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Original article

CYP2C19*2/ABCB1-C3435T polymorphism and risk of cardiovascular events in coronary artery disease patients on clopidogrel: Is clinical testing helpful?

Mukesh Singh, Tejaskumar Shah, Sasikanth Adigopula, Janos Molnar, Aziz Ahmed, Sandeep Khosla, Rohit Arora*

Department of Cardiology, Chicago Medical School, 3333 Green Bay Road, North Chicago, IL 60068, United States

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ABSTRACT

Background: Studies evaluating CYP2C19*2 and ABCB1-C3435T polymorphisms have shown conflicting results. We performed this meta-analysis to evaluate role of clinical testing for these polymorphisms in CAD patients on clopidogrel.

Methods: 19,601 patients from 14 trials were analyzed. The endpoints were major adverse cardiovascular events (MACE), cardiovascular (CV) death, stent thrombosis (ST), myocardial infarction (MI), stroke and major bleeding. Combined relative risks (RR) with 95% confidence intervals (CI) were computed for each outcome by using standard methods of meta-analysis and test parameters were computed.

Results: CYP2C19*2 polymorphism was associated with higher risk of MACE [RR: 1.28, CI: 1.06–1.54; $p = 0.009$], CV death [RR: 3.21, CI: 1.65–6.23; $p = 0.001$], MI [RR: 1.36, CI: 1.12–1.65; $p = 0.002$], ST [RR: 2.41, CI: 1.69–3.41; $p < 0.001$]. No difference was seen in major bleeding events [RR: 1.02, CI: 0.86–1.20; $p = 0.83$]. Subgroup analysis showed similar results for elective PCI [RR: 1.34, CI: 1.01–1.76; $p = 0.03$], and PCI with DES [RR: 1.53, CI: 1.029–1.269; $p = 0.03$]. CYP2C19*2 polymorphism has very low sensitivity (28–58%), specificity (71–73%), positive predictive value (3–10%) but good negative predictive value (92–99%). ABCB1-C3435T polymorphism analysis revealed similar MACE [RR: 1.13, CI: 0.99–1.29; $p = 0.06$], ST [RR: 0.88, CI: 0.52–1.47; $p = 0.63$] and major bleeding [RR: 1.04, CI: 0.87–1.25; $p = 0.62$] in both groups.

Conclusion: In CAD patients on clopidogrel therapy, CYP2C19*2 polymorphism is associated with significantly increased adverse cardiovascular events. However, due to the low positive predictive value, routine genetic testing cannot be recommended at present.

1. Background

Dual antiplatelet therapy of aspirin and clopidogrel is now established as a standard of care for patients undergoing percutaneous coronary intervention (PCI) or patient with acute coronary syndrome (ACS).[1] In Percutaneous Coronary Intervention in the Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) study, dual antiplatelet therapy (DAPT) in patients with non-ST elevation myocardial infarction (NSTEMI) lead to 31% reduction in cardiovascular death or

* *Corresponding author.*
E-mail address: drmukeshsingh@yahoo.com (M. Singh).
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myocardial infarction (MI).[2] Similarly, in ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), DAPT in patients with ST elevation myocardial infarction (STEMI) was shown to reduce all cause mortality, and major cardiovascular events (MACE) including reinfarction.[3]

However, despite the use of DAPT, nearly 10% patients still experience recurrent MACE.[4–7] Persistent occurrence of MACE during DAPT may be partially explained by inter-individual variability of clopidogrel response, especially in patients undergoing PCI.[8–10] One of the postulated non-modifiable factors for variability of response can be attributed to pharmacogenetics of clopidogrel metabolism.

Clopidogrel is a prodrug that requires to be converted in to active metabolites to irreversibly bind to the $P2Y_{12}$ receptor. Clopidogrel metabolism is a two steps process dependent on cytochrome P450 (CYP), with contributions from the isoenzymes like: CYP2C19, CYP3A4 or CYP3A5, CYP2C9, CYP1A2, and CYP2B6.[11–13] CYP2C19 is a key enzyme in this activation process. There are at least 9 LoF alleles in CYP2C19 gene: *2–*8 null-functioning, *9–*10 decreased functioning. The presence of carriers of the loss-of-function alleles of CYP2C19 polymorphism is associated with clopidogrel non-responsiveness in healthy people and in patients with coronary artery disease (CAD).[14–16] In addition to CYP2C19 polymorphism, variations in the gene regulating clopidogrel absorption and efflux by encoding the P-glycoprotein a multi drug resistant-1 efflux transporter (called ABCB1),[17] might also affect the rate of clinical events during treatment. According to ACC/AHA guidelines, current evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large sub-groups of patients and hence is not currently recommended.[18]

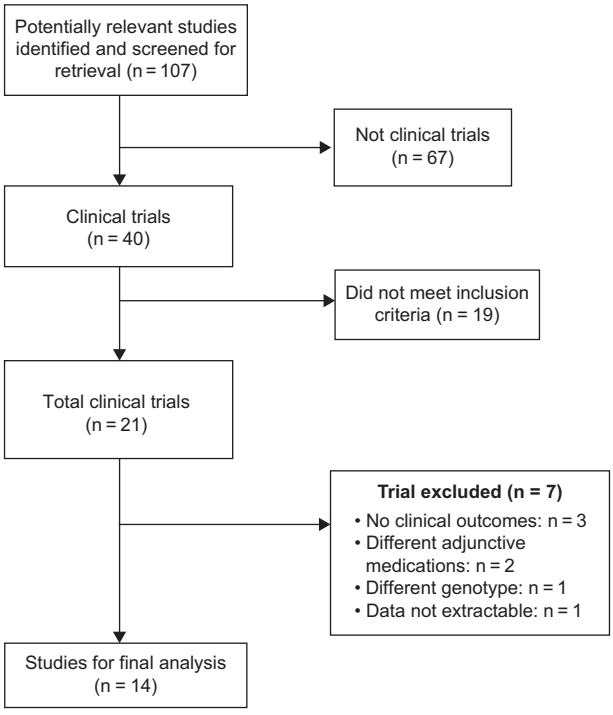

Fig. 1 – Study selection process for CYP2C19*2 polymorphism.

Table 1 – Study characteristics.

Name of study (year)	Total no of patients	F/UP	Study population	Study type	Treatment protocol	CYP 2 C19 (1*/1*)	CYP 2 C19 (1*/2*)	CYP 2 C19 (1*/2*)	Outcomes
SHULDINER (2009)	225	12	Elective PCI	Cohort	LD 300/600 mg MD 75 mg	158	63	4	MACE
MEGA TRINTON TIMI- 38 (2009)	1459	15	ACS undergoing PCI	Post hoc RCT	LD 600/300 mg MD 75 mg	1064	357	38	MACE, CV deaths, stroke, MI, ST and major bleeding
PARE CURE (2010)	2537	12	ACS undergoing PCI	Post hoc RCT	LD 300 mg MD 75 mg	NA	NA	NA	MACE and major bleeding
MALEK (2008)	105	12	ACS undergoing PCI	Cohort	LD 600/300 mg MD 75 mg	84	21	1	MACE, CV deaths, MI and ST
SIMON (2009)	2178	12	MI	Cohort	LD 300 mg MD 75 mg	1561	564	53	MACE
TRENK (2008)	797	12	Elective PCI	Cohort	LD 600 mg MD 75 mg	552	228	17	MACE
COLLETE (2009)	259	6	MI	Cohort	MD 75 mg	186	64	9	MACE, CV deaths, MI and ST
WALLENTINE (2010)	4904	12	ACS	Post hoc RCT	LD 600/300 mg MD 75 mg	NA	NA	NA	MACE, ST and major bleeding
BHATT (2009)	2428	12	Stable CAD	Post hoc RCT	LD 300 mg MD 75 mg	950	490	58	MACE
ANDERSON (2009)	1250	12	CAD undergoing PCI	Cohort	NA	NA	NA	NA	MACE and MI
WORRALL (2009)	104	12	ACS undergoing PCI	Post hoc RCT	NA	NA	NA	NA	MACE
SIBBING (2009)	2485	12	CAD undergoing PCI	Cohort	LD 600 mg MD 75 mg	1805	633	47	MACE, stroke, MI and ST
GIUSTI (2009)	772	6	CAD undergoing PCI	Cohort	LD 600 mg MD 75 mg	525	221	26	MACE, CV deaths and ST
Yamamoto (2011)	98	12	Elective PCI stable CAD	Cohort	LD 300 mg MD 75 mg	47	51	25	MACE, stroke, MI and CV deaths

[PCI = Percutaneous Coronary Interventions, ACS = Acute Coronary Syndrome, CAD = Coronary artery diseases, LD = Loading Dosage, MD = Maintenance Dose, MACE = Major Adverse Cardiovascular Event, CV = Cardiovascular and ST = Stent Thrombosis.]

Table 2 – Heterogeneity results for individual study outcomes and subgroup outcomes.

	Q-value	df (Q)	P-value	I-squared	Result	Publication bias (Funnel plots)
All studies of CYP219*2						
MACE	32.9	13	0.002	60.5	Heterogenic	None
CV deaths	2.0	4	0.730	0.0	Homogenic	None
MI	6.6	5	0.250	24.5	Homogenic	Possible
Stroke	1.7	2	0.425	0.0	Homogenic	None
Major bleeding	1.9	2	0.393	0.0	Homogenic	None
Stent thrombosis	7.3	5	0.199	31.5	Homogenic	Possible
All studies ABCB1						
MACE	7.2	2	0.027	72.4	Heterogenic	None
Stent thrombosis	0.2	1	0.692	0.0	Homogenic	Cannot be evaluate – only 2 studies
Major bleeding	1.2	1	0.269	18.0	Homogenic	Cannot be evaluate – only 2 studies
Elective PCI sub-groups of CYP219*2						
MACE	5.6	3	0.136	46.0	Homogenic	No
ACS sub-groups of CYP219*2						
MACE	20.6	6	0.002	70.9	Heterogenic	No
CV deaths	1.4	2	0.493	0.0	Homogenic	No
MI	4.7	2	0.095	57.4	Heterogenic	No
Major bleeding	1.9	2	0.393	0.0	Homogenic	No
Stent thrombosis	6.2	3	0.102	51.7	Homogenic	Possible
DES sub-groups of CYP219*2						
MACE	11.5	4	0.022	65.1	Heterogenic	No
MI	6.4	2	0.041	68.6	Heterogenic	Possible
Stent thrombosis	1.2	2	0.555	0.0	Homogenic	Possible

[PCI = Percutaneous Coronary Interventions, ACS = Acute Coronary Syndrome, CAD = Coronary artery diseases, MACE = Major Adverse Cardiovascular Event, CV = Cardiovascular and DES = Drug Eluting Stent.]

Individual studies evaluating role of CYP2C19*2 polymorphism and ABCB1-C3435T polymorphism have yielded mix results. Therefore we performed pooled analysis of prospective studies comparing clinical outcomes in patients with CYP2C19*2 and ABCB1 polymorphism on clopidogrel therapy to evaluate association and role of clinical testing for these polymorphisms in CAD patients on clopidogrel.

2. Methods

We performed this review in accordance with the Quality of Reporting of Meta-analysis (QUOROM) statement and the Consolidated Standards of Reporting Trials (CONSORT) Group recommendations.[19] A protocol was prospectively developed, detailing the objectives, criteria for study selection and approach to assessing the study quality, primary outcome and methodology.

2.1. Literature search

We searched the National Library of Medicine Pub Med, National Institutes of Health clinical trials registry and the Cochrane Central Register of Controlled Trials for prospective studies of CAD patients on clopidogrel treatment comparing clinical outcomes based on CYP2C19*2 and ABCB1 polymorphism. Selection process was similar both polymorphism. We also searched Internet-based sources of information on the results of clinical trials in cardiology (www.cardiosource.com/clinicaltrials, www.theheart.org, www.clinicaltrialresults.com and www.tctmd.com), as well as conference proceedings from meetings of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology. Searches were restricted to the period from January 2000 through May 2011. The key words used for search were: *coronary artery disease*, *acute coronary syndrome*, *percutaneous coronary interventions*, *STEMI*, *NSTEMI*, *Unstable Angina*, *stable angina*, *clopidogrel*, *prasugrel*, *ticagrelor*, *CYP2C19*, *CYP3A4* or *CYP3A5*, *CYP2C9*, *CYP1A2*, and *CYP2B6*, *ABCB1*.

2.2. Study selection

Two independent authors reviewed all titles and abstracts from the results of our computerized search. We also went into the related links of all relevant articles. In addition to our computerized search, we manually reviewed the reference list of all retrieved articles to complete our search. Study selection process is outlined in Fig. 1.

2.3. Inclusion criteria

We included in our analysis the results of randomized clinical trials or post hoc analysis of randomized control trial that compared clinical outcomes of patients with and without CYP2C19*2 and ABCB1 polymorphism in CAD patients on clopidogrel treatment.

All studies had to meet all the following criteria to be included in the analysis:

1. Randomized controlled trial or post hoc analysis of randomized controlled trials.
2. Include patients with coronary artery diseases mainly undergoing PCI.
3. Compare CYP2C19*2 carrier (variant) versus non-carrier (normal) and ABCB1 polymorphism (CT/TT) versus normal (CC).
4. Report at least one of the outcomes: MACE, CV death, ST, MI, stroke and major bleeding.

2.4. *Exclusion criteria*

Studies that did not meet the above criteria were excluded.

2.5. *Data abstraction*

After identifying all relevant articles, we extracted characteristics of the study like (author, year, design, duration, sample size, patient population, and genotype characteristics) and outcomes like (MACE, CV death, MI, ST, stroke, major bleeding complications and follow-up percentage). Two reviewers independently extracted data and assessed outcomes. The inter-rater agreement was 90%, and disagreements were resolved by consensus.

2.6. *Quality assessment*

All the trials reported adequate concealment of the randomized treatment sequence. In all studies, follow-up was more than 90% complete.

2.7. *Statistical analysis*

Combined relative risks (RR) across all the studies with 95% confidence intervals (CI) were computed for each endpoint by using the Comprehensive Meta-Analysis software package (version CM 2.2, Biostat, Englewood, NJ). Heterogeneity of the studies was assessed for each endpoint (Table 2). Those studies that were homogenous for an endpoint were analyzed by the Mantel–Haenszel fixed effect model, while those

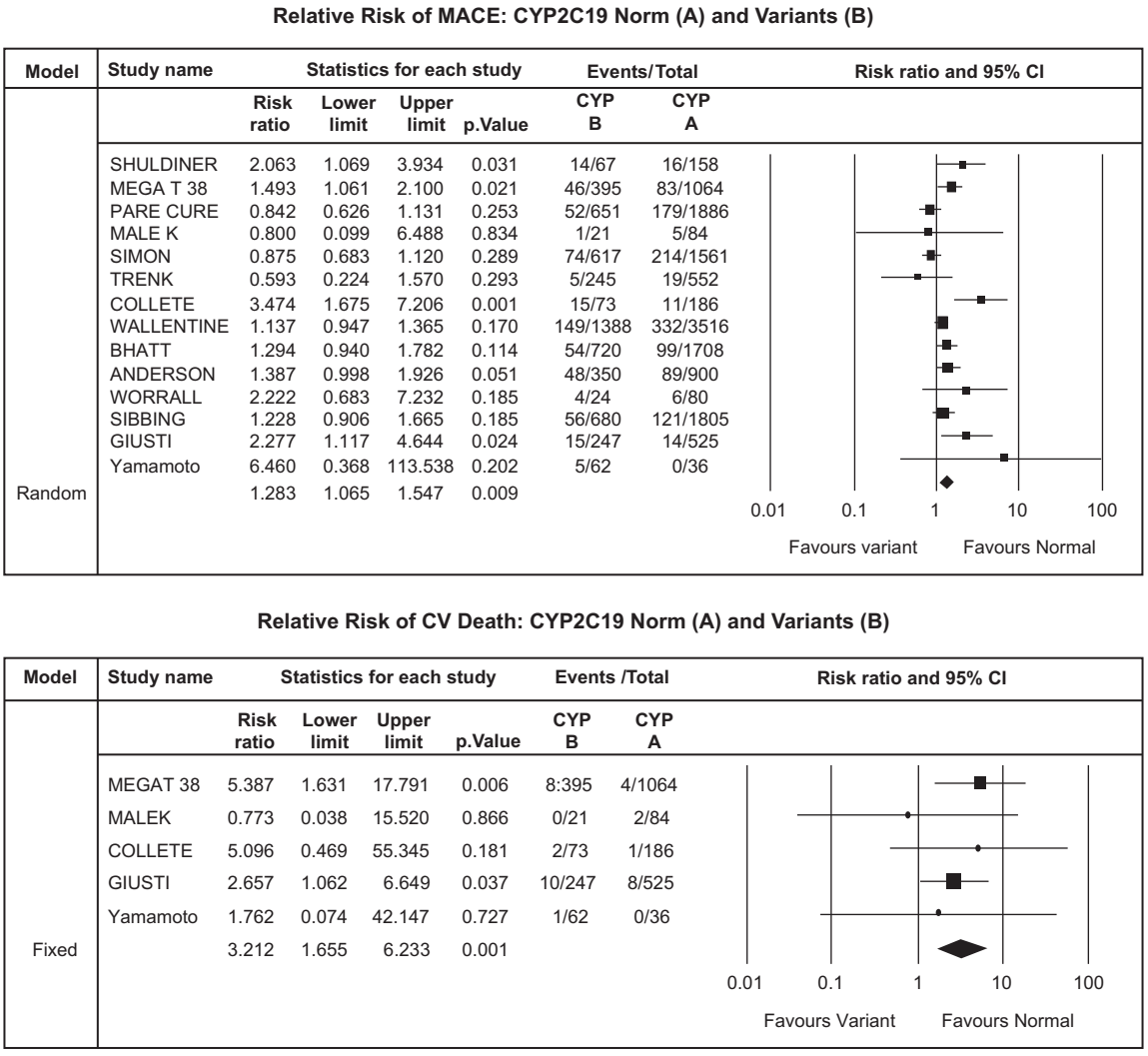

Fig. 2 – CYP2C19*2 analysis – major adverse cardiovascular events (upper panel) and cardiovascular death (lower panel).

studies that were heterogeneous for an endpoint were analyzed by the random effect model. A two-sided alpha error of <0.05 was considered to be statistically significant. The inverse variance method was used for study weighting. Potential publication biases were assessed by the funnel plot method and Egers test. Sensitivity, specificity, and the positive and negative predictive values of genetic testing were computed for each endpoint.

3. Results

3.1. *Literature search for CYP2C19*2 polymorphism*

A total of 107 articles were identified of which 40 were potentially relevant studies and screened for retrieval. After title and abstract evaluation, 19 studies were excluded and 21 studies were retrieved for a more detailed screening. Out of these 21 studies 7 studies were excluded and fourteen trials were included for final analysis [Fig. 1]. Among excluded seven studies, 3 studies were excluded, as they have demonstrated genotype polymorphism co-relation with platelet reactivity and no clinical outcomes assessed,[20–22] while other 3 studies were excluded as they have either compared the different genotype (CYP2C19*17)[23] or no clinical outcomes were evaluated.[24,25] Additionally, CLARITY TIMI 28 genomic study was excluded as data was not extractable.[26] Thus, fourteen trials were included in the final analysis.[26–40]

3.2. *Literature search for ABCB1 polymorphism*

A total of three studies identified which also looked in to ABCB1 polymorphism data and included in our meta-analysis comparing the effect of clopidogrel in CAD patients with or without ABCB1 polymorphism.[31,34,41]

3.3. *Overview of study and patient characteristics*

Study design was either RCT or post hoc analysis of RCT, comparison of clinical outcomes between a CYP2C19*2 or ABCB1 carrier with non-carrier in CAD patients on clopidogrel treatment. The characteristics of included trials are mentioned in Table 1. For simplicity, patient population was categorized as CYP2C19*2 carrier (defined as a variant) group who are either heterozygous (has at least one loss of *2 functional allele) or homozygous (has two loss of *2 functional alleles). Patients were categorized in CYP2C19*2 non-carrier (defined as normal) who are either carrying wild type (*1/*1) or none *2 alleles. Similarly, for ABCB1 polymorphism patient population was categorized in ABCB1 carrier (CT/TT) and ABCB1 non-carrier (CC).

3.4. *Endpoints*

All fourteen studies included in meta-analysis had MACE as a primary endpoint. Out of fourteen, six studies[28,30,33,34,38,39] included in the meta-analysis had stent thrombosis (ST) as

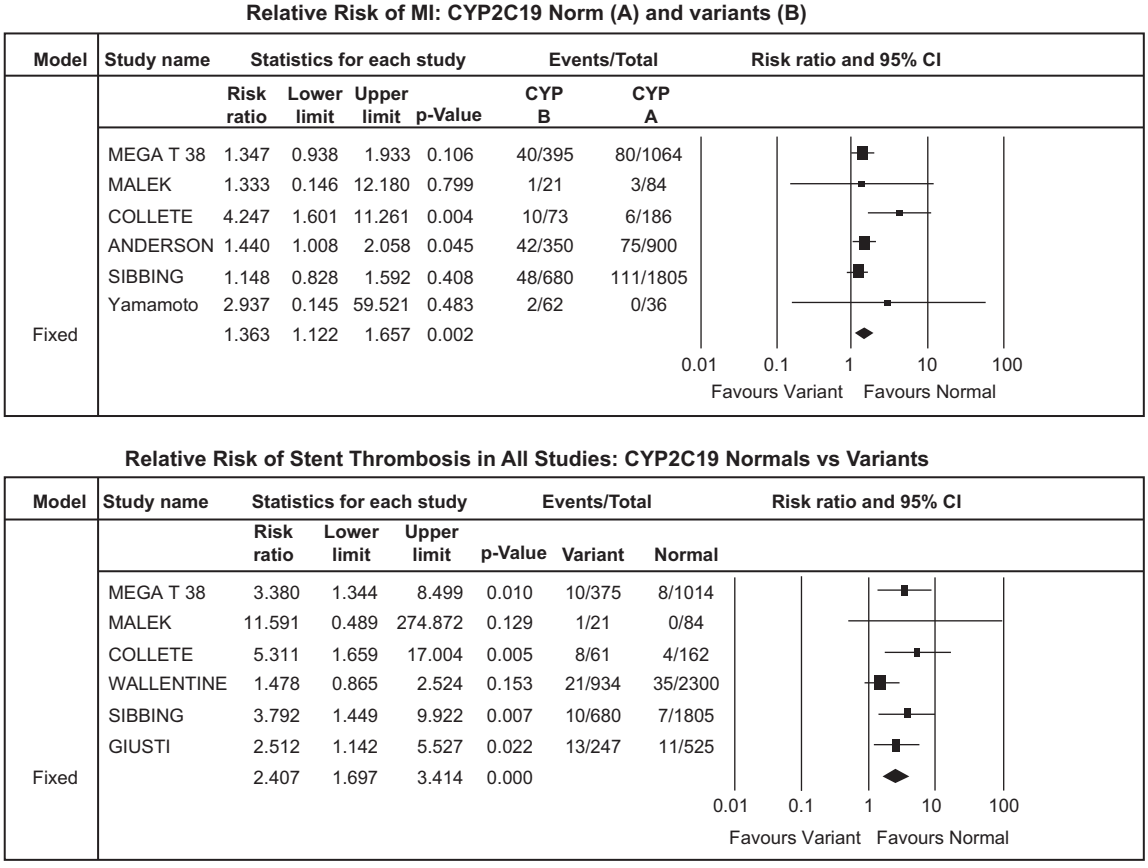

Fig. 3 – CYP2C19*2 analysis – myocardial infarction (upper panel) and stent thrombosis (lower panel).

an endpoint, while thee studies evaluated major bleeding[28,29,34] and stroke[28,38,40] as an endpoints. Outcomes for all studies included in our analysis are given in Table 1.

3.5. *Heterogeneity testing*

Results of heterogeneity testing for both CYP2C19*2 and ABCB1 polymorphisms are shown in Table 2. For heterogeneous outcomes random effect model and for homogenous outcomes fixed effect model was used. Publication bias analysis revealed no evidence of bias except for MI and ST (Table 2).

3.6. *Clinical outcomes of CYP2C19*2 polymorphism*

The trials included in this meta-analysis consisted of a total of 19,601 patients (CYP2C19*2 carrier group, $n = 5540$; non-carrier group, $n = 14{,}061$). The results of current meta-analysis are shown in Figs. 2–8.

3.6.1. *Major adverse cardiovascular event (MACE)*

Overall there were total of 1726 [8.8%] MACE of which 538 [9.71%] were in carrier group while 1188 [8.44%] in the non-carrier group. There was a significant increase of MACE in carrier group [RR: 1.28, CI: 1.06–1.54; $p = 0.009$] [Fig. 2].

3.6.2. *Cardiovascular (CV) death*

There were a total of 36 [17.54%] cardiovascular deaths of which 21 [2.63%] were in carrier group while 15 [0.79%] in the non-carrier group. The risk of cardiovascular mortality was higher in carrier groups than non-carrier group [RR: 3.21, CI: 1.65–6.23; $p = 0.001$] [Fig. 2].

3.6.3. *Myocardial infarction (MI)*

A total of 418 [7.39%] MI events occurred of which 143 [9.04%] were in carrier group while 275 [6.74%] in the non-carrier group. There was increase in MI events [RR: 1.36, CI: 1.12–1.65; $p = 0.002$] in carrier group compared to non-carrier group [Fig. 3].

3.6.4. *Stent thrombosis (ST)*

This includes a total of definite, probable and possible stent thrombosis. Incidence of ST was a total of 128 [1.56%]; out of which 63 [2.72%] were in carrier group while 65 [1.10%] in the non-carrier group. The risk of ST was significantly higher in carrier groups than non-carrier group [RR: 2.41, CI: 1.69–3.41; $p < 0.001$] [Fig. 3].

3.6.5. *Stroke*

Stroke outcome occurred only in 12 [0.29%] out of 4042 patients. The risk of stroke was also significantly higher in carrier group versus non-carrier group [RR: 4.13, CI: 1.16–14.71; $p = 0.029$] [Fig. 4].

3.6.6. *Major bleeding*

A total of 626 [5.54%] bleeding events occurred of which 175 [5.57%] were in Carrier group while 451 [5.53%] in the non-carrier group. Bleeding events did not differ between the two groups [RR: 1.02, CI: 0.86–1.20; $p = 0.84$] [Fig. 4].

3.7. *Subgroup analysis of CYP2C19*2 polymorphism*

3.7.1. *Major adverse cardiovascular event (MACE)*

There was a significant increase in incidence of MACE in carrier group in all patient populations irrespective of clinical

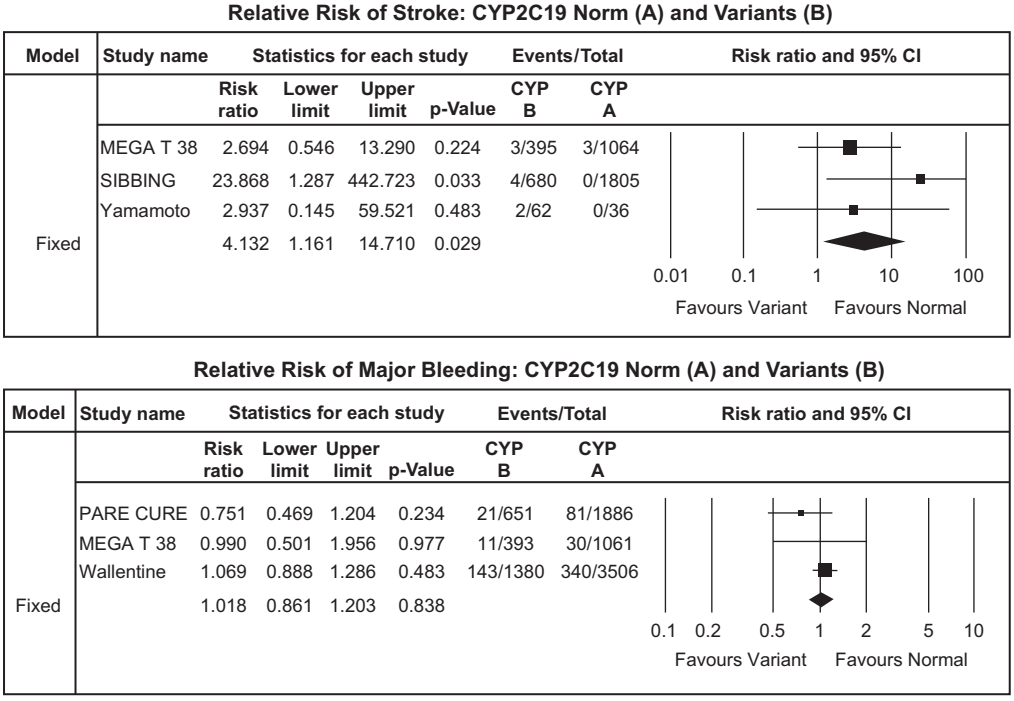

Fig. 4 – CYP2C19*2 analysis – stroke (upper panel) and major bleeding events (lower panel).

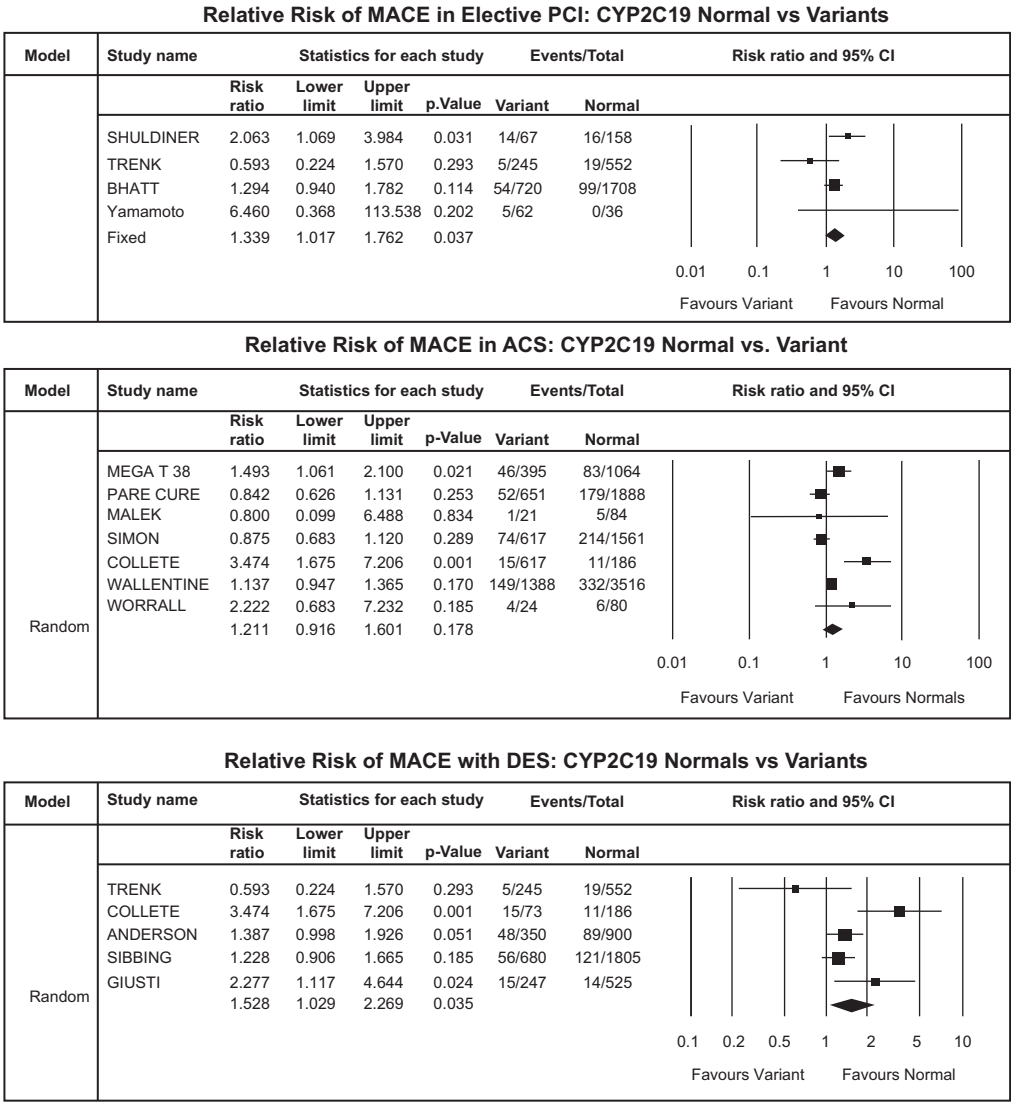

Fig. 5 – CYP2C19*2 subgroup analysis – MACE: elective PCI patients (upper panel), ACS patients (middle panel) and DES patients (lower panel).

sub-groups {stable CAD patients undergoing PCI [RR: 1.34, CI: 1.02–1.76; $p = 0.037$], ACS patients [RR: 1.21, CI: 0.91–1.60; $p = 0.178$] and patients undergoing PCI with DES [RR: 1.53, CI: 1.03–2.27; $p = 0.035$]} [Fig. 5].

3.7.2. *Myocardial infarction (MI)*

There was a significant increase of MI events in carrier group in ACS patients [RR: 1.98, CI: 0.84–4.67; $p = 0.118$] but no significant increase in MI events in carrier group in patients undergoing PCI with DES [RR: 1.56, CI: 0.97–2.53; $p = 0.067$] [Fig. 6].

3.7.3. *Stent thrombosis (ST)*

Stent thrombosis was significantly higher in carrier group of patients undergoing PCI with DES [RR: 3.36, CI: 1.96–5.77; $p < 0.001$] and ACS patients [RR: 2.17, CI: 1.42–3.33; $p < 0.001$] [Fig. 7].

3.8. *Test parameters of CYP2C19*2 polymorphism*

Test parameter analysis was done using 2 × 2 table. Genetic assay for CYP2C19*2 polymorphism was found to have sensitivity of (28–58%), specificity of (71–73%), negative predictive value of (92–99%) and positive predictive value of (3–10%) for various outcomes studied in this meta-analysis. Test parameters for individual outcomes are given in Table 3.

3.9. *Clinical outcomes of ABCB1 polymorphism*

The trials included in this meta-analysis consisted of a total of 8758 patients (non-carrier group, $n = 6384$; carrier group, $n = 2374$). The results of ABCB1-C3435T polymorphism summarized in Fig. 5. Overall there were a total of 930 [10.61%] MACE of which 274 [11.54%] were in carrier (CT/TT) group while 656 [10.27%] in the non-carrier (CC) group. This

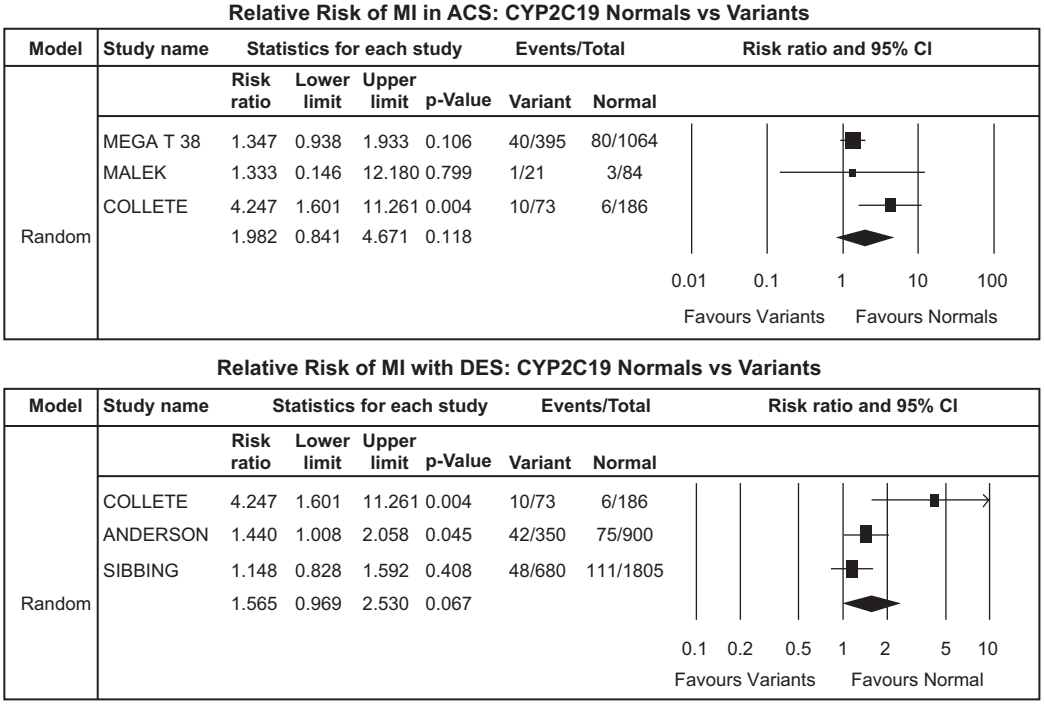

Fig. 6 – CYP2C19*2 subgroup analysis – MI: ACS patients (upper panel) and DES patients (lower panel).

difference between the two groups was not statistically significant [RR: 1.13, CI: 0.99–1.29; $p = 0.06$] [Fig. 8]. Similar results were obtained for ST [RR: 0.88, CI: 0.52–1.47; $p = 0.63$] and major bleeding events [RR: 1.04, CI: 0.87–1.25; $p = 0.62$] [Fig. 8].

4. Discussion

The present meta-analysis included nearly 19,600 patients from 14 prospective clinical trials conducted through May,

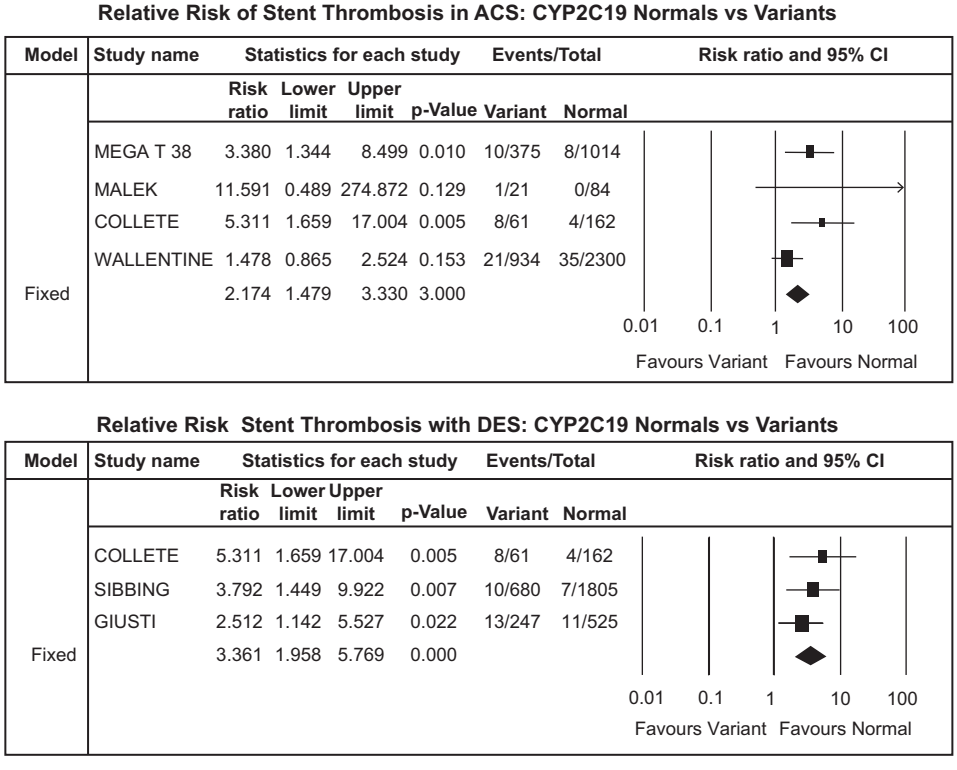

Fig. 7 – CYP2C19*2 subgroup analysis – ST: ACS patients (upper panel) and DES patients (lower panel).

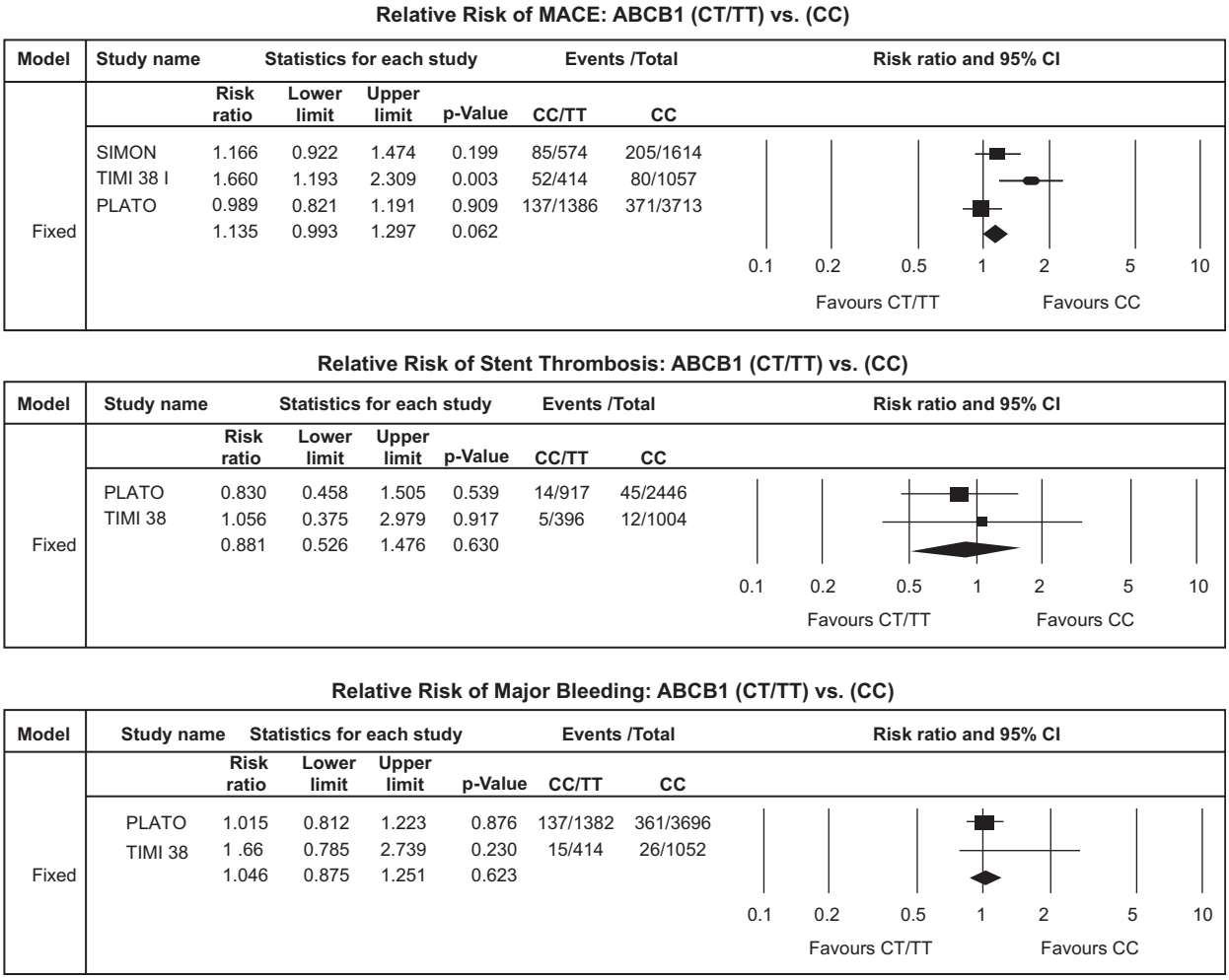

Fig. 8 – ABCB1-C3435T polymorphism analysis – MACE (upper panel), ST (middle panel) and major bleeding (lower panel).

2011. This pooled analysis is different from previous meta-analysis,[42–45] as we assessed not only the association but also the CYP2C19*2 genetic testing parameters for individual outcomes. We also analyzed the role of ABCB1 polymorphism in clopidogrel non-responsiveness and included separate sub-analysis of three different patient populations to identify the population at risk.

Results of our analysis show that CYP2C19*2 polymorphism is associated with significantly increased relative risk of MACE (1.28 fold), MI (1.3 fold), CVS death (3 fold), ST (2.4 fold) and stroke (4 fold) without any decrease or increase in the incidence of bleeding events. Moreover, stable patients undergoing elective PCI also have significantly increased risk for MACE (1.3 fold) with CYP2C19*2 polymorphism carrier state. Additionally, it shows ABCB1 polymorphism is not associated with increased incidence of MACE or ST.

Majority of stent thrombosis occur early (<30 days) and according to previous reports incidences are approximately 1% that causes serious consequences like MI, CVS deaths and strokes.[46] According to our analysis, compared to normal genotype, CYP2C19*2 polymorphism was associated with higher incidence of stent thrombosis, MI, CVS deaths and strokes. Overall, we found higher risk of ST (2.4 fold) as compared to MACE (1.28 fold). This could be due to the fact that MACE was reported in 14 studies while ST was reported by only six studies with wide confidence intervals.

Based on our data, CYP2C19*2 polymorphism genotyping has around 10% positive predictive value for almost each adverse outcomes (MI, MACE, CVS deaths etc.) which suggest that genotyping has no predictive value to detect studied outcomes. On the other hand, normal CYP2C19 had a very high (90–100%) negative predictive value for almost each adverse outcome. Thus, patients without CYP2C19*2

Table 3 – Test parameters of CYP2C19*2 polymorphism.

All studies of CYP219*2	MACE	CVS deaths	MI	ST	Major bleeding
Sensitivity %	31	58	34	43	28
Specificity %	72	71	73	73	72
NPV %	92	99	93	98	94
PPV %	10	3	9	4	6

[MACE = Major Adverse Cardiovascular Event, CV = Cardiovascular and MI = Myocardial Infarction, ST = Stent Thrombosis.]

polymorphism are at very low risk of having an adverse event while in case of polymorphisms, the negative outcome does not seem to be predictable. This is true despite that the overall RR values indicate higher risks in this patient group. Thus, it is reasonable to think that there are other (unknown?) factors that play the major role in the negative outcomes in CYP2C19*2 polymorphism group of patients. This finding indicates the potential role genotype testing may play in evaluating genetically non-modifiable factors responsible for clopidogrel non-responsiveness in patient with recurrent ischemic events. However, due to the poor sensitivity and low positive predictive value, routine genetic testing cannot be recommended at present.

Our data also shows that ABCB1 polymorphism has no clinical role in clopidogrel non-responsiveness in patient undergoing PCI or patients with ACS. Although, this data only compares, the 3435C → T heterozygous/homozygous variant (includes CT/TT) to normal (CC) while data comparing homozygous variant (TT) to normal (CC) is not known and is a subject to be evaluated in future study.

Subgroup analysis of stable CAD patients undergoing elective PCI shows higher incidence of MACE (1.3 fold) in variant group compared with normal group, which contradicts the conclusion drawn from CHARISMA genomic substudy that indicated no association with ischemic outcomes in CYP2C19*2 heterozygotes.[35] As previously mentioned, high on treatment platelet reactivity (HTPR) is the pathophysiologic phenomenon behind the development of recurrent ischemic events in ACS patients or patients undergoing PCI.[47] Apart from pharmacogenetic polymorphism, other factors also contributes to HTPR are non-compliance, underdosing, drug–drug interactions, co-morbidities (diabetes mellitus, abnormal renal function, hyperlipidemia, obesity) active smoking, clinical presentation, and procedural complexities.[7] According to initial data published in GRAVITAS trial (Price et al) shows that even after adjusting clopidogrel therapy (maintenance dose 150 mg), based on persistent HTPR assessed by platelet function test, did not result in change in clinical outcomes and persistent HTPR was attributed to non-modifiable risk factors like clinical presentation, procedural characteristics and genetic polymorphism.[48] Therefore, combining platelet function testing to identify the HTPR followed by genotyping to identify CYP2C19*2 polymorphism may give us guidance to use alternate anti-platelets like prasugrel[49] or ticagrelor.[33]

Overall, the prevalence of laboratory-defined clopidogrel non-responsiveness has been estimated at 21–26%.[50] Clinical implications to clopidogrel non-responsiveness of CYP2C19*2 polymorphism are obvious since significant number of population has at least one loss-of-function *CYP2C19* allele: ≈30–50% of Asians, 11–16% of Caucasians, and 14–25% of African-Americans.[51] Recently, FDA issued black box warning regarding use of clopidogrel in poor metabolizers but recommended against routine genotyping in patients on clopidogrel therapy.[52] Our meta-analysis indicates that CYP2C19*2 polymorphism results in significantly increased risk of cardiovascular events like MI, ST and CV deaths. Therefore it is imperative to have clinical trial designed to evaluate clinical benefit of personalizing antiplatelet therapy based on genotyping and platelet function test.

As with any meta-analysis, one of the limitations of our study is the difference in the definitions of the endpoints in the component trials, such as the definition of MACE, MI and CV death was different in various studies. Also, there was also heterogeneity in the study population, follows up duration, clopidogrel therapy protocol. Similarly, baseline characteristics between the two groups cannot be compared completely in most meta-analyses because of differences in the study protocols across the component trials. Also, there is a potential for publication bias but the trials in our analysis had different results and it should reduce this potential risk. Moreover, publication bias analysis was negative for all outcomes except for MI and ST indicating robustness of our results.

5. Conclusion

In CAD patients on clopidogrel therapy, CYP2C19*2 polymorphism is associated with significantly increased adverse cardiovascular events. However, due to the low positive predictive value, routine genetic testing cannot be recommended at present and should not be performed.

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Conflicts of interest

All authors have none to declare.

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