**Efficacy and safety of prasugrel and ticagrelor versus clopidogrel in patients with acute coronary syndrome (ACS): a network meta-analysis**

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**Introduction:** Newer P2Y12 inhibitors have greater potency compared with clopidogrel. However, their efficacy and safety in patients with ACS are not well-studied.

**Method:** We searched for randomised controlled trials comparing different P2Y12 inhibitors (clopidogrel, prasugrel and ticagrelor), in combination with aspirin, in ACS patients after percutaneous coronary intervention. The primary outcome was major adverse cardiovascular events (MACE), a composite of cardiovascular death, myocardial infarction and stroke. Secondary outcomes were the components of MACE, all-cause mortality, stent thrombosis, and Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding. Statistical analysis was performed using R. P-scores were generated to indicate the probability of the $P2Y_{12}$ inhibitor having the largest effect size for each outcome.

**Results:** Eleven RCTs with altogether 31795 patients were included. Compared to clopidogrel, both prasugrel and ticagrelor significantly decreased the risk of MACE (OR=0.88, 95% CI=0.79-0.97; OR=0.85, 95% CI=0.76-0.95, respectively), myocardial infarction (OR=0.86, 95% CI=0.76-0.98; OR=0.81, 95% CI=0.70-0.94, respectively), and stent thrombosis (OR=0.52, 95% CI=0.32-0.86; OR=0.62, 95% CI=0.45-0.85, respectively) (Fig.1). Ticagrelor, in addition, significantly reduced cardiovascular mortality (OR=0.83, 95% CI= 0.70-0.99) and all-cause mortality (OR=0.82, 95% CI=0.69-0.96). Neither prasugrel nor ticagrelor significantly increased TIMI major bleeding, but ticagrelor increased TIMI minor bleeding (OR=1.48, 95% CI=1.25-1.76). No significant relationship between $P2Y_{12}$ inhibitors and stroke was found. P-scores ranked ticagrelor the best for reducing MACE, myocardial infarction, cardiovascular and all-cause mortality, whereas having the highest likelihood to increase TIMI minor bleeding. Prasugrel was ranked the best for protecting against stroke and stent thrombosis (Table 1).

**Conclusions:** Compared to clopidogrel, both prasugrel and ticagrelor reduce MACE, myocardial infarction, and stent thrombosis. Ticagrelor also reduces mortality, although at the expense of increased minor bleeding. These results provide the evidence to justify recommending the newer drugs over clopidogrel in ACS patients.

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Table 1. P-scores indicating the likelihood that the P2Y12 inhibitor is the best for the outcome

|  | Clopidogrel | Prasugrel | Ticagrelor |
|---|---|---|---|
| **MACE** | 0.004 | 0.66 | 0.84 |
| **Cardiovascular mortality** | 0.02 | 0.67 | 0.81 |
| **Myocardial infarction** | 0.009 | 0.60 | 0.88 |
| **Stroke** | 0.39 | 0.92 | 0.20 |

| All-cause mortality | 0.05 | 0.54 | 0.91 |
|---|---|---|---|
| **Definite or probable stent thrombosis** | 0.003 | 0.86 | 0.64 |
| **TIMI major bleeding** | 0.57 | 0.48 | 0.45 |
| **TIMI minor bleeding** | 0.97 | 0.45 | 0.08 |

**Figure.1**



| Newer P2Y$_{12}$ inhibitor compared to clopidogrel | Trials (n) | OR (95% CI) |
|---|---|---|
| **MACE** | | |
| Prasugrel | 4 | 0.88 (0.79-0.97) |
| Ticagrelor | 4 | 0.85 (0.76-0.95) |
| **Myocardial infarction** | | |
| Prasugrel | 5 | 0.86 (0.76-0.98) |
| Ticagrelor | 4 | 0.81 (0.70-0.94) |
| **Stent thrombosis** | | |
| Prasugrel | 4 | 0.52 (0.32-0.86) |
| Ticagrelor | 2 | 0.62 (0.45-0.85) |
| **Cardiovascular mortality** | | |
| Prasugrel | 4 | 0.87 (0.75-1.00) |
| Ticagrelor | 4 | 0.83 (0.70-0.99) |
| **All-cause mortality** | | |
| Prasugrel | 5 | 0.91 (0.79-1.04) |
| Ticagrelor | 4 | 0.82 (0.69-0.96) |
| **Major bleeding** | | |
| Prasugrel | 6 | 1.01 (0.76-1.35) |
| Ticagrelor | 4 | 1.01 (0.91-1.13) |

0.5    1    1.5

Favours newer P2Y$_{12}$ inhibitor    Favours clopidogrel