Clopidogrel versus ticagrelor in East Asian patients aged 75 years or older with acute coronary syndrome: observations from the GF-APT registry

Ziwei Xi1*, Zifeng Qiu2*, Jianan Li3, Hong Qiu1, Tingting Guo4, Yong Wang1, Jianfeng Zheng1, Yanan Gao1, & Runlin Gao1

1Department of Cardiology, Coronary Artery Disease Center, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, HE, China, 2Peking University Health Science Center, Beijing, HE, China, 3Department of Cardiology and Macrovascular Disease, Beijing Tiantan Hospital, Capital Medical University, Beijing, HE, China, and 4Thrombosis Center, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, HE, China

Abstract
The benefits of potent antithrombotic therapy usually come at the expense of a higher risk of bleeding. The efficacy and safety of ticagrelor in elderly East Asian populations remains debated due to the concerns about the imbalance of ischemic and bleeding risks. This study aimed to compare the impact of clopidogrel with ticagrelor on clinical outcomes in East Asian patients aged ≥75 years with acute coronary syndrome (ACS) using data from an institutional registry. We assessed the treatment effect of ticagrelor versus clopidogrel based on propensity scores and multivariate Cox proportional hazards models. A total of 2775 ACS patients were included, of which 235 (8.5%) were treated with ticagrelor. The primary efficacy outcome occurred in 11.9% of patients treated with ticagrelor versus 8.8% treated with clopidogrel. There was no significant association between treatment with ticagrelor and a lower risk of the primary efficacy outcome (p = .156). However, the incidences of all-cause death (hazard ratio [HR] 1.69, 95% confidence interval [CI] 1.02 to 2.79) and major bleeding (adjusted HR 2.20, 95% CI 1.06 to 4.56) were significantly higher in patients treated with ticagrelor than clopidogrel. In elderly patients with ACS from East Asia, the efficacy of clopidogrel was comparable to ticagrelor, while ticagrelor is associated with an increased risk of mortality and major bleeding.

Plain Language Summary
What is the context?
- Current guidelines recommend ticagrelor over clopidogrel for patients with acute coronary syndrome (ACS).
- There are no specific guidelines concerning the elderly, and data on optimal antiplatelet therapy in elderly are quite scarce.
- Further study was necessary to identify the efficacy and safety of ticagrelor and clopidogrel in elderly patients from East Asian populations which are reported to be at a higher risk of bleeding.

What is new?
- The risk of major adverse cardiac events did not differ significantly between clopidogrel versus ticagrelor in patients aged ≥75 years from East Asia, while the use of ticagrelor might be associated with increased risk of mortality and major bleeding events.
- Analyses after propensity score matching showed consistent results on the safety and efficacy of clopidogrel versus ticagrelor.
- The benefit of potent P2Y12 inhibitor ticagrelor over clopidogrel is questionable in elderly East Asian patients with ACS.

Keywords
Acute coronary syndrome, antiplatelet therapy, clopidogrel, East Asian, elderly, ticagrelor

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*Both Ziwei Xi and Zifeng Qiu contributed to the article equally.

Correspondence: Hong Qiu, Department of Cardiology, Coronary artery disease center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 North Lishi Road, Xicheng District, Beijing, HE 100000, China. Telephone: 0016-13261179000. E-mail: qiu6780@sina.com
What is the impact?

- This study provides more information on the use of potent antiplatelet therapy in older patients from Asia. The individual assessment of ischemic and bleeding risk is necessary to guide decision-making on DAPT rather than applying the recommendations of guidelines directly.

Introduction

Dual antiplatelet therapy (DAPT) with a P2Y₁₂ receptor inhibitor and aspirin has been established as the standard of care for patients with acute coronary syndromes (ACS) [1,2]. Current guidelines recommend the use of ticagrelor which can provide more prompt, potent, and consistent platelet inhibition than clopidogrel in patients with ACS. This recommendation is primarily based on the results of the Platelet Inhibition and Patient Outcomes (PLATO) study, which showed the superiority of ticagrelor over clopidogrel in preventing adverse cardiovascular events compared to clopidogrel [3]. However, patients treated in everyday clinical practice might differ from highly selective cohorts in randomized trials in some ways, such as higher proportion of elderly patients and higher burden of comorbidities. Further, several observational studies conducted in a “real-world” setting have generated conflicting results [4–6].

A considerable amount of literature has described the association between advanced age and poor prognosis of ACS [7,8]. In routine practice, elderly patients with ACS are common and account for more than one-third of patients presenting with myocardial infarction. The elderly considered to have much higher risk of both ischemic and bleeding events than younger patients [9,10]. The benefit of potent antiplatelet therapy comes at the expense of an increase in bleeding risk [11,12], making the optimal choice of antithrombotic therapy for the elderly population challenging. There is no specific guideline for elderly patients and studies concerning the impact of the potent P2Y₁₂ inhibitors in older patients are limited.

Increased bleeding risk remains an important concern for elderly patients treated with DAPT, especially in East Asian patients who are reported to have a significantly higher risk of severe bleeding risk compared with Western patients [13]. Several studies conducted in Asian populations failed to confirm the superior efficacy of ticagrelor as observed in the PLATO study [14–17]. Whether the trade-off between decreased risk of ischemic events and increased risk of bleeding events could improve clinical outcomes is therefore uncertain for East Asian patients.

The fact that elderly and Asian patients are both obviously underrepresented in clinical trials including the PLATO study limits the direct extrapolation of the trial findings into clinical practice for elderly East Asian patients with ACS [3]. Some studies from Asian regions have indicated that the advice of European and American guidelines should be applied with caution in this specific population [18,19]. We hypothesized that ticagrelor had consistently significant benefit compared with clopidogrel among elderly ACS patients. The present study aimed to test our hypothesis by assessing the efficacy and safety of clopidogrel versus ticagrelor in elderly East Asian patients with ACS and provided more evidence on DAPT regimens for the elderly in a real-world setting.

Methods

Study population

The present study is a retrospective analysis using data from the efficacy and safety of Genetic and platelet Function testing for guiding AntiPlatelet Therapy after percutaneous coronary intervention (GF-APT) registry (ChiCTR2100047090). The GF-APT is a single-center registry that retrospectively enrolled a total of 41,090 consecutive patients admitted to Fuwai Hospital since January 2016 to December 2018 with symptoms suggestive of coronary artery disease and treated with percutaneous coronary intervention (PCI) during the index hospitalization. For patients with multiple hospital stays for PCI, only the first admission was included. Data on de-identified demographics, medical history, laboratory parameters at admission, angiographic features, procedural characteristics, in-hospital therapies, complications, and medication at discharge were collected from electronic medical records for all enrolled patients. There was no treatment intervention directed by the protocol in the registry. All patients enrolled in the registry were followed up for 1 year. Follow-up was performed by clinic visits or telephone interviews using standardized questionnaires at 1, 6 and 12 months after the index procedure. Adverse events were identified using physician-reported diagnosis.

Among patients included in this registry, patients aged ≥75 years and presenting with ACS at admission were eligible to constitute the present study population. Acute coronary syndrome was defined according to the diagnostic criteria established by the European Society of Cardiology [20,21]. We excluded patients who had any contraindication to the use of the P2Y₁₂ receptor and patients of whom the life expectancy of <1 year.

This study was approved by the ethics committee of Fuwai Hospital (No. 2021–1603) and done in accordance with the principles of the Declaration of Helsinki. The informed consent from each study participant was waived because of the observational and retrospective nature of the study.

Outcomes and definition

The primary efficacy outcome was a composite of major adverse cardiac events (MACEs) during follow-up, including all-cause death, myocardial infarction (MI), and repeat target vessel revascularization. We also assessed the net clinical benefit comprising MACEs plus major bleeding events within 12 months after the index PCI. Myocardial infarction was identified according to the Third Universal Definition of Myocardial Infarction [22]. All deaths caused by cardiac disease or the cause of which could not be determined by physician would be classified as cardiac deaths.

The safety outcome was major bleeding event, defined as Bleeding Academic Research Consortium criteria type 3 or a fatal bleeding event [23]. The secondary safety outcome was clinically significant bleeding which was a composite of major and minor bleeding events. The major criteria of major bleeding were the following: overt bleeding plus a hemoglobin decrease ≥ 3 g/dL, any transfusion with overt bleeding, cardiac tamponade, bleeding requiring surgical intervention for control, bleeding requiring intravenous vasoactive agents, intracranial hemorrhage, intraocular bleeding that compromised vision, or fatal bleeding. Minor bleeding events included any bleeding event that required medical intervention by a health-care professional but did not meet the criteria for major bleeding.

Statistical analysis

The patients were divided into a clopidogrel group and a ticagrelor group in accordance with the P2Y₁₂ receptor inhibitor administered after PCI. We performed an intention-to-treat
analysis and the patients who switched between ticagrelor and clopidogrel remained in the group in line with the initial choice of P2Y<sub>12</sub> receptor inhibitor. Descriptive analyses of patients’ baseline characteristics were conducted for the clopidogrel and ticagrelor groups. Continuous variables were presented as mean ± standard deviation or median (interquartile range [IQR]) based on their distributions. Categorical variables were presented as numbers (percentages). Continuous variables were compared with Student’s t-test or the Mann-Whitney U test and categorical variables with the chi-square test or Fisher exact.

The cumulative incidence of clinical outcomes was described using the Kaplan–Meier method and compared using the log-rank test. The adjusted hazard ratio (HR) and 95% confidence intervals (CIs) were calculated by Cox proportional hazard models to assess the association between DAPT regimens and clinical outcomes. The multivariable analyses included the following covariates to adjust for non-randomized selection of treatment: ticagrelor treatment, age, sex, body mass index, atrial fibrillation, cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, and ever-smoking), prior MI, prior PCI, prior ischemic stroke, renal insufficiency, type of ACS at admission and variables, which had statistical significance (p < .1) in the univariable analyses. The P values for interactions based on the joint test in the Cox regression models were used, in order to test the homogeneity of treatment effects of clopidogrel versus ticagrelor across subgroups defined by baseline participant characteristics.

An additional sensitivity analysis was performed using the propensity score matching (PSM) to adjust for baseline differences and potential confounders between the ticagrelor and clopidogrel groups due to unrandomized treatment decisions. A propensity score was calculated for each patient to estimate the probability of receiving clopidogrel versus ticagrelor by means of a non-parsimonious multivariate logistic regression. The logistic regression model was constructed by previously reported risk factors for adverse outcomes of ACS, including clinical variables and procedural data that might lead to biased estimates of outcomes, as well as covariates that obtained p values < .1 in the univariate analysis. The clinical outcomes of the two matched groups were then compared using the Cox proportional hazard regression to investigate the efficacy and safety of clopidogrel versus ticagrelor in the propensity score-matched cohort.

All tests were two-tailed and a p value < .05 was considered statistically significant. All calculations were performed with IBM SPSS Statistics version 25 (SPSS, Chicago, IL).

**Results**

**Study population and patient characteristics**

The study population consisted of 2,775 patients aged 75 years or older, of whom 91.5% (n = 2,540) were prescribed clopidogrel and 8.5% (n = 235) with ticagrelor. Figure 1 displayed a detailed flow chart for the present study. The overall clopidogrel prescription at discharge decreased significantly from 93.0% to 90.2% (p = .029) during 2016 to 2018. The temporal trends in clopidogrel use stratified by indication were shown in Figure 2. A total of 82 (3.0%) patients switched between clopidogrel and ticagrelor during 1-year follow-up, of which 69 patients were in the clopidogrel group and 13 in the ticagrelor group.

The baseline characteristics of the two treatment groups are presented in Table I. Patients prescribed ticagrelor were younger (78.7 years vs. 78.0 years, p < .001) and more frequently presented with STEMI (11.7% vs. 22.6%, p < .001). The proportion of patients with left main disease was considerably higher (13.3% vs. 20.9%, p = .002) and chronic total occlusion was more common (23.2% vs. 30.6%, p = .011) in the ticagrelor group compared with the clopidogrel group. Patients treated with ticagrelor had greater total stent length and more stents implanted than clopidogrel.

**Comparison of efficacy and safety outcomes**

The efficacy and safety outcomes of patients treated with clopidogrel versus ticagrelor from the overall cohort were summarized in Table II. The cumulative rate of the combined primary outcome of all-cause death, MI and repeat target vessel revascularization over 1-year follow-up was 8.8% vs. 11.9% in the clopidogrel and ticagrelor group, respectively. The net clinical benefit outcomes occurred in 9.6% of clopidogrel-treated patients and 12.3% of ticagrelor-treated patients. Figure 3 displays the Kaplan–Meier curves for MACEs, individual efficacy outcomes and net clinical benefit outcomes. The risk of MACEs (adjusted HR 1.33, 95% CI 0.90 to 1.99, p = .156) or net clinical benefit outcomes (adjusted HR 1.24, 95% CI 0.84 to 1.83, p = .281) did not differ significantly between the clopidogrel and ticagrelor groups after adjustment. With regard to each component of MACEs, ticagrelor was associated with an increased risk of all-cause mortality as compared with clopidogrel in the multivariable analyses (adjusted HR 1.69, 95% CI 1.02 to 2.79, p = .040).

![Figure 1. Study flow chart.](image-url)
Accordingly, a non-statistically significant numerical increase in the risk of cardiac death (adjusted HR 1.75, 95% CI 0.91 to 3.37, p = .095) was found in patients treated with ticagrelor. There were no statistically significant differences in occurrences of MI and repeat target vessel revascularization (TVR) between patients receiving ticagrelor and clopidogrel (MI: adjusted HR 1.36, 95% CI 0.70 to 2.64, p = .361; repeat TVR: adjusted HR 0.81, 95% CI 0.33 to 2.03, p = .655).

Although the rates of MACEs varied according to baseline characteristics including sex, body mass index, renal function, left ventricular ejection fraction, disease history, and lesion characteristics, the effects of clopidogrel versus ticagrelor on MACEs were mostly comparable across participant subgroups, as presented in Figure 4. We observed nominally significant interaction in patients with versus without chronic total occlusion disease (p for interaction = .045), which suggested that the treatment with ticagrelor was associated with a higher risk of MACEs (adjusted HR 2.03, 95% CI 1.16 to 3.55, p = .013) as compared with clopidogrel among patients with chronic total occlusion disease but not among patients without chronic total occlusion disease. With respect to safety outcomes, patients treated with ticagrelor had a higher risk of major bleeding event compared to clopidogrel.
Table II. Clinical outcomes at 1 year of patients treated with clopidogrel versus ticagrelor.

|                                | All patients (n = 2775) | Clopidogrel (n = 2540) | Ticagrelor (n = 235) | Adjusted HR (95% CI) | P value |
|--------------------------------|-------------------------|------------------------|----------------------|----------------------|---------|
| MACEs                          | 251 (9.0)               | 223 (8.8)              | 28 (11.9)            | 1.33 (0.90–1.99)     | .156    |
| All-cause death                | 137 (4.9)               | 119 (4.7)              | 18 (7.7)             | 1.69 (1.02–2.79)     | .04     |
| Cardiac death                  | 75 (2.7)                | 64 (2.5)               | 11 (4.7)             | 1.75 (0.91–3.37)     | .095    |
| Myocardial infarction          | 97 (3.5)                | 87 (3.4)               | 10 (4.3)             | 1.36 (0.70–2.64)     | .361    |
| Repeat TVR                     | 73 (2.6)                | 68 (2.7)               | 5 (2.1)              | 0.81 (0.33–2.03)     | .655    |
| Any repeat revascularization   | 190 (6.8)               | 172 (6.8)              | 18 (7.7)             | 1.03 (0.63–1.69)     | .893    |
| Major bleeding                 | 52 (1.9)                | 43 (1.7)               | 9 (3.8)              | 2.20 (1.06–4.56)     | .035    |
| Minor bleeding                 | 110 (4.0)               | 89 (3.5)               | 21 (8.9)             | 2.70 (1.67–4.38)     | <.001   |
| Net clinical benefit outcome   | 274 (9.9)               | 245 (9.6)              | 29 (12.3)            | 1.24 (0.84–1.83)     | .281    |

HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiac event; TVR, target vessel revascularization.

Figure 3. Incidence curves for outcomes at 1 year of patients treated with clopidogrel versus ticagrelor. Kaplan–Meier curves of patients stratified according to P2Y12 inhibitors for outcomes including (a) major adverse cardiac events, (b) all-cause death, (c) net clinical benefit outcomes, (d) and major bleeding events.

(adjusted HR 2.20, 95% CI 1.06 to 4.56, p = .035), which was mainly driven by an increase in gastrointestinal hemorrhage and cerebral hemorrhage (1.1% vs. 3.0%). The incidence of minor bleeding was also significantly higher in the ticagrelor group than in the clopidogrel group (adjusted HR 2.70, 95% CI 1.67 to 4.38, p < .001).

Comparison of outcomes in propensity score-matched cohort

After propensity score matching, 470 patients were successfully matched at a 1:1 ratio. Baseline clinical characteristics were well balanced between the ticagrelor group and the clopidogrel group, as shown in Table S1 in the Supplementary Materials. No significant differences in procedural characteristics were found between the two groups, except that ticagrelor-treated patients had a greater total stent length.

In the propensity score-matched cohort, the multivariate Cox proportional hazards models revealed that ticagrelor-treated patients were at a numerically but not statistically higher risk of MACEs (adjusted HR 1.62, 95% CI 0.87 to 3.02, p = .127) than clopidogrel-treated patients, corresponding to a numerically increase in net
clinical benefit outcomes (adjusted HR 1.71, 95% CI 0.93 to 3.17, \( p = .087 \)). In accordance with the results before propensity score matching, a significant increase in all-cause mortality was also observed in the ticagrelor group (adjusted HR 2.46, 95% CI 1.00 to 6.05, \( p = .049 \)) in adjusted analyses after propensity score matching. In terms of safety outcomes, ticagrelor remained significantly associated with an increased risk of minor bleeding (adjusted HR 2.14, 95% CI 1.01 to 4.53, \( p = .048 \)), while the risk of major bleeding tended to be numerically higher in the ticagrelor group (2.6% vs. 3.8%) but the low numbers of events limit meaningful conclusions (\( p = .425 \)). The incidences of clinical outcomes during follow-up of the propensity score-matched cohort were summarized in Table S2 in the Supplementary Materials. The Kaplan–Meier curves for MACEs, individual efficacy outcomes and net clinical benefit outcomes of the propensity score-matched cohort were displayed in Figure S1 in the Supplementary Materials.

**Discussion**

In the present analysis of 2775 patients aged ≥75 years from an institutional registry, we investigated the impact of clopidogrel versus ticagrelor on clinical outcomes after ACS. The results demonstrated that the risk of major adverse cardiac events did not differ significantly between the two treatments, while the overall net clinical benefit was consistently similar. Further, the use of ticagrelor was associated with increased

| Subgroup                      | No. of patients | Ticagrelor n/N | Clopidogrel n/N | HR (95% CI)       | P for interaction |
|-------------------------------|-----------------|----------------|----------------|-------------------|-------------------|
| Overall                       | 2775            | 28/235         | 223/2540       | 1.33 (0.90–1.99)  | 0.661             |
| Sex                           |                 |                |                |                   |                   |
| Female                        | 1121            | 9/97           | 82/1024        | 1.18 (0.58–2.39)  |                   |
| Male                          | 1654            | 19/138         | 141/1516       | 1.44 (0.89–2.34)  |                   |
| Body mass index, kg/m2        |                 |                |                |                   | 0.998             |
| >30                           | 139             | 1/11           | 10/128         | 1.46 (0.16–13.67) |                   |
| <30                           | 2636            | 27/224         | 213/2412       | 1.32 (0.68–1.97)  |                   |
| Baseline eGFR, ml/min/1.73 m2  |                 |                |                |                   | 0.733             |
| <60                           | 814             | 7/69           | 67/745         | 1.03 (0.46–2.28)  |                   |
| >=60                          | 1961            | 21/166         | 156/1795       | 1.45 (0.92–2.30)  |                   |
| LVEF, %                       |                 |                |                |                   | 0.884             |
| <50                           | 205             | 5/26           | 29/179         | 1.48 (0.55–3.98)  |                   |
| >=50                          | 2570            | 23/209         | 194/2361       | 1.28 (0.63–1.98)  |                   |
| Prior MI                      |                 |                |                |                   | 0.126             |
| Yes                           | 547             | 10/50          | 52/497         | 1.92 (0.95–3.87)  |                   |
| No                            | 2228            | 18/185         | 171/2043       | 1.08 (0.66–1.76)  |                   |
| Prior PCI                     |                 |                |                |                   | 0.986             |
| Yes                           | 602             | 7/59           | 56/543         | 1.21 (0.54–2.72)  |                   |
| No                            | 2173            | 21/176         | 167/1997       | 1.37 (0.86–2.16)  |                   |
| Diagnosis at admission        |                 |                |                |                   | 0.863             |
| Unstable angina               | 2118            | 16/161         | 152/1957       | 1.24 (0.74–2.09)  |                   |
| NSTEMI                         | 307             | 5/21           | 34/286         | 1.65 (0.58–4.70)  |                   |
| STEMI                          | 350             | 7/53           | 37/297         | 1.15 (0.50–2.63)  |                   |
| Multiple–vessel disease       |                 |                |                |                   | 0.641             |
| Yes                           | 1444            | 18/121         | 159/1323       | 1.25 (0.76–2.05)  |                   |
| No                            | 1331            | 10/114         | 64/1217        | 1.51 (0.76–2.99)  |                   |
| Left main disease             |                 |                |                |                   | 0.089             |
| Yes                           | 388             | 11/49          | 38/339         | 1.60 (0.80–3.19)  |                   |
| No                            | 2367            | 17/186         | 185/2201       | 1.06 (0.64–1.74)  |                   |
| Chronic total occlusion disease|               |                |                |                   | 0.045             |
| Yes                           | 662             | 16/72          | 59/590         | 2.03 (1.16–3.55)  |                   |
| No                            | 2113            | 12/153         | 154/1950       | 0.67 (0.48–1.56)  |                   |

Figure 4. Effects of ticagrelor and clopidogrel on major adverse cardiac events in subgroups defined by demographic and disease characteristics. eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.
risk of mortality and major bleeding events in elderly patients with ACS as compared to clopidogrel. Our findings indicate that the benefit of potent P2Y₁₂ inhibitor ticagrelor over clopidogrel is questionable in elderly East Asian patients with ACS and an individual assessment of ischemic and bleeding risk is necessary to guide decision-making on DAPT.

Current evidence on DAPT for elderly

Our results are in agreement with an observational analysis of all patients ≥80 years from the SWEDHEART Registry which suggested that ticagrelor use among elderly patients with MI might be associated with increased risk of death and bleeding, although the risk of stroke and MI alone was lower [24]. Similarly, the open-label, randomized controlled POPular AGE trial also found that clopidogrel is a favorable alternative to ticagrelor in older patients with non-ST elevation ACS considering that it results in a significantly lower bleeding rate without an increase in thrombotic events [25].

Our findings on the comparable ischemic risk and the increased bleeding risk in ticagrelor-treated elderly patients are, however, in contrast to the results of the prespecified subgroup analysis of the PLATO trial [26]. In the substudy, the clinical benefit of ticagrelor in ACS did not depend on age at all and the absolute reduction in all-cause mortality was even numerically greater in elderly. Moreover, a study with data from an all-comers STEMI registry has confirmed that ticagrelor was associated with a reduction in major adverse events but not an increase in bleeding events compared with clopidogrel in real-world cohort of elderly patients with STEMI [27]. While the multivariate analyses after propensity score matching and from different patient subgroups got similar results, the potential bias due to the non-randomized design of our study should be noted. Although we have included and addressed the important confounding factors on which there was adequate information available, the possibility of residual and unmeasurable bias could not be completely eliminated by propensity score matching, subgroup analyses, or additional statistical adjustments.

The discrepancy in efficacy of ticagrelor between our study and previous studies, which provided evidence for superiority of ticagrelor, could be partly explained by increased lesion and procedural complexity in patients prescribed ticagrelor in the overall cohort of our study. Complex lesion characteristics including multiple-vessel disease, left main disease, and chronic total occlusion were more common among ticagrelor-treated elderly patients in our study, while the lesion complexity has been reported to be significantly associated with increased risk of adverse outcomes [28]. Notably, numerically lower rates of myocardial infarction, repeat TVR and any repeat revascularization, albeit not significantly, were noted among patients treated with ticagrelor in the propensity score-matched cohort of our study. In addition, the use of the safer second-generation drug-eluting stents could also be a reason for non-significant benefit of ticagrelor in our study while bare-metal stents and first-generation drug-eluting stents were used in the PLATO trial [3]. As for bleeding events, it is noteworthy that the absolute increase in major bleeding events with ticagrelor versus clopidogrel was numerically greater in elderly versus younger patients in the substudy from the PLATO trial, with which our study was somewhat in good accordance [26].

Dilemma of antithrombotic therapy for the elderly

Our study focused on older patients who were frequently under-represented in clinical trials, which limits the application of findings from clinical trials to older patients. Due to the progressive aging of the population, the group of elderly ACS patients has continued to grow over the past decades. In a multicenter registry from European countries, patients over 65 years old represented about 45% of the ACS population [29]. Most current clinical guidelines are on the basis of relevant clinical trials of patients with mean age of around 65 years and most recommendations are not age-specific [1,2]. Despite the benefits of potent P2Y₁₂ inhibitors, their efficacy in elderly population is consequently uncertain. For instance, the preference for potent P2Y₁₂ inhibitors over clopidogrel in current guidelines for ACS was supported by the results from the PLATO and TRITON TIMI 38 trials, in which older adults ≥75 years only constituted 13% and 15% of the study population, respectively [3,30]. Therefore, there are still gaps in the evidence that pertain to the use of more potent P2Y₁₂ inhibitors in older population.

Increasing age has been identified as a risk factor in many stratification models of both ischemic and bleeding risk [31–33]. Older patients have been proved to be a vulnerable population with high mortality by numerous studies. According to the Global Registry of Acute Coronary Events (GRACE) score which was developed for risk stratification in patients with ACS, an ACS patient aged 80 years has a 3-fold higher risk of mortality as compared to a patient aged 60 years [33]. On the other hand, older patients are also at a substantially increased risk of major bleeding, which is strongly associated with mortality risk and makes it difficult to identify the optimal antithrombotic treatment.

Poor outcomes of elderly after suffering an ACS can be partly explained by increased prevalence and exposure time of other cardiovascular risk factors, as well as the age-related changes in structure and function of the cardiovascular system. Additionally, the elderly is more likely to receive conservative treatment rather than standard first-line therapy recommended by guidelines because of concerns about high risk of treatment-related complications [34,35]. Thus, it is reasonable to assume that the trade-off between the benefits and risks of potent DAPT comprising ticagrelor or prasugrel in elderly patients might differ from those observed in the selected patient cohorts of clinical trials, and needs to be further evaluated by studies that specifically examining the effects of aggressive antithrombotic strategy in elderly population.

Differential response to antithrombotic agents in the East Asians

The results of the present study were similar to several studies from China and other East Asian regions, which indicated that treatment with clopidogrel or ticagrelor had similar efficacy in preventing major vascular thrombotic outcomes at 12 months and ticagrelor consistently caused significantly more major bleeding [5,17]. In fact, whether the superiority of ticagrelor over clopidogrel in ACS patients varies according to geography or ethnicity is controversial yet and the results of previous studies are inconsistent [17,18,36]. Given that Asian population appears to be more resistant to thromboembolic events but have a greater propensity for major bleeding compared with Caucasian population [37], numerous studies challenged the applicability of recommendations from universal guidelines on ticagrelor over clopidogrel to East Asians [38]. A growing body of evidence demonstrated that the unique ischemia and bleeding risk profiles in East Asian population should be taken into consideration when tailoring antithrombotic therapy. Our study was conducted in an elderly East Asian cohort of ACS and provided an important insight into the efficacy and safety of newer-generation P2Y₁₂ inhibitors in this specific population. The results underline the importance of further validation for findings from randomized clinical trials in the elderly East Asian population.
There are several limitations worth mentioning in the present study. First, this is a retrospective analysis of data from an institutional registry and the selection of P2Y12 inhibitors between ticagrelor and clopidogrel was not randomized. Although we performed propensity score matching, subgroup analyses and multivariate analyses to lessen potential confounding effects, there still might be residual confounding inherent in the observational study design and our results need to be interpreted with caution. Hence, there remains a need for dedicated randomized trials on the efficacy of potent DAPT in elderly. Although nearly all patients included in our study were Chinese, our findings from the presents were consistent to a certain extent with previous studies from other East Asian regions [14,17]. Second, the follow-up period was relatively short in our study. However, DAPT is generally prescribed for 6 to 12 months to patients undergoing PCI and the difference in treatment effect of ticagrelor and clopidogrel is supposed to be apparent within the first 30 days of therapy. Thus, the 1-year follow-up period is acceptable in our analysis and a prolonged follow-up period might not have significant impact on our results. Third, intention to treat analyses were performed to examine the treatment effect of different P2Y12 inhibitors, whereas it should be noted that patients who switched between the two drugs might result in potential bias. Fourth, only 235 (8.5%) patients were treated with ticagrelor in our cohort and the study might be not powered to show significant differences due to the limited sample size of the ticagrelor group. Clopidogrel use is currently more common compared with ticagrelor use in East Asian countries due to the drug prices and concerns around bleeding risk, especially in patients at advanced age. While significant decrease in the use of guideline recommended therapies with increasing age, the enrollment of elderly patients treated with potent P2Y12 inhibitors was relatively difficult. Future study targeted at this population with more sufficient power is still required.

Conclusions

In conclusion, our study suggested that in elderly East Asian patients undergoing PCI for ACS, clopidogrel, and ticagrelor had comparable treatment effects in preventing ischemic events, while ticagrelor was associated with an increased risk of mortality. Moreover, elderly patients treated with clopidogrel after ACS had lower risk of bleeding events. An individualized antiplatelet therapy based on ischemic versus bleeding risk assessment are necessary in this population. Further studies are mandatory to confirm our findings and examine the adaptation of current recommendation on potent P2Y12 inhibitors among elderly Asian patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author Hong Qiu (Email: qiu-hong6780@sina.com) on reasonable request.

Ethics approval and consent to participate

This study has been approved by the ethics committee of Fuyui Hospital (No. 2021-1063). The informed consent from participants was waived by the Ethics Committee.

Supplementary material

Supplemental data for this article can be accessed online at https://doi.org/10.1080/09557104.2022.2118250

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