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Ticagrelor versus clopidogrel in East Asian patients with acute coronary syndrome: Systematic review and meta-analysis

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ABSTRACT

Background: Bleeding complications are associated with unfavorable outcomes in patients with acute coronary syndrome (ACS). Compared to Whites, several studies demonstrated a higher risk of bleeding in Asians who present with acute myocardial infarction. To date, the efficacy and safety of ticagrelor in East Asian population have not been well established.
Methods: We conducted a systematic review and meta-analysis of randomized controlled trials that compared ticagrelor and clopidogrel in East Asian patients with acute coronary syndrome (ACS). We systematically searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrial.gov database.
Results: Three randomized controlled trials, including a total of 1552 patients, met our inclusion criteria. Study countries included Japan, South Korea, and China. All studies defined primary efficacy endpoint and major bleeding events in accordance with the PLATO definition. Ticagrelor was associated with a numerically lower, albeit statistically nonsignificant, risk of primary efficacy endpoint defined as a composite of death from vascular causes, myocardial infarction, or stroke (odds ratio 0.84; 95% confidence interval 0.43–1.63; $p = 0.60$). Ticagrelor was associated with a significantly higher risk of PLATO-defined major bleeding compared to clopidogrel (odds ratio 1.52; 95% confidence interval 1.04–2.23; $p = 0.03$).
Conclusions: Our meta-analysis demonstrated that ticagrelor was associated with a higher risk of major bleeding compared to clopidogrel in East Asian patients with ACS. Further studies evaluating the role of ticagrelor in management of ACS in East Asian patients are warranted.

1. Introduction

Ticagrelor is a reversible non-thienopyridine oral P2Y12 antagonist that provides faster, more potent, and consistent platelet inhibition than clopidogrel [1]. In the large multi- national randomized controlled trial, the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was shown to be superior to clopidogrel in reducing the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the overall rate of major bleeding events [2]. Based on these results, the use of ticagrelor is preferred over clopidogrel in patients with acute coronary syndrome (ACS) [non-ST-elevation ACS or ST-elevation myocardial infarction] as a Class IIa recommendation in the current ACC/AHA guidelines for the management of ACS [3,4].

Despite its therapeutic benefits, the efficacy of antiplatelet agents should be carefully weighed against potential complications such as bleeding, since bleeding complications are associated with unfavorable short- and long-term outcomes in ACS [5–7]. This is of particular concern for Asian patients who tend to have lower body mass index and high prevalence of renal failure, both of which are associated with bleeding complications [6,8–12]. In addition, several studies demonstrated a higher risk of bleeding in Asians presenting with acute myocardial infarction compared to Whites [8,11,12].

To date, the efficacy and safety of ticagrelor in the East Asian population have not been well-established. While the subgroup analysis of the Asian patients enrolled in PLATO trial showed overall comparable efficacy and safety of ticagrelor in Asian population compared to non-Asian, the Study to Assess Safety and Efficacy of Ticagrelor Versus Clopidogrel in Asian/Japanese Patients With Non-ST or ST Elevation Acute Coronary Syndromes (PHILO trial), which was designed to mirror PLATO trial with 801 East Asian patients, showed a higher, albeit statistically non-significant, incidence of the primary efficacy and safety endpoints in the patients treated with ticagrelor compared to clopidogrel [13,14]. In this context, we conducted a systematic review and meta-analysis to evaluate the efficacy and safety of ticagrelor in East Asian patients with ACS.

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CI, confidence interval; PLATO, Platelet Inhibition and Patient Outcomes.

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2. Methods

We performed a meta-analysis of randomized trials in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guideline [15]. The protocol for this systematic review was registered in the PROSPERO database (www.crd.york.ac.uk/PROSPERO; CRD42017054800). We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrial.gov database through January 2017 using the following search terms and keywords: ticagrelor or AZD6140, clopidogrel or SR25990C, and "acute coronary syndrome" or "myocardial infarction". No language restrictions were applied. The search was restricted to randomized controlled trials. Studies were also identified through a search of references cited in the screened original articles and relevant review articles. Conference abstracts for the scientific sessions of the American College of Cardiology, American Heart Association, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics and Japanese Circulation Society within the last three years were also reviewed.

Eligible trials had to satisfy the following pre-specified criteria: 1) randomized controlled design, including subgroup analysis, that compared ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300 to 600 mg loading dose, 75 mg daily thereafter) in patients with ACS, 2) studies of East Asian patients, which include Japanese, South Korean, Chinese, and Mongolian patients, 3) median follow-up duration ≥ 6 months and 4) studies reporting the incidence of the primary efficacy and safety outcomes of interest (as described below). When ethnicity or nationality of the study participants was not specifically described in articles, it was inferred based on the study country and facility.

Two investigators (N.M. and S.A.) independently screened and assessed trial eligibility using the predefined inclusion criteria. After initial screening of all titles and abstracts, full-text articles of potentially relevant studies were reviewed to determine their eligibility. Disagreements were resolved through discussion between the two reviewers.

The primary efficacy outcome of interest was a composite of death from vascular causes, myocardial infarction, or stroke, which is in accordance with the primary efficacy endpoint in the PLATO trial. The primary safety outcome of interest was major bleeding events. Although we originally planned to accept the definition of major bleeding used in each study, all included studies used a common definition for major bleeding in accordance to the PLATO trial. The secondary outcomes of interest were all-cause death, a composite of major and minor bleeding, non-coronary artery bypass grafting (CABG)-related major bleeding, and net clinical benefit defined as a composite of death from vascular causes, myocardial infarction, stroke, or major bleeding.

Relevant data were independently extracted by two investigators (N.M. and S.A.). Disagreements were resolved through discussion between the two reviewers. Data were abstracted to include the following information: first author's name, year of publication, study period, country, study design, sample size, clinical characteristics of the study population, duration of follow-up, outcome definitions used in each study, and the incidence of primary and secondary outcomes that coincide with our study. When a potentially eligible study did not report the outcome of interest, the authors of the study were contacted via email. Quality assessment of the study was performed using the Cochrane Collaboration's risk of bias tool [16].

Summary estimates were calculated as odds ratios with 95% confidence intervals using the random effects model based on DerSimonian and Laird's meta-analytic statistical method [17]. Considering that the heterogeneity of the included trials might influence the treatment effects, we pre-specified the use of the random-effects model to assess effect sizes. As an exploratory analysis, we tested for an interaction between ticagrelor and East Asian ethnicity with respect to the primary efficacy and safety outcomes; we compared the estimated odds ratio in East Asians from this meta-analysis to that in non-East Asian patients from the PLATO trial, regarding these quantities as independent and approximately normally distributed on the logarithmic scale. The event rates in non-East Asian patients were obtained from the substudy of PLATO trial [13]. The I^2 index was used to summarize the proportion of the total variability in the estimate. The I^2 statistic is derived from the Q statistic and describes the percentage of total variation across studies that is due to heterogeneity; values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively [18,19]. Planned assessment for publication bias using Funnel plot and the Begg's test was not performed as the total number of the included studies was insufficient for such assessments. The statistical level of significance was 2-tailed $p < 0.05$. Analyses were performed using Review Manager version 5.3 (Revman; The Cochrane Collaboration, Oxford, UK) and SPSS version 24.0 (IBM Corp, Armonk, New York, United States).

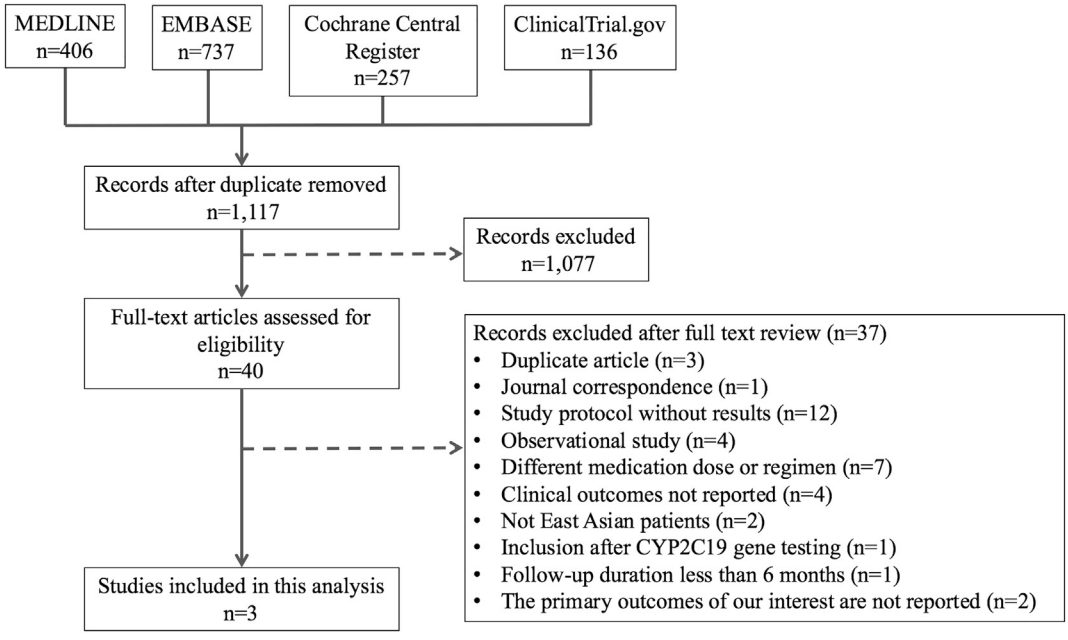

Fig. 1. Flow chart of search strategy.

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