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Review Article
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Clinical Efficacy and Safety of Reduced-Dose Prasugrel versus Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Objectives: This systematic review and meta-analysis of randomized controlled trials (RCTs) compared the clinical efficacy and safety of reduced-dose prasugrel (loading dose: 20 mg; daily maintenance dose: 3.75 mg) and clopidogrel in patients undergoing percutaneous coronary intervention (PCI).

Methods: PubMed, Embase, and the Cochrane Library database were searched for relevant articles from inception to March 8, 2021. Only RCTs that compared the clinical efficacy and safety of reduced-dose prasugrel and clopidogrel treatment in adult patients undergoing PCI were included. The primary outcome was the risk of major cardiovascular events (MACEs).

Results: Four RCTs involving 2464 patients were included. The overall risk of MACEs was 8.3% (102/1235) in the study group (reduced-dose prasugrel) and 9.8% (121/1229) in the control group (clopidogrel). No significant difference was observed in the risk of MACEs between the study and control groups (risk ratio: 0.84, 95% confidence interval: 0.65-1.08, I^2 = 0%). In addition, cardiovascular-related death, all-cause death, nonfatal myocardial infarction, nonfatal stroke, revascularization, and stent thrombosis did not differ significantly between the two groups. Apart from a higher risk of minor bleeding in the study group, reduced-dose prasugrel had a similar bleeding risk to clopidogrel.

Conclusions: The clinical efficacy of reduced-dose prasugrel is comparable to that of clopidogrel; however, the risk of minor bleeding should be considered when prescribing this regimen for patients undergoing PCI.

Key Words: Bleeding • Clopidogrel • Coronary artery disease • Major cardiovascular event • Prasugrel

INTRODUCTION

Although acute coronary artery syndrome (ACS), including acute myocardial infarction (MI), is a major cause of morbidity and mortality worldwide, its clinical outcomes have improved substantially.[1] This progress is attributable to many factors, including effective primary and secondary treatment strategies, implementation of care delivery systems, widespread use of percutaneous coronary intervention (PCI), and advances in antiplatelet agents and anticoagulants.[1] Dual antiplatelet therapy, consisting of aspirin and a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) is recommended for patients with ACS to reduce the rate of future cardiovascular events.[2,3]

Numerous large randomized control trials (RCTs) have compared the clinical efficacy and safety among

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these three P2Y12 inhibitors.[4-11] Wiviott et al. reported that in patients with ACS undergoing scheduled PCI, prasugrel therapy (loading dose: 60 mg; daily maintenance dose: 10 mg) was associated with significantly reduced rates of cardiovascular-related death, nonfatal MI, and nonfatal stroke compared with clopidogrel (loading dose: 300 mg; daily maintenance dose: 75 mg).[4] Another RCT demonstrated that the administration of prasugrel (60 mg) in patients with ST-segment elevation MI before PCI was associated with significantly faster platelet inhibition compared with clopidogrel (600 mg).[12] A real-world study of patients undergoing primary PCI demonstrated similar results; prasugrel was associated with a lower adjusted 30-day mortality rate compared with ticagrelor and clopidogrel, and it was associated with a reduced adjusted 12-month mortality rate compared with clopidogrel.[13] Although prasugrel was associated with a more favorable clinical outcome than clopidogrel in these studies,[4,12,13] it was sometimes associated with a higher risk of bleeding.[4,9,10] Because the risk of bleeding is a serious concern, a reduced dose of prasugrel (loading dose: 20 mg; maintenance dose: 3.75 mg) has been proposed as a possible antiplatelet treatment, particularly for East Asian patients.[14] Several further studies have been conducted to investigate the efficacy and safety of a reduced or adjusted dose of prasugrel compared with clopidogrel.[10,15-21] To provide more robust evidence, we conducted a systematic review and meta-analysis of RCTs to compare the clinical efficacy and safety of reduced-dose prasugrel (loading dose: 20 mg; daily maintenance dose: 3.75 mg) and clopidogrel in patients undergoing PCI.

METHODS

Study search and selection

PubMed, Embase, and the Cochrane Library database were searched for relevant articles from inception to March 8, 2021. The following search terms were used: “prasugrel hydrochloride,” “prasugrel,” “percutaneous coronary intervention,” and “randomized.” RCTs that compared the clinical efficacy and safety of reduced-dose prasugrel and clopidogrel treatment in adult patients undergoing PCI were included. The reference lists from relevant articles were also searched manually for additional eligible articles. No language limitations were applied. Studies were included if they met the following criteria: (1) patients underwent PCI, (2) patients were ≥ 18 years old, (3) the intervention was reduced-dose prasugrel, (4) the comparison group was treated with clopidogrel, (5) the study was an RCT, and (6) the outcomes of clinical efficacy and the risk of bleeding were available. We excluded in vitro research, animal studies, and pharmacokinetic-pharmacodynamic assessments. Two investigators independently screened and reviewed each study. If any disagreements arose, a third investigator was consulted. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[22]

Outcome measurements

The primary outcome was the incidence of major adverse cardiovascular events (MACEs) as well as individual events, namely cardiovascular death, all-cause death, nonfatal MI, nonfatal ischemic stroke, revascularization, and stent thrombosis. The secondary outcome was the risk of bleeding, including major bleeding, minor bleeding, clinically relevant bleeding, bleeding events leading to discontinuation, and other bleeding.

Data analysis

The Cochrane risk-of-bias tool[23] was used to evaluate the quality and risk of bias of the RCTs. Statistical analyses were performed using Review Manager version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). The degree of heterogeneity was evaluated using Q statistics generated from the χ^2 test, and the I^2 statistic was used to assess heterogeneity. Heterogeneity was considered significant when $p < 0.10$ or $I^2 > 50\%$. A fixed-effects model was used for homogeneous data, and a random-effects model was used for heterogeneous data. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for the outcome analyses.

RESULTS

Study selection

A total of 6778 studies were identified from the online databases, of which 2888 were duplicates and were

thus excluded. In addition, 3863 and 27 studies were excluded after title and abstract screening and after full-text screening, respectively. Finally, four RCTs[18-21] were included in the meta-analysis (Figure 1).

Characteristics of the included studies

The characteristics of the four included RCTs[18-21] are summarized in Table 1. Three were phase 3 RCTs,[18,20,21] and one was a phase 2 trial.[19] One RCT[18] was a single-center study, and three were multicenter studies.[19-21] All four RCTs[18-21] were conducted in Japan. A total of 2464 patients undergoing PCI were included in the current review, of whom 1235 received reduced-dose prasugrel (loading dose: 20 mg; daily maintenance dose: 3.75 mg) and 1229 received clopidogrel. The definitions of the outcomes of interest differed among the included studies (Supplemental Table 1). Three RCTs[18-20] had an unclear risk of selection bias in both random sequence generation and allocation concealment, and one RCT[21] had an unclear risk of selection bias in allocation concealment. Low risks of bias were observed in the other domains for all RCTs (Figure 2).

Primary outcomes

Overall, the risk of MACEs was 8.3% (102/1235) in the study group (reduced-dose prasugrel) and 9.8% (121/1229) in the control group (clopidogrel). The risk of MACEs between the study and control groups (RR: 0.84; 95% CI: 0.65-1.08; I^2 = 0%) did not differ significantly in the pooled analysis of the four RCTs (Figure 3).[18-21] In addition, no significant differences were noted for cardiovascular death (RR: 1.32; 95% CI: 0.55-3.22; I^2 = 0%), all-cause death (RR: 1.13; 95% CI: 0.53-2.42; I^2 = 0%), nonfatal MI (RR: 0.76; 95% CI: 0.57-1.02; I^2 = 0%), or

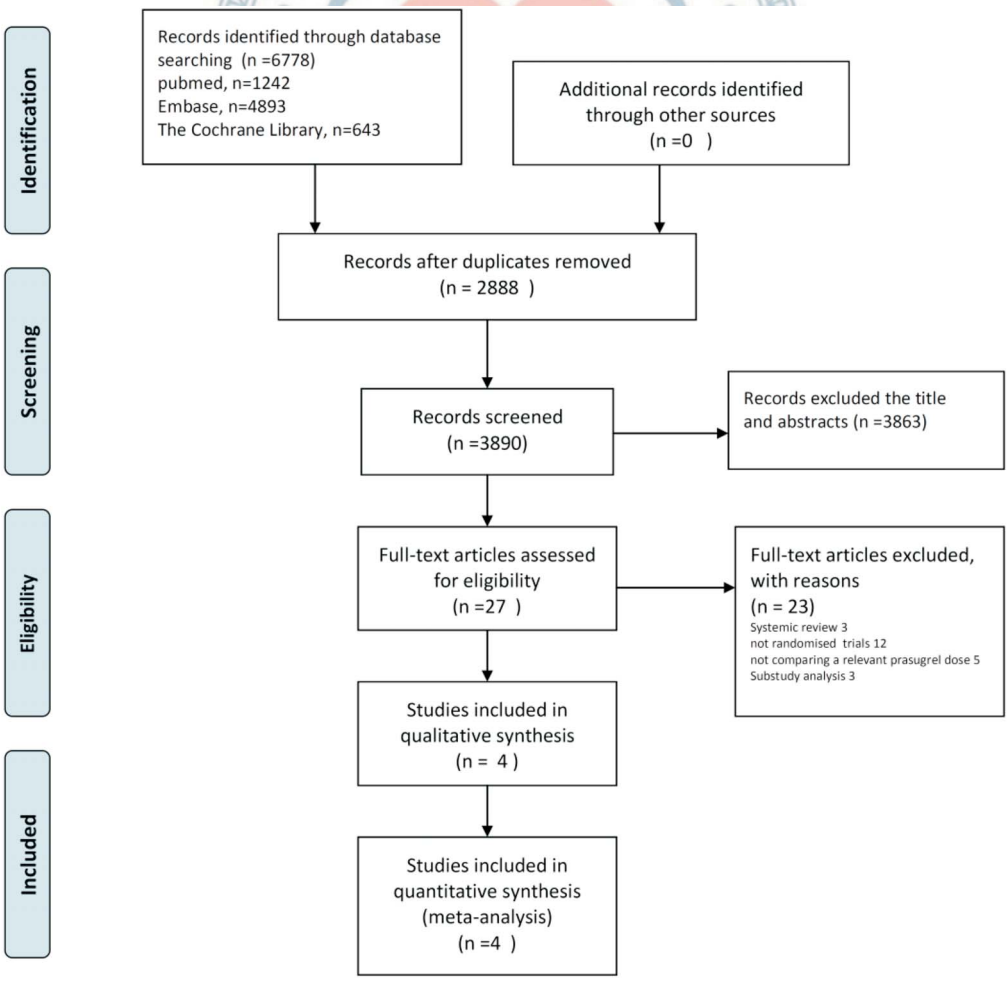

Figure 1. *Flowchart of study selection.*

Table 1. Characteristics of the included studies

Study	Study design	Study sites	Study period	Study population	Number of patients		Regimen of prasugrel, loading dose/maintenance dose
					Prasugrel	Clopidogrel	
Saito et al., 2014[21]	Randomized, double-blind, double-dummy, parallel-group phase 3 study	162 centers in Japan	December 2010-June 2012	Patients (aged ≥ 20 years) with ACS undergoing PCI	685	678	20 mg/3.75 mg
Isshiki et al., 2014[20]	Randomized, double-blind, double-dummy, parallel-group phase 3 study	Multicenter in Japan	August 2011-December 2012	Patients (aged ≥ 20 years) scheduled for elective PCI	370	372	20 mg/3.75 mg
Kimura et al., 2015[19]	Randomized, double-blind, double-dummy, parallel-group, phase 2 study	55 centers in Japan	June 2009-June 2010	Patients (aged 20-84 years, BW ≥ 40 kg) scheduled for elective PCI	141	140	20 mg/3.75 mg
Kitano et al., 2020[18]	Randomized controlled study	One center in Japan	December 2014-November 2016	Patients with ACS undergoing PCI	39	39	20 mg/3.75 mg

ACS, acute coronary syndrome; BW, body weight; PCI, percutaneous coronary intervention.

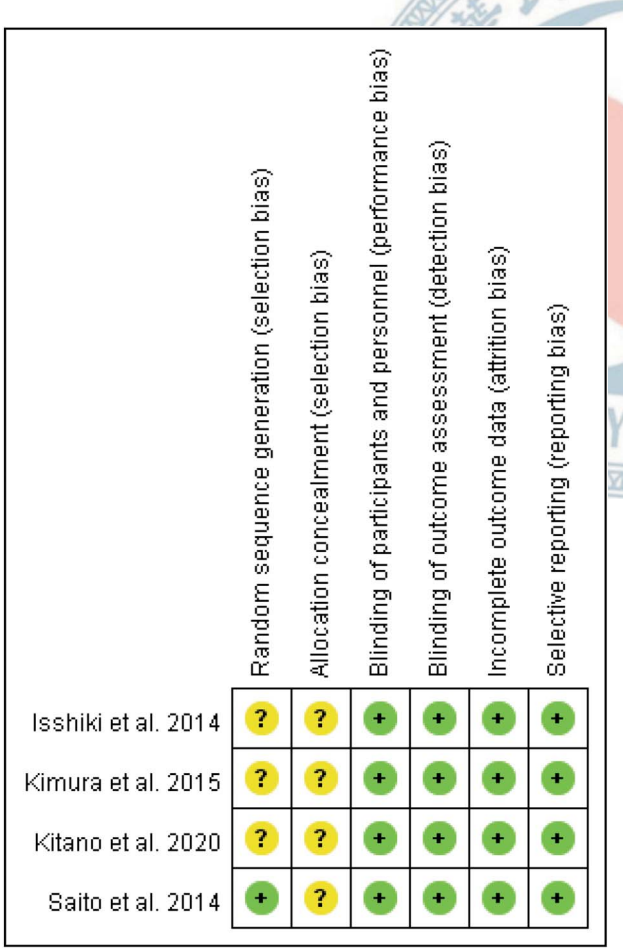

Figure 2. *Summary of risk-of-bias assessment.*

nonfatal stroke (RR: 0.76, 95% CI: 0.33-1.76, I^2 = 0%) between the two groups (Figure 3). Finally, no significant differences in revascularization (RR: 1.09; 95% CI: 0.85-1.39; I^2 = 0%) or stent thrombosis (RR: 0.70; 95% CI: 0.21-2.35; I^2 = 0%) were identified between the study and control groups (Figure 3).

Secondary outcomes

According to the pooled analysis of three RCTs,[19-21] the risk of major bleeding was lower (1.1%; 13/1196) in the study group than in the control group (2.1%; 25/1190); however, this difference was not statistically significant (RR: 0.33; 95% CI: 0.05-1.97; I^2 = 53%) (Figure 4). By contrast, the study group had a higher risk of minor bleeding than the control group [3.9% (32/826) vs. 2.1% (17/818); RR: 1.86; 95% CI: 1.04-3.32; I^2 = 0%] (Figure 4) in the pooled analysis of two RCTs.[19,21] However, no significant differences in the risk of major or minor bleeding were observed between the study and control groups (RR: 1.07; 95% CI: 0.64-1.81; I^2 = 22%). In addition, no significant differences in clinically relevant bleeding (RR: 0.73; 95% CI: 0.46-1.15; I^2 = 0%), bleeding events leading to discontinuation of drugs (RR: 0.86; 95% CI: 0.51-1.46; I^2 = 0%), or other bleeding (RR: 1.28; 95% CI: 0.98-1.69; I^2 = 51%) were noted between the two groups (Figure 4). Finally, the risk of overall major,

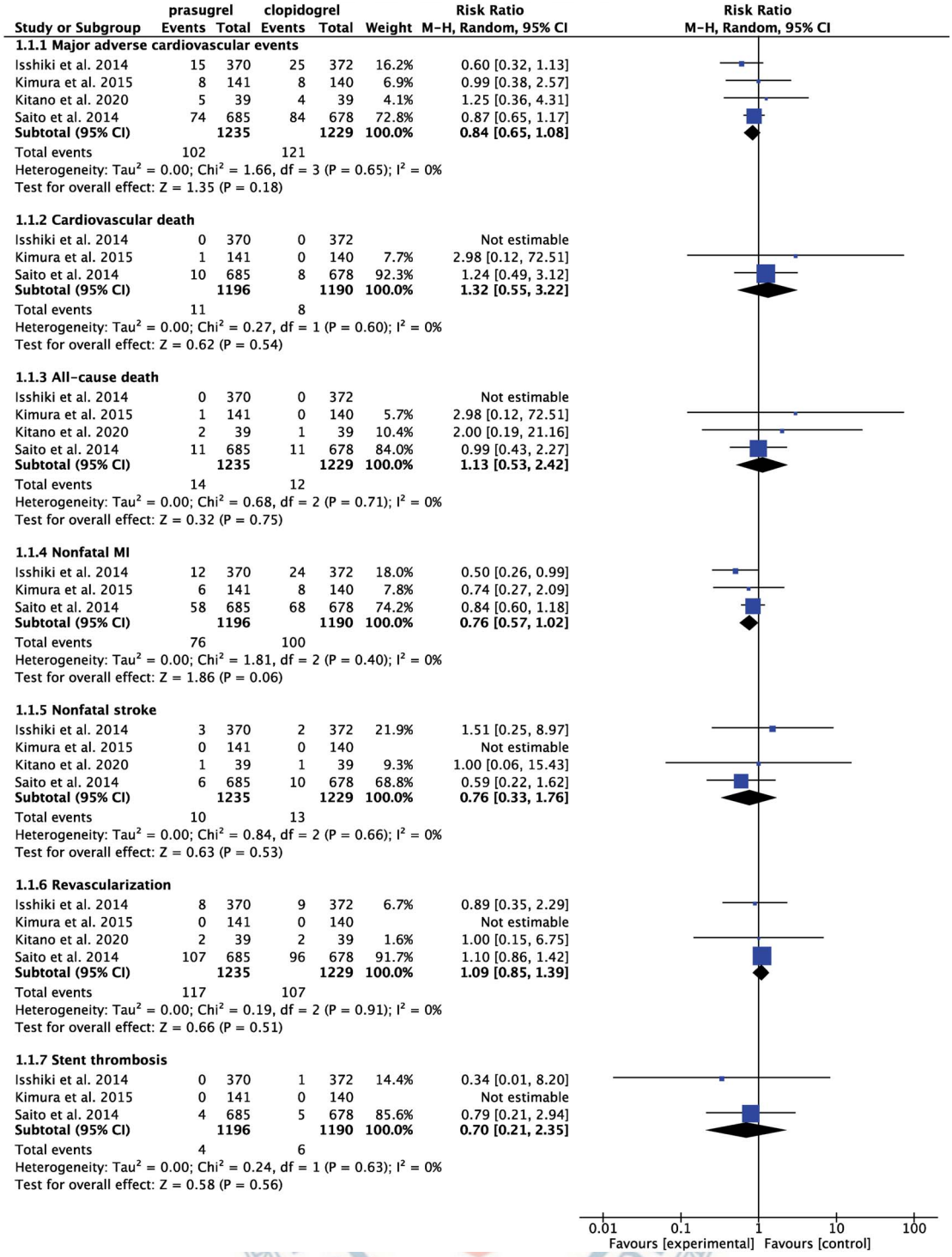

Figure 3. *Forest plot of the risk of major cardiovascular events and specific cardiovascular events in patients who received reduced-dose prasugrel compared with those who received clopidogrel.*

minor, or clinically relevant bleeding (RR: 0.97; 95% CI: 0.74-1.28; I^2 = 0%) did not differ significantly between the study and control groups (Figure 4).

Sensitivity analysis

Table 2 summarizes the findings of sensitivity analysis. First, the findings of overall MACEs were unchanged

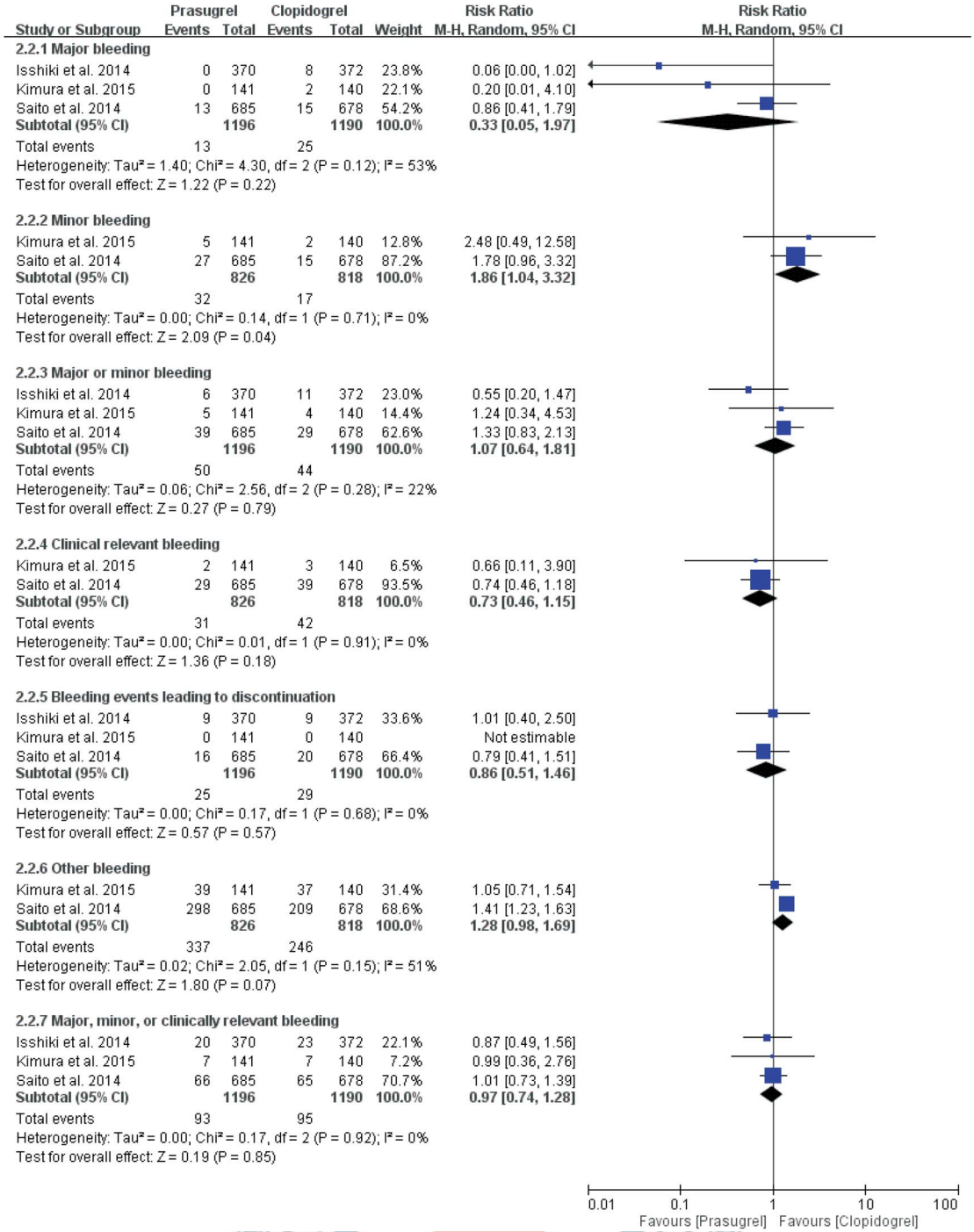

Figure 4. *Forest plot of the risk of bleeding in patients who received reduced-dose prasugrel compared with those who received clopidogrel.*

after performing leave-one-out sensitivity analysis, and in subgroup analysis of patients with ACS undergoing PCI compared with those receiving scheduled PCI (RR: 0.89; 95% CI: 0.67-1.18; I^2 = 0%). Second, we performed further analysis of two studies[20,21] according to the definition of MACEs as cardiovascular death, nonfatal MI, and nonfatal ischemic stroke. The results were the same in that the risk of MACEs using this definition did not differ between the study and control groups (RR: 0.81; 95% CI: 0.60-1.08; I^2 = 9%). Third, to minimize the con-

Table 2. The findings of sensitivity analysis

Outcome/subgroup	No. of study	RR	95% CI	I^2
MACE				
Including cardiovascular death, nonfatal MI, and nonfatal ischemic stroke	2	0.81	0.60-1.08	9%
Patients with ACS undergoing PCI	2	0.89	0.67-1.18	0%
Patients with standard risk group	4	0.84	0.65-1.08	0%
Specific cardiovascular outcome in patients with standard risk				
Cardiovascular death	3	1.33	0.55-3.22	0%
All-cause death	4	1.13	0.53-2.42	0%
Nonfatal MI	3	0.76	0.57-1.02	0%
Nonfatal stroke	4	0.76	0.33-1.76	0%
Revascularization	4	1.09	0.85-1.39	0%
Stent thrombosis	3	0.70	0.21-2.35	0%
Adverse events				
Minor bleeding	2	1.89	1.04-3.44	0%
Major bleeding	3	0.33	0.06-1.97	53%
Major or minor bleeding	3	1.07	0.62-1.85	23%
Clinically relevant bleeding	2	0.73	0.46-1.15	0%
Bleeding events leading to discontinuation	3	0.86	0.51-1.46	0%
Other bleeding	2	1.19	0.77-1.83	71%
Major, minor, or clinically relevant bleeding	3	0.97	0.74-1.28	0%

ACS, acute coronary syndrome; CI, confidence intervals; MACE, major cardiovascular events; MI, myocardial infarction; PCI, percutaneous intervention; RR, pooled risk ratios.

founding effect of different patients' characteristics, we performed subgroup analysis after excluding high-risk patients who were older (> 75 years) or had a low body weight (< 50 kg), and the results showed no significant difference in the risk of MACEs between the study and control groups (RR: 0.84; 95% CI: 0.65-1.08; I^2 = 0%). In addition, no significant differences were found between the study and control groups in cardiovascular death (RR: 1.33; 95% CI: 0.55-3.22; I^2 = 0%), all-cause death (RR: 1.13; 95% CI: 0.53-2.42; I^2 = 0%), nonfatal MI (RR: 0.76; 95% CI: 0.57-1.02; I^2 = 0%), nonfatal stroke (RR: 0.76, 95% CI: 0.33-1.76, I^2 = 0%), revascularization (RR: 1.09; 95% CI: 0.85-1.39; I^2 = 0%), or stent thrombosis (RR: 0.70; 95% CI: 0.21-2.35; I^2 = 0%).

After excluding high-risk patients, the other findings were also similar. Compared with the control group, the study group had a higher risk of minor bleeding (RR: 1.89; 95% CI: 1.04-3.44; I^2 = 0%), but a similar risk of major bleeding (RR: 0.33; 95% CI: 0.06-1.97; I^2 = 53%), major or minor bleeding (RR: 1.07; 95% CI: 0.62-1.85; I^2 = 23%), clinically relevant bleeding (RR: 0.73; 95% CI: 0.46-1.15; I^2 = 0%), bleeding events leading to discontinuation of drugs (RR: 0.86; 95% CI: 0.51-1.46; I^2 = 0%), other bleeding (RR: 1.19; 95% CI: 0.77-1.83; I^2 = 71%), and major, minor or clinically relevant bleeding (RR: 0.97; 95% CI: 0.74-1.28; I^2 = 0%).

DISCUSSION

This meta-analysis of four RCTs[18-21] compared the efficacy and safety of reduced-dose prasugrel with clopidogrel in patients with ACS who underwent PCI. The clinical effectiveness of reduced-dose prasugrel was comparable to that of clopidogrel in this population, as supported by the following evidence. First, reduced-dose prasugrel and clopidogrel were associated with a similar risk of MACEs. Second, the risk of cardiovascular death, all-cause death, nonfatal MI, nonfatal ischemic stroke, revascularization, and stent thrombosis did not differ significantly between the reduced-dose prasugrel and clopidogrel groups. Third, these findings remained unchanged in the leave-one-out sensitivity analysis and the subgroup analysis of patients with ACS undergoing PCI compared with patients receiving elective PCI. These findings are consistent with the results of a recent real-world study[24] in which total ischemic events were similar between the clopidogrel and reduced-dose prasugrel

groups (p = 0.385). However, Lee et al.'s recent meta-analysis of three RCTs and four observational studies demonstrated that reduced-dose prasugrel was associated with a lower risk of MACEs than clopidogrel [odds ratio (OR): 0.80, 95% CI: 0.67-0.97].[25] These results are different to those of our study, which may be because we included four RCTs that investigated a 3.75 mg dose of prasugrel. By contrast, Lee et al.'s meta-analysis included three RCTs, and one used a 5 mg dose of prasugrel.[25] In summary, these findings indicate that the clinical efficacy of reduced-dose prasugrel (3.75 mg) is equivalent to that of clopidogrel for patients receiving PCI.

In addition to clinical efficacy, this study also assessed the safety of reduced-dose prasugrel. No significant differences were observed between reduced-dose prasugrel and clopidogrel in the risk of major bleeding, clinically relevant bleeding, bleeding events leading to discontinuation of the study drug, other bleeding, and overall major, minor, or clinically relevant bleeding. However, our pooled analysis of two RCTs revealed that reduced-dose prasugrel was associated with a higher risk of minor bleeding compared with clopidogrel. These findings are in line with Lee et al.'s meta-analysis, in which the risk of minor bleeding was significantly higher in the reduced-dose prasugrel group (OR: 1.73, 95% CI: 1.25-2.41) despite the lack of a significant difference in all bleeding events between the reduced-dose prasugrel and clopidogrel groups (OR: 1.31, 95% CI: 0.87-1.98).[25] In both our study and Lee et al.'s study,[25] the risk of minor bleeding was significantly higher in the prasugrel group than in the clopidogrel group. By contrast, no significant difference in major bleeding was observed between the two groups. However, this finding should be interpreted cautiously. First, only two to three studies provided data for meta-analysis. Second, the findings with regards to major bleeding were based on analysis with high heterogeneity (I^2 > 50%). Although these findings indicated that prasugrel only increased the risk of minor bleeding but not major bleeding, and that the extent of prasugrel-associated bleeding was only mild, further studies are needed to clarify this issue. Our findings suggest that clinicians should be mindful of the risk of minor bleeding associated with prasugrel, even at a reduced dosage.

Although this meta-analysis only included RCTs to provide robust evidence, it has several limitations. First, the number of included studies was limited, and all were conducted in Japan. Thus, our findings may not be generalizable to larger populations in other countries. Second, many findings of this meta-analysis were associated with high heterogeneity, which may be due to variations in study populations or follow-up times. Finally, the definitions of MACE varied in each included study. Two studies[20,21] defined MACEs as a composite of cardiovascular death, non-fatal MI, and non-fatal ischemic stroke. One study[19] used the definition as a composite of all-cause death, non-fatal MI, non-fatal stroke, myocardial ischemia requiring rehospitalization and coronary revascularization. In addition, Kimura et al.'s study[19] included both a standard group and high-risk group. To avoid these heterogenicities, we performed further subgroup analysis. Therefore, our findings should be interpreted with caution. To address these limitations, further large-scale RCTs are warranted to validate our findings.

In conclusion, the clinical efficacy of reduced-dose prasugrel is comparable to that of clopidogrel; however, the risk of minor bleeding should be considered when prescribing this regimen for patients undergoing PCI.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplemental Table 1. The definition of outcome of interests in each study

Study	MACE	Major bleeding	Minor bleeding
Saito et al., 2014[21]	A composite of cardiovascular death, nonfatal MI, and nonfatal ischemic stroke.	Intracranial bleeding or clinically significant bleeding accompanied by a decrease in hemoglobin ≥ 5 g/dl.	Clinically significant bleeding accompanied by a decrease in hemoglobin of 3-< 5 g/dl.
Isshiki et al., 2014[20]	A composite of cardiovascular death, nonfatal MI, and nonfatal ischemic stroke.	Intracranial bleeding or clinically significant bleeding accompanied by a decrease in hemoglobin ≥ 5 g/dl.	Clinically significant bleeding accompanied by a decrease in hemoglobin of 3-< 5 g/dl.
Kimura et al., 2015[19]	A composite of all-cause death, non-fatal MI, non-fatal stroke, myocardial ischemia requiring rehospitalization and coronary revascularization.	Intracranial bleeding or clinically overt bleeding associated with a decrease in the hemoglobin level of ≥ 5 g/dL.	Clinically overt bleeding associated with a decrease in the hemoglobin level of 3-5 g/dL.
Kitano et al., 2020[18]	A composite of all-cause death, non-fatal MI, non-fatal stroke, myocardial ischemia requiring revascularization.	NA	NA

MACE, major cardiovascular events; MI, myocardial infarction; NA, not applicable.