Study Protocol

Title: Safety and Efficacy of Ticagrelor versus Clopidogrel in East Asian Patients with Acute Coronary Syndromes: A Patient-level Pooled Analysis of Randomized Trials

Study Principle investigator:

Duk-Woo Park, MD, PhD

Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Address:

Duk-Woo Park, MD, PhD

Department of Medicine, Asan Medical Center,

University of Ulsan College of Medicine,

388-1 Poongnap-dong, Songpa-gu, Seoul, 138-736, Korea.

Fax: (82-2)-475-6898, Tel: (82-2)-3010-3995,

E-mail: dwpark@amc.seoul.kr

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1. Research Key Summary

Owing to the differential propensity for bleeding and ischemic events with response to antiplatelet therapy, the safety and effectiveness of potent P2Y12 inhibitor ticagrelor in East Asian populations remain uncertain. This patient-level pooled analysis of randomized trials of the PHILO and TICAKOREA is designed to examine the comparative safety and efficacy of ticagrelor versus clopidogrel in East Asian patients with acute coronary syndromes.

2. Background

Dual antiplatelet therapy (DAPT) with a P2Y12 inhibitor and aspirin is the standard antithrombotic therapy in patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI). Ticagrelor is an oral, reversible, direct-acting, P2Y12 inhibitor that provides faster, greater, and more consistent P2Y12 inhibition compared to clopidogrel.[1] In the large international PLATelet inhibition and patient Outcomes (PLATO) trial, ticagrelor was revealed to be superior to clopidogrel in reducing the composite rate of death from vascular causes, myocardial infarction (MI), or stroke at 12 months without an increase in the overall rate of major bleeding events in patients hospitalized with ACS.[2] European and United States guidelines recommend that ticagrelor should be preferred to clopidogrel as a P2Y12 antagonist in ACS patients with or without PCI.[3]

East Asian populations are regarded as more susceptible to bleeding events but relatively resistant to atherothrombosis even a higher prevalence of high on-treatment reactivity, which is referred to as “East Asian paradox”.[4,5] Since the Asian subgroup of the PLATO population represented 6% of patients overall, direct extrapolation of the available evidence into clinical practice for the Asian population may not be appropriate. In the PHILO trial with East Asian population, patients treated with ticagrelor compared to clopidogrel had a higher incidence of bleeding events as well as major adverse cardiovascular events (MACE), albeit statistically non-

significant.[6] In addition, the TICAKOREA trials showed significant higher bleeding risks of ticagrelor with a non-significant trend of worse MACE, compared with clopidogrel in Korean ACS patients.[5] However, prior trials were underpowered to draw any confirmative conclusion regarding efficacy and safety of standard-dose ticagrelor compared to clopidogrel in East Asain patients presented with ACS who are intended for early invasive strategy. Thus, further studies with larger population are needed to confirm or refute these results in East Asian ACS patients.

3. Study Objectives

The primary objective of the study is to compare the safety and efficacy of standard-dose ticagrelor compared with clopidogrel, given as antiplatelet dual therapy, with regard to the event rate of major bleeding in East Asian patients with non–ST elevation or ST-elevation ACS for whom early invasive strategy was planned.

4. Study Methods

The protocol was developed according to the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data Development Group.[7] We did a meta-analysis of individual patient data from two randomized clinical trials of the PHILO and the TICAKOREA that compared standard-dose ticagrelor and clopidogrel in East-Asian patients presented with ACS. Two investigators (D.W. Park and J.S. Jang) assessed trial eligibility criteria and a third investigator (J.M. Ahn) could be consulted if eligibility could not be agreed. This work was partly supported by the Cardiovascular Research Foundation (CVRF), Seoul, Korea.

5. Study population

Patients at least 18 years of age who presented with ACS with or without ST elevation, with an onset of symptoms in the previous 24 hours, for whom invasive management was planned, were

enrolled.

5.1. Inclusion/exclusion Criteria

Inclusion or exclusion criteria for enrollment of the PHILO and the TICAKOREA were similar. Major exclusion criteria were any contraindication to aspirin, clopidogrel, or ticagrelor; chronic oral anticoagulant therapy; active bleeding or a history of bleeding; fibrinolytic therapy within 24 hours before randomization; need for oral anticoagulation therapy; increased risk of bradycardia; concomitant therapy with a strong CYP3A inhibitor or inducer; end-stage liver or kidney disease.

6. Study Endpoints

The primary safety outcome was the occurrence of clinically significant bleeding (a composite of major bleeding or minor bleeding according to the PLATO criteria[8]) at 12 months. Secondary safety endpoints included major, minor, or fatal bleeding defined by the PLATO criteria as well as intracranial bleeding. The primary efficacy outcome was major adverse cardiovascular events (MACE; defined as a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke). Secondary efficacy outcomes included individual components of MACE, as well as all-cause death, MI, stroke, repeat revascularization, and stent thrombosis (definite). Exploratory efficacy endpoints also included a composite of cardiovascular death, spontaneous MI, or stroke and a composite of Composite of all-cause death, MI or stroke.

7. Data collection and quality assessment

We contacted the principal investigators of the PHILO and the TICAKOREA trial to request data at the patient level in anonymized electronic datasets. For acquisition of individual patients data of the PHILO, we asked the access to database (DB) via Data Request Portal of the AstraZeneca

Group of Companies (https://astrazenecagroup-dt.pharmacm.com//DT/Home/Index/0) and received the data sharing agreement and data access. We checked data for completeness and consistency and compared them with the results of the original publications. The principal investigators of the included trials were contacted in case of missing data or if questions arose during the integrity checks. Once queries had been resolved, the clean data were uploaded to the main study dataset. Two investigators (D.W. Park and J.S. Jang) independently assessed the quality of included trials with the Cochrane Collaboration's tool for assessing risk of bias.

8. Data base information

All DB management process will be done by the SAS Multi-Sponsor Environment (MSE) using the SAS® Clinical Trial Data Transparency system. The DB import, export, and all analyses will be done by a remote desktop connection SAS Clinical Trial Data Transparency portal.

9. Statistical Analysis

We pooled data from all trials to provide baseline characteristics and comparative outcome data. All analyses were done by intention to treat. Baseline, procedural, and outcome data for individual patients were pooled. Continuous variables are presented as mean (SD) and were compared with with Student's t-test or the Wilcoxon rank-sum test; discrete data are presented as frequencies and were compared with with the chi-square test or Fisher's exact test. The cumulative event rates are calculated according to the Kaplan–Meier method, with event or censoring times calculated from the date of randomization and the between-group differences in outcomes is assessed using the log-rank test. The patients lost to follow-up are included in the analyses for all outcomes by censoring at the data of last follow-up. We also compare the safety and efficacy of ticagrelor and clopidogrel with random-effects Cox proportional hazards models stratified by trial and with inclusion of a γ frailty term to account for heterogeneity between trials. The proportional

hazards assumption in the Cox model for the overall group was assessed by visual inspection of the scaled Schoenfeld residuals over a Kaplan-Meier transform of time, as well as with the corresponding test for the correlation of the Schoenfeld residuals with time.[9] Subgroup analyses for primary safety and efficacy outcome according to baseline clinical, procedural, and anatomical characteristics were also done with the Cox models. A two-sided p value of less than 0·05 was considered to indicate statistical significance; we did not adjust for multiplicity. All statistical analyses were done with the SAS or R software. Reporting of this individual patient-data, pooled analysis concurs with specific PRISMA guidelines.[7]

10. Reference

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