Cardiovascular and Bleeding Risks in Acute Myocardial Infarction Newly Treated With Ticagrelor vs. Clopidogrel in Taiwan

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Background: There are few data on ticagrelor in Asian patients. This study evaluated clinical outcomes with ticagrelor and clopidogrel in Taiwanese patients with acute myocardial infarction (AMI).

Methods and Results: We used the Taiwan National Health Insurance Research Database to identify 27,339 AMI patients aged ≥18 years between January 2012 and December 2014, and only patients who survived greater than or equal to 30 days after AMI and took dual antiplatelet therapy were included. Cohorts of ticagrelor and clopidogrel were matched 1:8, based on propensity score matching, to balance baseline covariates. The primary efficacy endpoints were death from any cause, AMI, or stroke. The safety endpoints consisted of major gastrointestinal bleeding or intracerebral hemorrhage. Following propensity matching, the primary efficacy endpoint rate was 22% lower in the ticagrelor group than in the clopidogrel group (10.6% and 16.2%, respectively; adjusted HR, 0.779; 95% CI: 0.684–0.887). The safety endpoint rate was similar between the ticagrelor and clopidogrel groups (3.2% and 4.1% respectively; adjusted HR, 0.731; 95% CI: 0.522–1.026).

Conclusions: In real-world AMI Taiwanese patients, ticagrelor seemed to offer better anti-ischemic protection than clopidogrel, without an increase in the rate of major bleeding. A large-scale randomized trial is needed to assess the efficacy and safety of ticagrelor in East Asian AMI patients.

Key Words: Acute coronary syndrome; Acute myocardial infarction; Clopidogrel; Ticagrelor; Vascular disease
potent P2Y12 receptor inhibitors will provide similar benefits in Asian patients compared with other races. Because data on the clinical impact of ticagrelor in East Asian patients with AMI were limited, the current study was designed to investigate the efficacy and safety of ticagrelor vs. clopidogrel in Taiwanese patients with AMI.

Methods

Study Design
We retrospectively performed a nationwide population-based cohort study to compare the efficacy and safety of ticagrelor and clopidogrel in adult AMI patients in Taiwan during an 18-month follow-up. The study was approved by the institutional review board of National Cheng Kung University Hospital, Tainan, Taiwan.

Database
The Taiwan National Health Insurance Database used in this study included all inpatient and outpatient medical claims from 1 January 2007 to 30 June 2015. In both the inpatient and outpatient databases, medical information including disease diagnosis, prescription drugs, procedures, and surgery incurred during hospitalization or at an outpatient visit are documented. For processing by the National Health Insurance in Taiwan, all the health-care service providers are requested to submit all diagnosis information using the International Classification of Disease-Clinical Modification, ninth revision (ICD-9-CM) together with service claims.

Subjects
We selected all adult patients (≥18 years) who were admitted to hospital for AMI from 1 January 2012 to 31 December 2014. AMI admission was defined as hospitalization with a primary or secondary discharge diagnosis code of ICD9-CM 410.x. We retained only those patients who were admitted at an acute care hospital. For fear of wrongly selecting into the study patients who had not actually had AMI (e.g., prior AMI patients who were admitted for a diagnostic or therapeutic intervention and still coded for AMI), we excluded patients who were coded as AMI and survived but were hospitalized for <2 days. We also excluded AMI patients who died after less than 30 days or were prescribed more than 2 kinds of P2Y12 inhibitors after AMI (Figure 1). For each patient, the comorbidities were retrieved from both the inpatient and outpatient claim databases for 3 years before the index date. According to the internal validity of the ICD9-CM coding in the present study (Table S1), the positive predictive value of AMI was

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Figure 1. Participant selection.
Ticagrelor vs. Clopidogrel in Taiwanese AMI

converting enzyme inhibitors (ACEI), angiotensin receptor blockers [ARB], vitamin K-antagonist, and statins]. The index date was defined as 30 days after first AMI discharge after 1 January 2012 for each group. The follow-up period was from the index date until the first occurrence of any study outcome or the end of the study period (30 June 2015), whichever came first.

Treatment
In Taiwan, prasugrel was not available and ticagrelor and clopidogrel were both reimbursed for AMI patients for 9 months. Patients in the ticagrelor group received a loading dose of 180 mg followed by a dose of 90 mg twice daily. Patients in the clopidogrel group received a 300–600-mg loading dose followed by a dose of 75 mg daily. All patients

| Table 1. Baseline AMI Subject Characteristics Before Matching |
|---------------------|----------------------|----------------------|----------------------|----------------------|
| **Index year**      | **All**              | **Clopidogrel**       | **Ticagrelor**        | **SMD**              |
|                     | (n=27,339)           | (n=24,495)            | (n=2,844)             |                      |
| 2012                | 9,314 (34.0)         | 9,313 (38.0)          | 0                     | 1.68                 |
| 2013                | 9,647 (35.4)         | 9,240 (37.7)          | 408 (14.3)            |                      |
| 2014                | 8,376 (30.6)         | 5,942 (24.3)          | 2,436 (85.7)          |                      |
| Age (years)         | 63.7±13.8            | 64.2±13.8             | 60.1±12.8             | −0.30                |
| Male                | 21,267 (77.8)        | 18,892 (77.1)         | 2,375 (83.5)          | 0.16                 |
| **Risk factors**    |                      |                      |                       |                      |
| Hypertension        | 17,994 (65.8)        | 16,320 (66.6)         | 1,674 (58.9)          | −0.16                |
| Diabetes mellitus   | 10,797 (39.5)        | 9,833 (40.1)          | 964 (33.9)            | −0.13                |
| Dyslipidemia        | 11,608 (42.5)        | 10,432 (42.6)         | 1,176 (41.4)          | −0.03                |
| **Cardiovascular history** |                 |                      |                       |                      |
| CAD                 | 8,836 (32.3)         | 8,101 (33.1)          | 735 (25.8)            | −0.07                |
| AF                  | 853 (3.1)            | 822 (3.4)             | 32 (1.1)              | −0.02                |
| PAD                 | 997 (3.6)            | 940 (3.8)             | 57 (2.0)              | −0.11                |
| Ischemic stroke     | 2,394 (8.8)          | 2,229 (9.1)           | 165 (5.8)             | −0.13                |
| Intracerebral hemorrhage | 352 (1.3)           | 325 (1.3)             | 27 (1.0)              | −0.04                |
| Heart failure       | 3,769 (13.8)         | 3,554 (14.5)          | 215 (7.6)             | −0.22                |
| **Comorbidity**     |                      |                      |                       |                      |
| COPD                | 6,458 (23.6)         | 5,913 (24.1)          | 545 (19.2)            | −0.12                |
| Asthma              | 2,626 (9.6)          | 2,380 (9.7)           | 246 (8.7)             | −0.04                |
| CKD                 | 5,158 (18.9)         | 4,797 (19.6)          | 361 (12.7)            | −0.19                |
| ESRD                | 3,678 (13.5)         | 3,458 (14.1)          | 220 (7.7)             | −0.21                |
| Liver disease       | 3,616 (13.2)         | 3,231 (13.2)          | 385 (13.5)            | 0.01                 |
| Cancer              | 4,787 (17.5)         | 4,296 (17.5)          | 491 (17.3)            | −0.01                |
| Peptic ulcers       | 5,652 (20.7)         | 5,147 (21.0)          | 505 (17.8)            | −0.08                |
| Prior GI bleeding   | 1,429 (5.2)          | 1,317 (5.4)           | 112 (4.0)             | −0.07                |
| **In-hospital drug use** |                 |                      |                       |                      |
| GP IIb/IIa inhibitor| 5,047 (18.5)         | 4,323 (17.7)          | 724 (25.5)            | 0.19                 |
| β-blocker           | 19,139 (70.0)        | 16,999 (69.4)         | 2,140 (75.3)          | 0.13                 |
| ACEI or ARB         | 20,702 (75.7)        | 18,467 (75.4)         | 2,235 (78.8)          | 0.08                 |
| Statin              | 20,473 (74.9)        | 18,017 (73.6)         | 2,456 (86.4)          | 0.32                 |
| **In-hospital procedure or surgery** | | | | |
| IABP                | 1,382 (5.0)          | 1,219 (5.0)           | 163 (5.7)             | 0.03                 |
| ECMO                | 95 (0.3)             | 88 (0.4)              | 7 (0.2)               | −0.02                |
| PCI                 | 23,601 (86.3)        | 20,947 (85.5)         | 2,654 (93.3)          | 0.26                 |
| CABG                | 283 (1.0)            | 280 (1.1)             | 3 (0.1)               | −0.13                |

Data given as mean±SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; GI, gastrointestinal; GP, glycoprotein; IABP, intra-aortic balloon pump; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SMD, standardized mean difference.

0.88 and the percentage of consistency in comorbidity diagnoses was 95.9%/14–16 We obtained information on each patient at the index AMI admission, consisting of age, gender, days of hospitalization, and the use of AMI-related interventional procedures, including PCI and coronary artery bypass graft (CABG). During the same hospitalization, we also evaluated whether patients received other invasive procedures including ventilator support, intra-aortic balloon pump (IABP), and extracorporeal membrane oxygenation (ECMO). We ascertained medication use, both in-hospital and in the 180 days prior to the index date, as proxies for other comorbidities, using the anatomic therapeutic chemical classification system: oral anti-diabetic drugs, insulin, and several cardiovascular drug classes (β-blockers, calcium channel blockers, angiotensin-
received acetylsalicylic acid (aspirin) at a dose of 100mg daily. For those who had not previously been receiving aspirin, 300mg was the preferred loading dose. We enrolled only patients who received fixed DAPT during the AMI hospitalization and for greater than or equal to 30 days after discharge. Those who received different DAPT during hospitalization and/or who died less than 30 days after AMI were excluded from our study. Other medical treatments were also used based on the standard treatment regimen for patients with AMI in a non-restrictive manner.

### Study Endpoints

The primary efficacy endpoint was a major adverse cardiac event, defined as death from any causes, non-fatal AMI, and/or non-fatal stroke during the follow-up period. The secondary efficacy endpoints were the individual components of the primary efficacy endpoint variable. The primary safety endpoint was major bleeding requiring hospitalization, including gastrointestinal (GI) bleeding and/or intracerebral hemorrhage. The secondary safety endpoints were the individual components of the primary safety endpoint variable.

### Statistical Analysis

Demographic data are expressed as mean±SD or percentage. In general, differences in proportions were analyzed using chi-squared test or Fisher’s exact test, and differences in location parameters of continuous variables were analyzed using Student t-test.

Because of the non-randomized nature of the study, propensity score analysis was performed to minimize any selection bias due to the differences in clinical characteristics between the groups. Propensity scores for the likelihood of receiving ticagrelor or clopidogrel were computed using multivariate logistic regression analysis, conditional on covariates including age, gender, cardiovascular dis-

| Table 2. Baseline Propensity Score-Matched AMI Subject Characteristics |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Index year**  | **All** (n=21,501) | **Clopidogrel** (n=19,112) | **Ticagrelor** (n=2,389) | **SMD** |
| 2012            | 7,298 (33.9)     | 7,297 (38.2)     | 0                | 1.67 |
| 2013            | 7,568 (38.2)     | 7,213 (37.7)     | 356 (14.9)       |
| 2014            | 6,635 (30.9)     | 4,602 (24.1)     | 2,033 (85.1)     |
| **Age (years)** | 63.0±13.2        | 63.1±13.4        | 62.2±12.3        | −0.07 |
| **Male**        | 16,985 (79.0)    | 15,029 (78.6)    | 1,956 (81.9)     | 0.08 |
| **Risk factors**| **Cardiovascular history** |                   |                   |       |
| Hypertension    | 13,819 (64.3)    | 12,334 (64.5)    | 1,485 (62.2)     | −0.05 |
| Diabetes mellitus | 8,164 (38.0)    | 7,306 (38.2)     | 858 (35.9)       | −0.05 |
| Dyslipidemia    | 9,166 (42.6)     | 8,144 (42.6)     | 1,022 (42.8)     | 0.00 |
| **Comorbidity** | **COPD**         |                   |                   |       |
|                 | 4,811 (22.4)     | 4,313 (22.6)     | 498 (20.9)       | −0.04 |
| Asthma          | 1,960 (9.1)      | 1,736 (9.1)      | 224 (9.4)        | 0.01 |
| CKD             | 3,432 (16.0)     | 3,083 (16.1)     | 349 (14.6)       | −0.04 |
| ESRD            | 2,283 (10.6)     | 2,064 (10.8)     | 219 (9.2)        | −0.05 |
| Liver disease   | 2,790 (13.0)     | 2,462 (12.9)     | 328 (13.7)       | 0.02 |
| Cancer          | 3,713 (17.3)     | 3,275 (17.1)     | 438 (18.3)       | 0.03 |
| Peptic ulcer    | 4,269 (19.9)     | 3,827 (20.0)     | 442 (18.5)       | −0.04 |
| Prior GI bleeding | 1,029 (4.8) | 928 (4.9)        | 101 (4.2)        | −0.03 |
| **In-hospital drug use** |                   |                   |                   |       |
| GP IIb/IIa inhibitor | 3,942 (18.3)   | 3,496 (18.3)     | 446 (18.7)       | 0.01 |
| β-blocker       | 15,277 (71.1)    | 13,573 (71.1)    | 1,704 (71.3)     | 0.01 |
| ACEI or ARB     | 16,447 (76.5)    | 14,610 (76.4)    | 1,837 (76.9)     | 0.01 |
| Statin          | 17,105 (79.6)    | 15,104 (79.0)    | 2,001 (83.8)     | 0.12 |
| **In-hospital procedure or surgery** |                   |                   |                   |       |
| IABP            | 1,104 (5.1)      | 965 (5.1)        | 139 (5.8)        | 0.03 |
| ECMO            | 71 (0.3)         | 64 (0.3)         | 7 (0.3)          | −0.01 |
| PCI             | 19,477 (90.6)    | 17,278 (90.4)    | 2,199 (92.1)     | 0.06 |
| CABG            | 47 (0.2)         | 44 (0.2)         | 3 (0.1)          | −0.02 |

Data given as mean±SD or n (%). Abbreviations as in Table 1.
cases, diabetes mellitus, chronic kidney disease, in-hospital cardiovascular drugs (β-blockers, statins, glycoprotein IIb/IIIa inhibitors, ACEI/ARB), and in-hospital procedures (PCI, IABP, ECMO, and CABG). Then, using the Greedy 5→1 digit technique, the propensity score was used to present the balance of continuous and binary variables between groups. Intent-to-treat analysis was used to evaluate the association between different DAPT and risk of efficacy and safety endpoints. Once a patient met the definition for exposure to ticagrelor or clopidogrel, he/she was considered exposed from that point forward, even if he/she discontinued therapy. Time-to-event Kaplan-Meier curves for each cohort were constructed for death from any cause, non-fatal AMI, stroke, and a composite of primary efficacy and safety endpoints and were compared using log-rank test. The estimates of relative risk, with 95% CI, were derived from Cox proportional hazards models, adjusted for potential confounders including medication and comorbidities (before propensity score matching), with matching analysis for propensity score matching.

We conducted several sensitivity analyses to test the robustness of the findings. First, we performed propensity score assessment, which was used to match both ticagrelor and clopidogrel patients in 1:1 and 1:4 ratios. Intent-to-treat analysis was used to evaluate the association between different DAPT and risk of efficacy and safety endpoints again. Second, we enrolled only clopidogrel users in 2012, before ticagrelor was available in Taiwan, which means that we could minimize selection bias in both groups. All analysis was performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

### Results

#### Baseline Characteristics

From 2012 to 2014, 40,253 AMI patients were identified for potential placement into either the ticagrelor or the clopidogrel cohort. Of these, 32,137 patients (79.8%) received clopidogrel and 3,715 patients (9.2%) received ticagrelor. At least 30 days after discharge, 24,495 patients continued clopidogrel and 2,844 patients continued ticagrelor (Figure 1). Baseline clinical characteristics are listed in Table 1. The patients who received ticagrelor were younger than those who received clopidogrel. There was also a higher percentage of comorbid diseases, including diabetes, heart failure, old cerebrovascular events, chronic kidney disease, and end-stage renal disease, in the clopidogrel cohort than in the ticagrelor cohort.

Before propensity score matching, patients who received ticagrelor and clopidogrel also significantly differed with regard to in-hospital medication. After propensity score matching, 21,501 AMI patients were selected and baseline characteristics and in-hospital medications better matched (Table 2). Of these, 19,477 (90.0%) received PCI and 47 (0.22%) received CABG during the index hospitalization. Moreover, 76.5% received ACEI/ARB, 71.1% received β-blockers, 79.6% received statins, and 18.3% received i.v. glycoprotein IIb/IIIa inhibitors.

#### Clinical Outcomes

Mean exposure to the study drug was different in the 2 groups: 225±103 days for ticagrelor and 256±106 days for clopidogrel (P<0.001). During the 1-year follow-up, 636 ticagrelor users (22.4%) would be switched to clopidogrel and 416 clopidogrel users (1.69%) would be switched to ticagrelor. Before propensity score matching, the incidence of primary efficacy endpoints (death from any cause/AMI/stroke) was 10.1% in the ticagrelor users and 18.3% in the clopidogrel users (adjusted HR, 0.887; 95% CI: 0.777–0.990). The incidence of primary safety endpoints (major GI bleed and/or intracerebral hemorrhage) was 2.9% in the ticagrelor users and 4.7% in the clopidogrel users (adjusted HR, 0.731; 95% CI: 0.522–1.026). The incidence of ischemic stroke was 1.4% in the ticagrelor users and 3.0% in the clopidogrel users (adjusted HR, 0.811; 95% CI: 0.586–1.123). The incidence of non-fatal AMI was 7.5% in the ticagrelor users and 9.9% in the clopidogrel users (adjusted HR, 0.984; 95% CI: 0.807–1.199; Table S2).

We therefore used the propensity-score method to create ticagrelor (n=2,389) and clopidogrel (n=19,112) cohorts (Table 3). During follow-up, the incidence of primary efficacy endpoints (death from any cause/AMI/stroke) was 10.6% in the ticagrelor users and 16.2% in the clopidogrel users (adjusted HR, 0.779; 95% CI: 0.684–0.887; Figure 2A). The incidence of primary safety endpoints (major GI bleeding and/or intracerebral hemorrhage) was 3.2% in the ticagrelor users and 4.1% in the clopidogrel users (adjusted HR, 0.731; 95% CI: 0.522–1.026; Figure 2B). In the subgroup analysis, we found that ticagrelor has benefits for some groups, including those aged <75 years, female,
with an AMI history, with diabetes mellitus history, without chronic kidney disease history, without heart failure history, and who used statin at admission (Figure 3). We also found that ticagrelor had a lower bleeding risk among patients with heart failure history in subgroup analysis (Figure 4).

**Sensitivity Analysis**

We calculated propensity scores to match both ticagrelor and clopidogrel patients in 1:1 and 1:4 ratios. Intent-to-treat analysis was used to re-evaluate the association between different DAPT and risk of the primary efficacy and safety endpoints. For ticagrelor or clopidogrel patients in the 1:1 cohort, the incidence of primary efficacy endpoints (death from any cause/AMI/stroke) was 10.2% in the ticagrelor users and 13.7% in the clopidogrel users (adjusted HR, 0.876; 95% CI: 0.742–1.034). The incidence of major bleeding complications (GI bleeding and/or intracerebral hemorrhage) was 2.9% in the ticagrelor users and 3.2% in the clopidogrel users (adjusted HR, 1.072; 95% CI: 0.773–1.489; Table 4). For ticagrelor or clopidogrel patients in the 1:4 cohort, the incidence of primary efficacy endpoints (death from any cause/AMI/stroke) was 10.2% in the ticagrelor users and 13.4% in the clopidogrel users (adjusted HR, 0.900; 95% CI: 0.791–1.024). The incidence of major bleed-
Taiwanese patients with AMI. The major finding of this retrospective study is that ticagrelor offered better cardiovascular protection than clopidogrel and was similar to clopidogrel for major bleeding events. Therefore, ticagrelor should be used in most AMI patients, but they must be carefully monitored for major bleeding events. Additionally, a further large-scale randomized trial should be conducted to assess the efficacy and safety of ticagrelor in East Asian patients with AMI.

Ticagrelor is an oral direct-acting P2Y12 receptor antagonist that does not require metabolic activation and has a unique mode of action that encompasses inhibition of both P2Y12 and equilibrative nucleoside transporter 1 (ENT1). Therefore, compared with clopidogrel, ticagrelor results in faster and greater platelet inhibition, with less patient-to-patient variation. In the PLATO study, as compared with clopidogrel, ticagrelor was associated with a 16% relative risk reduction with regard to the primary efficacy endpoint – a composite of death from cardiovascular causes, AMI, and stroke – but with a significant

### Table 4

|         | Ticagrelor (%) | Clopidogrel (%) | Ticagrelor vs Clopidogrel | Hazard Ratio (95%CI) |
|---------|----------------|----------------|--------------------------|---------------------|
| Overall |                |                |                         | 0.78 (0.68–0.89)    |
| Age     |                |                |                         |                     |
| <75 Yr  | 170 (9.1)      | 162 (12.9)     |                         | 0.85 (0.73–0.99)    |
| >=75 Yr | 168 (17.6)     | 119 (27.7)     |                         | 0.80 (0.63–1.04)    |
| Sex     |                |                |                         |                     |
| Female  | 53 (12.2)      | 89 (21.9)      |                         | 0.64 (0.46–0.89)    |
| Male    | 201 (10.3)     | 220 (14.7)     |                         | 0.87 (0.75–1.01)    |
| CKD     |                |                |                         |                     |
| Yes     | 124 (14.3)     | 167 (22.9)     |                         | 0.73 (0.60–0.90)    |
| No      | 130 (8.5)      | 142 (12.1)     |                         | 0.82 (0.68–0.99)    |
| CHF     |                |                |                         |                     |
| Yes     | 61 (17.5)      | 91 (29.6)      |                         | 0.85 (0.61–1.18)    |
| No      | 193 (9.5)      | 218 (13.6)     |                         | 0.81 (0.70–0.94)    |
| Statin use at admission |            |                |                         |                     |
| Yes     | 48 (21.6)      | 61 (30.3)      |                         | 0.80 (0.54–1.17)    |
| No      | 200 (9.6)      | 248 (14.5)     |                         | 0.76 (0.67–0.90)    |

**Discussion**

This nationwide population-based, real-world study was conducted to compare the efficacy and safety between ticagrelor and clopidogrel in East Asian patients, especially in the subgroup analyses. Similar patterns of results were found for different matching ratios.
Table 4. Sensitivity Analysis

| Subgroup                          | Clopidogrel (%) | Ticagrelor (%) | Ticagrelor vs Clopidogrel | Hazard Ratio (95% CI) |
|-----------------------------------|----------------|---------------|---------------------------|---------------------|
| Overall                           |                |               |                           | 0.78 (0.68–0.89)    |
| Age                               |                |               |                           |                     |
| <75 Yr                            | 42(2.1)        | 435(2.9)      |                           | 0.57 (0.63–1.22)    |
| >=75 Yr                           | 34(7.9)        | 344(7.9)      |                           | 1.19 (0.79–1.78)    |
| Sex                               |                |               |                           |                     |
| Female                            | 30(6.9)        | 237(5.8)      |                           | 1.66 (1.01–2.73)    |
| Male                              | 46(2.4)        | 552(3.7)      |                           | 0.90 (0.59–1.09)    |
| Old MI                            |                |               |                           |                     |
| Yes                               | 59(3.2)        | 562(3.9)      |                           | 1.02 (0.77–1.35)    |
| No                                | 17(3.2)        | 217(4.5)      |                           | 0.77 (0.46–1.47)    |
| DM                                |                |               |                           |                     |
| Yes                               | 42(4.9)        | 451(5.7)      |                           | 0.52 (0.31–0.88)    |
| No                                | 34(2.2)        | 364(3.1)      |                           | 0.88 (0.60–1.28)    |
| CKD                               |                |               |                           |                     |
| Yes                               | 19(5.4)        | 245(7.9)      |                           | 0.90 (0.51–1.57)    |
| No                                | 53(2.5)        | 534(3.3)      |                           | 1.04 (0.78–1.38)    |
| CHF                               |                |               |                           |                     |
| Yes                               | 22(10.3)       | 136(6.8)      |                           | 2.05 (1.10–3.80)    |
| No                                | 54(2.5)        | 643(3.8)      |                           | 0.81 (0.61–1.07)    |
| Statin use at admission           |                |               |                           |                     |
| Yes                               | 58(2.9)        | 577(3.8)      |                           | 0.91 (0.69–1.21)    |
| No                                | 18(4.6)        | 202(5.0)      |                           | 1.21 (0.70–2.08)    |

Data given as n (%). †Death from any cause/AMI/stroke; ‡major GI bleeding/ICH. Abbreviations as in Tables 1,3.
increase in non-procedure-related PLATO major bleeding (4.5% vs. 3.8%, P=0.026). Although the consistency of effects of ticagrelor was also observed in Asian patients of the PLATO study, the Asian/Australian subgroup of the PLATO population represented 6% of patients overall. Only limited data exist on the comparison between the newer P2Y12 inhibitors (prasugrel and ticagrelor) and clopidogrel in East Asian patients with ACS. The PHILo trial, which was designed to mirror PLATO, was a multicenter, randomized, double-blind, non-event-driven study conducted in Japan and East Asian countries (Japan, 90%; Taiwan, 4%).21 The incidence of primary efficacy endpoints was 10.2% per year with ticagrelor and 8.1% per year with clopidogrel (HR, 1.54; 95% CI: 0.88-2.44). The incidence of major bleeding was 10.3% per year for ticagrelor and 6.8% per year for clopidogrel (HR, 1.54; 95% CI: 0.94-2.53). Due to the small number of patients, however, PHILo was not statistically powered to detect treatment differences between groups. The KAMIR-NIH registry was an observational cohort study to compare the short-term clinical outcomes between ticagrelor and clopidogrel in Korean patients with AMI undergoing successful PCI.22 In that study, there was no significant difference in the incidence of primary efficacy endpoints between ticagrelor and clopidogrel at 6-month follow-up (3.7% vs. 4.2%, P=0.637). Ticagrelor, compared with clopidogrel, however, was associated with higher incidences of in-hospital major bleeding (2.6% vs. 1.2%, P=0.008). In the KAMIR-NIH registry, the incidence of the primary efficacy endpoint was much lower compared with previous AMI studies. That was because the study excluded the patients who discontinued anti-platelet agents or switched DAPT in-hospital and, given that patients who had ischemic or hemorrhagic events during hospitalization tended to discontinue or switch anti-platelet agents, mainly relatively stable patients with AMI after successful revascularization were included in the study. Therefore, the effect between ticagrelor and clopidogrel on real-world AMI patients in East Asian countries is still unclear and unanswered.

The recently published ESTATE study was a multicenter retrospective pilot study to evaluate the efficacy and safety of ticagrelor (n=324) and clopidogrel in 928 ACS Taiwanese patients. At 5.5-month follow-up, ticagrelor, compared with clopidogrel, was associated with a lower incidence of composite PLATO efficacy endpoint (7.1% vs. 11.6%, P=0.07). Ticagrelor, compared with clopidogrel, was associated with similar incidences of in-hospital major bleeding (4.5% vs. 6.3%, P=0.4). Because the patient number was relatively small, ticagrelor treatment was seen to have a marginally favorable effect on the occurrence of primary efficacy outcomes with a similar incidence of major bleeding. The present study is the first and largest nationwide population-based study in Asian countries, and the occurrence of primary efficacy endpoints was similar in the ticagrelor groups in this and the PLATO trial (10.6% vs. 10.2%, respectively). When compared with the PLATO trial, a relative risk reduction was observed with ticagrelor regarding the occurrence of primary efficacy endpoints (21% vs. 16%) in the present study. When all the aforementioned results are taken together, the effect of ticagrelor probably differs across East Asian populations.

Bleeding events in patients with ACS are relatively frequent and appear to be associated with poor prognosis. One study, based on the PLATO trial population, showed that only major bleeding, regardless of the definition used, was associated with a marked increase in short-term but not long-term mortality.24 The incidence of major bleeding was higher with ticagrelor treatment in the PHILO trial (10.3% vs. 6.8%) but not in the PLATO trial (11.6% vs. 11.2%) nor the current study (4.5% vs. 6.3%). The ESTATE trial indicated that the incidence of all bleeding was not significantly different between ticagrelor and clopidogrel (19.6% vs. 14.3%, P=0.13). The lower major bleeding rate observed in the present study was similar to the ESTATE trial, which may be attributable to missing information or incomplete patient records. Because minor bleeding events were possibly unrecorded and incomplete in the Taiwan National Health Insurance Database, we could not obtain the incidences of minor bleeding or total bleeding in the present study. In the present subgroup analysis, however, ticagrelor had consistently similar major bleeding complications to clopidogrel.

There are several limitations in the present investigation. First, this was a non-randomized study. It was a retrospective cohort study and, therefore, selection bias was hardly avoidable, even though it was partially compensated by propensity-score matched analysis and several sensitivity analyses. Second, we could not accurately evaluate the minor bleeding complications and other adverse effects of P2Y12 inhibitors including dyspnea, hyperuricemia, and asymptomatic heart block. Nor could we confirm whether recurrent AMI was due to stent thrombosis. Third, the health-care claims data did not contain body mass index (BMI) and smoking status data. Because information on BMI for all patients was unavailable, we could not adjust the analysis in this aspect; but we assumed that obesity differential bias would be absent due to the population-level comparison in this study. Also, the database did not include some variables such as coronary artery disease extension and revascularization details.

Conclusions

In Taiwanese patients with AMI, treatment with ticagrelor as compared with clopidogrel seemed to reduce the rate of death from any cause, AMI, or stroke without an increase in the rate of major bleeding during an 18-month follow-up. The results are very different to those from Japan and Korea. Therefore, dedicated research for East Asian patients is required before we can apply Western recommendations for potent P2Y12 inhibitors in the former population.

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Disclosures

The authors declare no conflict of interest.

References

1. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al; ESC Committee for Practice Guidelines. 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.

2. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cerneck B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. *J Am Coll Cardiol* 2016; 67: 1235–1250.

3. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al; ACC/AHA Task Force Members; Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *Circulation* 2014; 130: 2344–2394.

4. Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, et al; Working Group on On-Treatment Platelet Reactivity. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol* 2015; 62: 2261–2273.

5. 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.

6. Goto S, Toda E. Antiplatelet therapy after coronary intervention in Asia and Japan: The Asian perspective of antiplatelet intervention. *Hamostaseologie* 2009; 29: 321–325.

7. Mak KH, Bhatt DL, Shao M, Hankey GJ, Easton JD, Fox KA, et al. Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. *Am Heart J* 2009; 157: 658–665.

8. Park DW, Yun SC, Lee SW. 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 vs bare-metal stents. *JACC Cardiovasc Interv* 2008; 1: 494–503.

9. Kimura T, Morimoto T, Nakagawa Y, Tamura T, Kadota K, Yasumoto H, et al; J-Cypher Registry Investigators. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. *Circulation* 2009; 119: 987–995.

10. Kumar RS, Douglas PS, Peterson ED, Anstrom KJ, Dai D, Brennan JM, et al. Effect of race and ethnicity on outcomes with drug-eluting and bare metal stents: Results in 423,965 patients in the linked National Cardiovascular Data Registry and centers for Medicare & Medicaid services payer databases. *Circulation* 2013; 127: 1395–1403.

11. Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol* 2007; 50: 1852–1856.

12. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: A double-blind comparison to clopidogrel with aspirin. *Eur Heart J* 2006; 27: 1038–1047.

13. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361: 1045–1057.

14. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the national health insurance research database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf* 2011; 20: 236–242.

15. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Kao YH. Validation of the National Health Insurance Research Database with acute myocardial infarction cases in Taiwan. *J Epidemiol* 2014; 24: 500–507.

16. Cheng CL, Chien HC, Lee CH, Lin SJ, Yang YK. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in National Health Insurance Research Database in Taiwan. *Int J Cardiol* 2015; 201: 96–101.

17. Bonello L, Laine M, Kipson N, Mancini J, Helal O, Fromnot J, et al. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. *J Am Coll Cardiol* 2014; 63: 872–877.

18. 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.

19. 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.

20. Chen IC, Lee CH, Fang CC, Chao TH, Cheng CL, Chen Y, et al; ESTATE Investigators. Efficacy and safety of ticagrelor versus clopidogrel in acute coronary syndrome in Taiwan: A multicenter retrospective pilot study. *J Chin Med Assoc* 2016; 79: 521–530.

21. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome: Randomized, double-blind, phase III PHILO study. *Circ J* 2015; 29: 2452–2460.

22. Park KH, Jeong MH, Ahn Y, Ahn TH, Seung KB, Oh DJ, et al; KAMIR-NIH registry investigators. Comparison of short-term clinical outcomes between ticagrelor versus clopidogrel in patients with acute myocardial infarction undergoing successful revascularization; from Korea Acute Myocardial Infarction Registry-National Institute of Health. *Int J Cardiol* 2016; 215: 193–200.

23. Saito S, Ishikawa T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. *Circ J* 2014; 78: 1684–1692.

24. Ducrocq G, Schulte PJ, Becker RC, Cannon CP, Harrington RA, Held C, et al. Association of spontaneous and procedure-related bleeds with short- and long-term mortality after acute coronary syndromes: An analysis from the PLATO trial. *EuroIntervention* 2015; 11: 737–745.

**Supplementary Files**

**Supplementary File 1**

**Table S1.** WHO ICD-9-CM codes

**Table S2.** Ticagrelor: efficacy and safety outcomes of AMI before propensity score matching

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