Received: 13 January 2020 | Revised: 25 February 2020 | Accepted: 20 March 2020

DOI: 10.1111/bcp.14317

SYSTEMATIC REVIEW AND META-ANALYSIS

Efficacy and safety of clopidogrel versus prasugrel and ticagrelor for coronary artery disease treatment in patients with CYP2C19 LoF alleles: a systemic review and meta-analysis

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Aim: We performed a systematic review and meta-analysis to compare the efficacy and safety of ticagrelor and prasugrel with those of clopidogrel in CYP2C19 reduced-metabolizers.

Methods: PubMed, Cochrane and Web of Science were systematically searched for randomized controlled trials or cohort studies up to January 2020. The primary endpoint was major adverse cardiovascular events (MACE), including cardiovascular (CV) death, all-cause death, myocardial infarction (MI), stent thrombosis and stroke. The secondary endpoint was bleeding. Pooled effects were measured by relative risk (RR) with 95% confidence intervals (CIs). Publication bias was evaluated with Egger's regression test and adjusted by trim and fill method.

Results: Twelve studies comprising 5829 CV patients with CYP2C19 loss-of-function alleles were included. Patients who received ticagrelor or prasugrel showed a lower risk of MACE than those who received clopidogrel (RR 0.524; 95% CI: 0.375, 0.731). The former also had lower risks of CV death (RR 0.409; 95% CI: 0.177, 0.946), all-cause death (RR 0.441; 95% CI: 0.263, 0.739), MI (RR 0.554; 95% CI: 0.414, 0.741) and stent thrombosis (RR 0.587; 95% CI: 0.348, 0.988) than the latter patient group. The risk of stroke was not significantly different between patients receiving the alternatives and those receiving clopidogrel (RR 0.605; 95% CI: 0.257, 1.425). Major and minor bleeding risk was not significantly different between patients treated with alternatives and clopidogrel (RR 1.019; 95% CI: 0.827, 1.260 and RR 1.235; 95% CI: 0.581, 2.628, respectively).

Conclusion: CYP2C19 reduced-metabolizers can expect better clinical outcome on using prasugrel or ticagrelor rather than clopidogrel.

KEYWORDS

bleeding, CYP2C19 reduced-metabolizers, major adverse cardiovascular events, meta-analysis, P2Y12 receptor inhibitors

Ha Young Yoon and Nari Lee contributed equally to this work.

1 | INTRODUCTION

P2Y12 receptor inhibitors, such as clopidogrel, prasugrel or ticagrelor, play a key role in secondary prevention of thrombotic events in patients with coronary artery disease (CAD).[1] Clopidogrel is converted to an active metabolite by hepatic enzyme cytochrome P450 (CYP) 2C19. Therefore, CYP2C19 polymorphisms could alter patients' responses to clopidogrel.[2] Patients with CYP2C19 loss-of-function (LoF) alleles (*2, *3, *4, *5, *6, *7 and *8) have shown decreased concentration of the active metabolite (reduced-metabolizers, RM) and have been associated with an increased risk of major adverse cardiovascular events (MACE).[3] The US Food and Drug Administration proposed that healthcare professionals consider the use of other antiplatelet medications or dosing strategies as an alternative to clopidogrel in patients with CYP2C19 LoF alleles.[4]

Prasugrel and ticagrelor are alternative P2Y12 inhibitors; prasugrel is a prodrug that irreversibly inhibits the P2Y12 receptor, whereas ticagrelor is a reversible direct-acting inhibitor of the P2Y12 receptor. Both drugs are less susceptible to CYP2C19 status and show less variability across patients so that they are prescribed as an alternative to clopidogrel-resistant patients.[5,6] These alternatives show more consistent, faster and greater inhibition of platelet reactivity than clopidogrel.[7–9]

Although some adverse events among CYP2C19 reduced-metabolizers (RM) have been reported, standard-dose clopidogrel is widely used regardless of clopidogrel resistance.[10] Additionally, not many studies have been published regarding a comparative analysis of the efficacy and safety of clopidogrel with those of alternative antiplatelet agents in CYP2C19 RMs. Therefore, this meta-analysis aimed to examine the necessity of prospective CYP2C19 genotyping by comparing the risk of MACE and bleeding between CYP2C19 RMs who were treated with the alternatives and those treated with clopidogrel.

2 | METHODS

The paper was written based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

2.1 | Search strategy

Two investigators (N.R.L. and H.Y.Y.) independently conducted a systemic search of all studies published before January 2020 using PubMed, Cochrane and Web of Science. The following search terms were included: (clopidogrel OR prasugrel OR ticagrelor OR cangrelor OR antiplatelet* OR purinergic P2Y12 receptor antagonist OR thienopyridine*) AND (percutaneous coronary intervention OR stent thrombosis OR cardiovascular disease OR acute coronary syndrome OR myocardial ischemia) AND (MACE OR major adverse cardiac events OR bleeding) AND (cytochrome P450 2C19 OR CYP2C19 OR polymorphi* OR genetic OR genotype OR mutation). Additionally, the references of the searched studies were also screened.

2.2 | Selection criteria and data extraction

Studies were selected if (1) cardiovascular (CV) patients had CYP2C19 LoF alleles; (2) standard-dose or high-dose clopidogrel was compared with prasugrel or ticagrelor; (3) the study evaluated adverse cardiovascular events such as death, stroke, myocardial infarction, stent thrombosis or bleeding; (4) the study design was randomized controlled trial (RCT) or cohort study. Studies were excluded if (1) outcome data were not predefined and extractable; (2) it was not an original article; (3) it was not written in English.

The primary endpoint is MACE, which is defined as the composite of CV death, all-cause death, myocardial infarction (MI), stent thrombosis and stroke. The risk of each component of MACE was also assessed. The secondary endpoint is bleeding classified as major and minor bleeding. Major bleeding included "severe bleeding" as defined in the GUSTO study and "major bleeding" as defined in the TIMI and PLATO studies (see Table S1 in the supplementary material0.[12] Minor bleeding consisted of other bleeding types that did not meet the major bleeding criteria. The following parameters were extracted independently by two investigators: study design, name of first author, year of publication, country, mean age, medication dose, follow-up duration, genotyping method and endpoints as well as the total number of MACE and bleeding.

The quality of RCT studies was assessed by Cochrane Collaboration's tool: a lower risk of bias was allotted a score of 2, unclear bias risk was allotted a score of 1, and high risk of bias was allotted a score of 0.[13,14] For cohort studies, the Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies.[15] A scoring system on this scale was based on three components: selection of subjects (0–4 points); comparability of study groups (0–2 points); and determination of outcomes of interest (0–3). Disagreements were discussed and consensus was reached on all points after carrying out discussions with a third investigator (J.-M.S.).

2.3 | Statistical analysis

Relative risk (RR) with 95% confidence intervals (CIs) was calculated to compare the risk of MACE and bleeding using the Mantel–Haenszel method. Heterogeneity was evaluated by Cochran's Q statistic and Higgins' and Thompson's I^2 statistics.[16] Depending on the heterogeneity results, a fixed-effects or random-effects model was used to calculate the effect size.[17] The random-effects model was applied when heterogeneity existed ($P < .1$, $I^2 > 50\%$); otherwise, the fixed-effects model was applied. Egger's regression test for evaluating funnel plot asymmetry was

performed to identify potential publication bias, while the "trim and fill" method was used to adjust publication bias.[18,19] Sensitivity analysis was conducted, by sequential omission of each study, to validate robustness of the results. Additional subgroup analysis of the primary endpoint was performed on studies with RCT design.

Statistical analyses were performed using Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ, USA).

3 | RESULTS

3.1 | Overviews of studies

The literature search resulted in 7761 articles. Of these, 1107 duplicates were removed, and 6562 articles were excluded based on the title of the articles. Finally, after screening abstract or full-text articles, 12 articles remained (Figure 1). The characteristics of these studies are presented in Table 1.[20–31] A total of 12 studies encompassing 5829 CV patients with CYP2C19 LoF alleles were included in primary analysis. Patients, who were treated with clopidogrel at a dose range of 75–150 mg/day, prasugrel at a dose range of 3.75–10 mg/day, and ticagrelor at a dose of 180 mg/day, were diagnosed with stable CAD or acute coronary syndrome (ACS). Patients were enrolled between 2004 and 2017 and studies were published between 2010 and 2019. The risk scores of bias for RCT ranged from 7 to 10, and those for cohort studies ranged from 8 to 9 (Table 1).

3.2 | The primary endpoint (efficacy)

Patients who received alternatives showed a lower risk of composite MACE than those receiving clopidogrel (RR 0.524; 95% CI: 0.375, 0.731) (Figure 2A). Heterogeneity was detected among studies (I^2 = 56%; P = .02) and publication bias was evaluated via Egger's test (P = .02). The corrected effect size for publication bias was 0.687 (95% CI: 0.473, 0.995) (Table 2).

For the risk of CV death and all-cause death, patients receiving alternatives showed lower risk than those receiving clopidogrel (RR 0.409; 95% CI: 0.177, 0.946 and RR 0.441; 95% CI: 0.263, 0.739, respectively) (Figure 2B and 2C). Both groups showed no heterogeneity (I^2 = 0%; P = .84 and I^2 = 0%; P = .99, respectively). Egger's test and the trim and fill method were not applicable for CV death because only two studies had been included; for all-cause death, the trim and fill method estimated a corrected effect size of 0.414 for publication bias (95% CI: 0.258, 0.664).

Patients receiving alternatives had a lower risk of MI and stent thrombosis than those receiving clopidogrel (RR 0.554; 95% CI: 0.414, 0.741 and RR 0.587; 95% CI: 0.348, 0.988, respectively) (Figure 2D and 2E) and no heterogeneity was noted. Egger's test revealed a possible publication bias for MI (P = .049), and thus, the effect size adjusted by trim and fill method was 0.603 (95% CI: 0.459, 0.793). Publication bias for stent thrombosis was not detected (P = .11).

The risk of stroke was not significantly different between patients receiving the alternatives and those receiving clopidogrel (RR 0.605; 95% CI: 0.257, 1.425) (Figure 2F), with no heterogeneity (I^2 = 0%; P = .94). Publication bias was not detected and RR was found to be similar before and after implementation of the trim and fill method (RR 0.632; 95% CI: 0.276, 1.444).

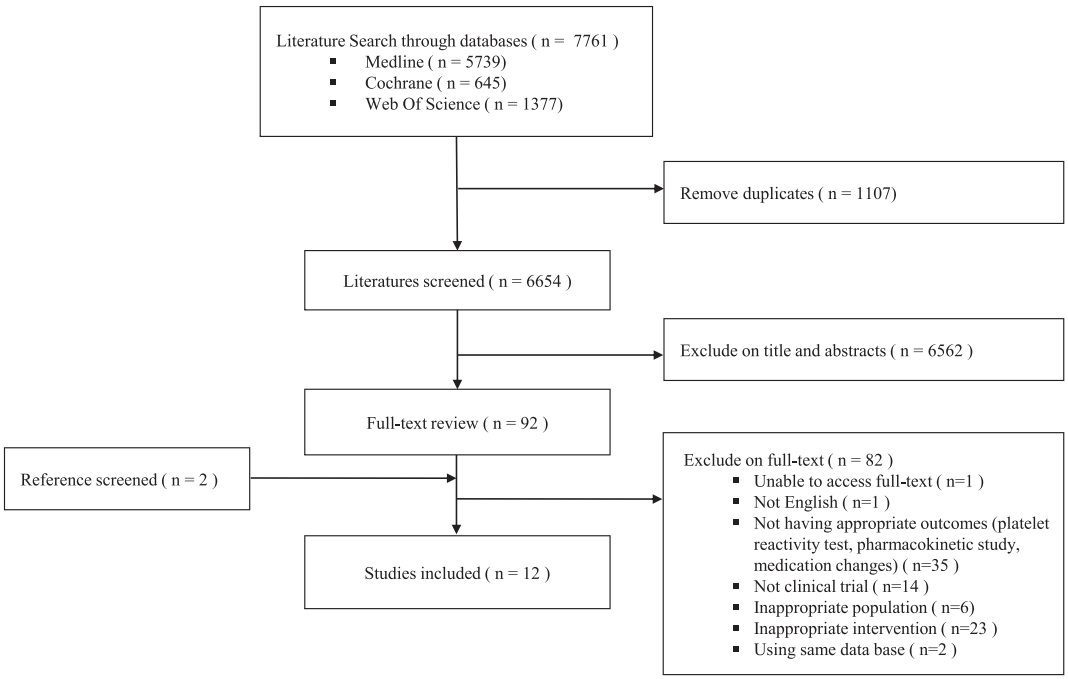


FIGURE 1 Flow diagram of the study selection process

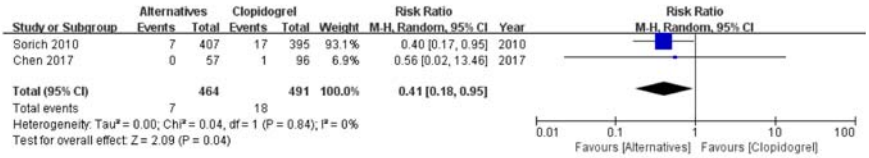
TABLE 1 Characteristics of studies and participants included in systematic review

Author	Country	Study population	Age	Medication (dose/day)		Follow-up duration (month)	Genetic variant	Endpoint	Study design	Risk of bias
				Clopidogrel	Alternatives					
Sorich et al. (2010)[20]	Austrailia	ACS	61	Clopidogrel (75 mg)	Prasugrel (10 mg)	15	*2A, *3, *4, *5A, *6,*7 *8	Composite, CV death, MI	RCT	9
Wallentin et al. (2010)[21]	Sweden	ACS	62.5	Clopidogrel (75 mg)	Ticagrelor (180 mg)	12	*2,*3, *4,*5, *6*7,*8	Composite, CV death, stent thrombosis, major bleeding	RCT	7
Gurbel et al. (2014)[22]	US	Stable CAD	62.7	Clopidogrel (75 mg)	Prasugrel (5 mg/10 mg)	1	*2,*3, *4,*5, *6*7,*8	Mild bleeding	RCT	7
Xiong et al. (2015)[23]	China	ACS	67	Clopidogrel (150 mg)	Ticagrelor (180 mg)	1	*2	Minor bleeding	RCT	9
Zhang et al. (2016)[24]	China	ACS	71.7	Clopidogrel (150 mg)	Ticagrelor (180 mg)	6	*2,*3	Composite, all-cause death, MI, stroke, stent thrombosis, major bleeding, minor bleeding	RCT	7
Dong et al. (2016)[25]	China	ACS	67	Clopidogrel (75 mg)	Ticagrelor (180 mg)	1	*2,*3	All-cause death, MI, stroke	RCT	8
Ogawa et al. (2016)[26]	Japan	ACS	64.3	Clopidogrel (75 mg)	Prasugrel (3.75 mg)	6	*2, *3	Composite, CV death, all-cause death, MI, stent thrombosis, major bleeding, minor bleeding	RCT	10
Deiman et al. (2016)[27]	Netherlands	ACS	65.2	Clopidogrel (75 mg)	Prasugrel (10 mg)	18	*2, *3	Composite, MI, stent thrombosis	Cohort	8
Chen et al. (2017)[28]	China	ACS/stable CAD	59.6	Clopidogrel (75 mg/150 mg)	Ticagrelor (180 mg)	12	*2	Composite, CV death, MI, stent thrombosis, mild bleeding	RCT	9
Lee et al. (2018)[29]	US	ACS/stable CAD	63	Clopidogrel (75 mg)	Ticagrelor (180 mg)/ Prasugrel (10 mg)	12	*2, *3	Composite, all-cause death, MI, stent thrombosis, severe bleeding, moderate bleeding	Cohort	9
Cavallari et al. (2018)[30]	US	ACS/stable CAD	64.3	Clopidogrel (75 mg)	Ticagrelor (180 mg)/ Prasugrel (10 mg)	12	*2, *3	Composite, all-cause death, MI, stroke, stent thrombosis	Cohort	9
Tatarunas et al. (2019)[31]	Lithuania	ACS	65.8	Clopidogrel (75 mg)	Ticagrelor (180 mg)	6	*2	Major bleeding	Cohort	8

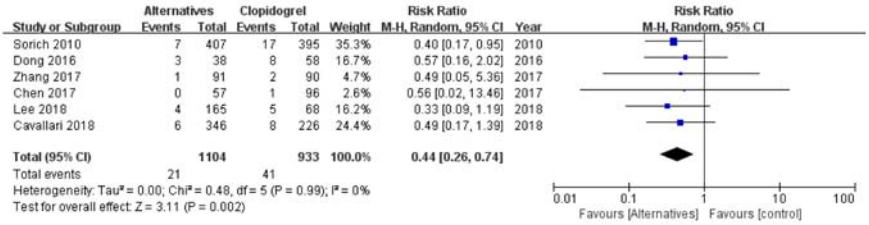
ACS: acute coronary syndrome; CAD: coronary artery disease; CV: cardiovascular; MACE: major cardiovascular events; MI: myocardial infarction; RCT: randomized controlled trial.

(A) Composite MACE

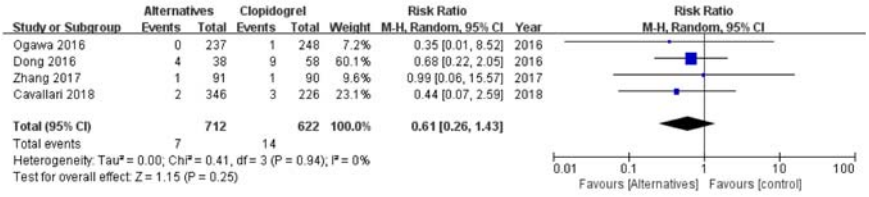
(B) CV death



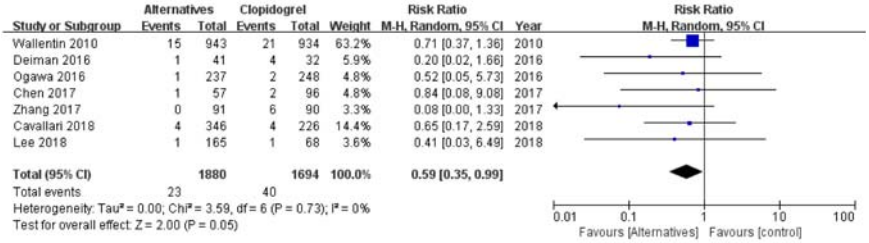
(C) All cause death



(D) Stroke



(E) Myocardial infarction



(F) Stent thrombosis

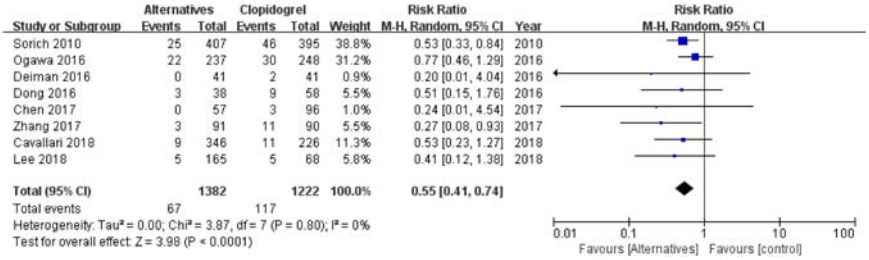


FIGURE 2 Forest plot for comparing the risk of major adverse cardiovascular events between clopidogrel and its alternatives: A, composite MACE, B, CV death, C, all-cause death, D, stroke, E, MI and F, stent thrombosis

TABLE 2 Analysis of publication bias

Effect magnitudes	Egger's test	Studies trimmed	Before trim and fill	After trim and fill
			Point estimation (95% CI)	Point estimation (95% CI)
RR of composite MACE	P = .02	4	0.524 (0.375–0.731)	0.687 (0.473–0.995)
RR of CV death	N/A	N/A	0.409 (0.177–0.946)	N/A
RR of all cause death	P = .57	2	0.441 (0.263–0.739)	0.414 (0.258–0.664)
RR of myocardial infarction	p = .049	4	0.554 (0.414–0.741)	0.603 (0.459–0.793)
RR of stent thrombosis	p = .11	3	0.587 (0.348–0.988)	0.693 (0.424–1.133)
RR of stroke	P = .705	1	0.605 (0.257–1.425)	0.632 (0.276–1.444)
RR of major bleeding	p = .02	2	1.018 (0.822–1.260)	1.034 (0.837–1.278)
RR of minor bleeding	p = .37	1	1.235 (0.581–2.628)	1.159 (0.565–2.378)

CV: cardiovascular; MACE: major adverse cardiovascular events; N/A: not applicable; RR: relative risk; 95% CI: 95% confidence intervals.

3.3 | The second endpoint (safety)

With regard to major bleeding, the risk was not significantly different between patients treated with the alternatives and those treated with clopidogrel (RR 1.019; 95% CI: 0.827, 1.260) (Figure 3A). No heterogeneity was noted (I^2 = 0%; P = .81), but Egger's test indicated that there was publication bias (P = .02). The trim and fill method estimated a corrected effect size of 1.034 for bias (95% CI: 0.837, 1.278).

A significant difference was not observed in the risk of minor bleeding between patients receiving alternatives and those receiving clopidogrel (RR 1.235; 95% CI: 0.581, 2.628) (Figure 3B). There was some evidence of heterogeneity (I^2 = 74%; P = .004). Egger's test was not significant (P = .37), and the trim and fill method estimated a corrected effect size of 1.159 for bias (95% CI: 0.565, 2.378).

3.4 | Sensitivity analysis

To assess the stability of the results, sensitivity analysis was performed by sequentially excluding each study; however, the results of this analysis were robust. There were no significant effects on RRs for composite MACE (RR range 0.46–0.60), CV death (0.40–0.51), all-cause death (0.42–0.47), MI (0.48–0.58), stent thrombosis (0.43–0.63) and stroke (0.51–0.67). Heterogeneity of composite MACE decreased from 56% to 42% after eliminating the study by Wallentin et al.[21]

Sensitivity analysis of major bleeding indicated that RR ranged from 0.84 (95% CI: 0.42, 1.69) to 1.03 (0.83, 1.27) on omission of a single study under the random-effects model. Regarding minor bleeding, RR ranged from 0.99 (0.46, 2.11) to 1.62 (0.91, 2.90). Heterogeneity decreased from 71% to 36% after excluding the study by Xiong et al.[23] and it indicated that carriage of two LoF alleles and medication dose were factors affecting heterogeneity.

3.5 | Subgroup analysis

Subgroup analysis of the primary endpoint was performed on RCT studies. The RRs for composite MACE, CV death, all cause death and myocardial infarction were 0.64 (95% CI: 0.47, 0.86), 0.41 (95% CI: 0.18, 0.95), 0.46 (95% CI: 0.23, 0.89) and 0.57 (95% CI: 0.42, 0.79), respectively. The risk of stroke and stent thrombosis were not

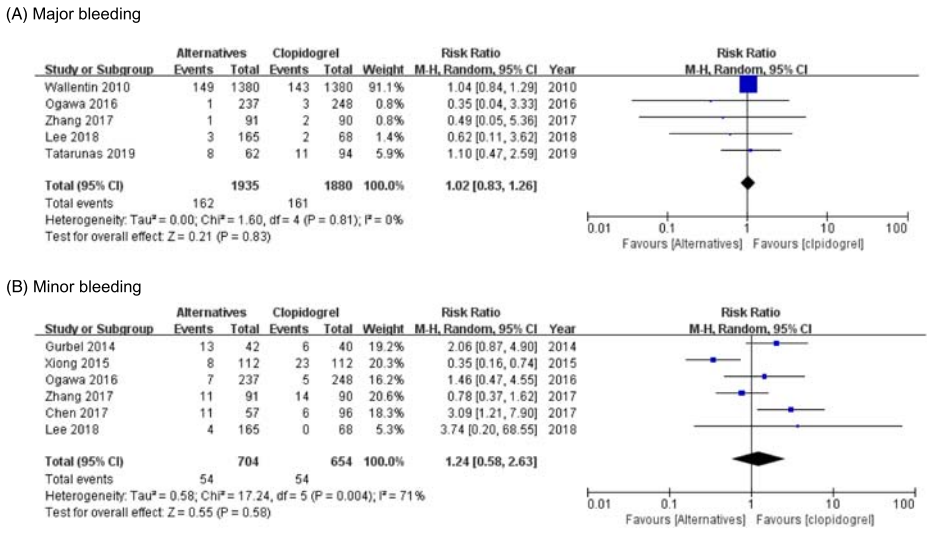


FIGURE 3 Forest plot for comparing the risk of bleeding between clopidogrel and its alternatives: A, major bleeding and B, minor bleeding

significantly different between patients receiving clopidogrel and the alternatives (Figure 4).

4 | DISCUSSION

This meta-analysis evaluated the extent to which the alternative antiplatelet agents, such as prasugrel and ticagrelor, can improve clinical outcomes of CYP2C19 RM in comparison with clopidogrel. In comparison with clopidogrel, the alternatives showed more clinical benefits for CAD treatment in patients with CYP2C19 LoF alleles. The alternatives reduced the risk of MACE; meanwhile, the risk of bleeding was not significantly different.

Clopidogrel is a second-generation thienopyridine, which has replaced ticlopidine because of its better safety profile.[32] Many patients with CAD benefited from clopidogrel; however, they

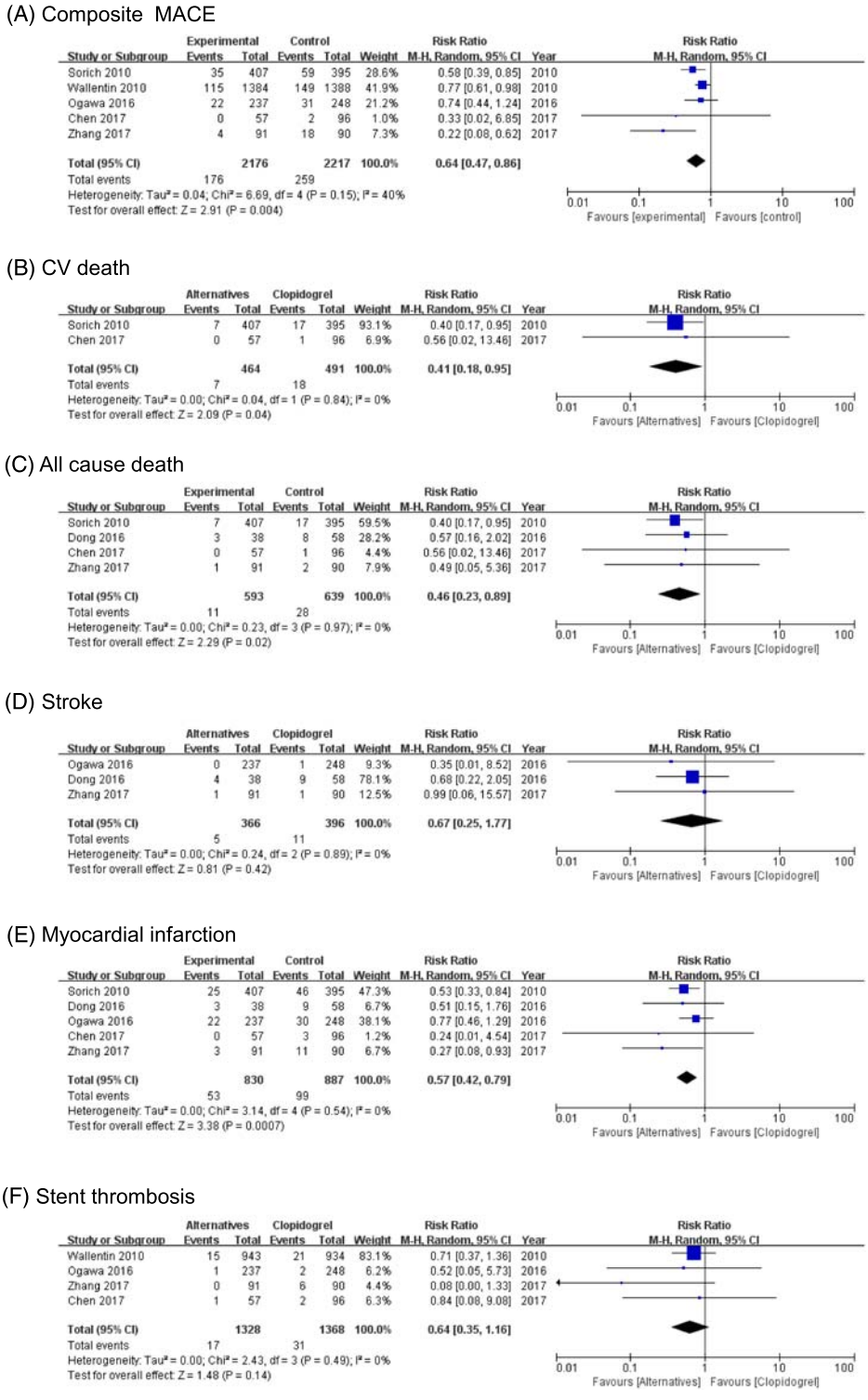


FIGURE 4 Forest plot for subgroup analysis including only RCTs: A, composite MACE, B, CV death, C, all-cause death, D, stroke, E, MI and F, stent thrombosis

continued to have recurrent CV events as a result of its pharmacogenetic limitations.[33] A previous meta-analysis demonstrated that CYP2C19 LoF carriers showed a higher risk of composite ischaemic and vascular events than non-carriers.[34] CYP2C19 genotype might have a prominent effect on adverse CV outcome, especially among Asians, because the frequency of LoF allele in East Asians is higher than that in Caucasian and Africans.[35] Other platelet inhibitors, including prasugrel and ticagrelor, were developed to overcome pharmacogenetic limitations of clopidogrel. In a randomized controlled trial that compared prasugrel with clopidogrel, it was found that prasugrel therapy caused a significant reduction in the risk of ischaemia.[36] In the PLATO study, treatment with ticagrelor as compared with clopidogrel significantly reduced the risk of CV death, MI or stroke.[37]

CYP2C19 genotype-based treatment can contribute to cost-effectiveness and better quality of life in patients with CAD. In a clinical trial, the conventional group was treated with clopidogrel based on routine clinical practice and the genotype-guided group was treated with prasugrel if they carried more than one CYP2C19 LoF allele; consequently, the genotype-guided group had better Quality Adjusted Life Years (QALYs) and lower treatment costs than the conventional group.[38] In accordance with this result, other studies have also demonstrated that the implementation of a pharmacogenetic approach to antiplatelet therapy was effective in terms of cost, QALYs, and clinical outcomes for CYP2C19 RMs.[27,39]

The result of bleeding was not significant in our meta-analysis. Consistent with our results, many studies have reported that there was no significant difference in bleeding between clopidogrel and ticagrelor or prasugrel. In the PLATO sub-study, the risk of major bleeding events was similar between patients who received ticagrelor and those who received clopidogrel.[40] Another study also revealed that the risk of major and minor TIMI bleeding in patients treated with prasugrel was similar to that in those treated with clopidogrel.[41] In a recent network meta-analysis comparing oral P2Y12 inhibitors, the risks of major bleeding were not significantly different between ticagrelor, prasugrel, high dose clopidogrel and standard dose clopidogrel.[7]

There are limitations to this meta-analysis. First, we were unable to access individual patient data. Some studies included both types of patients, namely those with stable CAD and those with ACS, and they were prescribed different concomitant medication. Second, many of the included research articles pertained to single-centre, open-label and underpowered studies, and each study had different follow-up durations. Third, some element of bias may have existed because each study implemented different bleeding criteria. Furthermore, in current clinical implementation, genetic test for CYP2C19 LoF alleles is conducted on a case-by-case basis. Due to lack of clinical evidence and feasibility of genotyping, clinicians prescribed alternative antiplatelet agents based on genetic test if patients experienced recurrent ACS events or if the committee suggested that genotyping might result in better outcomes.[42] In addition, the prevalence of RM varies depending on ethnicity, ranging from 3–5% (Caucasians) to 12–23% (Asians), thereby showing different responses to clopidogrel. Despite shortcomings, this study provides compelling evidence for the treatment of CYP2C19 LoF carriers with clopidogrel or its alternatives.

5 | CONCLUSION

Our analysis suggested that alternative antiplatelet treatments instead of clopidogrel based on genotyping test can induce better clinical outcomes on LoF allele carriers; however, this medication should be tailored according to the balance between patients' ischaemic and bleeding risk.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

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How to cite this article: Yoon HY, Lee N, Seong J-M, Gwak HS. Efficacy and safety of clopidogrel versus prasugrel and ticagrelor for coronary artery disease treatment in patients with CYP2C19 LoF alleles: a systemic review and meta-analysis. *Br J Clin Pharmacol*. 2020;86:1489–1498. https://doi.org/10.1111/bcp.14317