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Original Article

Efficacy and safety of ticagrelor versus clopidogrel in acute coronary syndrome in Taiwan: A multicenter retrospective pilot study

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Abstract

Background: The efficacy and safety of ticagrelor compared with clopidogrel in acute coronary syndrome has not previously been evaluated in an Eastern Asian population, which is recognized to have a different response to $P2Y_{12}$ antagonists compared with the Caucasian population in real-life situations.

Methods: A multicenter retrospective pilot study was performed to evaluate 928 consecutive patients with acute coronary syndrome, receiving aspirin and one $P2Y_{12}$ antagonist (324 ticagrelor or 604 clopidogrel). Using propensity score matching, 448 patients were selected and divided into two equal groups. Kaplan−Meier analysis was used to study patient survival and event-free status using the log-rank test. Independent covariates were identified using univariate in a multivariate Cox proportional hazard model.

Results: In the overall cohort, significant differences were observed for certain variables between the two groups. During the mean 164.3 (±116.4)-day follow-up in the overall cohort, ticagrelor treatment had no significant effect on the primary efficacy endpoint (myocardial infarction, stroke, or vascular death); however, in the matched cohort, ticagrelor showed a lower incidence of primary endpoint (hazard ratio: 0.56; 95% confidence interval: 0.30−1.04; $p = 0.07$) and stroke (hazard ratio: 0.15; 95% confidence interval: 0.02−1.24; $p = 0.08$) with marginal statistical significance, and a similar bleeding rate. The protective effect of ticagrelor treatment was consistent for all subgroups. More patients treated with ticagrelor experienced dyspnea (21.0% vs. 11.6%, $p = 0.007$), and $P2Y_{12}$ antagonist treatment was consequently discontinued.

Conclusion: Ticagrelor treatment could provide a marginally favorable effect at the expense of an increased risk of dyspnea in real-life situations. This pilot study provides a scientific basis to call for a larger, suitably powered Phase 4 prospective or observational study in this ethnic population.

Keywords: acute coronary syndrome; antiplatelet therapy; clopidogrel; outcomes; ticagrelor

Conflicts of interest: I.-C.C., C.-H.L., and C.-C.F. have been on the speakers' bureau for AstraZeneca and Sanofi. T.-H.C. has been on the speakers' bureau for AstraZeneca and Sanofi, and ever received travel expenses and others, which are unrelated to research, to attend Annual Scientific Meetings of the European Society of Cardiology from AstraZeneca and Sanofi. Y.-H.L. has been on the speakers' bureau for AstraZeneca and Sanofi and ever received travel expenses and others, which are unrelated to research, to attend Annual Scientific Meetings of the American College of Cardiology from AstraZeneca. The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Dual antiplatelet therapy with aspirin and clopidogrel is used in patients with acute coronary syndrome (ACS), owing in part to an increased incidence of thrombogenesis. This therapy has been proved to be beneficial both with and without percutaneous coronary intervention (PCI),[1–3] and is endorsed by numerous clinical management guidelines.[4–9] However, clinical application of clopidogrel is hampered by its pharmacodynamic characteristics because its biotransformation into active metabolites results in a slow onset of action, and a variable response[10,11] with a potentially increased risk of stent thrombosis and myocardial infarction (MI).[12] The argument that clopidogrel treatment in Asian patients may not be as effective as that in Caucasian patients is ongoing, based on the observation that the frequency of the cytochrome P450 2C19 loss-of-function allele accompanied by high platelet reactivity is more prevalent in the Asian population.[13]

Ticagrelor, a novel oral $P2Y_{12}$ antagonist that does not undergo biotransformation to active metabolites, has many favorable pharmacodynamic characteristics, including rapid onset of action and being reversible, and consistent inhibition of platelet function.[14,15] In the Platelet Inhibition and Patient Outcomes (PLATO) study, compared with the treatment with a therapeutic dose of 75 mg/d clopidogrel, treatment with 90 mg ticagrelor twice daily significantly reduced the rate of death from vascular causes, MI, and stroke without increasing the overall major bleeding, but with an increase in non-procedure-related bleeding in ACS patients with or without ST-segment elevation.[15] Therefore, certain clinical management guidelines recommend ticagrelor over clopidogrel for $P2Y_{12}$ inhibition in patients with ACS.[5,7–9]

Recently, the possibility of a paradox with regard to antiplatelet treatment in the East Asian population has been reported.[16,17] Some studies have shown a higher prevalence of on-treatment platelet reactivity, but with a similar thrombotic event rate after PCI in East Asian patients compared with Caucasian patients.[16,17] In contrast to ischemic events, the risk of serious bleeding in the East Asian population appears to be greater than that in the Caucasian population.[16,17] Therefore, the superior efficacy and acceptable safety profile of ticagrelor to that of clopidogrel, as demonstrated in the PLATO trial, may not be reproducible in an East Asian population, particularly a Chinese population. A recently published study that enrolled 801 East Asian individuals (90% of whom were Japanese) showed that the incidence of composite primary endpoints and PLATO-defined major bleeding tended to be higher in ACS patients treated with ticagrelor than in those treated with clopidogrel.[18] Based on clinical experience and evidence with anticoagulants, the expected responses of Japanese and Chinese patients to antithrombotic treatments may not be similar.[19,20] To the best of our knowledge, no previous studies have investigated the efficacy and safety of ticagrelor compared with clopidogrel in an Asian population in real-life situations. Therefore, the present Efficacy and Safety of Ticagrelor versus Clopidogrel in Acute Coronary Syndrome in Taiwanese (ESTATE) study aimed to determine whether ticagrelor is superior to clopidogrel for the prevention of vascular events and death in Taiwanese patients with ACS.

2. Methods

2.1. Study population

Eligible patients were consecutively enrolled in this multicenter, retrospective study. The study protocol did not require informed consent and was approved by the Institutional Review Board of the National Cheng Kung University Hospital, Tainan, Taiwan (identifier: NCKUH B-ER-104-112) and Tainan Municipal Hospital, Tainan, Taiwan (identifier: SCMH 1040801). In order to make a parallel comparison of ticagrelor versus clopidogrel during the same study period, we screened eligible patients from July 2013 in the Tainan Municipal Hospital and from June 2014 in the National Cheng Kung University Hospital until February 2015. Ticagrelor had been listed and available in both of these hospitals since the given dates. The eligible patients were selected according to the following screening criteria: (1) selection of patients with discharge codes 410.xx and 411.xx, using ICD-9 version; (2) limiting the patient population to those with primary or secondary discharge diagnosis of ACS, including acute ST-segment-elevation MI (STEMI), non-ST-segment-elevation MI (NSTEMI), unstable angina, and undifferentiated ACS (including undetermined MI, apical ballooning syndrome, coronary spasm with elevated cardiac-specific enzymes, and typical ST-segment deviation in electrocardiography); (3) including only those patients who were taking ticagrelor or clopidogrel on or before discharge; and (4) limiting the number of patients hospitalized via the emergency department with an initial manifestation of ACS, symptom onset <24 hours, and duration of symptoms ≥ 10 minutes at rest. Patients were categorized into two groups based on drug administration at admission: ticagrelor ($n = 324$) and clopidogrel ($n = 604$). The clinical and endpoint data were collected and recorded by a medical chart review if patients were regularly followed up in our hospital; however, telephone calls or direct contact with the participants or their families was made for patients without regular medical follow-up. However, the authors received the data in an anonymous manner with no direct reference to medical charts and no direct contact with participants or their families.

2.2. Outcome measurement

The minimum follow-up period was 1 month and the maximum 1 year. We performed a prespecified analysis of the primary PLATO composite efficacy endpoints (death from vascular causes, MI, or stroke).[21] Secondary endpoints included individual occurrence of components of the primary PLATO efficacy endpoints. Additional efficacy endpoints included stent thrombosis, among others.

The primary ESTATE composite safety endpoint was timed to the first PLATO-defined and PLATO-adjudicated major bleeding event.[21] Occurrences of major, minor, and minimal