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ARTICLE

Risk of major adverse cardiovascular events in *CYP2C19* LoF genotype guided clopidogrel against alternative antiplatelets for CAD patients undergoing PCI: Meta-analysis

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Abstract

Selection of rational antagonists of $P2Y_{12}$ receptor for CAD patients who inherit *CYP2C19* LoF alleles remains still conflicting. This study compared the clinical outcomes in CAD patients inheriting *CYP2C19* LoF alleles undergoing PCI and treated with clopidogrel against alternative antagonists of $P2Y_{12}$ receptor. A thorough literature search was performed across multiple scientific databases following the PRISMA guidelines and PICO model. Setting the statistical significance at $p < 0.05$ and RevMan software was used to calculate the risk ratios (RRs). Estimation of the pooled analysis revealed a significant 62% increased risk of major adverse cardiovascular events (MACE) in CAD patients inheriting *CYP2C19* LoF alleles and treated with clopidogrel against those treated with alternative $P2Y_{12}$ receptor antagonists such as prasugrel or ticagrelor (RR 1.62; 95% CI 1.42–1.86; $p < 0.00001$). In addition, Asian CAD patients were found at a significantly higher risk of MACE (RR 1.93; 95% CI: 1.49–2.49; $p < 0.00001$) juxtaposed to CAD patients of other ethnicities (RR 1.51; 95% CI: 1.29–1.78; $p < 0.00001$). Conversely, between these two treatment groups, taking clopidogrel against prasugrel/ticagrelor, who possess *CYP2C19* LoF alleles, no significant differences in bleeding events were observed (RR 0.94; 95% CI 0.79–1.11; $p = 0.47$). CAD patients undergoing PCI who inherited *CYP2C19* LoF alleles and treated with clopidogrel were associated with significantly higher risk of MACE against those treated with alternative antagonists of $P2Y_{12}$ receptor, that is, prasugrel or ticagrelor.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Although some meta-analyses reported the reduced aggregated risk in ACS patients undergoing PCI and taking alternative antiplatelets against clopidogrel in

CYP2C19 LoF carriers, however, no study appears in the literature that has directly head to head compared the increased risk of MACE for the patients carrying *CYP2C19* LoF alleles treated with clopidogrel against alternative antiplatelets such as prasugrel or ticagrelor.

WHAT QUESTION DID THIS STUDY ADDRESS?

What was the aggregated risk of MACE for the CAD patients underwent PCI and inherited *CYP2C19* LoF alleles treated with clopidogrel against alternative antiplatelets, that is, prasugrel or ticagrelor?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This meta-analysis after pooled estimation found that CAD patients with PCI taking clopidogrel and inherited *CYP2C19* LoF alleles were associated with a 62% significantly increased risk of MACE compared to the patients taking prasugrel or ticagrelor, also inherited *CYP2C19* LoF alleles. This risk was driven by cardiovascular death, MI, stroke, and stent thrombosis. Further, the increased risk of MACE was considerably higher in Asian patients compared to other ethnic patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

CYP2C19 genotype guided therapy of alternative antiplatelets, that is, prasugrel or ticagrelor in CAD patients undergoing PCI may be beneficial to these patients and may help to reduce MACE substantially. The findings of this analysis may facilitate the rapid translation of precision antiplatelets from bench to bedsides.

BACKGROUND

Precision medicine considers regulatory genetic characteristics of pharmacodynamics or pharmacokinetics properties of many clinically significant medications such as antiplatelets. For instance, genetic variability of cytochrome P450 (CYP) in a subset of patients may be considered for the optimization of effectiveness and the safety of concerning medications.[1–4] Multiple previous studies have established a significantly higher risk of major adverse cardiovascular events (MACE) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) with clopidogrel inheriting *CYP2C19* loss-of-function (LoF) alleles compared to the patients carrying no *CYP2C19* LoF alleles.[5–10] For improved clinical outcomes of CAD patients, the use of *CYP2C19* genotype-guided alternative $P2Y_{12}$ receptor antagonists (antiplatelets) therapy was encouraged by these studies. These studies suggested to administer alternative antagonists of $P2Y_{12}$ receptor (i.e., ticagrelor or prasugrel) to the patients carrying one or two *CYP2C19* LoF alleles (*CYP2C19*2*, **3*, **4*, **5*, **6* or **8*) for the reduction of adverse clinical effects. The use of ticagrelor or prasugrel against clopidogrel in patients possessing LoF alleles of *CYP2C19* is advised in pharmacogenomics guidelines for clopidogrel dosing by the clinical pharmacogenetics implementation consortium (CPIC).[11]

Thus far, no study in the literature was identified that directly comparing the aggregated risk of MACE in CAD patients inheriting *CYP2C19* LoF alleles and treated with clopidogrel against treatment with $P2Y_{12}$ receptor antagonists like prasugrel or ticagrelor. Nonetheless, few meta-analyses reveal a lower aggregated risk associated with alternative antiplatelets (ticagrelor or prasugrel) compared to clopidogrel in *CYP2C19* LoF carrier patients.[12–15]

However, in patients with CAD or acute coronary syndrome (ACS), the clinical advantages of implementing *CYP2C19* genotype-guided antiplatelet therapy with ticagrelor or prasugrel rather with clopidogrel remain debated and conflicted,[16–18] hindering its use as a common clinical practice. Some of these studies administered clopidogrel as standard therapy while others used prasugrel/ticagrelor as standard care; therefore, the findings were conflicting. Without proper risk assessment associated with the standard antiplatelet therapy with clopidogrel against prasugrel or ticagrelor in CAD/ACS patients with *CYP2C19* LoF alleles, judging the aptitude of *CYP2C19* genotype-guided antiplatelets therapy renders impractical. Clinicians might not prefer of using ticagrelor or prasugrel as first line therapy over clopidogrel without considering *CYP2C19* genetic impacts because of cost and the risk of bleeding as well.

The current study therefore aimed to determine the aggregated risk through estimation of pooled risk by

performing meta-analyses of the published articles detailing the adverse clinical effects of clopidogrel and alternative antiplatelet therapy in CAD patients inherited *CYP2C19* LoF alleles.

METHODS

Literature search was conducted following PICO model in Cochrane library and PubMed since the inception to 30 June, 2023 by using different keywords.[19] Table S1 lists the keywords used in identification of the relevant studies. To track down additional studies of interest, Scinapse and 1000 Genomes databases were explored.[20,21] In the current analysis, the studies that met the following criteria were included; (i) two treatment groups of *CYP2C19* LoF alleles (**2*, **3*, **4*, **5*, **6*, **8*) inherited in CAD patients (one received clopidogrel while other was administered with alternative antagonists of $P2Y_{12}$ receptor i.e. prasugrel or ticagrelor) must report adverse clinical effects; (ii) minimum of one of the adverse clinical outcome, that is, safety or efficacy endpoints was reported in the study where MACE like myocardial infarction (MI), cardiovascular (CV) death, stent thrombosis (ST), stroke, unstable angina (UA), or revascularization were represented by efficacy endpoints and safety endpoint demonstrated bleeding toxicity where clinically significant bleeding events defined bleeding as described by the Global Use of Strategies to open Occluded Arteries (GUSTO) criteria.[22] Studies were omitted based on the following criteria (i) had poor study design where either alternative antiplatelets or clopidogrel was reported for clinical outcomes; (ii) if the outcomes of the two treatment groups, where both patients inherited *CYP2C19* LoF alleles were not reported clearly; (iii) if the studies were case reports, reviews, or letter to the editor.

For the selection of primary studies from searched literatures, Rayyan QCRI, a systematic tool for review was utilized.[23] Full texts of all primarily selected studies were then downloaded, and extensive checking was conducted before selecting the final studies. Two independent investigators selected the studies using Rayyan QCRI software separately and to resolve any disagreement interposed with the investigators in the selection process was eliminated by thorough discussion. Complying with the Newcastle Ottawa Scale (NOS) guidelines, the integrity of the observational studies was determined as discussed in details elsewhere.[24] Conversely, as outlined elsewhere, the quality of the involved randomized control trials (RCTs) was assessed by applying a 5-point Jadad scale.[25] For the estimation of the pooled relative risk (RR) and 95% confidence interval (CI), Review-Manager software was employed, subsequently followed by random/fixed effect model in accordance with the heterogeneity levels of the relevant studies (I^2 statistics). The distribution of RR of MACE was visually inspected in the funnel plot for determining the publication bias. All analyses considered a p-value of <0.05 as indicative of statistical significance.

Ethics statement

This is not required since it was a meta-analysis of published results.

RESULTS

General characteristics and quality of included studies

Figure 1 illustrates the whole identification process of the studies included in the current analysis. This meta-analysis included a total of 28,741 CAD patients undergoing PCI (mean age 63.6 ± 11.2; 71.1% male), eight and seven of the studies being observational and RCTs, respectively. Outcomes data collection follow-up period in the evaluated studies varied, ranging from 1 to 18 months. Among CAD patients inheriting *CYP2C19* LoF alleles (e.g., *CYP2C19*2*, **3*, **4*, **5*, **6*, **8*) a total of 13,195 patients were treated with clopidogrel while 15,546 of them received alternative antiplatelets, that is, ticagrelor or prasugrel.[26–40] Table 1 illustrates the major baseline characteristics of the assessed studies. Almost all of the included studies carried two LoF alleles (*CYP2C19*2* or **3*) except two studies[33,34] where patients carried more than two *CYP2C19* LoF alleles.

The majority of the included observational studies as assessed by the NOS criteria were high quality (NOS score 6–8), barring one with NOS score of 4, deemed as moderate quality. Similarly, the Jaded scale determined all the included RTCs as high quality.

Comparison of clinical outcomes for *CYP2C19* LoF genotype-guided therapy of clopidogrel vs. alternative antiplatelets

Pooled estimation of this analysis demonstrated a 62% significantly higher risk of MACE (RR 1.62; 95% CI 1.42–1.86; $p < 0.00001$) in CAD patients inherited *CYP2C19* LoF alleles taking clopidogrel compared to those who administered alternative antiplatelets, that is, ticagrelor or prasugrel (Figure 2). As illustrated in Figure 2, the

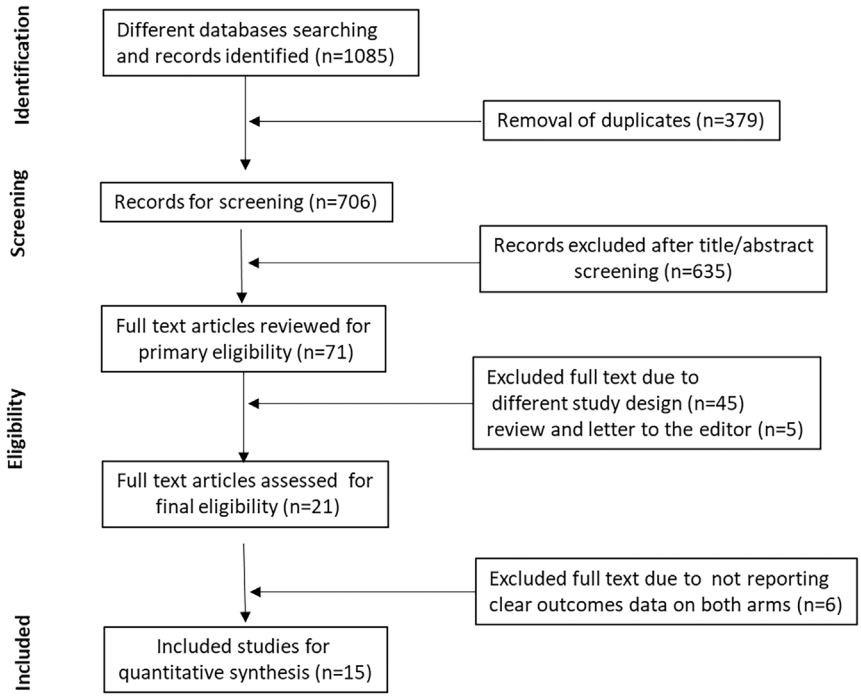

FIGURE 1 Flowchart for the identification of studies following PRISMA guidelines.

significantly elevated MACE risk was originated from MI (RR 1.71; 95% CI: 1.31–2.24; $p < 0.0001$), CV death (RR 2.03; 95% CI: 1.36–3.03; $p = 0.0005$), ST (RR 1.64; 95% CI: 1.08–2.48; $p = 0.02$), and stroke (RR 1.72; 95% CI: 1.08–2.75; $p = 0.02$).

Comparison of clinical outcomes in Asian vs. other ethnicities for *CYP2C19* LoF genotype-guided therapy of clopidogrel against alternative antiplatelets

The current study additionally investigated the impacts of *CYP2C19* LoF alleles affecting Asian CAD patients against CAD patients of other ethnic groups, that is, Europeans and Americans, and found a statistically significant higher risk of MACE in Asian patients when compared with other ethnicities (RR 1.93; 95% CI: 1.49–2.49; $p < 0.00001$ vs. RR 1.51; 95% CI: 1.29–1.78; $p < 0.00001$), as highlighted in Figure 3.

Bleeding events

Inheritance of *CYP2C19* LoF alleles has been linked to the bleeding events as assessed in 10 out of the 15 studies considered for this analysis. However, no significant difference (RR 0.94; 95% CI 0.79–1.11; $p = 0.47$) in bleeding events were found between two treatment groups of CAD patients (clopidogrel vs. ticagrelor/prasugrel), both inherited *CYP2C19* LoF alleles (Figure 4).

Heterogeneity, sensitivity analysis, and publication bias

When MACE was compared between two treatment groups, this study revealed a moderate level of heterogeneity ($I^2 = 48\%$), making the analysis sensitive. The sensitivity analysis was conducted by removal of one by one study in a chronological order, and no difference in clinical outcomes was found. Inspecting the funnel plot visually, it was determined that there was no publication bias affecting this study, as detailed in Figure 5.

To summarize the findings, CAD patients inherited *CYP2C19* LoF alleles underwent PCI showed a significant risk of MACE following clopidogrel administration compared to those treated with prasugrel/ticagrelor. Between these two treatment groups, bleeding toxicity risk was not significant. The results of this study recommend the implementations of the *CYP2C19* LoF genotype-guided alternative antiplatelets like ticagrelor or prasugrel for better optimization of the effectiveness of the antiplatelet therapy in CAD patients following PCI to achieve precision medicine of antiplatelets.

DISCUSSION

The final outcomes of this study strongly reinforce the medical significance of considering the appropriate selection of antiplatelets based on the *CYP2C19* LoF genotype for the CAD patients following PCI. This analysis emphasizes the implementation of *CYP2C19* LoF

TABLE 1 Characteristics of included studies for the analysis.

Author, Year	Study design	Clinical settings	Country	Age ± SD; % of Female	Sample size	*CYP2C19* Non-LoF carriers		*CYP2C19* LoF carriers		Clinical outcomes measured	Follow-up period, months
						n (%)	Allele	*n* (%)	Allele		
Claassens et al. (2021)	RCT	PCI for ACS	Multiethnic	77.3 ± 5.3; 37%	1073	401 (37.4)	*1	672 (62.4)	*2, *3	MACE, CV death, MI, ST, stroke, bleeding	12
Zhang et al. (2021)	Observational	PCI for ACS	China	60.2 ± 9.7; 24.3%	1361	535 (39.3)	*1, *17	826 (60.7)	*2, *3	MACCE, death, MI, ST, stroke, TVR, bleeding	12
Tuteja et al. (2020)	Pragmatic RCT	PCI for CAD	USA	63 ± 10; 27%	468	326 (69.7)	*1, *17	142 (30.3)	*2, *3	MACE, CV death, MI, ST, stroke, bleeding	16.4 ± 7.8
Martin et al. (2020)	Observational	PCI for ACS	USA	63 ± 12; 32.5%	1063	734 (69)	*1, *17	329 (31.0)	*2, *3	MACCE, bleeding	12
Xi et al. (2020)	Observational	PCI for CAD	China	60 ± 9.9; 24.4	1336	698 (52.2)	*1, *17	638 (47.8)	*2, *3	MACE, CV death, MI, ST, stroke	12
Cavallari et al. (2018)	Pragmatic RCT	PCI for ACS	USA	62.7 ± 11.8; 32.6%	1815	1243 (68.5)	*1	572 (39.5)	*2, *3	MACE, death, MI, stroke, ST	12
Lee et al. (2018)	Observational	PCI for ACS	USA	63 ± 12; 32.4%	868	605 (69.7)	*1, *17	263 (30.4)	*2, *3	MACCE, death, MI, ST, stroke, bleeding	12
Chen et al. (2017)	Observational	PCI for CAD	China	59.8 ± 9.9; 20%	458	227 (49.6)	*1	231 (50.4)	*2	MACE, CV death, MI, ST, UA, TVR, bleeding	12
Ogawa et al. (2016)	RCT	PCI for ACS	Japan	64.3 ± 10.9; 20%	773	288 (37.3)	*1	485 (62.7)	*2, *3	MACE, CV death, MI, ST, stroke, bleeding	12
Shen et al. (2016)	Observational	PCI for CAD	China	68.5 ± 10.4; 35%	628	133 (43)	*1	176 (57)	*2, *3	MACE, death, MI, bleeding	12
Deiman et al. (2016)	Observational	PCI for ACS	Netherlands	64.7 ± 10.7; 29%	3260	2233 (68.5)	*1, *17	1027 (31.5)	*2, *3	MACE, death, MI, ST	18
Dong et al. (2016)	Observational	PCI for ACS	China	67 ± 13.5; 20.5%	166	70 (42.2)	*1	96 (57.8)	*2, *3	MACE, death, MI, stroke	01
Zhang et al. (2016)	RCT	PCI for ACS	China	70.3 ± 9.4; 49.7%	329	148 (45)	*1	181 (55)	*2, *3	MACE, death, MI, stroke, ST	06
Wallentin et al. (2010)	RCT	PCI for ACS	Sweden	62.5 ± 10.9; 31%	10,285	7513 (73)	*1, *17	2772 (27)	*2, *3, *4, *5, *6, *8	CV death, MI, ST stroke, bleeding	12
Sorich et al. (2010)	RCT	PCI for ACS	USA	60.3 ± 10.7; 27.3%	2943	2141 (72.7)	*1	802 (27.3)	*2, *3, *4, *5, *6, *8	CV death, MI, ST stroke, bleeding	15

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CV, cardiovascular; LoF, Loss-of-function; MACCE, major adverse cardiovascular or cerebrovascular events; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; ST, stent thrombosis, TVR, target vessel revascularization.

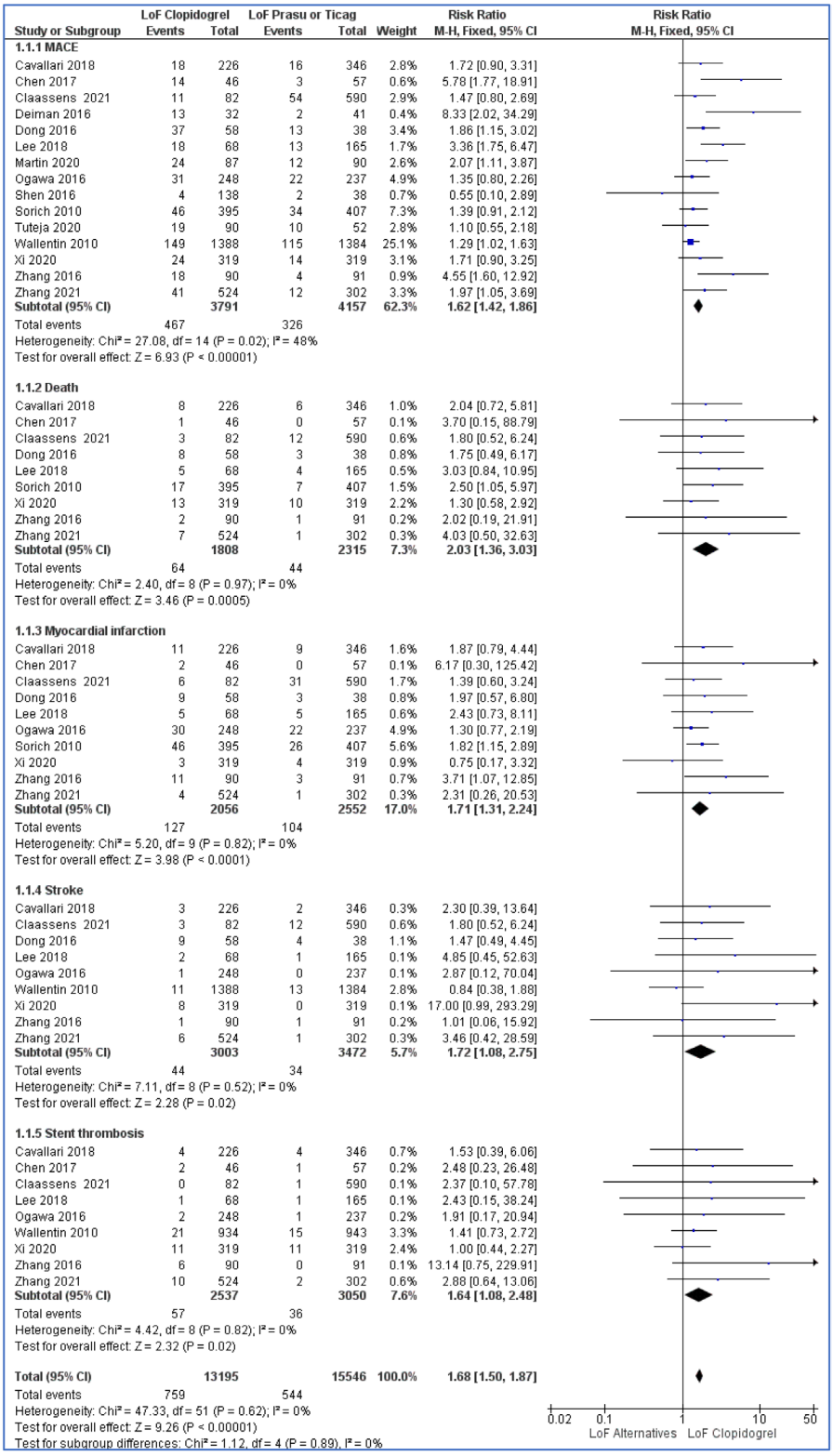

FIGURE 2 Forest plot of MACE for CAD patients inheriting *CYP2C19* LoF alleles taking clopidogrel against the patients with alternative antiplatelets.

genotype-guided precision antiplatelets therapy with prasugrel or ticagrelor in clinical practice, as the administration of clopidogrel substantially elevates the risk of MACE by over 60% in patients inheriting *CYP2C19* LoF alleles over those treated with alternative antiplatelets, that is, prasugrel/ticagrelor.

So far, no studies have been identified in the literature directly assessing the aggregated risk for the safety and

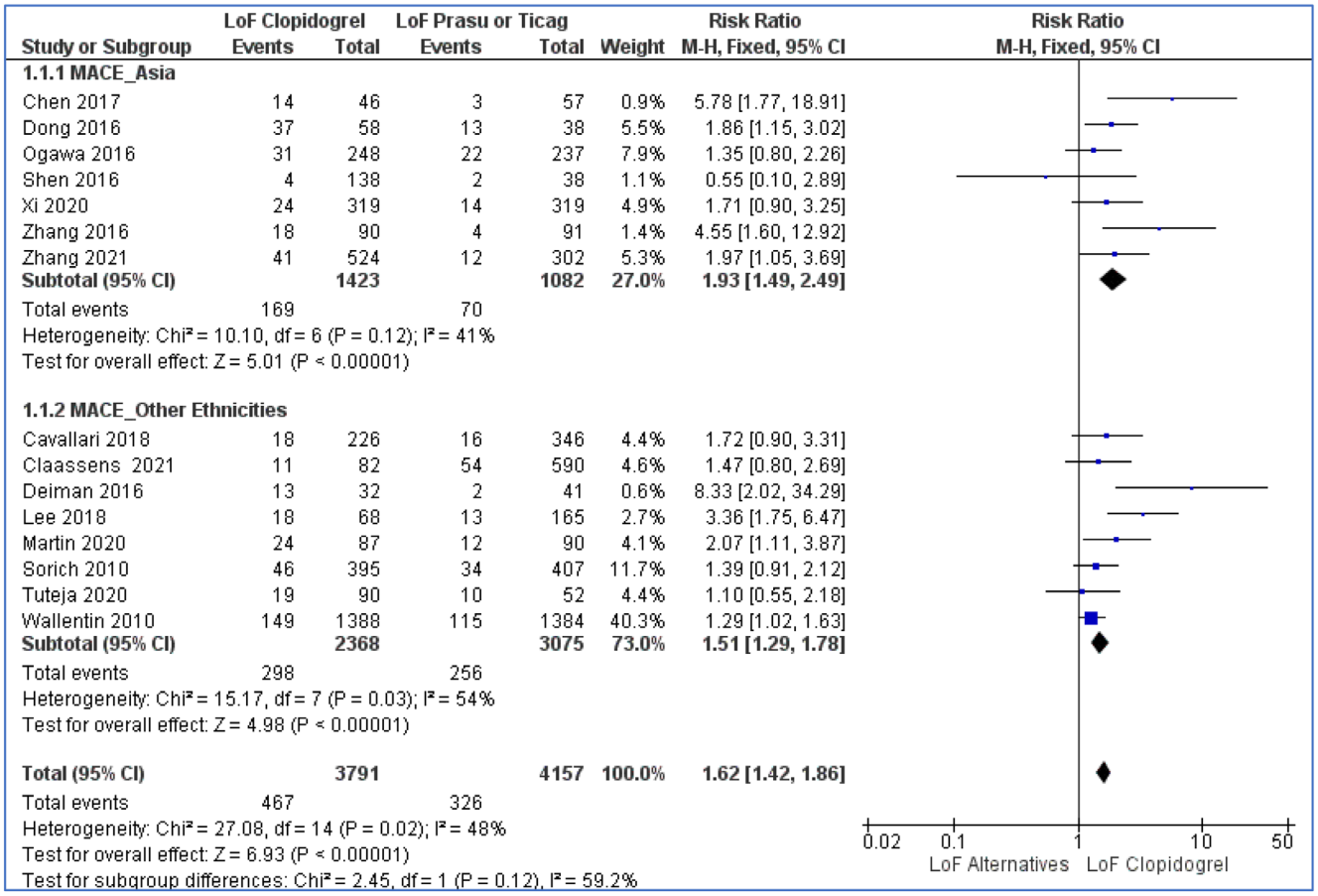

FIGURE 3 Forest plot of MACE for Asian CAD patients against CAD patients of other ethnicities, both inheriting *CYP2C19* LoF alleles.

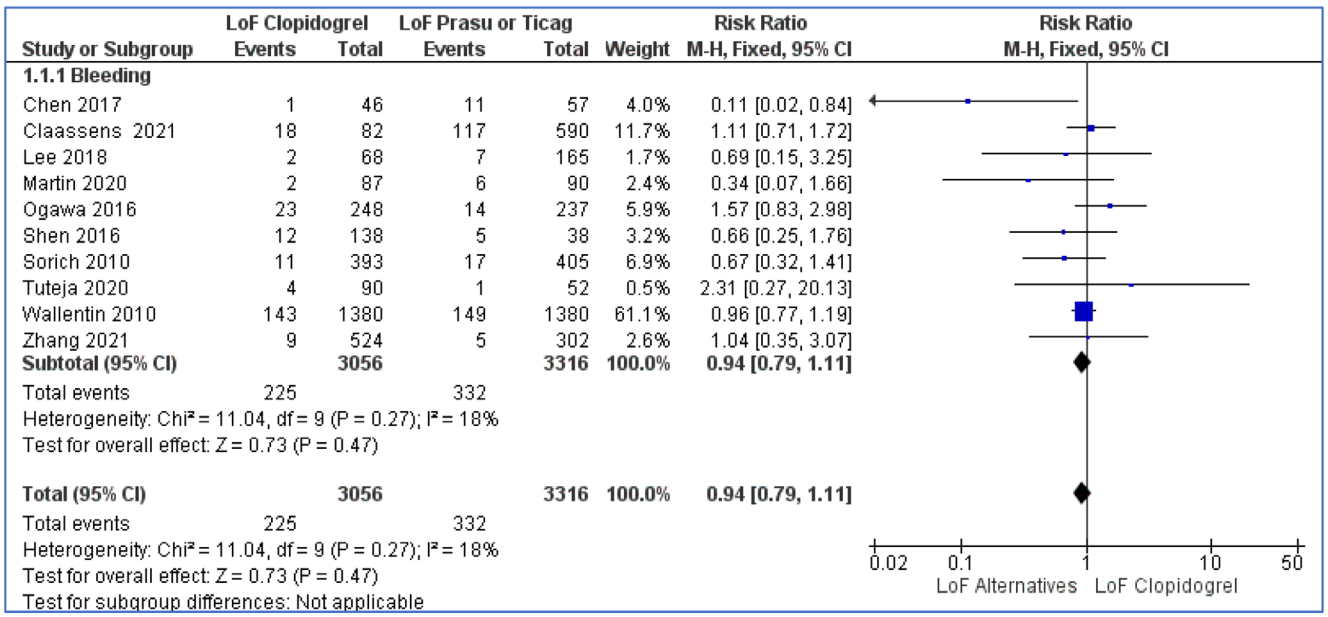

FIGURE 4 Forest plot of bleeding events for CAD patients inheriting *CYP2C19* LoF alleles taking clopidogrel against alternative antiplatelets.

efficacy endpoints of clopidogrel with alternative antiplatelets (i.e., ticagrelor/prasugrel) in a side by side comparison for CAD patients inheriting *CYP2C19* LoF alleles. This is the supportive evidence of existing literature which indicates an over 60% substantially increased risk of MACE associated with clopidogrel in comparison with prasugrel

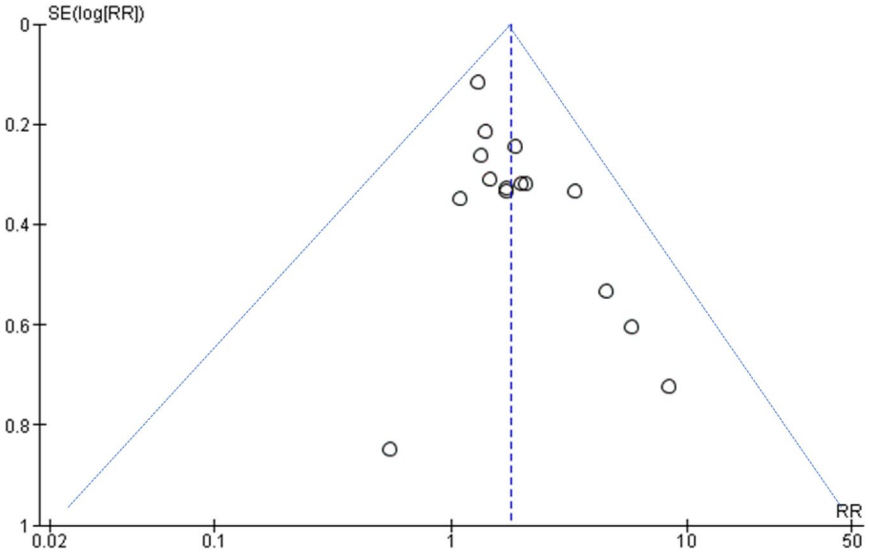

FIGURE 5 Funnel plot for the detection of publication bias.

or ticagrelor for CAD patients following PCI who inherited *CYP2C19* LoF alleles. As between two treatment groups, no significant risk of bleeding was found, and the overall findings of current analysis encourage the clinical implementation of alternative antiplatelets, that is, ticagrelor or prasugrel for CAD patients undergoing PCI. Genotype-guided clinical implementation of alternative antiplatelets might be even more practical and effective for Asian patients since the risk of MACE was striking in Asian CAD patients compared to other ethnic patients (RR: 93% vs. 51%). Higher risk of MACE in Asian CAD patients was observed which might be due the carrying of high percentage of *CYP2C19* LoF alleles in these patients (~50–65%) compared to other ethnic patients (~25–30%). However, it is important to note that the comparison groups in the included studies in the current meta-analysis had unequal number of *CYP2C19* LoF alleles between the clopidogrel and prasugrel/ticagrelor groups, which might have affected the accurate estimation of RR. It is assumed that patients carrying two *CYP2C19* LoF alleles, that is, poor metabolizers may be associated with higher estimation of RR. In contrast, patients carrying one *CYP2C19* LoF allele, that is, intermediate metabolizers may be associated with lower estimation of RR. Higher or lower estimation of RR may need further consideration about the changes in the dosing of clopidogrel or alternative antiplatelets based on the metabolizer status, that is, intermediate or poor metabolizers.

Few studies comparing clinical effects of clopidogrel against prasugrel or ticagrelor without the consideration of the *CYP2C19* genotypes effects, were identified in the literature which were also indicative of prasugrel/ticagrelor being better clinical option than clopidogrel.[41–43] The findings of the current analysis serve as a supplement to those well-established evidence along with numerous other studies illustrating an elevated risk of MACE associated with clopidogrel therapy in patients possessing *CYP2C19* LoF alleles and were suggestive of the implementation of alternative antiplatelets like prasugrel or ticagrelor for these patients.[5–10] As in comparison with alternative antiplatelets like prasugrel or ticagrelor, clopidogrel was found to be associated with a significantly higher MACE risk in *CYP2C19* LoF alleles carrying patients, it should not be considered a rational treatment choice of using clopidogrel for CAD patients undergoing PCI. Clopidogrel is a pro-drug which needs bio-activation mainly by the CYP2C19 enzyme. Patients inheriting *CYP2C19* LoF alleles may not convert clopidogrel to its pharmacologically active metabolite, which may in turn lead to therapeutic ineffectiveness and subsequently may lead to higher risk of MACE. Instead, prasugrel and ticagrelor are preferable alternative treatment options since there was no safety concern associated with using these drugs and they can reduce MACE significantly as evidenced in other studies.[12–15] For the selection of rational and precise antiplatelets taking both efficacy and safety endpoints into consideration for CAD patients following PCI inheriting *CYP2C19* LoF alleles, the robust findings of the present study could be viewed as the gold standard since this analysis estimated the aggregated risk from ~29,000 CAD patients in a head-to-head comparison, where one arm was treated with clopidogrel inherited *CYP2C19* LoF alleles and the other arm was treated with prasugrel/ticagrelor and also inheriting *CYP2C19* LoF alleles.

Despite few studies not favoring the *CYP2C19* genotype-guided antiplatelets therapy against the standard treatment care, their findings may not be deemed as robust evidence due to the inadequacies in study design.[16,44] These studies administered both arms with clopidogrel and/or alternative antiplatelets, however, most importantly these studies did not provide any clear information of the number of *CYP2C19* LoF alleles

carrying patients treating with clopidogrel versus alternative antiplatelets, for example, ticagrelor or prasugrel. Some studies offered this information in a limited perspective, but none presented the clinical outcomes associated with *CYP2C19* LoF allele carriers treating with clopidogrel against alternative antiplatelets, that is, ticagrelor or prasugrel and therefore, it was not possible to compare their findings with the current analysis. However, a recent trial conducted by Claassens et al. study[17] showed non-inferiority of genotype guided therapy (patients with *CYP2C19* LoF alleles were administered prasugrel/ticagrelor and non-carriers of *CYP2C19* LoF allele were administered clopidogrel) compared to the standard treatment group (patients received prasugrel/ticagrelor) in respect to reducing the thrombotic events (5.1% vs. 5.9%; $p < 0.001$ for noninferiority). As it is assumed that the *CYP2C19* genetics may not affect the clinical effectiveness of prasugrel/ticagrelor since these drugs are not primarily metabolized by the CYP2C19, therefore, may reduce net adverse clinical effects as found with the genotype-guided therapy. The inconsistencies in results as found in our analysis could be due to inconsistencies in the standard treatment group being considered in the study.

Without considering the genetic effects of *CYP2C19*, the bleeding toxicity risk among patients administering clopidogrel against alternative antiplatelets remains conflicted and hence may not be considered as conclusive evidence. Some studies reported an elevated bleeding risk in patients treated with alternative antiplatelets like ticagrelor or prasugrel against those administered with clopidogrel without consideration the genetic effects of *CYP2C19*.[41–43] Conversely, certain studies observe no notable differences in bleeding events within these two treatment groups.[45–47] Nonetheless, the present study did not find any statistically significant bleeding events between two treatment groups of *CYP2C19* LoF alleles carrying patients treating with clopidogrel against alternative antiplatelets, that is, ticagrelor or prasugrel. The mechanism for this no difference bleeding outcome is not clear which warranted further investigation to be elucidated. This finding of the present study recommends the clinical implications of alternative antiplatelets, that is, prasugrel or ticagrelor instead of clopidogrel for CAD patients following PCI inheriting *CYP2C19* LoF alleles as it imposes no safety concern. The findings of the current analysis can be served as supporting evidence for the utility of genotype guided antiplatelet dosing in these patients.

Considering the comprehensive findings of this study, cardiologists are expected to rationalize the *CYP2C19* genotype-guided precision antiplatelets therapy using the robust evidence of the present analysis derived from a comparatively large sample size as well as considering other clinical conditions of the patients to fully implement precision antiplatelet therapy in clinical use.

Limitations

The findings of this study are likely to be limited for CAD patients undergoing PCI inheriting *CYP2C19* LoF allele due to a lack of studies regarding the effects of administering clopidogrel against alternative antiplatelets such as prasugrel or ticagrelor in other clinical conditions like CAD patients without PCI or stroke patients inheriting *CYP2C19* LoF alleles.

Future directions

For accurate assessment of the clinical outcomes, future RCTs or longitudinal studies are necessary for CAD patients, specifically for the ACS patients with or without PCI or for stroke patients inheriting *CYP2C19* LoF alleles treating with clopidogrel against alternative antiplatelets, that is, prasugrel/ticagrelor.

CONCLUSIONS

A significant higher risk of MACE was found in CAD patients undergoing PCI, inherited *CYP2C19* LoF alleles, and treated with clopidogrel compared to those treated with ticagrelor or prasugrel. In these two treatment groups, both inheriting *CYP2C19* LoF alleles, no significantly different bleeding events were observed. Key findings of the current study suggest the clinical implementations of alternative antiplatelets (ticagrelor or prasugrel) for the optimization of the effectiveness of antiplatelets in CAD patients undergoing PCI and inheriting *CYP2C19* LoF alleles to expedite precision medicine in routine clinical practice.

AUTHOR CONTRIBUTIONS

C.S. and M.B. designed the research; M.B., M.A.M., M.E., and M.S.K.K. performed the research; M.B. analyzed the data. M.B., and M.A.M. wrote the manuscript. C.S. critically reviewed the manuscript to improve overall quality.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

This manuscript does not contain any associated data. However, the raw data supporting the findings of this study are freely available upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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