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

Min Jia
Zaibo Li
Hongtao Chu
Lin Li
Keyong Chen

Corresponding Author: Min Jia, e-mail: jm681005@163.com
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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, I²=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, I²=0%) and the risk of total major and minor bleeding (Pooled RR: 1.30; 95% CI: 1.15–1.48, p<0.0001, I²=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, I²=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

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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 (χ²) test and I². Primary assessment was performed with a fixed-effects model. P≤0.1 and I²≤ 50% means the studies have no significant heterogeneity and a fixed-effects model was used, while P>0.1 and I²>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...
Some of the selected characteristics of the included RCTs are shown in Table 1. Among the 6 studies, five 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 to those who took clopidogrel (708/10,414, 6.80%) (Pooled RR: 0.83; 95% CI: 0.64–1.06, p=0.14, I²=55%) (Figure 2A).
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.
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, R²=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, R²=0%) (Figure 3B). This result is consistent in both prospective and retrospective studies (p=0.47, R²=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, R²=0%) (Figure 4).
Patients can be divided into ST-segment elevation MI (STEMI) or 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.
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.

References:

1. Yusuf S, Zhao F, Mehta SR et al: Clopidogrel in unstable angina to prevent recurrent events trial I: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without st-segment elevation. N Engl J Med, 2001; 345: 494–502
2. Sabatine MS, Cannon CP, Gibson CM et al., CLARITY-TIMI 28 Investigators: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with st-segment elevation. N Engl J Med, 2005, 352: 1179–89
3. Chen ZM, Jiang LX, Chen YP et al., COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. Lancet, 2005; 366: 1607–21
4. Serebruany VL, Steinbuhler SR, Berger PB et al: Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol, 2005; 45: 246–51
5. Suri MF, Hussein HM, Abdelmoula MM et al: Safety and tolerability of 600 mg clopidogrel bolus in patients with acute ischemic stroke: Preliminary experience. Med Sci Monit, 2008; 14(10): P93–44
6. Serebruany VL, Malinin AI, Ziai W et al: Effects of clopidogrel and aspirin in combination versus aspirin alone on platelet activation and major receptor expression in patients after recent ischemic stroke: For the plavix use for treatment of stroke (pluto-stroke) trial. Stroke, 2005; 36: 2289–92
7. Mehta SR, Tanguay JF, Elkeboom JW et al., CURRENT-OASIS 7 trial investigators: Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (current-oasis 7): A randomised factorial trial. Lancet, 2010; 376: 1233–43
8. Wallentin L, Varenhorst C, James S et al: Prasugrel achieves greater and faster P2Y12 receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. Eur Heart J, 2008; 29: 21–30
9. Gurbe P, Belden KP, Butler K et al: Randomized double-blind assessment of the onset and offset of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: The onset/offset study. Circulation, 2009; 120: 2577–85
10. Berger JS, Roe MT, Gibson CM et al: Safety and feasibility of adjunctive antithrombotic therapy with intravenous elinogrel, a direct-acting and reversible P2Y12 ADP-receptor antagonist, before primary percutaneous intervention in patients with ST-elevation myocardial infarction: The Early Rapid Reversal of platelet thrombosis with intravenous Elinogrel before PCI to optimize reperfusion in acute Myocardial Infarction (ERASE MI) pilot trial. Am Heart J, 2009; 158: 998–1004e1
11. Wiviott SD, Braunwald E, McCabe CH et al., TRITON-TIMI 38 Investigators: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med, 2007; 357: 2001–15
12. Pandit A, Aryal MR, Pandit AA et al: Cangrelor versus clopidogrel in percutaneous coronary intervention: A systematic review and meta-analysis. EuroIntervention, 2014; 9(11): 1350–58
13. Korostovska L, Sviyaev Y, Zvaratu N et al: New insights into the management of rhythm and conduction disorders after acute myocardial infarction. Am J Case Rep, 2014; 15: 159–62
14. Aradi D, Komocsi A, Verobucsko A, Serebruany VL: Impact of clopidogrel and potent P2Y12-inhibitors on mortality and stroke in patients with acute coronary syndrome or undergoing percutaneous coronary intervention: A systematic review and meta-analysis. Thromb Haemost, 2013; 109: 93–101
15. Bellemain-Appaix A, Brierger D, Beygui F et al: New P2Y12 inhibitors versus clopidogrel in percutaneous coronary intervention: A meta-analysis. J Am Coll Cardiol, 2010; 56: 1542–51
16. Liberati A, Altman DG, Tetzlaff J et al: The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. J Clin Epidemiol, 2009; 62: e1–34
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMI, 2003; 327: 557–60
18. Zeymer U, Mochmann HC, Mark B et al: Double-blind, randomized, prospective comparison of loading doses of 600 mg clopidogrel versus 60 mg prasugrel in patients with acute ST-segment elevation myocardial infarction scheduled for primary percutaneous intervention: The ETAMI trial (early thienopyridine treatment to improve primary PCI in patients with acute myocardial infarction). JACC Cardiovasc Interv, 2015; 8: 147–54
19. Brer SI, Oldroyd KG, Maehara A et al: Outcomes in patients with ST-segment elevation acute myocardial infarction treated with clopidogrel versus prasugrel (from the infuse-ami trial). Am J Cardiol, 2014; 113: 1457–60
20. Roe MT, Armstrong PW, Fox KA et al., TRILOGY ACS Investigators: Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med, 2012; 367: 1297–309
21. Cannon CP, Husted S, Harrington RA et al., DISPERSE-2 Investigators: Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: Primary results of the DISPERSE-2 trial. J Am Coll Cardiol, 2007; 50: 1844–51
22. Kurz DI, Radovanovic D, Seifert B et al: Comparison of prasugrel and clopidogrel-treated patients with acute coronary syndrome undergoing percutaneous coronary intervention: A propensity score-match analysis of the acute myocardial infarction in Switzerland (AMIS)-plus registry. Eur Heart J Acute Cardiovasc Care, 2015; [Epub ahead of print]
23. Levine GN, Bates ER, Blankenship JC et al: 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv, 2013; 82: E266–35
24. Gurum HS, Eagle KA: Defining the optimal dose of aspirin and clopidogrel in acute coronary syndromes. Evaluation of ‘Dose comparisons of clopidogrel and aspirin in acute coronary syndromes,’ N Engl J Med 2010; 363: 930–42. Expert Opin Pharmacother, 2011; 12: 149–51
25. Price MJ, Berger PB, Teirstein PS et al., GRAVITAS Investigators: Standard- vs. high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: The GRAVITAS randomized trial. JAMA, 2011; 305: 1097–102
26. Aradi D, Komocsi A, Verobucsko A, Serebruany VL: Impact of clopidogrel and potent P2Y12-inhibitors on mortality and stroke in patients with acute coronary syndrome or undergoing percutaneous coronary intervention: A systematic review and meta-analysis. Thromb Haemost, 2013; 109: 93–101
27. Clark MG, Beavers C, Osborne J: Managing the acute coronary syndrome patient: Evidence based recommendations for anti-platelet therapy. Heart Lung, 2015; 44(2): 141–49
28. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D et al: ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J, 2012; 33: 2569–619