Efficacy and safety of potent P2Y12 inhibitors vs. clopidogrel in elderly patients with acute coronary syndrome

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To the Editor: Current guidelines recommended that patients with acute coronary syndrome (ACS) should receive dual anti-platelet therapy of aspirin plus P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) if without contraindication. Up to now, information on the clinical efficacy and safety of potent anti-platelet drugs in the elderly patients with ACS is limited, especially in very older people (age ≥75 years). We searched PubMed, the Cochrane library, Web of Science, EMBASE (Excerpt Medical Database) from January 2000 to December 2019. Analysis of the data was performed using Stata software, Version 12.0 (StataCorp LP, College Station, TX, USA). The overall polled results were recorded as risk ratios (RRs) and 95% confidence intervals (CIs) with two-sided P values. Finally, seven clinical studies included 8848 patients of potent oral P2Y12-inhibitors versus clopidogrel in elderly patients (age ≥65 years old) with ACS were included in this meta-analysis.1-7 Patients older than 65 years in the included trials were mainly treated with aspirin combined with ticagrelor, and those over 75 years were mainly treated with aspirin plus prasugrel. Five thousand six hundred and forty-eight (63.8%) received aspirin plus prasugrel, and 3839 patients (43.4%) received reduced maintenance dose prasugrel (<10 mg). The seven included studies were all high-quality studies.

All seven included studies discussed the effect of anti-platelet therapy on the incidence of major adverse cardiovascular events (MACEs) in elderly ACS patients. There was no significantly difference between the group treated with potent P2Y12 inhibitors and that with clopidogrel in reducing MACEs, whether it was older than 65 years or 75 years (RR = 0.95, 95% confidence interval [CI] 0.86–1.05) [Table 1]. In the sub-group analysis, there was no significant difference in MACEs between the group treated with the standard-dose potent ticagrelor and that with clopidogrel (RR = 0.81, 95% CI 0.30–1.31, P = 0.026). Reduced-dose prasugrel did not increase the incidence of MACE (RR = 1.02, 95% CI 0.86–1.18, P = 0.921). Data on all-cause mortality was provided in five studies,1,2,4-6 and one was patients older than 65 years. No significant heterogeneity was presented in these studies (P = 0.0215). As expected, aspirin plus potent P2Y12 inhibitors may reduce all-cause mortality, with a RR = 0.82, 95% CI 0.66 to 0.97. Six randomized controlled studies1,2,4-6,7 reported the risk of major bleeding. Patients treated with potent anti-platelet P2Y12 inhibitors (ticagrelor or clopidogrel) showed a strong tendency to increase the risk of major bleeding (RR 1.25, 95% CI 0.99–1.51) compared with those with clopidogrel. In the sub-group analysis, patients received reduced-dose prasugrel did not differ significantly in the bleeding risk from those received clopidogrel (RR 1.23, 95% CI 0.68–1.78, P = 0.422).

The choice of anti-platelet drugs in elderly patients is extremely interesting and requires more effective treatment strategies to reduce thrombotic events without increasing the risk of bleeding complication.8 The principal findings from this meta-analysis, available to date to examine the outcomes of more potent P2Y12 inhibitors vs. clopidogrel in elderly ACS patients, are as follows: (1) Dual anti-platelet therapy with more potent P2Y12 receptor antagonists compared with clopidogrel demonstrated a similar protective ischemic effect determined by MACEs and all-cause mortality in elderly patients presenting with ACS. (2) The dosage of potent P2Y12 inhibitors (both standard and reduced dose) did not affect the protective ischemic effects, compared with that of clopidogrel. (3) Potent P2Y12 inhibitors indeed showed a strong tendency to increase the risk of major bleeding, compared with clopidogrel. In addition, this analysis included the maintenance of different dosage of prasugrel as a subgroup, which showed that the reduced dose of prasugrel...
had no significant difference in the occurrence of MACEs and all-cause mortality in comparison with clopidogrel, but it did have the tendency to reduce the risk of major bleeding. There was no sufficient data to confirm this effect, so it still needs to be further explored. Experts consensus clearly expresses that the patients with high risk of bleeding is cautious with prasugrel, which is also a proof of this meta-analysis. Although the sub-group analysis showed no significant increase in the risk of bleeding at lower maintenance doses, the tendency of overall risk of major bleeding from potent anti-platelet agents was still increased. Therefore, the use of potent anti-platelet drugs in high-risk elderly patients should be cautious.

Certainly, this study has common potential limitations, potent P2Y12 inhibitors refers to two different drugs that may have different biological and clinical effects, and only 17.2% of patients included in the study received ticagrelor. It is necessary to conduct special tests to confirm these results and increase the sample size as appropriate.

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**Conflict of interest**

None.

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**Table 1:** Ischemia and bleeding outcomes from randomization to the end of follow-up in elderly ACS patients (n = 8848).

| Clinical Outcomes | Sub-group | RR (95% CI) | P  |  \( \hat{f} \) (%) |
|-------------------|-----------|-------------|----|-------------------|
| MACE              | ≥ 65 years old | 0.95 (0.86, 1.05) | 0.844 | 0  |
|                   | ≥ 75 years old | 1.38 (0.83, 3.60) | 0.034 | 77.7 |
|                   | Overall      | 0.91 (0.77, 1.06) | 0.109 | 42.3 |
| All-cause mortality | Overall     | 0.82 (0.66, 0.97) | 0.215 | 31.0 |
| Major bleeding    | ≥ 65 years old | 1.21 (0.94, 1.49) | 0.872 | 0  |
|                   | ≥ 75 years old | 1.58 (0.77, 2.39) | 0.597 | 0  |
|                   | Overall      | 1.25 (0.99, 1.51) | 0.890 | 0  |

CIs: Confidence intervals; MACE: Major adverse cardiovascular events; RR: Risk ratio.