (0.9) |
| Pericardial effusion | 1 (0.9) |
| Vascular disorders | 1 (0.9) |
| Lymphorrhea | 1 (0.9) |
| Respiratory, thoracic and mediastinal disorders | 2 (1.9) |
| Acute pulmonary edema | 1 (0.9) |
| Chronic obstructive pulmonary disease | 1 (0.9) |
| Pleural effusion | 1 (0.9) |
| Gastrointestinal disorders | 1 (0.9) |
| Gastrointestinal hemorrhage | 1 (0.9) |
| Skin and subcutaneous tissue disorders | 1 (0.9) |
| Rash | 1 (0.9) |
| General disorders and administration site conditions | 5 (4.6) |
| Catheter site hematoma | 1 (0.9) |
| Death | 1 (0.9) |
| Pyrexia | 1 (0.9) |
| Sudden death | 1 (0.9) |
| Vascular stent restenosis | 1 (0.9) |
| Injury, poisoning and procedural complications | 3 (2.8) |
| Procedural hemorrhage | 1 (0.9) |
| Subdural hemorrhage[#] | 1 (0.9) |
| Tendon injury | 1 (0.9) |

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SOC, system organ class.
* Number (%) of patients with SAEs, sorted by international order for SOC and descending frequency for PT. [#] Patients with intracranial hemorrhage.
SAEs were coded using MedDRA version 19.1. A patient could have ≥ one SAE by PT reported under a given SOC. SAEs with an onset date on or after the date of the first dose of ticagrelor and up to and including 7 days following the date of the last dose of ticagrelor were included.