MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 1131-1137
DOI: 10.12659/MSM.893914

Received: 2015.02.20
Accepted: 2015.03.30
Published: 2015.04.20

# Novel Oral P2Y12 Inhibitor Prasugrel *vs.* Clopidogrel in Patients with Acute Coronary Syndrome: Evidence Based on 6 Studies

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Source of support:** Departmental sources

**Background:** Whether prasugrel can take the place of clopidogrel for patients with acute coronary syndrome (ACS) is not clear. The aim of this study was to perform a meta-analysis for systematically reviewing the evidence on prasugrel in comparison to clopidogrel in patients with ACS.

**Material/Methods:** Relevant prospective and retrospective studies were searched in databases. Six studies were finally included. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated to assess all causes of death, myocardial infarction (MI), stroke, major bleeding, major/minor bleeding, and stent thrombosis (for PCI performed).

**Results:** Compared with clopidogrel, prasugrel had similar risks of all cause of death (Pooled RR: 0.83; 95% CI: 0.64–1.06, p=0.14, $I^2$=55%), MI (Pooled RR: 0.86; 95% CI: 0.71–1.04, p=0.12) and stroke (pooled RR: 0.88; 95% CI: 0.70–1.10, p=0.25). However, prasugrel was associated with significantly higher risk of both major bleeding (Pooled RR: 1.19; 95% CI: 0.99–1.44, p=0.06, $I^2$=0%) and the risk of total major and minor bleeding (Pooled RR: 1.30; 95% CI: 1.15–1.48, p<0.0001, $I^2$=0%). For the patients who underwent percutaneous coronary intervention (PCI), prasugrel was associated with significantly lower risk of stent thrombosis (Pooled RR: 0.47; 95% CI: 0.34–0.61, p<0.00001, $I^2$=0%).

**Conclusions:** Prasugrel has similar effects as clopidogrel in terms of all causes of death, MI, and stroke in ACS patients. For the patients who underwent PCI, prasugrel contributes to lower risk of stent thrombosis. However, prasugrel is associated with significantly higher risk of bleeding. For the patients with active pathological bleeding or a history of stroke and/or TIA, prasugrel should not be recommended.

**MeSH Keywords:** Acute Coronary Syndrome • Evidence-Based Medicine • Purinergic P2Y Receptor Agonists

**Full-text PDF:** http://www.medscimonit.com/abstract/index/idArt/893914







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## Background

Currently, combination of aspirin and clopidogrel (dual antiplatelet therapy) is a common adjunctive therapy to reduce adverse cardiac events for patients with acute coronary syndrome (ACS) and for those undergoing percutaneous coronary intervention (PCI) [1,2]. Dual therapy may significantly reduce the risk of death, stent thrombosis, and myocardial infarction (MI) compared with aspirin alone [3]. However, the effect of clopidogrel on platelet inhibition is highly variable due to slow variable transformation of the prodrug to the active metabolite [4,5]. In addition, the ischemic benefit obtained from platelet blockade is at the expense of increased risk of bleeding complications [6,7]. Newly developed P2Y12 receptor inhibitors such as prasugrel, ticagrelor, cangrelor, and elinogrel have been shown to be more potent agents in P2Y12 inhibition than clopidogrel due to the faster, greater, and more consistent effect [8–11]. However, it is unclear whether these agents can take the place of clopidogrel for patients with ACS, and conditions of acute myocardial ischemia caused by occlusion of a coronary artery are not well recognized [12,13]. Results of recent meta-analyses still have some controversial issues due to significant heterogeneity of trials pooled for analysis [14,15]. The aim of this study is to perform a meta-analysis for systematically reviewing the evidence on the efficacy of novel oral P2Y12 inhibitor prasugrel in comparison to clopidogrel in patients with ACS.

## Material and Methods

### Study design

The PRISMA statement recommended by the Cochrane Collaboration [16] was used as the basic framework to conduct this meta-analysis. Relevant studies published between January 1, 1990 and Feb 1, 2015 was searched in PubMed, Web of Science, Cochrane Library, EMBASE, and ClinicalTrials.gov. A manual search was performed for additional relevant studies through the reference lists of important RCTs identified. Only studies published in English were retrieved. The following search strategy was used to identify suitable studies: ("prasugrel" [All Fields]) AND ("clopidogrel" [All Fields]) AND ("trial" [All Fields]) and ("acute coronary syndrome" OR "acute myocardial ischemia" [All Fields]). Two authors (MJ and ZL) independently performed the search process and assessed the eligibility of the studies. Disagreements were resolved through group discussion. One author was responsible for extracting original data and another author crosschecked the data.

### Study selection and data extraction

Studies were included for this meta-analysis has to meet the following criteria at the same time: (1) prospective or retrospective studies; (2) for prospective studies, intention-to-treat cohorts were used for study; (3) patients with acute coronary syndrome; (4) comparison between prasugrel and clopidogrel in patients; (5) studies included outcomes measured during follow-up ≥1 month (30 days). Studies involving mixed patients with stable chronic heart disease and acute coronary syndrome were excluded. The basic data extracted include study name, year of publication, study design, number of patients involved, syndrome of ACS, dose of prasugrel and clopidogrel, including loading and maintaining dose, the length of follow-up, and results of efficacy and safety outcomes (primary and secondary efficacy endpoints). If the required data was not available in the full text, supplemental data were searched. The major end points of this meta-analysis include all cause of death, MI, stroke, major bleeding, major/minor bleeding and stent thrombosis (for PCI performed). Major/minor bleeding needs to be defined according to TIMI criteria and cases related CABG surgery were excluded. Both definite and probable stent thrombosis was calculated for stent thrombosis. For studies with several intervention arms, the outcomes of each experimental group were extracted separately.

### Statistical analysis

Review Manager 5.2 (Cochrane Collaboration, Oxford, United Kingdom) was used for calculation and comparison of treatment effects. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a fixed-effects or random-effects model, depending on the heterogeneity. A 2-tailed p value ≤0.05 was used to denote statistical significance. Between-study heterogeneity was assessed by using the chi-square ($\chi^2$) test and $I^2$. Primary assessment was performed with a fixed-effects model. $P \geq 0.1$ and $I^2 \leq 50\%$ means the studies have no significant heterogeneity and a fixed-effects model was used, while $P < 0.1$ and $I^2 > 50\%$ suggests the studies have significant heterogeneity [17]. The source of the heterogeneity was then further analyzed. If there was no significant clinical heterogeneity, a secondary confirmatory analysis was done with a random-effects model. Otherwise, descriptive analysis was performed. Since the original studies had both prospective and retrospective design, subgroup analysis was performed according to this stratification.

## Results

The systematic search found 54 studies of potential interest. Among them, 6 were excluded because the full text was not in English; 25 were excluded because they did not meet the inclusion criteria; and 10 reviews, 5 duplicate studies, and 2 meta-analyses were excluded. The process of screening potential studies for inclusion is summarized in a flow chart in Figure 1. As shown in Table 1, a total of 6 studies were finally





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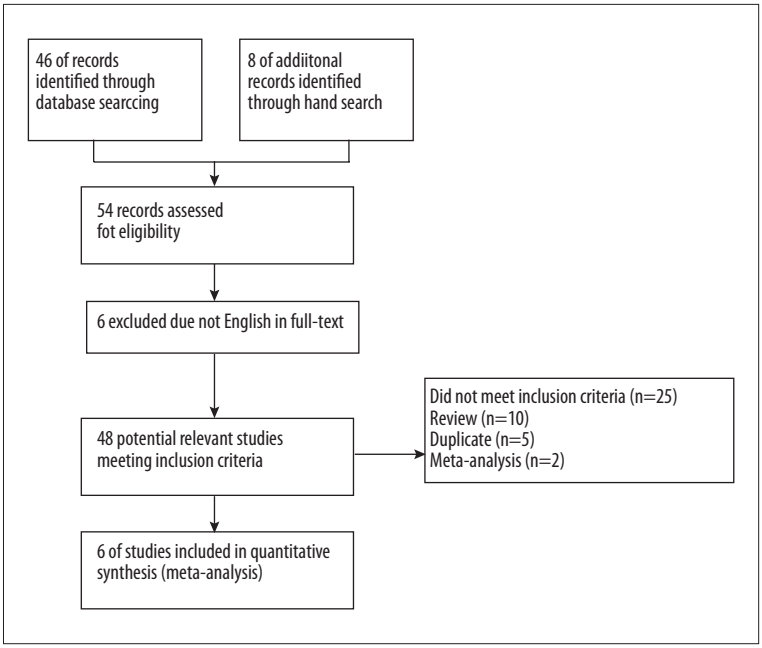


**Figure 1.** Flow chart of searching and screening process.

**Table 1.** The basic characteristics of studies included.

| Author/year | Study design | No. patient | Syndrome | Oral P2Y12 drug | Oral P2Y12 intervention | Clopidogrel intervention | Follow-up |
|---|---|---|---|---|---|---|---|
| ETAMI Trial 2015 | Prosp | 63 | STEMI | Prasugrel | 60 mg loading, 10 mg maintenance | 600 mg loading and 75 mg daily | 30 days |
| INFUSE-AMI Trial 2014 | Prosp | 452 | STEMI | Prasugrel | N/A | N/A | 12 months |
| TRILOGY ACS 2012 | Prosp | 9,326 | STEMI | Prasugrel | 30 mg loading, 10/5 mg maintenance | 300 mg loading and 100 mg daily | Median 17.1 months |
| DISPERSE-2 Trial 2007(a) | Prosp | 498 | NSTE-ACS | Prasugrel | 90 mg twice daily | 300 mg loading and 75 mg daily | 3 months |
| DISPERSE-2 Trial 2007(b) | Prosp | 492 | NSTE-ACS | Prasugrel | 180 mg twice daily | 300 mg loading and 75 mg daily | 3 months |
| TRITON–TIMI 2007 | Prosp | 13,608 | STE-ACS/ NSTE-ACS | Prasugrel | 60 mg loading, 10 mg maintenance | 300 mg loading and 75 mg daily | 15 months |
| AMIS-Plus 2015 | Retro | 4,602 | ACS | Prasugrel | N/A | N/A | 30 days |

STEMI – ST-elevation myocardial infarction; NSTEMI – non ST-elevation myocardial infarction; ACS – acute coronary syndrome; N/A – not available; TIMI – thrombolysis in myocardial; MACE – major adverse cardiac events; prosp – prospective; retro – retrospective.

included in the meta-analysis [11,18–22]. Some of the selected characteristics of the included RCTs are shown in Table 1. Among the 6 studies, five5 are prospective [11,18–21] and 1 is retrospective [22]. A total of 29 041 patients were involved in this study. The follow-up period ranged from 1 month to a median of 17.1 months in the 6 studies.

### Comparison of death/MI/Stroke between prasugrel and clopidogrel

Generally, the patients who received prasugrel had similar risks of all causes of death (630/14,626, 4.31%) compared those who took clopidogrel (708/10 414, 6.80%) (Pooled RR: 0.83; 95% CI: 0.64–1.06, p=0.14, $I^2$=55%) (Figure 2A). However, the





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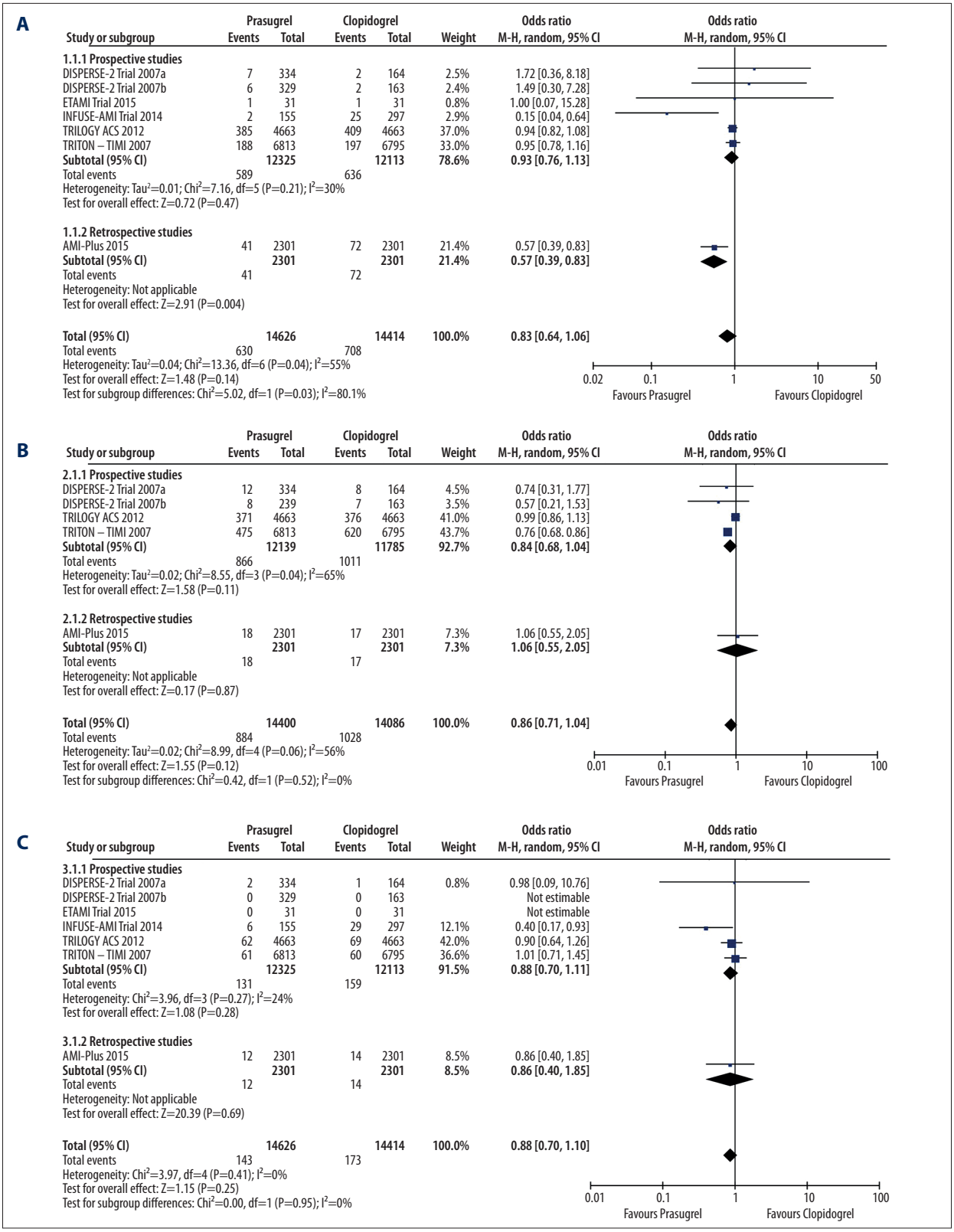


**Figure 2.** Comparison of death/MI/Stroke between prasugrel and clopidogrel. (**A**) Comparison of death between prasugrel and clopidogrel. (**B**) Comparison of MI between prasugrel and clopidogrel. (**C**) Comparison of Stroke between prasugrel and clopidogrel.





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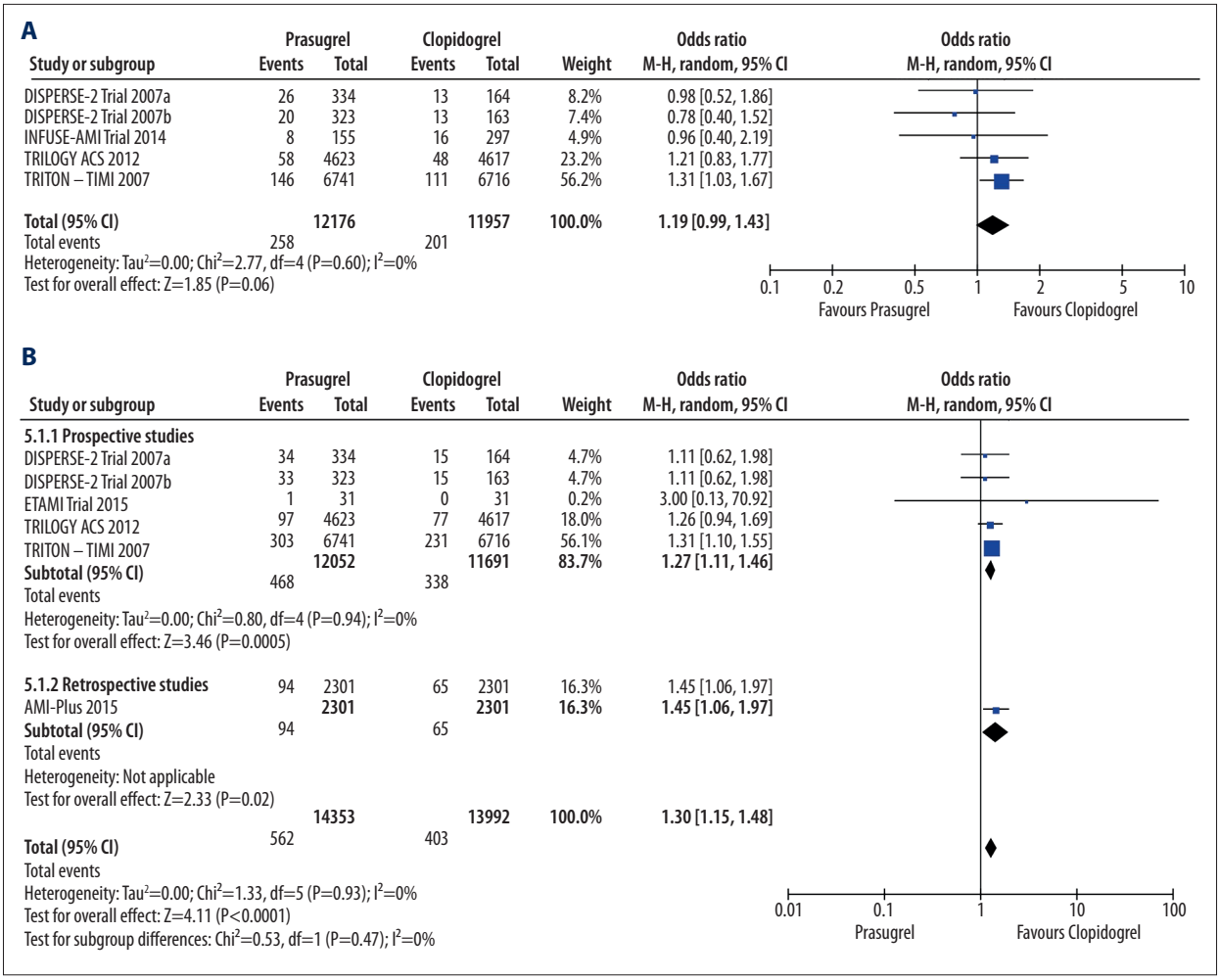


**Figure 3.** Comparison of bleeding risk between prasugrel and clopidogrel. (**A**) Comparison of major bleeding risk between prasugrel and clopidogrel. (**B**) Comparison of both major and minor bleeding risk between prasugrel and clopidogrel.

retrospective study found prasugrel contributed to lower risk of death (pooled RR: 0.57; 95% CI: 0.39-0.83, p=0.004), but the effect was not observed in prospective studies (pooled RR: 0.93; 95% CI: 0.76–1.13, p=0.47, $I^2$=56%) (Figure 2A). Prasugrel was associated with similar risk of MI as clopidogrel (884/14 440, 6.12% *vs.* 1028/14,086, 7.30%) (Pooled RR: 0.86; 95% CI: 0.71–1.04, p=0.12) (Figure 2B). No significant difference was observed in subgroup analysis (p=0.52, $I^2$=0%) (Figure 2B). The risk of stroke was also similar in both prasugrel and clopidogrel group (143/14 626, 0.98% *vs.* 173/14,414, 1.20%) (Pooled RR: 0.88; 95% CI: 0.70–1.10, p=0.25, $I^2$=0%) (Figure 2C). No significant difference was observed in subgroup analysis (p=0.95, $I^2$=0%) (Figure 2C).

## Comparison of bleeding risk between prasugrel and clopidogrel

Generally, major bleeding risk was significantly higher at borderline level in the prasugrel group (258/12 176, 2.12%) than in the clopidogrel group (201/11 957, 1.68%) (Pooled RR: 1.19; 95% CI: 0.99–1.44, p=0.06, $I^2$=0%) (Figure 3A). If the cases of minor bleeding were considered, the risk of total major and minor bleeding in the prasugrel group (562/14 353, 3.92%) was significantly higher than in the clopidogrel group (403/13 992, 2.88%) (Pooled RR: 1.30; 95% CI: 1.15–1.48, p<0.0001, $I^2$=0%) (Figure 3B). This result is consistent in both prospective and retrospective studies (p=0.47, $I^2$=0%) (Figure 3B).

## Comparison of stent thrombosis between prasugrel and clopidogrel

For the ACS patients who received PCI, stent thrombosis rate was 68/6999 (0.97%) and 149/7123 (2.01%) in the prasugrel and clopidogrel group, respectively (Figure 4). Therefore, for the patients who underwent PCI, prasugrel was associated with significantly lower risk of stent thrombosis (Pooled RR: 0.46; 95% CI: 0.34–0.61, p<0.00001, $I^2$=0%) (Figure 4).





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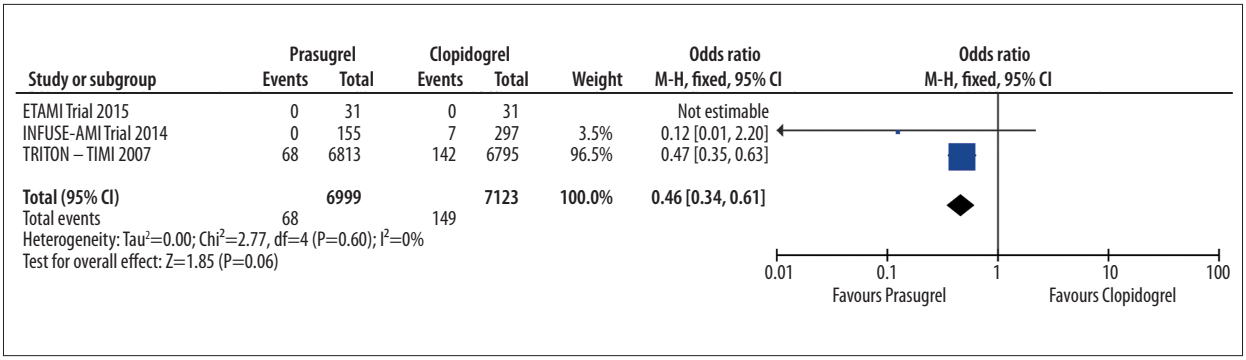


**Figure 4.** Comparison of stent thrombosis between prasugrel and clopidogrel.

## Discussion

In this study, we observed that compared with clopidogrel, prasugrel has similar effect as clopidogrel in terms of all causes of death, MI, and stroke in ACS patients. In addition, for the patients who received PCI, prasugrel contributed to lower risk of stent thrombosis. However, prasugrel was associated with significantly higher risk of bleeding.

Dual antiplatelet therapy (aspirin and clopidogrel) has been used as the standard therapy for patients with ACS or those undergoing PCI [23]. However, the use of clopidogrel has many limitations, such as high variability, delayed onset of action, and inhibiting platelets [24]. Some recent studies observed that increasing the loading dose of clopidogrel helped control the inter-individual variability and reduce the effect of platelet inhibition [7]. However, this dose increase could not decrease the risk of ischemic events and the randomized clinical trials also did not observe a significant effect on survival [25]. Thus, with the desire to further improve the outcomes for patients with ACS, exploring drugs that more rapidly inhibit platelet aggregation has been the target for developing new antiplatelet agents. Compared with clopidogrel, the new P2Y12 inhibitors, including prasugrel, ticagrelor, cangrelor, and elinogrel, demonstrate more rapid, potent, and consistent inhibition of platelet aggregation [8–11]. However, previous meta-analyses of new P2Y12 inhibitors had conflicting results due to significant heterogeneity among trials involved [15,26]. In the present study, we only focused on prasugrel and included both prospective and retrospective studies, which helped to appropriately stratify trials and reduce heterogeneity.

Faster and stronger antiplatelet therapy may be associated with a higher risk of bleeding complications, and this study confirmed significantly higher bleeding risk in ACS patients. However, the different types of ACS have distinctive characteristics. Thus, use of prasugrel in these patients requires more detailed assessment. According to electrocardiograph (ECG) diagnosis, MI patients can be divided into ST-segment elevation MI (STEMI) and non-ST segment elevation MI (NSTEMI). The former have the infarct-related artery totally occluded and patients usually have more severe and distressing signs and symptoms. Therefore, to limit the size of the infarction in these patients, there is an urgent need to recanalize the artery and restore blood flow [27]. Unstable angina (UA) and NSTEMI are known collectively as NSTE-ACS. For this group of patients, revascularization is also required. However, since these patients only have platelet-rich clots and do not have completely occluded arteries, the aim of revascularization is to increase blood flow and prevent reocclusion [27]. Approximately 50% of STEMI patients have significant multivessel disease [28]. Due to the need for potent antithrombotic and antiplatelet agents for PCI, bleeding is more frequent in this group of patients, especially in the arterial puncture site [28]. Thus, appropriate choice of antiplatelet agent is quite important. For patients with active pathological bleeding or a history of stroke and/or TIA, prasugrel should not be recommended. This finding is consistent with new guidelines for the management of STEMI patients [28]. However, the short half-life of prasugrel (around 7 h) requires patients have twice-daily administration. This is a significant disadvantage of this agent, especially for selected subjects, such as those with implantation of multiple stents.

This study had several limitations. One major limitation is the small number of original studies involved. However, since some trials involved in this study are mid-sized or large randomized controlled trials (RCTs), the final number of patients for meta-analysis is large, which helped to offset the disadvantage of a small number of studies. To confirm the findings of this study, more RCTs with large sample size are required. In addition, significant heterogeneity in the duration of therapies, inclusion criteria, endpoints, lengths of follow-up, and different endpoints might hamper reliability of the findings. Furthermore, lack of patient-level data made covariate-adjusted or time-to-event analysis impossible in this study. Considering the different features of STE-ACS and NSTE-ACS, more detailed comparison and analysis of prasugrel in these subgroups of ACS should be conducted.





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## Conclusions

This study found that prasugrel has similar effects as clopidogrel in terms of all causes of death, MI, and stroke in ACS patients. For the patients who received PCI, prasugrel contributes to lower risk of stent thrombosis; however, prasugrel is associated with significantly higher risk of bleeding. For the patients with active pathological bleeding or a history of stroke and/or TIA, prasugrel should not be recommended.

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