Efficacy and Safety of P2Y12 Receptor Antagonists in Acute Coronary Syndrome: Network Meta-analysis of Asian and Non-Asian Randomized Controlled Trials

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Abstract

Background and aims: Dual antiplatelet therapy (DAPT) including aspirin and another P2Y12 receptor antagonist (clopidogrel, prasugrel or ticagrelor) is a cornerstone of acute coronary syndrome (ACS) treatment. However, direct comparative evidence between clopidogrel, prasugrel and ticagrelor is limited. This network meta-analysis aimed to compare the effectiveness and safety of three different P2Y12 inhibitors for ACS patients.

Methods: We conducted a database search for randomized controlled trials (RCTs) comparing clopidogrel, prasugrel and ticagrelor in ACS patients. We then analyzed and compared the effectiveness and safety outcomes of mixed treatments under a frequentist approach using multivariate meta-analysis with a random-effects model. We drew direct and indirect comparisons to determine the primary cardiovascular (CV) efficacy and bleeding risks and performed subgroup analyses of major adverse cardiac events (MACE) according to baseline characteristics (sex, age and body weight), underlying disease (with or without DM, with or without CKD), and ACS presentation (NSTEMI/UA or STEMI). We also analyzed Asian and non-Asian trials for efficacy and safety.

Results: The literature search yielded 5 RCTs, including a total of 35,196 ACS patients, that met the inclusion criteria. We applied network meta-analysis to compare efficacy and safety endpoints, with follow-up intervals ranging from 6 to 15 months. The efficacy evaluation indicated that clopidogrel, prasugrel and ticagrelor had similar rates of MACE, CV death and all-cause mortality. However, while both prasugrel and ticagrelor had comparable rates of stent thrombosis, these were lower than with clopidogrel. Regarding safety, only ticagrelor had significantly higher risks of non-CABG TIMI criteria major bleeding and intracranial hemorrhage

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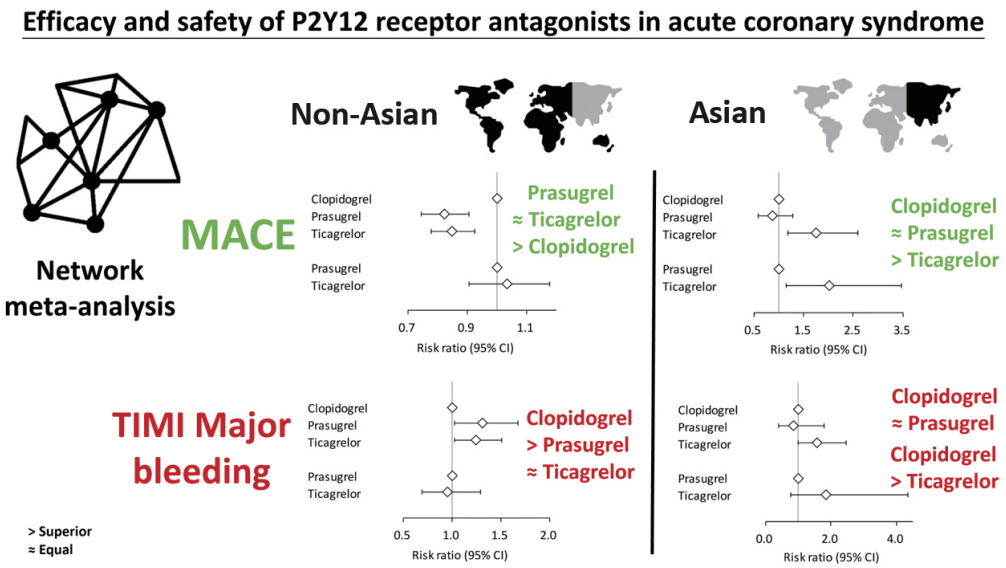
than clopidogrel, while ticagrelor and prasugrel showed no safety difference in comparison. In the MACE subgroup analysis, prasugrel was protective compared to clopidogrel, but only for males, those under 75 years, with BW >= 60 kg, NSTEMI/UA, non-DM and regardless of CKD status. Ticagrelor was protective compared to clopidogrel only in females and the non-CKD subgroup. Prasugrel was protective compared to ticagrelor only in those with BW >= 60 kg. In contrast to the overall analysis, in exclusively Asian trial analysis, clopidogrel and prasugrel had lower rates of MACE than ticagrelor, while there was no difference in stent thrombosis rates.

Conclusions: In this network meta-analysis, the three P2Y12 inhibitors clopidogrel, prasugrel and ticagrelor were not associated with differences in MACE reduction. However, prasugrel and ticagrelor had a lower stent thrombosis rate than clopidogrel. In contrast to the overall analysis, exclusively Asian trial analysis showed ticagrelor had a higher MACE rate than clopidogrel and prasugrel, while all three P2Y12 inhibitors showed comparable stent thrombosis rates.

Keywords: acute coronary syndrome, clopidogrel, prasugrel, ticagrelor



Introduction

Atherosclerotic plaque rupture followed by platelet aggregation and thrombotic occlusion result in acute coronary syndrome (ACS).[1] An antiplatelet agent should be given to treat ACS, as confirmed by the ISIS-2 trial which showed that in acute myocardial infarction (AMI), aspirin results in decreased mortality and reinfarction.[2] Moreover, dual antiplatelet therapy (DAPT), which combines aspirin and another oral P2Y12 receptor antagonist, brings even greater benefits. The CURE trial and the COMMIT trial demonstrated that adding clopidogrel to aspirin can further lower major adverse cardiac events (MACE); specifically, death, reinfarction, or stroke.[3,4] Meanwhile, the development of more rapid and potent P2Y12 receptor antagonists has overcome clopidogrel's drawback of delayed onset of action and CYP2C19 polymorphisms related to variable platelet inhibition. The TRITON-TIMI 38 trial first showed that prasugrel can further decrease MACE in comparison to clopidogrel,[5] and the PLATO trial first confirmed that ticagrelor

is associated with MACE reduction in comparison to clopidogrel.[6]

Current guidelines also recognize the importance of DAPT. The 2017 European Society of Cardiology (ESC) Guidelines for the management of AMI in patients presenting with ST-segment elevation (STEMI) recommend a potent P2Y12 inhibitor (prasugrel or ticagrelor) over clopidogrel ahead of percutaneous coronary intervention (PCI), and that such an inhibitor should be continued for 12 months.[7] The 2020 ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation recommend that prasugrel be considered in preference even to ticagrelor for non-ST segment elevation acute coronary syndrome (NSTE-ACS) patients.[8]

To date, the efficacy levels of the three P2Y12 receptor antagonists clopidogrel, prasugrel and ticagrelor have not been directly compared in clinical trials. Furthermore, the two more potent P2Y12 receptor antagonists (prasugrel and ticagrelor) pose a higher bleeding risk. We conducted this network meta-analysis (NMA) to evaluate the treatment effectiveness and safety of all three P2Y12 receptor antagonists (clopidogrel, prasugrel and ticagrelor) in combination with aspirin in ACS patients.

Methods and Materials

The protocol of this study was registered in PROSPERO (ID: CRD42020222068). The meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols statement (PRISMA-P). The current study is a meta-analysis and study approval by a local ethics committee was not required.

Literature search

We searched the EMBASE, MEDLINE, www.ClincalTrials.gov and Cochrane Central databases using the following keywords: "clopidogrel", "ticagrelor", "prasugrel", "P2Y12 inhibitor", "percutaneous coronary intervention", "randomized controlled trial (RCT)", and "acute coronary syndrome (ACS)", covering the period from database inception to Dec. 31st, 2020. The inclusion criteria were randomized controlled trials (RCTs) investigating at least one of the three oral P2Y12 receptor antagonists of interest (clopidogrel, prasugrel and ticagrelor) in ACS patients over 18 years of age, with endpoints including MACE, all-cause mortality, and major- and minor bleeding. Pharmacokinetic or pharmacodynamic studies were not included. Two authors (HY Tseng and JK Lee) independently screened the titles and abstracts of all the identified articles and subsequently reviewed a number of full-text articles based on that screening to identify potentially relevant studies. Disagreements related to the identification or eligibility of studies were resolved through consensus.

Outcomes

The primary cardiovascular (CV) efficacy endpoint was MACE, which included stroke, myocardial infarction (MI), and death. The secondary efficacy outcomes were stent thrombosis, cardiovascular death and all-cause mortality. The safety outcomes were non-CABG TIMI criteria major bleeding, fatal bleeding, and intracranial hemorrhage (ICH).

Data extraction

Data extracted from the included studies were the trial name (if available), last name of first author, year of publication, recruitment period, follow-up duration, maintenance dose of the study arms, and number of patients in the intention-to-treat cohort. Data on subgroup variables of interest were also collected, including the study region (Asian vs. non-Asian), sex, age group (<75 yrs vs. ≥ 75 yrs), body weight (<60 kg vs. ≥ 60 kg), type of ACS (non-ST segment elevation myocardial infarction or unstable angina (NSTEMI/UA) vs. STEMI), and the presence or absence of diabetes and chronic kidney disease (CKD) (Table 1). For the outcome data, we extracted the tabulated

Table 1.

First author	Trial	Year	Enrollment	Size	Treatment	Asian	Population	Follow-up
Wiviott	TRITON–TIMI 38	2007	2004-2007	13,608	Prasugrel vs. Clopidogrel	< 28 (0.2%)	ACS (STEMI: 26%, NSTE-ACS: 74%)	Up to 15 months
Wallentin	PLATO	2009	2006-2008	18,624	Ticagrelor vs. Clopidogrel	1086 (5.83%)	ACS (STEMI: 38%, NSTE-ACS: 62%)	12 months
Saito	PRASFIT-ACS	2014	2010-2012	1363	Prasugrel vs. Clopidogrel	1363 (100%)	ACS (STEMI: 50%, NSTEM: 50%)	6 months
Goto	PHILO	2015	2011-2012	801	Ticagrelor vs. Clopidogrel	801 (100%)	ACS (STEMI: 51.8%, NSTE-ACS: 46%)	12 months
Park	TICAKOREA	2019	2014-2017	800	Ticagrelor vs. Clopidogrel	800 (100%)	ACS (STEMI: 40.7%, NSTE-ACS: 9.3%)	12 months

data, which included the sample size and number of events in each study arm. Finally, two authors (HY Tseng and JK Lee) assessed the risk of bias of the included trials using the Cochrane Risk of Bias tool, whereby disagreements were resolved through consensus.

Statistical analysis

The comparison of outcomes among the three P2Y12 agents was made under the frequentist approach using multivariate meta-analysis estimated by restricted maximum likelihood. As the summary statistics we chose pooled random-effects risk ratios (relative risks) calculated directly from the reported tabular data (sample size and number of events). Pairwise comparison among the three P2Y12 agents was made using a visual forest plot, rather than using a table. The overall heterogeneity of all comparisons was assessed using the I^2 statistic, in which a value > 50% was considered indicative of substantial heterogeneity. Focusing on the primary endpoint (MACE), we conducted several subgroup analyses according to pre-specified subgroup variables, including the study region, sex, age group, body weight group, type of MI, and the presence or absence of diabetes and CKD. We also conducted analyses of exclusively Asian and non-Asian populations. The network meta-analysis was carried out using the netmeta statistical package (version 1.3-0; updated on January 18, 2021) in R (version 4.0.3).

Results

Search results

A total of 745 articles were identified, of which 698 were subsequently removed because they did not meet the inclusion criteria. The remaining 47 articles were further screened for eligibility. Ultimately, 5 RCTs including 35,196 patients were included in this network meta-analysis. The years of publication ranged from 2004 to 2019, and the sample sizes ranged from 800 to 18,624 patients. All of the studies included ACS patients only. Three of the five studies, including the PRASFIT-ACS, PHILO and TICAKOREA studies, exclusively enrolled Asian populations (Supplemental Figure 1).

Risk of bias

All five of the included trials met the criteria for low risk of bias. Detailed results of the risk-of-bias assessments are provided in the supplemental materials (Supplemental Figure 2).

Overall comparison

Supplemental Figure 3 depicts the network diagram. MACE developed in 3,587 patients (10.2%) out of the total of 35,196 patients in the 5 RCTs. No statistically significant difference was noted between any two of the three P2Y12 receptor antagonist agents. However, compared to clopidogrel, prasugrel was associated with a numerically lower risk of MACE (risk ratio [RR]: 0.84, 95% confidence interval [CI]: 0.53-1.34), while ticagrelor was associated with a numerically higher risk of MACE (RR: 1.27, 95% CI: 0.84-1.92). In addition, ticagrelor also had a numerically higher risk of MACE (RR: 1.50, 95% CI: 0.81-2.80) when compared with prasugrel (Figure 1A).

CV death and all-cause mortality occurred in 1,133 patients (3.2%) and 1,388 patients (3.9%), respectively. Neither a significant nor a numerical difference was noted between any two of the three agents (Figure 1B, 1C). Stent thrombosis was reported to have developed in 402 patients (1.1%) in 4 of the RCTs with a total of 34,395 patients. Compared with clopidogrel, significantly lower stent thrombosis risk was noted for both prasugrel (RR: 0.49, 95% CI: 0.37-0.65) and ticagrelor (RR: 0.66, 95% CI: 0.49-0.89). Remarkably, ticagrelor was associated with a borderline higher risk of stent thrombosis (RR: 1.35, 95% CI: 0.90-2.03) than prasugrel (Figure 1D).

Non-CABG TIMI criteria major bleeding developed in 758 patients (2.2%) out of the total of 35,196 patients in all 5 RCTs. Compared with clopidogrel, a borderline higher risk of non-CABG

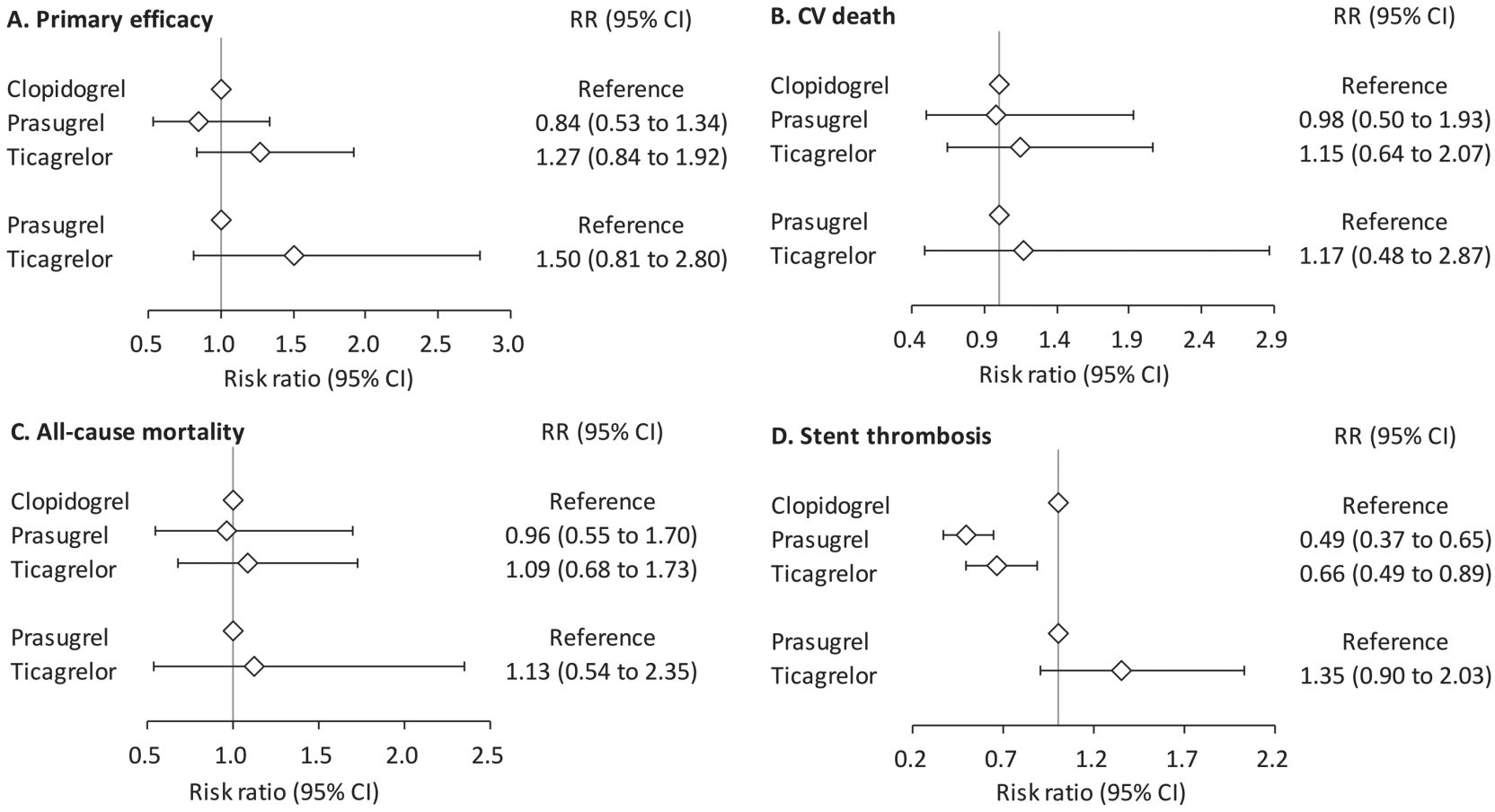


Figure 1. Summary of network meta-analysis of the efficacy outcomes. (A) Primary efficacy (B) CV death (C) All-cause mortality (D) Stent thrombosis.

TIMI criteria major bleeding was noted with both prasugrel (RR: 1.26, 95% CI: 0.996-1.58) and ticagrelor, where the increase was significant (RR: 1.29, 95% CI: 1.08-1.54). The risks with prasugrel and ticagrelor were quite similar (Figure 2A). Fatal bleeding was reported in 76 patients (0.2%) in 5 of the RCTs covering a total of 34,041 patients.

The risk was numerically higher with prasugrel when compared to clopidogrel (RR: 3.94, 95% CI: 0.94-12.96). Ticagrelor showed a difference in risk of fatal bleeding compared to clopidogrel (RR: 1.22, 95% CI: 0.37-4.04) and prasugrel (RR: 0.35%, 95% CI: 0.06-2.07) (Figure 2B). Intracranial hemorrhage (ICH) was reported in 81 patients (0.2%) from 3 of the RCTs with a total of 32,678 patients. The risks with prasugrel and clopidogrel were quite similar (RR: 1.11, 95% CI: 0.58-2.14). However, the risk of ICH with ticagrelor was significantly and numerically greater than with clopidogrel (RR: 1.97, 95% CI: 1.06-3.66) and prasugrel (RR: 1.77, 95% CI: 0.72-4.35) (Figure 2C).

MACE subgroup analysis

The results showed differences between the sexes. Prasugrel showed a significant protective effect in males, when compared to clopidogrel (RR: 0.75, 95% CI: 0.56-0.097), while ticagrelor showed no such benefits, compared to clopidogrel (RR: 1.03, 95% CI: 0.77-1.40). By contrast, ticagrelor showed significantly lower risk in females, compared to clopidogrel (RR: 0.85, 95% CI: 0.74-0.98), while prasugrel showed only numerically lower risk, compared to clopidogrel (RR: 0.87, 95% CI: 0.74-1.02). Comparing ticagrelor and prasugrel, no significant difference was noted between the male and female subgroups. Noticeably, ticagrelor showed numerically higher harmful effect in comparison to prasugrel in male patients (RR: 1.38, 95% CI: 0.99-1.93), almost reaching statistical significance (Figure 3A).

The results differentiated by body weight (BW) were quite different. In patients with BW < 60 kg, no statistically significant difference was noted between any two of the three agents. However, in patients with BW ≥ 60 kg, prasugrel was associated with a significantly lower risk than clopidogrel (RR: 0.64, 95% CI: 0.46-0.89). Moreover, the risk was significantly higher with ticagrelor than with prasugrel (RR: 1.41, 95% CI: 1.05-1.90) (Figure 3B).

In terms of age, the results were generally similar for the older (over 75 years of age) and younger (under 75 years) cohorts. The risks with ticagrelor and clopidogrel were quite similar in both age cohorts. One major difference was that a significantly lower risk was observed with prasugrel than with clopidogrel in the younger cohort (RR: 0.72, 95% CI: 0.57-0.92), but not in the older cohort. Moreover, the risk with ticagrelor was borderline higher than with prasugrel in the younger cohort (RR: 1.27, 95% CI: 0.95-1.71), but not in the older cohort (Supplemental Figure 4).

As regards the ACS presentation, the results were generally similar for the NSTEMI/UA and STEMI cohorts. In both NSTEMI/UA and STEMI patients, ticagrelor showed no difference, whether comparing to clopidogrel or to prasugrel. Prasugrel showed a lower risk compared to clopidogrel (RR: 0.75, 95% CI: 0.64-0.88) only in NSTEMI/UA patients, but no significant difference in STEMI patients (RR: 0.86, 95% CI: 0.63-1.17) (Supplemental Figure 5).

Regarding the diabetes status, the results were generally similar for the DM and non-DM cohorts. In both DM and non-DM patients, ticagrelor showed no difference, compared to either clopidogrel or prasugrel. Prasugrel showed lower risk compared to clopidogrel (RR: 0.68, 95% CI: 0.46-0.99) only in non-DM patients but not in DM patients (RR: 0.90, 95% CI: 0.64-1.25) (Supplemental Figure 6).

Some differences were noted between the CKD and non-CKD cohorts. While the protective effect of prasugrel compared to clopidogrel was significant in both the CKD and non-CKD cohorts, the reduced risk with ticagrelor compared

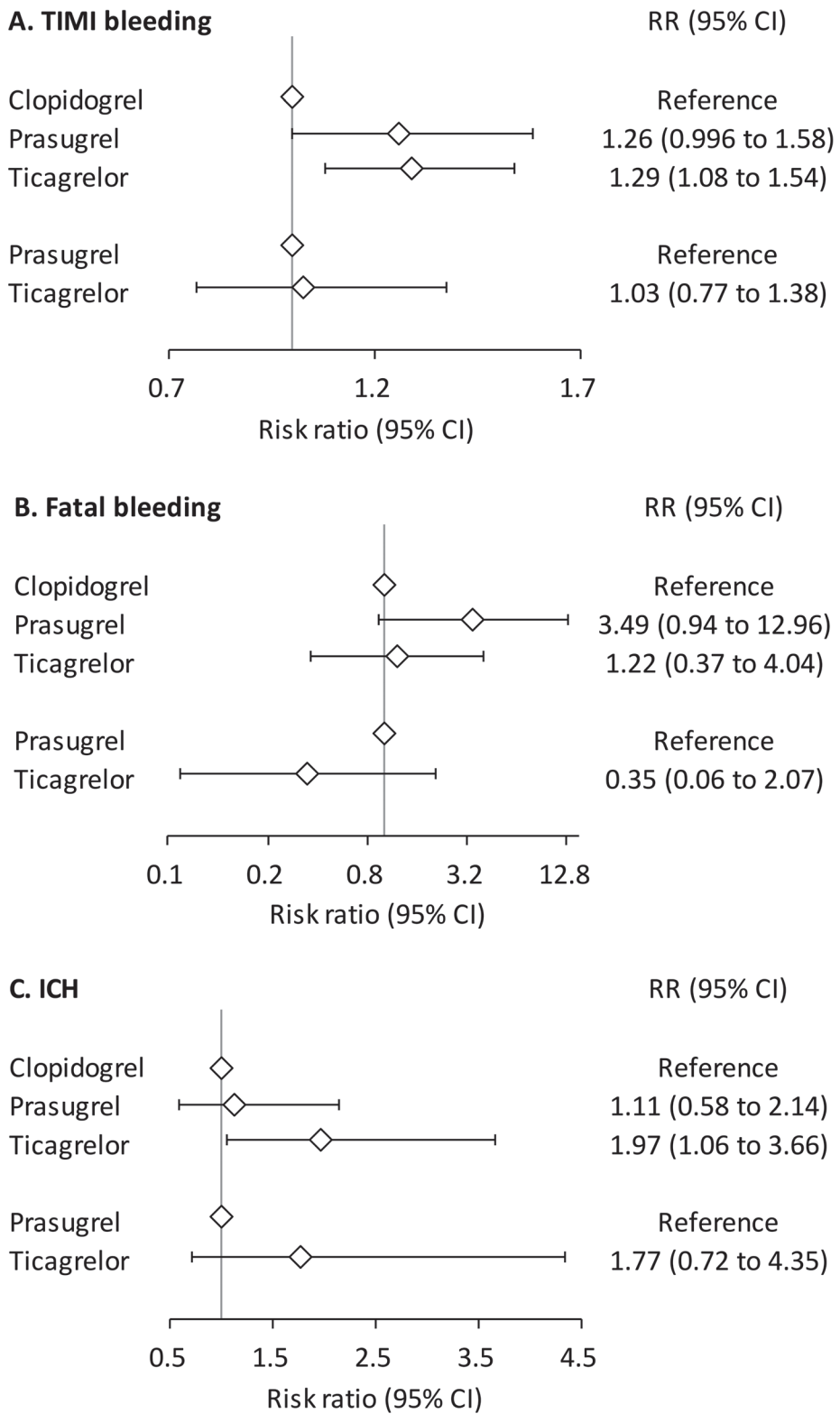


Figure 2. Summary of network meta-analysis of the safety outcomes. (A) TIMI major bleeding (B) Fatal bleeding (C) ICH.

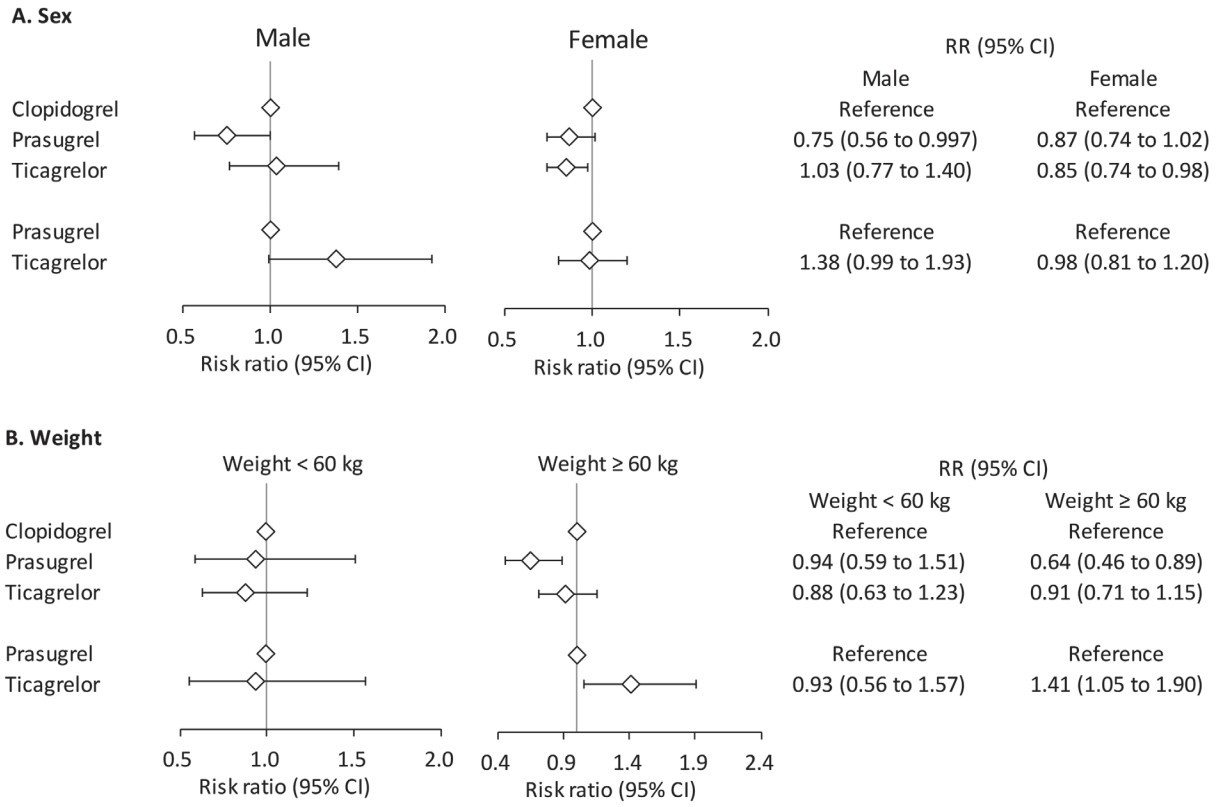


Figure 3. Summary of network meta-analysis of major adverse cardiac events stratified by (A) sex and (B) body weight.

to clopidogrel was only observed in the non-CKD cohort (RR: 0.81, 95% CI: 0.70-0.93), but not in the CKD cohort (RR: 0.95, 95% CI: 0.78-1.16). Interestingly, the risks for prasugrel and ticagrelor were similar in the non-CKD cohort, while the risk was borderline higher for ticagrelor than prasugrel in the CKD cohort (Supplemental Figure 7).

Asian and non-Asian trials subgroup analysis

The three P2Y12 inhibitors showed tremendous differences in MACE when separated into Asian and non-Asian regions (Figure 4A). Prasugrel showed a significant protective effect in comparison to clopidogrel (RR: 0.82, 95% CI: 0.74-0.91) in the non-Asian trials, while prasugrel and clopidogrel retained similar MACE rates (RR: 0.87, 95% CI: 0.59-1.28) in Asian trials. More interestingly, the effect of ticagrelor compared to clopidogrel was protective in the non-Asian trials (RR: 0.85, 95% CI: 0.78-0.92), but harmful in the Asian trials (RR: 1.75, 95% CI: 1.18-2.59). The risks were comparable with ticagrelor and prasugrel in the non-Asian trials (RR: 1.03, 95% CI: 0.91-1.18), but higher with ticagrelor than prasugrel in the Asian trials (RR: 2.01, 95% CI: 1.16-3.48).

In terms of CV death and all-cause mortality, the risks remained quite comparable between prasugrel and clopidogrel in both Asian and non-Asian trials (Figures 4B, 4C). The effect of ticagrelor compared to clopidogrel was significantly protective in the non-Asian trials, whereas it remained similar in the Asian trials. When comparing ticagrelor to prasugrel between

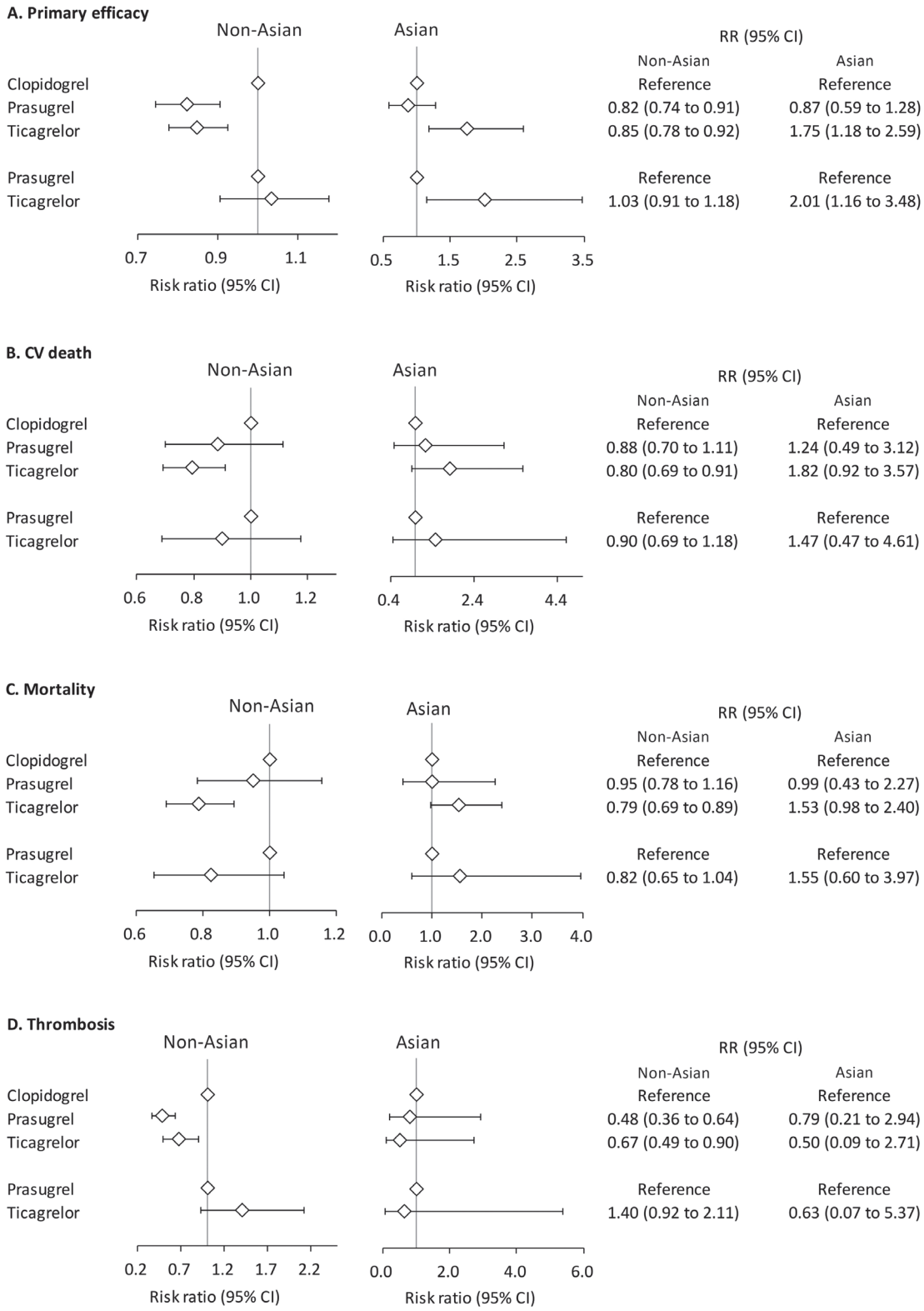


Figure 4. Summary of network meta-analysis of the efficacy outcomes in Asian and non-Asian trials. (A) Primary efficacy (B) CV death (C) All-cause mortality (D) Stent thrombosis.

the Asian and non-Asian trials, ticagrelor trended toward being more protective in the non-Asian trials and toward harmful in the Asian trials, but without reaching statistical significance.

Regarding stent thrombosis, none of the comparisons between any two agents showed a statistically significant difference in the Asian trials (Figure 4D). In the non-Asian trials, the risk with prasugrel and ticagrelor was lower than with clopidogrel, while the risk with ticagrelor was still numerically higher than with prasugrel (RR: 1.40, 95% CI: 0.92-2.11).

The risks of TIMI bleeding with prasugrel relative to clopidogrel were higher in the non-Asian trials (RR: 1.31, 95% CI: 1.03-1.67) but were comparable in the Asian trials (RR: 0.86, 95% CI: 0.41-1.79) (Figure 5A). Ticagrelor carried significantly greater risk of TIMI bleeding than clopidogrel in both non-Asian (RR: 1.24, 95% CI: 1.02-1.51) and Asian trials (RR: 1.57, 95% CI: 1.001-2.48). Moreover, the risks with prasugrel and ticagrelor were quite comparable in the non-Asian trials (RR: 0.95, 95% CI: 0.69-1.30) and the Asian trials (RR: 1.84, 95% CI: 0.77-4.35).

Fatal bleeding outcomes were differed notably between the Asian and non-Asian trials (Figure 5B). The risks with prasugrel were significantly higher than with clopidogrel in the non-Asian trials (RR: 4.18, 95% CI: 0.77-4.35), but were comparable in the Asian trials (RR: 1.84, 95% CI: 0.77-4.35). The risks with ticagrelor and clopidogrel were quite comparable in the non-Asian trials (RR: 0.87, 95% CI: 0.48-1.57) and the Asian trials (RR: 9.00, 95% CI: 0.49-166.61). The risks with ticagrelor were significantly lower than with prasugrel in the non-Asian trials (RR: 0.21, 95% CI: 0.07-0.65), but similar in the Asian trials (RR: 4.55, 95% CI: 0.10-198.68).

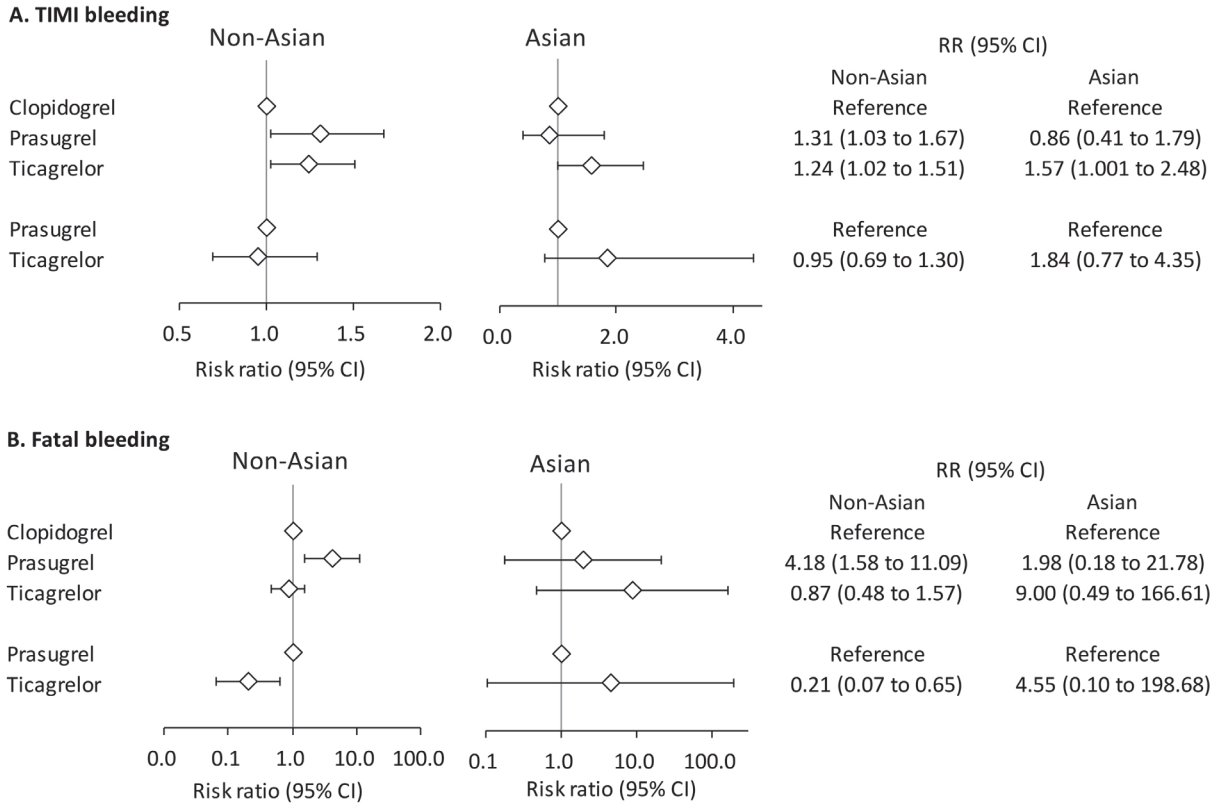


Figure 5. Summary of network meta-analysis of the safety outcomes in Asian and non-Asian trials. (A) TIMI major bleeding (B) Fatal bleeding.

Discussion

In our network meta-analysis (NMA), there was no difference in risks of MACE between clopidogrel, prasugrel and ticagrelor when treating ACS. However, the risks of stent thrombosis with both prasugrel and ticagrelor were lower in comparison to clopidogrel. As for safety concerns, ticagrelor showed significantly higher rates of non-CABG TIMI criteria major bleeding and ICH than clopidogrel. Interestingly, when analyzed by Asian and non-Asian trials, prasugrel and ticagrelor showed lower MACE rates than clopidogrel in non-Asian trials, while ticagrelor had higher MACE rates than clopidogrel and prasugrel in Asian trials. Stent thrombosis rates were comparable across the three P2Y12 inhibitors in Asian trials.

To the best of our knowledge, no randomized controlled trial (RCT) has undertaken a direct comparison of clopidogrel, prasugrel and ticagrelor in an ACS setting, and previously published meta-analyses have mainly compared only two of the three P2Y12 inhibitors. A previous meta-analysis comparing prasugrel and clopidogrel in ACS patients showed similar rates of all-cause death, MI and stroke; however, no analysis of MACE was reported in that study.[9] Similarly, a previous meta-analysis of ticagrelor and clopidogrel showed comparable MACE rates, but only in ACS patients who underwent PCI.[10] Two previous meta-analyses were conducted on ticagrelor and prasugrel in an ACS setting. One analysis reported ticagrelor associated with higher short-term stent thrombosis and long-term all-cause mortality compared to ticagrelor in ACS patients who received PCI.[11] The other analysis reported no difference in 1 year MACE between ticagrelor and prasugrel.[12] Therefore, we used network meta-analysis to compare clopidogrel, prasugrel and ticagrelor and discovered no difference in the risks of MACE in an ACS setting.

Two RCTs comparing prasugrel and ticagrelor that were not included in our NMA deserve mention. One RCT was the ISAR-REACT 5 trial, a multicenter, open-label RCT with ACS patients randomized to ticagrelor or prasugrel, in which prasugrel had a lower rate of the composite outcome of stroke, MI or death in the first year.[13] This study was excluded because 19% of the patients were not receiving a trial drug at discharge and one third of the study cohort no longer received the initial treatment by the end of the study. The other RCT was the PRAGUE-18 trial, a multicenter RCT with AMI patients randomized to ticagrelor or prasugrel which found prasugrel and ticagrelor to have similar combined endpoints of cardiovascular death, MI and stroke at one year.[14] However, high rates of crossover to clopidogrel were noted, namely 34.1% in the prasugrel group and 44.4% in the ticagrelor group. For these reasons, we did not include these two studies in our network meta-analysis.

There are very few NMAs comparing clopidogrel, prasugrel and ticagrelor with regard to MACE in ACS. Two NMAs were conducted before publication of the TICA KOREA trial. In 2016, Rafique et al. reported an NMA including 37 studies with a total of 88,402 STEMI patients that discovered that prasugrel was associated with lower rates of MACE within one year than clopidogrel and ticagrelor.[15] However, that NMA only included studies with STEMI patients and consisted of observational studies and registry data. In 2017, Shah et al. conducted similar studies of ACS patients and found that both prasugrel and ticagrelor had decreased rates of MACE compared with clopidogrel, but there was no significant difference between the agents upon direct comparison.[16] That NMA included 9 RCTs with a total of 106,288 patients, but half of the patients were initially allocated to clinical trials that compared place and clopidogrel, such as the CURE,[3] COMMIT[4] and CLARITY TIMI-28 studies.[17]

Two further NMAs were conducted recently. In 2020, Navarese et al. analyzed 12 RCTs with a total of 52,816 patients with ACS[18] and found that, compared with clopidogrel, ticagrelor

significantly reduced CV mortality and all-cause mortality, whereas prasugrel had no statistically significant mortality reduction, compared with clopidogrel. However, MACE was not reported in the Navarese et al. study. Most importantly, that study included RCTs focusing exclusively on special populations. For example, the Elderly ACS 2 trial,[19] the POPular Age trial[20] and a trial conducted by Wang et al.[21] only included elderly ACS patients. Another example of a study involving a special population was the TRICOLOGY ACS trial,[22] which only enrolled ACS patients without revascularization. These drawbacks might limit the applicability of the results of the studies in question to the whole ACS population. In 2020, Baldetti et al. conducted a similar study and found no significant differences between clopidogrel, prasugrel and ticagrelor with respect to 1-year MACE outcomes,[23] a finding which was similar to that of our NMA. However, the Baldetti et al. study included some prospective studies and some studies with short follow-up durations. Most importantly, no authors reported subgroup analyses in any of these previous NMAs, and none of them conducted analysis with regard to Asian and non-Asian populations.

With regard to safety concerns, our NMA confirmed the suspicions that the more potent the P2Y12 inhibitors are, the higher the bleeding rate will be. Prasugrel had a borderline higher risk of TIMI major bleeding than clopidogrel, almost reaching statistical significance. Higher major bleeding risks with ticagrelor, compared to clopidogrel, were also confirmed. Our finding was similar to previous meta-analyses reporting similar results with prasugrel[9] and ticagrelor[10] in comparison to clopidogrel. Our meta-analysis also showed that, in direct comparison, prasugrel and ticagrelor had no difference in this regard, consistent with previous meta-analyses.[11,12]

Thrombogenicity and hemorrhagic diathesis In Asian ACS populations differ from those in their Western counterparts. However, global clinical trials have included only low numbers of Asian patients. Focusing on studies which enrolled only Asian populations, only three RCTs were found, all of which were included in our analysis. The PRASFIT-ACS trial compared low-dose prasugrel (loading dose of 20 mg and maintenance doses of 3.75 mg) and clopidogrel.[24] The PHILO trial and TICAKOREA trial compared ticagrelor and clopidogrel.[26,27] However, no RCTs have directly compared prasugrel and ticagrelor in Asian populations. Overall, Asian populations showed differences in MACE and stent thrombosis rates, while non-Asian populations showed differences in MACE, CV death, mortality, TIMI bleeding and fatal bleeding rates.

Regarding MACE, our overall NMA showed no difference between the three different P2Y12 inhibitors. However, the analysis of Asian trials showed ticagrelor to be more harmful than clopidogrel and prasugrel. A similar result whereby ticagrelor had higher MACE rates than clopidogrel can be found in the PHILO trial and the TICAKOREA trial, which both reported a trend with ticagrelor toward higher MACE rates, though the difference did not reach statistical significance.[26,27] However, observational studies have reported a different result. In the KAMIR-NIH study, conducted in south Korea, Ticagrelor showed a similar MACE rate compared to clopidogrel.[35] In addition, ticagrelor even showed superiority in terms of MACE in the COSTIC study performed in China[36] and the ESTATE study conducted in Taiwan.[37] However, the conclusion that ticagrelor had a higher MACE rate than prasugrel in Asian populations was reached in the context of a lack of direct comparison trials. Comparing clopidogrel and low-dose prasugrel in an Asian population, no significant difference was noted, as evidenced by the PRASFIT-ACS trial and also observed in a real-world observational study,[24] the KiCS-PCI registry study performed in Japan.[38]

With regard to stent thrombosis, in our overall NMA, prasugrel and ticagrelor both showed lower stent thrombosis rates, compared to clopidogrel. By contrast, in Asian populations, the three P2Y12 receptor antagonists showed

comparable stent thrombosis rates. This was also observed in real-world observational studies. In the J-PCI registry study conducted in Japan, low-dose prasugrel and clopidogrel showed no difference in stent thrombosis rate. In the ESTATE study from Taiwan[37] and the KAMIR-NIH study from Korea,[36] ticagrelor and clopidogrel showed no difference in stent thrombosis rates. Based on the databases of the Korean national health insurance service, prasugrel and ticagrelor showed no difference in stent thrombosis rate, compared to clopidogrel.[39] However, no study has previously compared prasugrel and ticagrelor in Asian populations. Notably, the above results should be interpreted with caution since the standard dose of prasugrel used in the global trials (loading 60 mg and maintenance 10 mg) differed from the lower dose of prasugrel used in the Asian studies (loading 20 mg and maintenance 3.75 mg).

In summary, considering Asian populations, clopidogrel and low-dose prasugrel offered similar effects with regard to MACE reduction and stent thrombosis prevention. Ticagrelor, however, was harmful as regards MACE when compared with clopidogrel and low-dose prasugrel. The three P2Y12 inhibitors showed no difference as regards CV death, mortality, stent thrombosis rate, TIMI major bleeding and fatal bleeding in Asian populations. Therefore, clopidogrel and low-dose prasugrel should be favored over ticagrelor in Asian ACS populations. However, further studies are warranted to determine the optimal antiplatelet regimen and dosage in Asian ACS patients.

The importance and value of this study lay in its comparison of ticagrelor and prasugrel for which there is a lack of robust RCTs. Our overall NMA showed no difference regarding MACE, CV death, all-cause mortality, stent thrombosis, TIMI bleeding, fatal bleeding and ICH. However, the analysis of exclusively Asian RCTs showed ticagrelor associated with significantly higher MACE rates, but less fatal bleeding, compared to prasugrel.

Limitations

This NMA had several limitations. First, the results were analyzed on the clinical trial scale; not in terms of individual participant data. There were various sources of heterogenicity among the ACS treatments, such as dose and duration of P2Y12 inhibitor therapy, vascular access routes, glycoprotein IIb/IIIa inhibitors, drug-eluting stents, and degrees of operator experience. In particular, the differences in dosages should be noted. Regarding clopidogrel, most studies used 300 mg as the loading dose, but 20% of the patients in the PLATO trial and all of the participants in the TICAKOREA trial received 600 mg as a loading dose. More notably, there were two different loading and maintenance regimens for prasugrel. One was 60 mg loading with 10 mg maintenance, which was adopted in the TRITON–TIMI 38 trial; the other was 20 mg loading with 3.75 mg maintenance, as used in the PRASFIT-ACS trial. Dosing of clopidogrel were reduced in elderly patients and patients with low body weight. Furthermore, prasugrel should only be given when coronary anatomy is known and it is contraindicated in cases with a history of cerebrovascular accident.

Second, the included RCTs used different definitions of clinical events, different follow-up durations, and different sample sizes. Only RCTs were enrolled in our NMA, which increased the reliability of our study but limited its clinical implications in terms of real-world practice. Our study underscores the need for further RCTs to directly compare the clinical efficacy and safety outcomes of various P2Y12 receptor antagonists in ACS patients.

Conclusion

Our NMA suggested that clopidogrel, prasugrel and ticagrelor carried similar risks regarding MACE, CV death and all-cause mortality. Only ticagrelor was associated with increased risks of major bleeding events and

ICH when compared to clopidogrel. In Asian patients, ticagrelor was found to be harmful with regard to MACE when compared to clopidogrel and ticagrelor. Results from further RCTs are needed to further evaluate the efficacy and safety differences between clopidogrel, prasugrel and ticagrelor.

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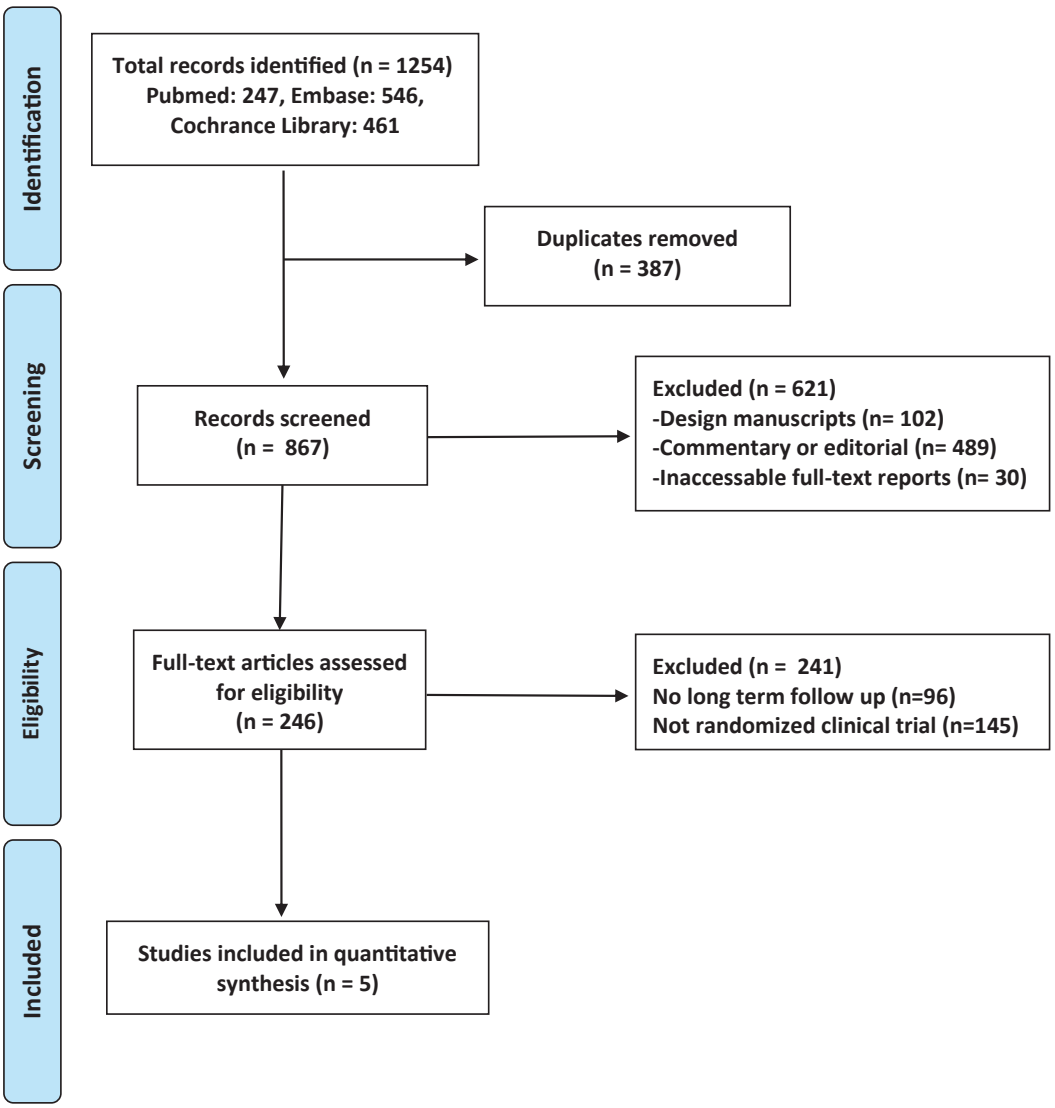
SUPPLEMENT



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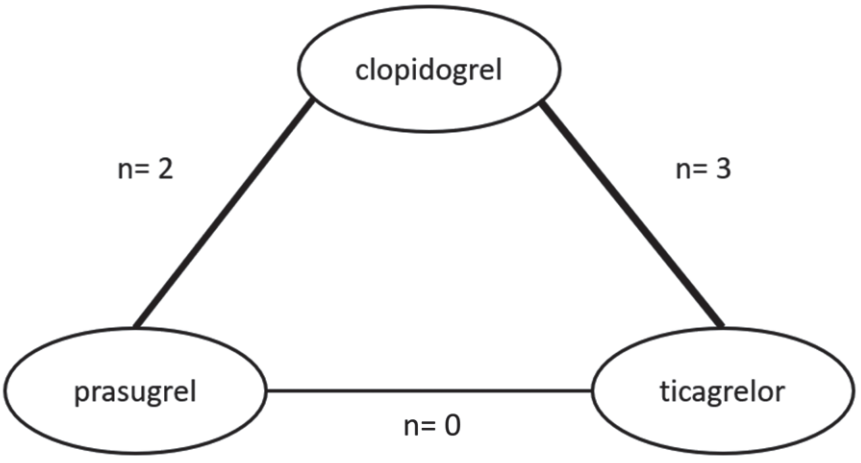
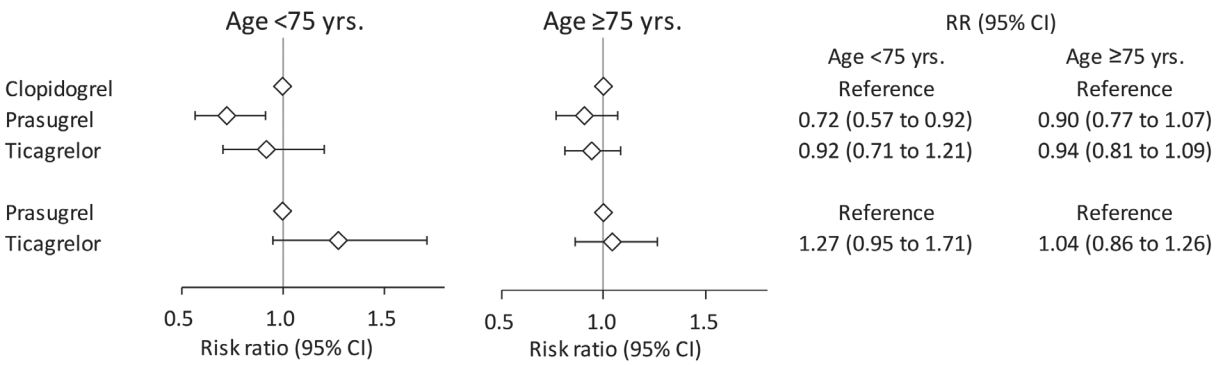
Supplemental Figure 1. Flowchart for inclusion and exclusion of studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias) (Mortality)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Selective reporting (reporting bias)
TRITON-TIMI 38	Low	Low	Low	Low	Low	Low	Low	Low
PLATO	Low	Low	Low	Low	Low	Low	Low	Low
PRASFIT-ACS	Low	Low	Low	Low	Low	Low	Low	Low
PHILO	Low	Low	Low	Low	Low	Low	Low	Low
TICAKOREA	Low	Low	Low	Low	Low	Low	Low	Low

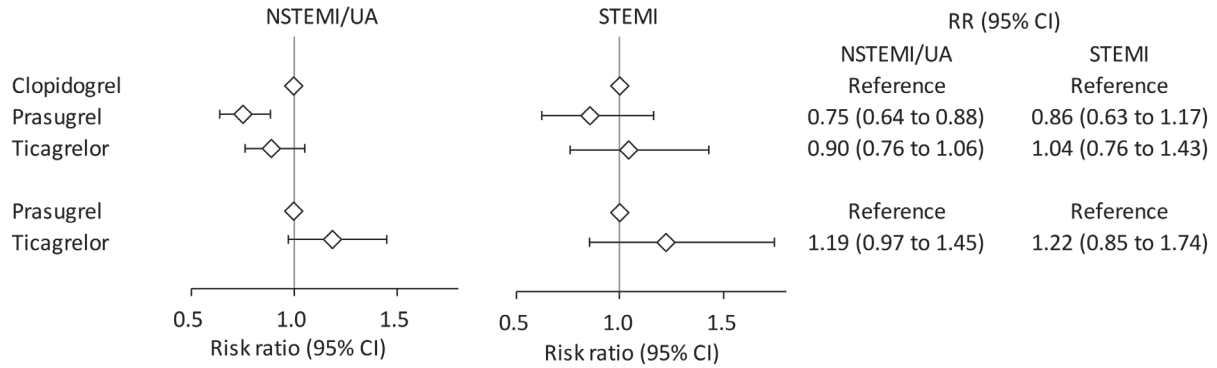
Supplemental Figure 2. Assessment of risk of bias in the included studies.



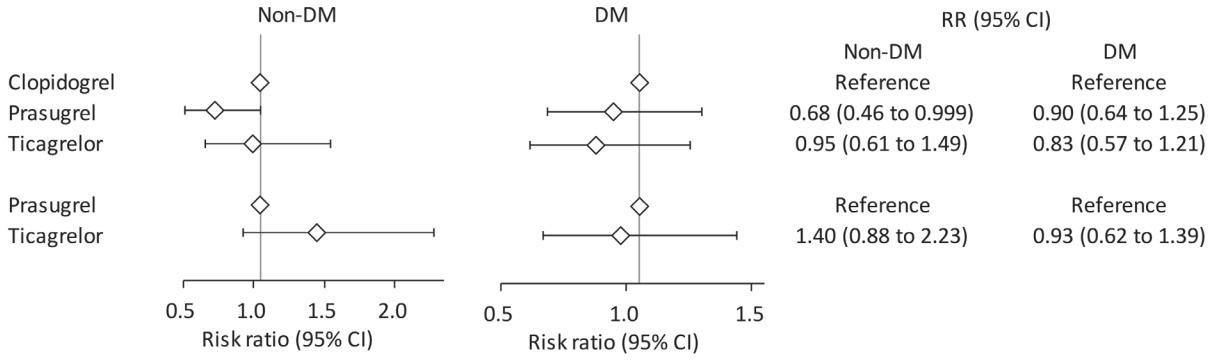
Supplemental Figure 3. Network diagram of treatment comparisons included in this study. The link thickness between treatments reflects the number of studies.



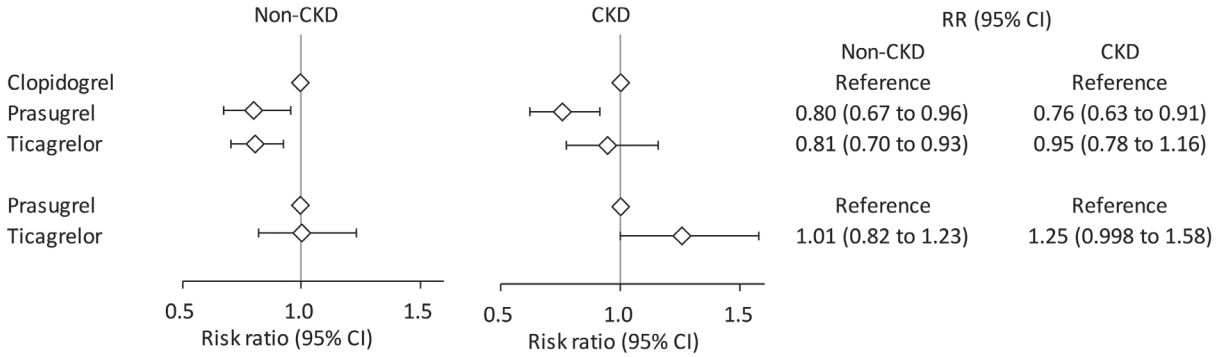
Supplemental Figure 4. Summary of network meta-analysis of major adverse cardiac events stratified by age, above or below 75 years old.



Supplemental Figure 5. Summary of network meta-analysis of major adverse cardiac events stratified by etiology of acute coronary syndrome.



Supplemental Figure 6. Summary of network meta-analysis of major adverse cardiac events stratified by the presence or absence of diabetes.



Supplemental Figure 7. Summary of network meta-analysis of major adverse cardiac events stratified by the presence or absence of chronic kidney disease.