Reduced-Dose Prasugrel versus Clopidogrel for Patients Undergoing Percutaneous Coronary Intervention
A Meta-Analysis of Randomized and Observational Studies

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Summary
Whether reduced-dose prasugrel has a better efficacy or safety than standard-dose clopidogrel remains unknown in patients undergoing percutaneous coronary intervention (PCI).

A systematic search of PubMed, EMBASE, Google Scholar, and Cochrane Library from database inception to May 1, 2021 was performed to compare the clinical outcomes in patients with acute coronary syndrome or stable coronary artery disease undergoing PCI between those treated with reduced-dose prasugrel and clopidogrel. The pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using the fixed-effect or random-effect model if significant heterogeneity was observed. The primary efficacy endpoint was major adverse cardiovascular events (MACE), including cardiovascular (CV) death, myocardial infarction (MI), or ischemic stroke. The primary safety endpoint was all bleeding events.

Overall, seven studies with 32,951 patients with PCI were included in the analysis. Reduced-dose prasugrel was associated with a lower risk of MACE than clopidogrel (OR 0.80, 95% CI 0.67-0.97). Except for MI (OR 0.74, 95% CI 0.56-0.98), the secondary efficacy endpoints of CV death, ischemic stroke, all-cause death, and stent thrombosis were similar. For the primary safety endpoint of all bleeding events, there was no significant difference between reduced-dose prasugrel and clopidogrel (OR 1.31, 95% CI 0.87-1.98), but the risk of minor bleeding was significantly higher in reduced-dose prasugrel (OR 1.73, 95% CI 1.25-2.41).

In patients undergoing PCI, a lower risk of MACE was found in patients receiving reduced-dose prasugrel than in those with clopidogrel, but a higher risk of minor bleeding events was noted.

Key words: Platelet aggregation inhibitors, Coronary heart disease, Acute coronary syndrome

Dual antiplatelet therapy (DAPT) with aspirin plus P2Y12 inhibitor is the current standard treatment for patients receiving percutaneous coronary intervention (PCI).¹² For patients with stable coronary artery disease (CAD) receiving PCI, the choice of the P2Y12 inhibitor is clopidogrel; however, the European guidelines also suggest that ticagrelor or prasugrel may be considered in patients with high ischemic risk.¹³ In the case of acute coronary syndrome (ACS), ticagrelor or prasugrel are recommended as the first-line treatment. In comparison with clopidogrel, standard-dose prasugrel (loading dose 60 mg, maintenance dose 10 mg QD) was demonstrated to have a lower risk of recurrent ischemic events in the TRITON-TIMI 38 trial; however, the risk of bleeding is a major concern of prasugrel.¹⁴,³ In the European guidelines, reduced-dose prasugrel (5 mg QD) is recommended in patients ≥75 years of age or body weight <60 kg.¹⁵ In Japan, reduced-dose prasugrel (3.75 mg QD) has been approved to be used for PCI in both ACS and stable CAD, based on the findings from the PRASFIT-ACS and PRASFIT-Selective studies.³⁶ In these two studies from Japan, there was a trend toward a better efficacy and the risk of major bleeding was not increased in reduced-dose prasugrel compared to standard-dose clopidogrel, but the sample sizes were not large enough to reach a final conclusion.³⁶ Recently, several observational studies were published to compare the safety and efficacy of reduced-dose prasugrel and standard-dose clopidogrel, with conflicting results. Therefore, there is a strong rationale to prove the efficacy and safety of reduced-dose prasugrel.

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The purpose of this study is to conduct a systematic review and meta-analysis of the randomized and non-randomized observational studies to compare the efficacy and safety of reduced-dose prasugrel and standard-dose clopidogrel in patients undergoing PCI.

Methods

Search Strategies: The meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-Analysis Of Observational Studies in Epidemiology: a proposal for reporting) guidelines for reporting systematic reviews and meta-analyses. A comprehensive search was conducted by two independent authors (CHL and MSH) through PubMed, EMBASE, Google Scholar, and Cochrane Library up to May 1, 2020, to identify studies comparing clinical outcomes of both efficacy and safety between reduced-dose prasugrel and standard-dose clopidogrel among patients undergoing PCI. The following search terms were used: “prasugrel,” “clopidogrel,” “P2Y12 inhibitor,” “acute coronary syndrome,” “myocardial infarction,” “coronary intervention,” and “coronary revascularization” (Supplemental Table). Studies meeting the following criteria were regarded as eligible: (1) randomized controlled trials or observational studies comparing clinical outcomes in those treated with reduced-dose prasugrel and standard-dose clopidogrel among patients undergoing PCI. The following search terms were used: “prasugrel,” “clopidogrel,” “P2Y12 inhibitor,” “acute coronary syndrome,” “myocardial infarction,” “coronary intervention,” and “coronary revascularization” (Supplemental Table). Studies meeting the following criteria were regarded as eligible: (1) randomized controlled trials or observational studies comparing clinical outcomes in those treated with reduced-dose prasugrel (loading dose 30 or 20 mg and maintenance dose 5 or 3.75 mg QD) versus standard-dose clopidogrel (loading dose 300-600 mg and maintenance dose 75 mg QD); (2) study participants including patients with stable CAD or ACS undergoing PCI; (3) reporting at least one of our specified clinical outcomes of interest, including major adverse cardiovascular events (MACE), cardiovascular (CV) death, myocardial infarction (MI), ischemic stroke, all-cause death, and stent thrombosis; and (4) reporting bleeding outcomes. There were no restrictions on the publication date, country, and patient characteristics. However, non-English publications, patient who were not undergoing PCI, review articles, letter to editors, pharmacokinetic or pharmacodynamics studies, or studies investigating different doses of the same agent were excluded. We also performed a search in ClinicalTrials.gov; however, there were no ongoing studies that focused on head-to-head comparisons of the clinical outcomes between reduced-dose prasugrel and clopidogrel after PCI. Two independent reviewers assessed the risk of bias (low, unclear, or high) of the studies included using the Cochrane risk of bias tool (9) or non-randomized studies (Supplemental Figure 1).

Data Extraction: Two independent authors (CHL and MSH) reviewed the publications included and extracted the following data: (1) the country in which the study was performed, (2) the year of publication, (3) the study design, (4) indications for PCI, (5) the prasugrel dose, (6) the total numbers of participants (if propensity-matched analysis was applied, the number of post-matched groups that were used), (7) the follow-up duration, and (8) clinical outcomes. The data were further cross-checked after
Saito, et al.\(^6\) Japan 2014 Multicenter, randomized, clinical trial (PRASFIT–ACS study) PCI for ACS 3.75 mg 685/678 24 weeks

Ishiki, et al.\(^6\) Japan 2014 Multicenter, randomized, clinical trial (PRASFIT-Elective study) PCI for stable CAD 3.75 mg 370/372 24 weeks

Koyabu, et al.\(^6\) Japan 2019 Retrospective, single-center, observational, matched cohort PCI for ACS (43.6%) or stable CAD (56.4%) 3.75 mg 250/250 (balanced between groups) 12 months

Yasuda, et al.\(^6\) Japan 2019 Prospective, multicenter registry (JAMIR study) PCI for AMI 3.75 mg 2607/462 (unmatched) No matching number was reported Median 12 months (range 9–13 months) In-hospital outcome

Akita, et al.\(^6\) Japan 2019 Prospective, multicenter registry (J-PCI study) PCI for ACS 3.75 mg 42735/20002 (unmatched) 12016/12016 (PS matched) In-hospital outcome

Shoji, et al.\(^6\) Japan 2020 Retrospective, multicenter registry (JCD-KiCS study) PCI for ACS 3.75 mg 1297/1262 (unmatched) 901/901 (PS matched) In-hospital outcome

Savonitto, et al.\(^6\) Italy 2018 Multicenter, randomized, clinical trial (Elderly ACS 2 study) PCI for ACS 5 mg 713/730 Median 12.1 months (range 3–13 months) In-hospital outcome

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; JAMIR, Japan Acute Myocardial Infarction Registry; JCD-KiCS, Japan Cardiovascular Database–Keio Interhospital Cardiovascular Studies; J-PCI, Japanese percutaneous coronary intervention; PCI, percutaneous coronary intervention; PS, propensity score; and PRASFIT, PRASugrel compared with clopidogrel For Japanese patients.

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; JAMIR, Japan Acute Myocardial Infarction Registry; JCD-KiCS, Japan Cardiovascular Database–Keio Interhospital Cardiovascular Studies; J-PCI, Japanese percutaneous coronary intervention; PCI, percutaneous coronary intervention; PS, propensity score; and PRASFIT, PRASugrel compared with clopidogrel For Japanese patients.

Results

Included studies: Figure 1 shows the flow diagram of the selection process used in this study. Searching in the electronic databases (PubMed, EMBASE, Google Scholar, and
Cochrane Library) retrieved a total of 2836 publications. After the removal of 2820 duplicate or irrelevant studies, we extracted 16 full-text articles for review. After excluding studies that did not fulfill the inclusion criteria of this study, seven publications were selected for qualitative and quantitative analyses.5,6,10-14) The characteristics of the seven studies included are summarized in the Table. There were differences among the studies included with regard to the study design and patient characteristics. Among them, four were observational studies and three were randomized clinical trials. Six studies originated from Japan and used prasugrel 3.75 mg QD. The other one, the Elderly ACS 2 study, was from Italy and evaluated prasugrel 5 mg QD in elderly patients.14 Five studies included only patients with ACS, one study included only those with stable CAD, and the other was a mixed study with patients with both ACS and stable CAD. Overall, by adding the non-matched cohort in the JAMIR study11) and the matched groups in the other six studies, there were a total of 32,951 patients (17,542 in the reduced-dose prasugrel arm and 15,409 in the clopidogrel arm). The follow-up duration in these studies was from in-hospital up to 1-year clinical outcomes.

Outcome analyses: For analysis of the primary efficacy endpoint of MACE, the study by Akita, et al.15) was excluded because only in-hospital mortality and stent throm-
sensitivity analyses revealed no significant differences of the MACE rate between randomized versus observational studies and 3.75 versus 5 mg prasugrel studies (Figure 5). In the subgroup of randomized clinical trials, there was a lower risk of MACE (OR 0.78, 95% CI 0.61-0.98) in the reduced-dose prasugrel group. The subgroup analysis of 3.75 mg prasugrel showed a borderline significantly lower risk of MACE (OR 0.82, 95% CI 0.67-1.01) in the reduced-dose prasugrel group. For sensitivity analyses of the primary safety endpoint, there was a higher bleeding risk of the reduced-dose prasugrel group from the in-hospital outcome studies than in the follow-up studies after discharge. No significant differences of the primary safety endpoint between randomized versus observational studies were found (Supplemental Figure 4).

Discussion

To our knowledge, this is the first meta-analysis to perform a direct head-to-head comparison of reduced-dose prasugrel versus standard-dose clopidogrel in patients undergoing PCI. The main findings of our study were that (1) the risk of MACE with reduced-dose prasugrel was lower than clopidogrel, which was driven mainly by the reduction of MI; (2) there were no differences in CV death, ischemic stroke, all-cause death, and stent thrombosis between the groups; and (3) although there was no increase of major bleeding, the use of reduced-dose prasugrel was associated with a higher risk of minor bleeding than that with clopidogrel.

For patients with ACS undergoing PCI, the TRITON-TIMI 38 study found that the efficacy of standard-dose prasugrel (60 mg loading and 10 mg daily dose) was superior to clopidogrel in improving clinical outcomes. But the bleeding risk of prasugrel was higher in patients with a history of ischemic stroke or transient ischemic attack, elderly patients (aged 75 years or older), and those weighing less than 60 kg. Bleeding complications negatively influence the clinical outcomes after PCI, and especially become a major concern for East Asian patients receiving antiplatelet therapy. After an early dose-finding trial with platelet function tests, reduced-dose prasugrel (20 mg loading and 3.75 mg QD) was developed in Japan. In the phase 3 clinical trial, the PRASFIT-ACS study, reduced-dose prasugrel showed a nonsignificant reduction of MACE (hazard ratio 0.77, 95% CI 0.56-1.07) compared with standard-dose clopidogrel. The risk of TIMI major bleeding was similar between the groups. Currently, reduced-dose prasugrel is recommended as the first-line P2Y12 inhibitor in the Japanese ACS guidelines and is prescribed widely to patients with ACS undergoing PCI in Japan. However, the real-world observational studies published subsequently from Japan that compared reduced-dose prasugrel and standard-dose clopidogrel in patients with ACS undergoing PCI demonstrated conflicting results. The pooled analyses of these studies in our meta-analysis found that the risk of MACE in the reduced-dosed prasugrel group was comparable to the clopidogrel group in ACS. There was a higher risk of all bleeding events of reduced-dose prasugrel in patients with ACS (Figure 4). However, we found trends toward better
### Secondary efficacy endpoints

| Study or Subgroup | Prasugrel | Clopidogrel | Odds Ratio | Weight | Mat. Reaction | 95% CI | Year |
|-------------------|-----------|-------------|------------|--------|---------------|--------|------|
| Overall mortality | 22 | 23 | 1.09 (0.33, 3.29) | 0.96 | Not estimable | 2014 |
| **Secondary endpoints** | | | | | | | |
| **Atrial fibrillation** | 22 | 23 | 1.09 (0.33, 3.29) | 0.96 | Not estimable | 2014 |
| **Stroke** | 22 | 23 | 1.09 (0.33, 3.29) | 0.96 | Not estimable | 2014 |
| **Bleeding** | 22 | 23 | 1.09 (0.33, 3.29) | 0.96 | Not estimable | 2014 |

**Figure 3.** Forest plot of the secondary efficacy (A) and safety (B) endpoints between reduced-dose prasugrel and clopidogrel.
**A** Major adverse cardiovascular events

| Study or Subgroup | Prasugrel Events | Clopidogrel Events | Odds Ratio M-H, Fixed, 95% CI Year |
|-------------------|------------------|-------------------|-----------------------------------|
| **1.3.1 Acute coronary syndrome studies** |                  |                    |                                   |
| Salto et al. 2014 | 74 685           | 84 678            | 0.68 [0.61, 1.19] 2014            |
| Savonitto et al. 2018 | 47 713           | 83 730            | 0.75 [0.60, 1.11] 2018            |
| Shoji et al. 2020 | 40 901           | 32 901            | 1.26 [0.79, 2.03] 2020            |
| Subtotal (95% CI) | 2239 2309        | 83.8%             | 0.89 [0.71, 1.12]                |
| **Total events**  | 161 179          |                   |                                   |
| Heterogeneity: $\chi^2 = 2.89, \text{df} = 2 (P = 0.24), \text{I}^2 = 31\%$ |
| Test for overall effect: $Z = 0.99 (P = 0.32)$ |

**1.3.2 Elective coronary intervention studies**

| Study or Subgroup | Prasugrel Events | Clopidogrel Events | Odds Ratio M-H, Fixed, 95% CI Year |
|-------------------|------------------|-------------------|-----------------------------------|
| Ishihaki et al. 2014 | 15 370           | 25 372            | 0.59 [0.30, 1.13] 2014            |
| Koyabu et al. 2019 | 4 250            | 8 250             | 0.49 [0.15, 1.65] 2019            |
| Subtotal (95% CI) | 620 622          | 16.2%             | 0.56 [0.32, 1.00]                 |
| **Total events**  | 19 33            |                   |                                   |
| Heterogeneity: $\chi^2 = 0.08, \text{df} = 1 (P = 0.80), \text{I}^2 = 0\%$ |
| Test for overall effect: $Z = 1.95 (P = 0.05)$ |

**B** All bleeding events

| Study or Subgroup | Prasugrel Events | Clopidogrel Events | Odds Ratio M-H, Fixed, 95% CI Year |
|-------------------|------------------|-------------------|-----------------------------------|
| **2.2.1 Acute coronary syndrome studies** |                  |                    |                                   |
| Salto et al. 2014 | 341 668          | 247 676           | 1.73 [1.38, 2.15] 2014            |
| Savonitto et al. 2018 | 29 713           | 20 730            | 1.51 [0.84, 2.69] 2018            |
| Akita et al. 2020 | 61 12016         | 37 12016          | 1.65 [1.10, 2.49] 2020            |
| Shoji et al. 2020 | 194 901          | 87 901            | 2.08 [1.68, 2.45] 2020            |
| Subtotal (95% CI) | 14315 14325      | 98.8%             | 1.80 [1.55, 2.10]                 |
| **Total events**  | 595 391          |                   |                                   |
| Heterogeneity: $\chi^2 = 1.72, \text{df} = 3 (P = 0.63), \text{I}^2 = 0\%$ |
| Test for overall effect: $Z = 7.58 (P < 0.000001)$ |

**2.2.2 Elective coronary intervention studies**

| Study or Subgroup | Prasugrel Events | Clopidogrel Events | Odds Ratio M-H, Fixed, 95% CI Year |
|-------------------|------------------|-------------------|-----------------------------------|
| Ishihaki et al. 2014 | 20 370           | 23 372            | 0.67 [0.47, 1.16] 2014            |
| Koyabu et al. 2019 | 7 250            | 4 250             | 1.77 [0.51, 6.13] 2019            |
| Subtotal (95% CI) | 629 622          | 9.2%              | 1.00 [0.58, 1.74]                 |
| **Total events**  | 27 27            |                   |                                   |
| Heterogeneity: $\chi^2 = 1.02, \text{df} = 1 (P = 0.31), \text{I}^2 = 2\%$ |
| Test for overall effect: $Z = 0.02 (P = 0.98)$ |

**Figure 4.** Forest plot of the primary efficacy (A) and safety (B) endpoints between reduced-dose prasugrel and clopidogrel without the JAMIR study.

Clinical outcomes in prasugrel users who were younger (<75 years), with higher body weight (>50 kg), and without chronic kidney disease (Supplemental Figure 3), most likely because of the reduction of bleeding complications. These study results could be applied to our clinical practice when choosing between reduced-dose prasugrel and clopidogrel for patients with ACS.

For elective PCI in stable CAD, we found a significantly lower risk of MACE of reduced-dose prasugrel than clopidogrel. Platelet activation occurs in patients with stable CAD undergoing PCI, because angioplasty induces the mechanical disruption of the atherosclerotic plaque that exposes the subendothelium to circulating blood. The intensity and persistence of platelet activation determine the recurrent ischemic events after PCI. Our meta-analysis results showed that reduced-dose prasugrel seems to be a better choice than clopidogrel in elective PCI for stable CAD, because reduced-dose prasugrel has a lower risk of MACE than clopidogrel and there is no increased risk of bleeding. Currently, prasugrel is used in elective PCI only in Japan and it is indicated only for PCI in ACS in most other countries in the world. A large-scale clinical trial is necessary to further confirm the benefits of reduced-dose prasugrel for elective PCI that we observed in this meta-analysis.

Although the risk of TIMI major or minor bleeding
was similar between reduced-dose prasugrel and clopidogrel in the PRASFIT-ACS study, the real-world observational studies showed quite conflicting results regarding the bleeding risk of reduced-dose prasugrel. For those studies considering only in-hospital outcomes, there was a higher bleeding risk of reduced-dose prasugrel (Supplemental Figure 4). Akita, et al. showed that bleeding complications, defined as bleeding events requiring blood transfusion, were higher in the reduced-dose prasugrel group than in the clopidogrel group (OR 1.65, 95% CI 1.10-2.51). Shoji, et al. also showed that the primary bleeding events, defined as bleeding complications within 72 hours after PCI requirement for transfusion or procedural intervention or surgery to stop the bleeding, were significantly higher among patients receiving reduced-dose prasugrel (OR 2.91, 95% CI 1.63-5.18). However, if look at the follow-up data after discharge and up to 1 year, the bleeding risk became similar between the reduced-dose prasugrel and clopidogrel groups. By observing the bleeding events in both acute and chronic phases, the data from Koyabu, et al. clearly indicated that the risk of PCI-related bleeding complications was higher in the acute phase in the reduced-dose prasugrel group than in the clopidogrel group. But the incidence of non-PCI-related bleeding complications over 12 months was comparable between the two groups. Pooled analyses of
these studies demonstrated that all bleeding and major bleeding events were similar, but minor bleeding events were increased significantly in the reduced-dose prasugrel group. Our data indicated that the judicious use of prasugrel is necessary even when the dose is decreased, especially during the perioperative period of PCI. Moreover, choosing patients with more benefits of prasugrel, such as those who are younger, with higher body weight, and without chronic kidney disease, is also necessary. Finally, prasugrel should be given to patients with ACS after the coronary anatomy is known and PCI is planned, because there was no ischemic benefit and the bleeding risk was increased with the pretreatment of prasugrel in patients with ACS.26) The recently published ISAR-REACT 5 trial showed that the clinical outcomes were better in patients with ACS with prasugrel loading after the knowledge of coronary anatomy was obtained than in those with the routine pretreatment of ticagrelor.26) Therefore, the new 2020 European guidelines of non-ST elevation ACS do not recommend routine pretreatment with a P2Y12 inhibitor in patients with ACS in whom coronary anatomy is unknown and early invasive management is planned.26)

There are several study limitations of the current meta-analysis. First, as the published studies that specifically compared the clinical outcomes of reduced-dose prasugrel with clopidogrel in patients with PCI were limited, we had to include both randomized and non-randomized observational studies. Although most observational studies that we selected used a matching process to eliminate unbalances between groups, the unmeasured confounding factors could not be ruled out completely. We used those values from propensity score matching in our meta-analysis, except for the JAMIR study that did not report the incidence after matching. Therefore, we removed the JAMIR study and reanalyzed the data that showed similar trends for efficacy and safety outcomes. The two large observational studies from Akita, et al. and Shoji, et al. used propensity-matched scores and reported the incidence of clinical outcomes. Both studies found that the risk of all bleeding events was higher in reduced-dose prasugrel than in clopidogrel, and the efficacy outcomes were similar (mortality and stent thrombosis in the study of Akita, et al. and MACE in the study of Shoji, et al.) between the groups.12,13) However, both studies reported only the in-hospital clinical outcomes. If we consider the longer follow-up results over 12 months, such as in the JAMIR registry, PRASFIT-ACS study, and the study by Koyabu, et al., the bleeding risk of reduced-dose prasugrel became similar to that of clopidogrel. The different follow-up durations probably also influence the clinical outcomes. As the detailed bleeding outcomes were unavailable in most of the studies included, the subgroup analysis of bleeding outcomes between reduced-dose prasugrel and clopidogrel by gender, age, body weight, or renal function could not be performed in our study. Finally, the sensitivity analyses were performed according to randomized versus observational studies and 3.75 versus 5 mg prasugrel. There was no significant heterogeneity in the overall analyses.

Conclusions

Based on the meta-analysis of the observational and randomized studies, reduced-dose prasugrel seems to be superior to standard-dose clopidogrel in patients with PCI, especially in those with stable CAD. The use of reduced-dose prasugrel was associated with a higher risk of minor bleeding events than that of clopidogrel. Larger randomized clinical trials with longer follow-up durations are necessary to determine the superiority of one agent versus the other.

Disclosure

Conflicts of interest: None.

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Supplemental Files
Supplemental Table
Supplemental Figures 1-4
Please see supplemental files; https://doi.org/10.1536/ihj.20-508