ORIGINAL ARTICLE

Coronary artery event and *CYP2C19*LoF polymorphism analysis using clopidogrel: A meta-analysis

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Abstract

Background: Clopidogrel (CLOP) has been used as an antiplatelet medication for many years to treat strokes; however, CLOP resistance may increase the risk of stroke recurrence. The poor metabolism of CLOP, which leads to resistance, is thought to be caused by the CYP2C19 (C-19) loss of function (LoF) polymorphism. It was impossible to draw firm conclusions from earlier research since the data were so inconsistent and diverse. **Aim:** The current study was conducted to gather conclusive data from an updated meta-analysis about the relationship between C-19LoF(C-19-LoF) polymorphism and coronary artery (CA) events in individuals using CLOP. **Methodology:** Electronic databases PubMed, EMBASE, SciHub, and Google Scholar were used to extract data till November 2024. RevMan 5 software was used for the analysis of extracted data. **Results:** Out of 7582 articles, we used 90 carefully selected to conduct our meta-analysis, which comprised 52,748 patients with CA disease undergoing CLOP medication. **Conclusion:** Our results indicate that CA events and composite events are significantly more common in individuals with one or more C-19-LoF alleles worldwide than in those without these alleles, particularly in Asian populations. The C-19-LoF alleles put the entire population at risk for composite events and recurrent CA events, especially Asians on CLOP, according to our meta-analysis. For people with poor or intermediate metabolic activity, more study is needed on alternate antiplatelet treatments.

Key words: Clopidogrel resistance, Clopidogrel sensitivity, Myocardial infarction, Omics, Platelet reactivity Cardiovascular

INTRODUCTION

Cardiovascular (CV) disease is a leading cause of death and morbidity worldwide. The exact etiology is unknown; however, various factors play an imperative role in the development of various types of CV disorders. The hyperactivation of platelets triggers the development of thrombus and

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severe ischemic episodes, one of the major contributors to these types of disorders.[1,2] Therefore, the preferred treatment for all individuals with coronary artery (CA) disease is the use of antiplatelets. Inhibitors of the purinergic receptor12 (P2Y12) are crucial for both preventing and treating CV disease. P2Y12 inhibitors lessen ischaemic consequences by suppressing platelet activities through a complementary mechanism.[2] Therefore, antiplatelet drugs are being used in the management of various CV disorders through a reduction in myocardial infarction. Clopidogrel (CLOP) is one of the antiplatelet drugs which is a P2Y12 inhibitor used in the management of ACS patients.[3,4]

CLOP is a pro-drug which is mainly activated by *C-19*in the presence of many genes, including *CYP1A2, CYP2B6, CYP2C9*, and *CYP3A4*.[5] Other variables, including age, sex, comorbidities, along with genetic variations, also influence the individual's response. The varied and gradual platelet inhibitory properties have led to the development of third-generation P2Y12 inhibitors, including ticagrelor and prasugrel. However, these medications are linked to problems and an elevated risk of bleeding.

The Loss of function (LoF) variations *2 and *3 result in proteins that are impaired or left nonfunctional due to the high polymorphism of the *C-19* gene, which is mainly made up of intronic variants. The haplotype *C-19**2 variation, for instance, is common in Asians, followed by other racial groups, and it results in a nonfunctional truncated protein.[6] Similarly, a premature stop codon and a nonfunctional shortened protein are produced by the *C-19*3* haplotype variant, which is common among Asians, followed by those with African and European heritage.[7,8]

These are the most frequently researched alleles, and thanks to technological advancements, it is now feasible to investigate differences among single nucleotide polymorphisms (SNPs) to create a personalized treatment plan. Similar to this, appropriate laboratory tests can be used to determine whether platelet function is suppressed, although they are not ideal tools for identifying patients who have "true" high platelet reactivity. CLOP resistance occurs in certain people, indicating that the medication is ineffective against its intended target. These individuals also have repeated ischemic episodes and myocardial infarction. Furthermore, Asian countries have a higher prevalence of CLOP resistance than Western countries.[8-10]

Ultra, Rapid, Normal, Intermediate, and Poor metabolizers are the five categories of metabolizers based on increased function alleles and LoF.[11] While intermediate and poor metabolizers have a decreased antiplatelet response to CLOP, ultra, rapid, and normal metabolizers have augmented or usual antiplatelet activity. The high frequency of LoF alleles in people with Asian heritage may aid in the recommendation of genotype-based guided antiplatelet medication. It is advised to use ticagrelor or prasugrel for intermediate and poor metabolizers. The current recommendations for genetic testing differ because of the rise in Asian immigration to other countries. Clinicians should, therefore, take into account inter-individual variability in CLOP response.[12] We intend to perform meta-analyses involving a variety of racial communities because of the intricate interactions among genetic variants, medication metabolism, and the varying response to antiplatelet therapy. Such research could offer a thorough grasp of how genetic differences affect CLOP response in various racial groups.

METHODS

Search strategy

To find pertinent studies with the appropriate MeSH terms through November 2024, the preprint database servers of PubMed, EMBASE, SciHub, and Google Scholar were searched. The following MeSH terms with Boolean operators were used: "genome" OR OR "genomes" OR "genome's" OR "genomically" OR "genomics" OR "genomic" OR ("cytochrom" OR "cytochromes" OR "cytochromes" OR "cytochrome" OR "cytochromic") OR "genetic variation" OR ("genetic" AND "variation") AND ("cytochrome p 450"OR "CYP2C19"OR "SNP" OR "polymorphic" OR "polymorphics" OR "polymorphism" OR "genetic polymorphism"OR "polymorphisms". PRISMA-2020[13] and STROBE[14] guidelines were followed in the conduct of this study.

Eligibility criteria

Inclusion criteria were established following the PICOS recommendations. All cohort, randomized control trials (RCTs), and case–control reports that evaluated the association between *C-19* polymorphisms and the risk of CA disease are included. The current study included data from participants who were diagnosed according to recognized protocols, regardless of their age, gender, and place of study. However, the eligibility criteria were subject to the following exclusion conditions. The review papers, case studies, conference abstracts, and research conducted on animals or *in vitro.* Studies that failed to disclose allele frequencies or genotypic data for the samples. Studies that have been published in other languages (other than English) were excluded.

Screening of data

Relevant research was independently searched by two authors (MI and MIS) following the inclusion and exclusion criteria. Titles, abstracts, and full texts were utilized to collect data following the PRISMA-2020 recommendations. After careful consideration, disagreements among the authors were resolved with the third author (AK).

Evaluation of quality

The Newcastle–Ottawa scale was used for the cohort and case–control studies, and the Jadad scale was used for the RCTs.[15] Two reviewers (MI and MIS) independently evaluated the quality of the included studies, and disagreements were resolved with the third author (AK).

Data extraction

The year of publication, author name, sample size, place of study, and age of each study population, as well as the genotype distribution of the *C-19* SNPs, were all collected from each carefully evaluated research article. If an article's data seemed incomplete or unconvincing, the author was emailed to ask for clarification.

Statistical analysis

RevMan 5 was used for data analysis. The odds ratio (OR) and related confidence interval (95%) were used to assess the relationship between *C-19* polymorphisms and CAD susceptibility. The random effect model was preferred over the fixed effect model due to the variations among the included studies for the analysis. As a result, the random effect model was chosen instead of the fixed effect one. The chi-square statistic and the I^2 z test were used to quantify heterogeneity. To determine whether there was any bias in publication, the funnel plot was utilised.

Sensitivity analysis

Sensitivity analysis was used to examine how outliers affected the estimate as a whole.

RESULTS

Search outcomes and study parameters

A total of 7,582 studies were discovered in the first search. Further, 1,293 papers were screened based on the titles. One hundred and ninety-six studies were found to be pertinent following additional screening based on the abstracts. The full texts of 143 articles were also obtained; following a thorough assessment, 90 papers were used in the current investigation. Figure 1 displays the systematic screening and selection of studies.

A total of eighty-four cohort studies[16-99] and Six RCT trials[100-105] made up the remaining ninety chosen studies including 52,748 patients in all. Table 1 lists the characteristics of the study.

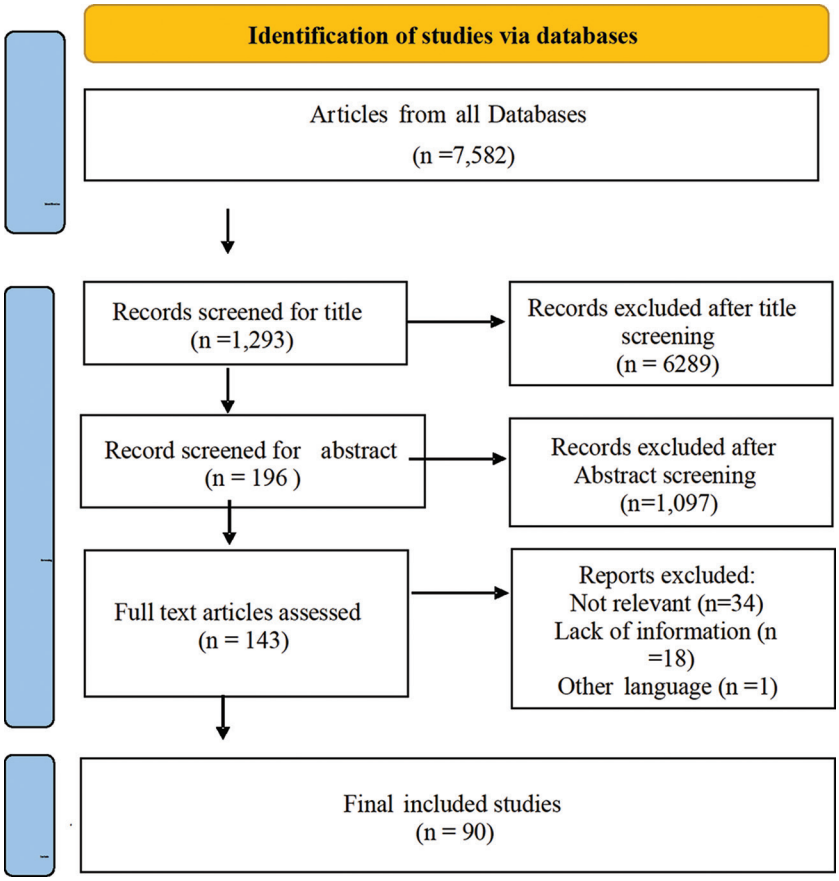

Figure 1: PRISMA chart for screening of articles

Table 1: Characteristics of the included studies

S. No.	Name of Author (year)	Type of Study	Place of study	Age	Dose (mg)	Total sample size	LOF carriers Event	LOF -carriers Total	LOF noncarriers Event	LOF noncarriers Total	Allele studied	Quality assessment (Newcastle-Ottawa Scale and Jadad Scale)
1	Abid *et al.* (2013)[16]	Prospective	Tunisia	56.7±10.5	300/600	100	4	23	4	77	2	9
2	Adel Alhazzani *et al.* (2017)[17]	Cohort	Saudi Arabia	57.8±11.9	75	80	15	19	13	33	2, 3	9
3	Al Azzam *et al.* (2013)[18]	Cross Section	Jordan	59.8±10.8	75	281	54	144	22	96	2	7
4	Arima *et al.* (2015)[19]	Cohort	Japan	69.9±10.5	300	518	65	345	16	173	2,3	9
5	Ayesh *et al.* (2019)[20]	Prospective	Europe	NR	NR	138	7	33	8	105	2, 3	8
6	Bhatt *et al.* (2012)[21]	Cohort	Multi Centre	64.0±9.5	NR	2428	48	665	92	1601	2,3,17	9
7	Zhu *et al.* (2016)[22]	Cohort	China	64.3±0.0	75	241	27	152	7	89	2,4	9
8	Bouman *et al.* (2011)[23]	Cohort	Germany	61.2±0.0	75	112	15	37	26	75	2,3,4,5,6,7,8,17	9
9	Campo *et al.* (2011)[24]	Cohort	Italy	66.00±13.0	600	300	10	81	11	219	2,17	7
10	Cavallari *et al.* (2018)[25]	Cohort	USA	62.7±0.0	NR	1815	18	226	74	1243	NR	8
11	Chen *et al.* (2015)[26]	Cohort	China	66.5±10.5	300	336	39	191	10	145	2	8
12	Chen *et al.* (2012)[27]	Cohort	China	65.2±9.6	NR	654	19	348	10	306	2	9
13	Chen *et al.* (2019)[28]	Observational	China	66.5±0.0	75	259	43	108	30	81	2,3	9
14	Choi *et al.* (2016)[29]	Cohort	Korea	63.4±10.6	600	2062	38	1237	16	825	2,3	9
15	Da Costa (2020)[30]	Cohort	Brazil	NR	NR	24	10	18	3	6	1,2	7
16	Dai *et al.* (2012)[31]	Cohort	China	61.5±0.0	NR	520	11	77	20	443	17	7

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Table 1: *(Continued)*

S. No.	Name of Author (year)	Type of Study	Place of study	Age	Dose (mg)	Total sample size	LOF carriers Event	LOF -carriers Total	LOF noncarriers Event	LOF noncarriers Total	Allele studied	Quality assessment (Newcastle-Ottawa Scale and Jadad Scale)
17	Delaney *et al.* (2012)[32]	Cohort	US	68.0±12.0	NR	693	80	202	145	488	2,3,4,17	8
18	Dong *et al.* (2016)[33]	Observational	China	67±0.0	75	102	37	58	8	44	2, 3	8
19	El-Khodary *et al.* (2021)[34]	Cohort	Egypt	58.54±10.30	75	50	6	11	1	39	2	9
20	Fang *et al.* (2015)[35]	Cohort	China	66±0.0	NR	114	19	75	4	39	2, 3, 17	8
21	Fathy *et al.* (2018)[36]	Case-Control	Egypt	56.2±0.0	75	230	35	57	79	173	2	9
22	Fu *et al.* (2020)[37]	Observational	China	61.45±0.0	75	131	8	53	9	78	2, 3	9
23	Giusti *et al.* (2009)[38]	Cohort	Italy	68.3±11.0	600	772	15	247	14	525	2	9
24	Han *et al.* (2015)[39]	Cohort	China	68.1±0.0	75	247	35	150	17	97	2,3	8
25	Harmsze *et al.* (2011)[40]	Cohort	Multi Centre	63.2±10.18	300/600	725	22	200	42	525	2,17	9
26	Harmsze *et al.* (2010)[41]	Case-Control	Netherland	62.1±0.0	NR	596	70	193	106	403	2,3	8
27	Hoh *et al.* (2016)[42]	Cohort	USA	67±0.0	NR	188	4	51	24	137	2,3,8,17	9
28	Hokimoto *et al.* (2014)[43]	Cohort	Japan	69.0±10.3	300	174	14	111	1	63	2,3	8
29	Jeong *et al.* (2015)[44]	Cohort	Korea	61.6±0.0	75	76	29	49	7	27	NR	8
30	Jia *et al.* (2013)[45]	Cohort	China	66.3±0.0	75	259	5	160	1	99	2,3	7
31	Kang *et al.* (2013)[46]	Cohort	China	63.4±8.9	NR	538	31	297	12	240	2	9
32	Khalil *et al.* (2016)[47]	Cohort	Chicago	57.1±9.12	75	190	26	45	63	136	2, 17	9

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Table 1: *(Continued)*

S. No.	Name of Author (year)	Type of Study	Place of study	Age	Dose (mg)	Total sample size	LOF carriers Event	LOF -carriers Total	LOF noncarriers Event	LOF noncarriers Total	Allele studied	Quality assessment (Newcastle-Ottawa Scale and Jadad Scale)
33	Kim *et al.* (2013)[48]	Cohort	Korea	63.5±10.6	300–600	2188	60	1316	27	872	2,3,17	9
34	Kubica *et al.* (2013)[49]	Prospective	Poland	60±0.0	75	191	7	35	26	143	2, 17	9
35	Lee *et al.* (2018)[50]	Observational	USA	63.3±0.0	75	868	18	68	53	405	2	9
36	Liang *et al.* (2013)[51]	Cohort	China	NR	600	1016	57	603	21	413	2,3,17	9
37	Lin *et al.* (2021)[52]	Observational	China	65.1±14.1	NR	122	13	51	2	38	2,3	9
38	Lin *et al.* (2018)[53]	Cohort	China	69±0.0	75	375	77	222	21	153	2,3	8
39	Liu *et al.* (2013)[54]	Cohort	China	66.2±8.9	300	109	18	72	3	37	2,3	7
40	Liu *et al.* (2020)[55]	Retrospective	China	66.6±0.0	75	289	31	159	10	130	2,3	9
41	Luo *et al.* (2011)[56]	Cohort	China	70.7±9.5	300	1738	115	802	67	936	2	8
42	Malek *et al.* (2008)[57]	Cohort	Jordani	60.00±11.1	300/600	105	1	21	5	84	2	8
43	Marcucci *et al.* (2012)[58]	Cohort	Italy	69.00±12.0	600	1187	39	295	76	892	2	8
44	Martin *et al.* (2020)[59]	Observational	USA	64.36±0.0	NR	612	23	177	59	435	NR	9
45	Mega *et al.* (2009)[60]	Cohort	Multi Centre	60.1±11.2	300	1459	46	395	83	1064	2,3,4,5,8	9
46	Mohammad and Al-Allawi *et al.* (2018)[61]	Prospective	Iraq	NR	NR	201	7	29	3	60	2, 17	8
47	Nagashima *et al.* (2013)[62]	Cohort	Japan	65.3±11.9	300	177	20	131	8	46	2,3	9

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Table 1: *(Continued)*

S. No.	Name of Author (year)	Type of Study	Place of study	Age	Dose (mg)	Total sample size	LOF carriers Event	LOF -carriers Total	LOF noncarriers Event	LOF noncarriers Total	Allele studied	Quality assessment (Newcastle-Ottawa Scale and Jadad Scale)
48	Nishio *et al.* (2012)[63]	Cohort	Japan	69.7±9.2	300	160	24	100	3	60	2,3	9
49	Nozari *et al.* (2015)[64]	Cohort	Iran	60.09±10.29	75	100	7	11	43	89	1,2	7
50	Oh *et al.* (2012)[65]	Cohort	Korea	60.8±9.8	300–600	2146	108	1011	100	1135	2	9
51	Pan *et al.* (2021)[66]	Cohort	China	61.9±9.73	NR	1716	30	233	17	202	2,3	8
52	Collet *et al.* (2009)[67]	Observational	France	40.1±0.1	75	259	15	73	11	186	2,3	9
53	Pare *et al.* (2010)[68]	Cohort	Multi Centre	63.8±10.15	300	2530	52	650	178	1880	2,3,17	9
54	Park *et al.* (2013)[69]	Cohort	Korea	NR	NR	2188	28	622	23	902	17	7
55	Patel *et al.* (2021)[70]	Cohort	USA	68±0.0	75	337	16	73	13	133	2, 3, 4, 5,7	8
56	Peng *et al.* (2013)[71]	Observational	China	64.9±0.0	75	506	23	271	11	235	2	9
57	Qiu *et al.* (2015)[72]	Cohort	China	67±0.0	75	211	12	125	3	73	2,3	9
58	Rao *et al.* (2017)[73]	Prospective	China	58.05±0.0	75	278	14	142	7	100	NR	8
59	Sawayama *et al.* (2020)[74]	Cohort	Japan	70.0±10.8	75	193	9	36	2	53	2,3,17	9
60	Shen *et al.* (2016)[75]	Cohort	China	68.48±0.0	NR	309	6	176	7	133	NR	8
61	Sibbing *et al.* (2009)[76]	Cohort	Germany	66.5±10.16	600	2485	55	680	119	1805	2	9
62	Sibbing *et al.* (2010)[77]	Cohort	Germany	67.4±0.0	NR	1523	1	302	3	138	17	7
63	Simon *et al.* (2009)[78]	Cohort	France	66.2±13.67	300–900	2208	63	635	193	1573	2,3,4,5,17	9

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Table 1: *(Continued)*

S. No.	Name of Author (year)	Type of Study	Place of study	Age	Dose (mg)	Total sample size	LOF carriers Event	LOF -carriers Total	LOF noncarriers Event	LOF noncarriers Total	Allele studied	Quality assessment (Newcastle-Ottawa Scale and Jadad Scale)
64	Sreedharan *et al.* (2020)[79]	Cohort	Australia	57 *et al.* (5065)	75	229	32	75	43	139	2,3	9
65	Sun *et al.* (2016)[80]	Cohort	China	64.6±10.8	300	559	55	338	14	181	2,3	9
66	Tabata *et al.* (2014)[81]	Cohort	Japan	70.0±9.9	300	331	32	220	8	111	2,3	9
67	Tabata *et al.* (2016)[82]	Cohort	Japan	69.0±10.3	300	434	43	285	12	149	2,3	9
68	Tanaka *et al.* (2019)[83]	Cohort	Japan	68±0.0	NA	518	18	319	10	182	2,3	7
69	Tang *et al.* (2013)[84]	Cohort	China	58.9±11.2	300	670	21	384	5	286	2,3,17	9
70	Tiroch *et al.* (2010)[85]	Cohort	Germany	64.8±0.2	600	928	14	248	68	680	2,17	9
71	Tomek *et al.* (2018)[86]	Cohort	Caucasian	64.5±0.0	NR	130	7	32	4	40	2	7
72	Trenk *et al.* (2008)[87]	Cohort	Germany	66.4±9.1	600	797	5	243	7	554	2	9
73	Verschuren *et al.* (2013)[88]	Cohort	Netherlands	60.80±00	600	1327	30	400	55	916	2,3,17	9
74	Wei *et al.* (2015)[89]	Cohort	China	65.7±11.7	300	110	21	51	4	59	2	9
75	Wirth *et al.* (2018)[90]	Cohort	Malta	64.58±9.2	NR	82	12	22	17	60	2	7
76	Xie *et al.* (2013)[91]	Cohort	China	59.5±11.0	600	1068	66	614	26	454	2, 3	9
77	Yi *et al.* (2016)[92]	Cohort	China	68.2±0.0	75	363	30	215	7	148	NR	9
78	Yi *et al.* (2018)[93]	Cohort	China	69.1±0.0	75	523	44	281	25	221	2	9
79	Yu *et al.* (2021)[94]	Cohort	China	58.2±9.0	300	351	22	101	55	250	2,3,17	8

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Table 1: *(Continued)*

S. No.	Name of Author (year)	Type of Study	Place of study	Age	Dose (mg)	Total sample size	LOF carriers Event	LOF -carriers Total	LOF noncarriers Event	LOF noncarriers Total	Allele studied	Quality assessment (Newcastle-Ottawa Scale and Jadad Scale)
80	McDonough *et al.* (2015)[95]	Retrospective	worldwide	62.5±0.0	75	522	4	107	19	386	2,17	9
81	Zhang *et al.* (2014)[96]	Cohort	China	64.8±0.0	75	95	16	53	5	42	2	9
82	Zhang *et al.* (2020a)[97]	Cohort	China	62.35±12.76	75	160	61	120	4	40	2, 3	9
83	Zhang *et al.* (2020b)[98]	Cohort	China	60.16±9.73	75	1361	62	524	56	397	2, 3, 17	9
84	Zhong *et al.* (2018)[99]	Retrospective	China	63.4±0.0	75/150	934	147	557	104	377	2,3	8
85	Wang *et al.* (2019)[100]	RCT	China	64.1±5.62)	75/300	1704	48	478	29	360	2, 3	5
86	Gonzalez *et al.* (2016)[101]	RCT	Spain	69±0.0	75/150	772	1	53	1	95	2	3
87	Mega *et al.* (2011)[102]	RCT	USA	60.2±0.0	75/300	333	3	86	5	247	2	3
88	Ogawa *et al.* (2016)[103]	RCT	Japan	64.2±0.0	75/300	383	31	248	16	135	2	5
89	Wallentin *et al.* (2010)[104]	RCT	Multi Centre	62.5±11.0	300/600	4904	48	437	146	1250	2,3,4,5,6,7,8	5
90	Yi *et al.* (2018)[105]	RCT	China	69.3±0.0	75	284	24	128	26	156	2	4

*NR: not reported

Evaluation of quality

The studies were assessed on a scale of 0–10, with low risk (7–10), moderate risk (5–6), and high risk (0–4) allocated to each group for cohort and case–control. However, RCTs were evaluated on a scale of 0–5 (Jadad scale). Table 1 indicates that six studies were judged to be of excellent and 84 studies to be of outstanding quality.

The outcome of *C-19* polymorphism and its efficacy for the world population

In all 90 studies, there were 30,950 individuals in the *C-19-LoF* noncarrier group and 21,798 patients in the *C-19-LoF* carrier group. Because there was a considerable amount of heterogeneity among the included studies (I^2 = 62%, $P < 0.001$), the random effects model was selected for further analysis. Figure 2 shows a significant correlation between the usage of CLOP in patients in the carrier group and those in the noncarrier group, with a pooled OR of 1.72 [1.53, 1.94]. Thus, *C-19-LoF* allele carriers were more vulnerable than *C-19-LoF* allele noncarriers, according to the primary study.

Publication bias

The funnel plots for the qualitative rating exhibit visual asymmetry in Figure 3, which is a sign of publishing bias.

The outcome of *C-19* polymorphism and its efficacy for the Asian population

From a total of 50 studies, including 26,444 patients from the Asian population, data were analyzed to assess the impact of *C-19-LoF* carrier versus *C-19-LoF* noncarrier and CLOP use on the outcome of CA events. In Figure 4, the Chi-square test ($P < 0.001$) showed that the heterogeneity (I^2) among studies was 61%, which is a quite significant level. *C-19-LoF* allele carriers were shown to be at higher risk than *C-19-LoF* allele noncarriers, with a pooled OR of 1.95 [1.66, 2.28], indicating a significant relationship.

Publicationbias

A funnel plot was used for the qualitative assessment of publication bias shows some asymmetry in the plot's form (Figure 5), which suggests publishing bias.

Sensitivity analysis

We conducted a sensitivity analysis on the meta-analysis results for the world and Asian populations (Figures S1 and S2). Even though the pooled OR dropped for all groups, *C-19-LoF* alleles were still significantly associated with CA events compared to those who do not carry these alleles, particularly in Asian populations. Furthermore, even after removing studies with large sample sizes and very small sample sizes, a significant connection was still seen in the population with *C-19-LoF* alleles using CLOP medication.

DISCUSSION

Prior studies demonstrating a link between *C-19-LoF* allele carriers and the incidence of adverse clinical outcomes in Asian and international patients on CLOP treatment were evaluated in the current systematic review and meta-analysis. This is the largest systematic review that addresses this topic and provides both qualitative and quantitative results. In total, 52,748 patients were recruited for the 90 trials that we included in our article. According to our results, Asian patients with any *C-19-LoF* allele are less likely to experience bleeding events; nevertheless, because of the nonsignificant increasing tendency, more extensive prospective studies are required to validate the impact on various CV events.[106] We observed that patients with *C-19-LoF* alleles were more likely to experience CA events than those without the alleles, even when taking CLOP medication. With an OR of 1.7 from our global pooled analysis, CAD patients treated with CLOP are more likely to experience CAD events worldwide. Further, our study also found that in the Asian population, the OR increases, suggesting that people taking higher dosages of CLOP have a markedly higher risk of cardiac events. Similar findings were made by Sharma *et al.*, who discovered that individuals with one or more *C-19-LoF* alleles have a much higher risk of composite events and CA events than those without these alleles, particularly in Asian populations.[107] Furthermore, the patients' country had a substantial impact on the consequences of *C-19-LoF* alleles. Our study's findings also demonstrated that a higher loading dose of CLOP was insufficient to overcome the CLOP resistance of Asian individuals. Niu *et al*. found that the *C-19* polymorphism affects CLOP's efficacy differently in Asians and Westerners.[108] The *C-19* genotype status test of interaction was also shown to be statistically significant by Pereira *et al.*, suggesting that the *C-19* genotype altered the effect.[109] According to Saito *et al.*, in Japanese patients undergoing PCI, the ABCD-GENE score demonstrated a significant and moderate diagnostic potential for HPR on CLOP.[110] Similarly, Angiolillo *et al*. found that the ABCD-GENE score provides a straightforward way to identify HPR patients taking CLOP who are more likely to experience serious ischemic events, like death, after an acute myocardial infarction. In patients with a high ABCD-GENE score, long-term oral P2Y12 inhibitors other than CLOP should be investigated.[111]

Heterogeneity is one of the important parameters in any type of meta-analysis.[112-114] Nevertheless, the substantial heterogeneity seen in these meta-analyses undoubtedly

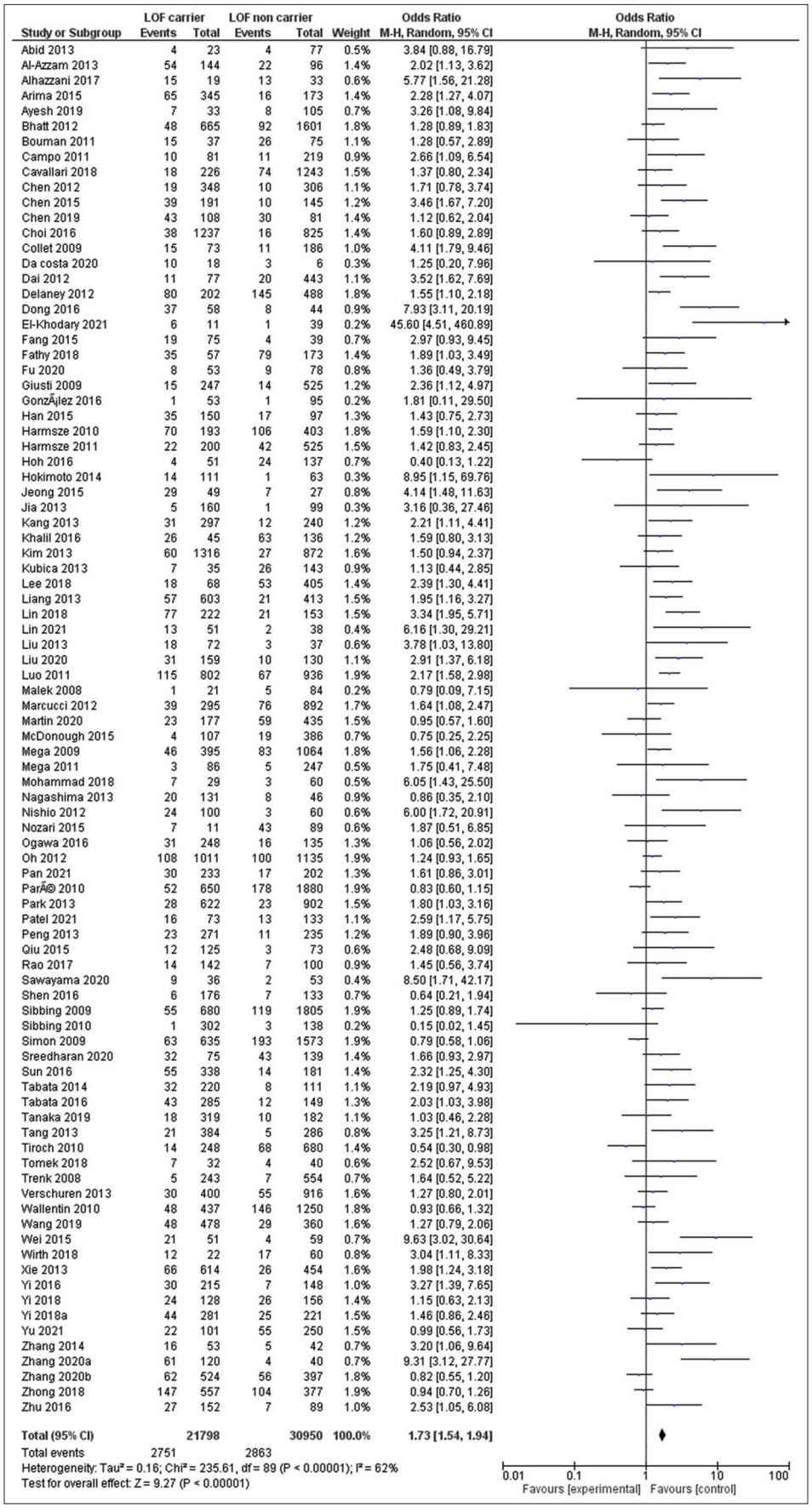

Figure 2: Correlation between *C-19-LoF* alleles and CA events (Worldwide patients receiving CLOP)

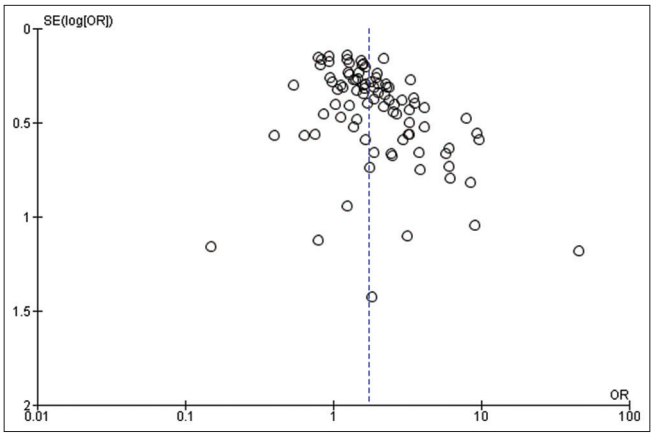

Figure 3: Funnel diagram for qualitative assessment of publication bias of included studies related to the patients receiving CLOP worldwide

indicates that there is a complex interaction between *C-19-LoF* alleles and the result of interest, one that may differ among studies and populations. The significance of taking population stratification into account in genetic studies is highlighted by this observation. Ignoring population stratification in genetic research can result in erroneous connections and incorrect interpretations of findings. Thus, it is appropriate to stress the importance of *C-19-LoF* allele genetic testing. Based on each patient's unique genetic profile, this individualized approach to treatment can assist in better customizing medical interventions for them.

To maximize medication efficacy and achieve precision medicine, especially in the Asian population, our study will assist clinicians in choosing appropriate alternative antiplatelet medications, such as ticagrelor or prasugrel, for the treatment

Study or Subgroup	LOF carrier Events	LOF carrier Total	LOF non carrier Events	LOF non carrier Total	Weight	Odds Ratio M-H, Random, 95% CI
Arima 2015	65	345	16	173	2.5%	2.28 [1.27, 4.07]
Chen 2012	19	348	10	306	2.0%	1.71 [0.78, 3.74]
Chen 2015	39	191	10	145	2.1%	3.46 [1.67, 7.20]
Chen 2019	43	108	30	81	2.5%	1.12 [0.62, 2.04]
Choi 2016	38	1237	16	825	2.5%	1.60 [0.89, 2.89]
Dai 2012	11	77	20	443	2.0%	3.52 [1.62, 7.69]
Dong 2016	37	58	8	44	1.6%	7.93 [3.11, 20.19]
Fang 2015	19	75	4	39	1.2%	2.97 [0.93, 9.45]
Fathy 2018	35	57	79	173	2.4%	1.89 [1.03, 3.49]
Fu 2020	8	53	9	78	1.5%	1.36 [0.49, 3.79]
Han 2015	35	150	17	97	2.3%	1.43 [0.75, 2.73]
Hokimoto 2014	14	111	1	63	0.5%	8.95 [1.15, 69.76]
Jeong 2015	29	49	7	27	1.4%	4.14 [1.48, 11.63]
Jia 2013	5	160	1	99	0.5%	3.16 [0.36, 27.46]
Kang 2013	31	297	12	240	2.2%	2.21 [1.11, 4.41]
Kim 2013	60	1316	27	872	2.9%	1.50 [0.94, 2.37]
Liang 2013	57	603	21	413	2.7%	1.95 [1.16, 3.27]
Lin 2018	77	222	21	153	2.6%	3.34 [1.95, 5.71]
Lin 2021	13	51	2	38	0.8%	6.16 [1.30, 29.21]
Liu 2013	18	72	3	37	1.1%	3.78 [1.03, 13.80]
Liu 2020	31	159	10	130	2.0%	2.91 [1.37, 6.18]
Luo 2011	115	802	67	936	3.3%	2.17 [1.58, 2.98]
Nagashima 2013	20	131	8	46	1.7%	0.86 [0.35, 2.10]
Nishio 2012	24	100	3	60	1.1%	6.00 [1.72, 20.91]
Ogawa 2016	31	248	16	135	2.3%	1.06 [0.56, 2.02]
Oh 2012	108	1011	100	1135	3.4%	1.24 [0.93, 1.65]
Pan 2021	30	233	17	202	2.4%	1.61 [0.86, 3.01]
Park 2013	28	622	23	902	2.6%	1.80 [1.03, 3.16]
Peng 2013	23	271	11	235	2.1%	1.89 [0.90, 3.96]
Qiu 2015	12	125	3	73	1.1%	2.48 [0.68, 9.09]
Rao 2017	14	142	7	100	1.6%	1.45 [0.56, 3.74]
Sawayama 2020	9	36	2	53	0.8%	8.50 [1.71, 42.17]
Shen 2016	6	176	7	133	1.3%	0.64 [0.21, 1.94]
Sun 2016	55	338	14	181	2.4%	2.32 [1.25, 4.30]
Tabata 2014	32	220	8	111	1.9%	2.19 [0.97, 4.93]
Tabata 2016	43	285	12	149	2.2%	2.03 [1.03, 3.98]
Tanaka 2019	18	319	10	182	1.9%	1.03 [0.46, 2.28]
Tang 2013	21	384	5	286	1.5%	3.25 [1.21, 8.73]
Wang 2019	48	478	29	360	2.8%	1.27 [0.79, 2.06]
Wei 2015	21	51	4	59	1.2%	9.63 [3.02, 30.64]
Xie 2013	66	614	26	454	2.8%	1.98 [1.24, 3.18]
Yi 2016	30	215	7	148	1.8%	3.27 [1.39, 7.65]
Yi 2018	24	128	26	156	2.4%	1.15 [0.63, 2.13]
Yi 2018a	44	281	25	221	2.7%	1.46 [0.86, 2.46]
Yu 2021	22	101	55	250	2.6%	0.99 [0.56, 1.73]
Zhang 2014	16	53	5	42	1.3%	3.20 [1.06, 9.64]
Zhang 2020	61	120	4	40	1.3%	9.31 [3.12, 27.77]
Zhang 2020a	62	524	56	397	3.1%	0.82 [0.55, 1.20]
Zhong 2018	147	557	104	377	3.4%	0.94 [0.70, 1.26]
Zhu 2016	27	152	7	89	1.7%	2.53 [1.05, 6.08]
Total (95% CI)		**14456**		**11988**	**100.0%**	**1.95 [1.66, 2.28]**
Total events	1841		985			

Heterogeneity: Tau² = 0.17; Chi² = 127.27, df = 49 (P < 0.00001); I² = 61%
Test for overall effect: Z = 8.33 (P < 0.00001)

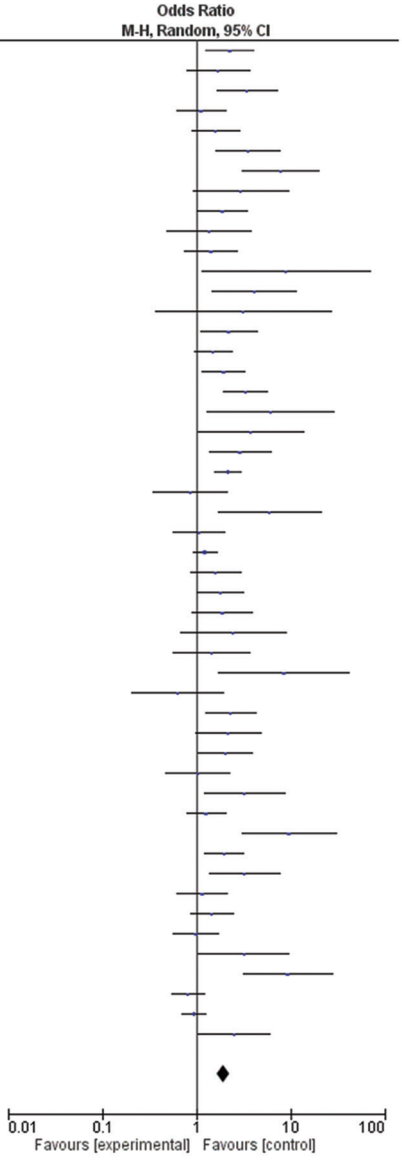

Figure 4: Correlation between *C-19-LoF* alleles and CA events (Asian patients receiving CLOP)

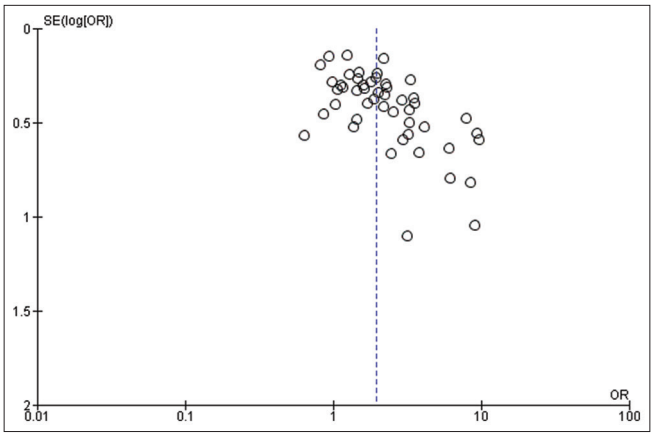

Figure 5: Funnel diagram for qualitative assessment of publication bias of included studies related to the patients receiving CLOP Asian population

of patients with CA disease who have *C-19-LoF*. The findings of the current investigation may have applications since physicians can, if available, determine a patient's *C-19* genetic status before administering CLOP to treat CAD.

CONCLUSION

Current investigations conclude that individuals having different polymorphisms for *C-19-LoF* alleles contribute to the variation in how well a patient responds to CLOP therapy. *C-19-LoF* allele carriers in the Asian population are far more likely than noncarriers to experience a CA event while taking CLOP than people in other populations. The high-loading dosage CLOP strategy is not clinically beneficial for patients with the *C-19-LoF* allele. Therefore, the present study supports that genetic testing for *C-19* variations may enable clinicians to customize antiplatelet medicine.

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ETHICAL DISCLOSURE

None.

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