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Association of Clopidogrel Genetic Polymorphism With Efficacy and Safety for Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Updated Meta-Analysis

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Background and Purpose Research suggests that *CYP2C19* loss-of-function (LoF) alleles impede the metabolism of clopidogrel. However, there is limited research on the relationship between these alleles and the risk of stroke or transient ischemic attack (TIA) recurrence in patients taking clopidogrel. This updated meta-analysis aims to evaluate the relationship between *CYP2C19* LoF alleles and the risk of stroke or TIA recurrence among patients receiving clopidogrel.

Methods Relevant literature was obtained from searches of PubMed, Scopus, Cochrane Central Register Controlled Trials (CENTRAL), and Embase. The outcome measures of included studies were stroke or TIA, composite vascular events as an efficacy, and bleeding as a safety outcome. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO ID: CRD42024564771).

Results An analysis of 28 studies encompassing 11,401 patients treated with clopidogrel following stroke or TIA revealed that carriers of *CYP2C19* LoF alleles had significantly higher risk of stroke recurrence compared to non-carriers (risk ratio [RR], 1.89; 95% confidence interval [CI]: 1.55−2.32). Composite vascular events were also significantly more frequent in carriers of the *CYP2C19* LoF allele than in non-carriers (RR, 1.54; 95% CI: 1.16−2.04). Both observational studies (RR, 2.20; 95% CI: 1.74−2.79) and post-hoc analyses of randomized controlled trials (RR, 1.44; 95% CI: 1.04−1.99) demonstrated significantly increased recurrence risk among carriers of these alleles. This risk was especially pronounced in Asian populations (RR, 1.97; 95% CI: 1.60−2.43). There was insufficient data specific to other ethnic groups for definite conclusions. The incidence of bleeding events was similar between groups.

Conclusions Carriers of *CYP2C19* LoF alleles treated with clopidogrel had a higher risk of stroke or TIA recurrence than non-carriers. This risk was higher in Asian populations.

Keywords humans; alleles; clopidogrel; ischemic stroke; transient ischemic attack; cytochrome.

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INTRODUCTION

Clopidogrel is a P2Y12 inhibitor prodrug that is metabolized into its active form, primarily by cytochrome P450 2C19 (CYP2C19), which irreversibly inhibits platelet aggregation.[1] When used alone or in combination with aspirin, clopidogrel has proven effective for secondary prevention after ischemic stroke or transient ischemic attack (TIA).[2] However, the *CYP2C19* gene exhibits polymorphism, and its loss-of-function (LoF) alleles are associated with the poor metabolism of clopidogrel. This genetic variant alters individual responses to clopidogrel, resulting in a significant stroke recurrence rate among those treated with clopidogrel, including patients receiving dual-antiplatelet treatment.[3]

Previous research has found that carriers of the *CYP2C19* LoF alleles with either stable coronary artery disease (CAD) or acute coronary syndrome (ACS) have an increased risk of mortality or the recurrence of cardiovascular diseases when treated with clopidogrel.[4,5] Consequently, the latest clinical guidelines recommend using *CYP2C19* genotyping to guide the selection of P2Y12 inhibitors in patients with ACS.[6]

In contrast, data on patients with ischemic stroke, including TIA are limited. The underlying mechanisms of stroke appear to be less dependent on platelet activation than those of CAD, and antiplatelet therapy following stroke carries a higher risk of intracranial hemorrhage.[7] Therefore, the impact of CYP polymorphism on ischemic stroke or TIA may differ from its impact on CAD. Two previous studies suggest that reduced *CYP2C19* function is linked to higher rates of stroke recurrence and worse outcomes in ischemic stroke patients.[8,9] However, another study found no such association.[10] As a result, the relationship between genetic polymorphisms and diminished clopidogrel response in patients with ischemic stroke or TIA remains unclear.

The recent PLATELET trial was a genetic study on the impact of the *CYP2C19* genotype on cardiovascular events among a large sample of approximately 2,500 Korean stroke patients.[11] While this study provided valuable insights into the effects of the *CYP2C19* genotype on cardiovascular outcomes, the broader applicability of its findings to the global population and existing evidence base is uncertain. By updating this meta-analysis to include this trial and other recent studies, we aim to address gaps in the literature, enhance the statistical power of our results, and provide a more comprehensive assessment of the relationship between *CYP2C19* polymorphisms and clinical outcomes in clopidogrel-treated patients who have suffered an ischemic stroke or TIA. We conducted a systematic review and updated meta-analysis of existing studies to evaluate the relationship between *CYP2C19* genetic polymorphisms, and stroke or TIA recurrence, composite vascular events, and bleeding in ischemic stroke or TIA patients receiving clopidogrel.

METHODS

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the methodologies detailed in the Cochrane Handbook for Systematic Reviews for reviewing intervention studies.[12,13] We systematically extracted data and evaluated the validity of the studies following these protocols. The protocol for this review was registered with PROSPERO (PROSPERO ID: CRD42024564771).

Search strategy and eligibility criteria

We performed a comprehensive search of the PubMed (MEDLINE), Scopus, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases, and a manual review of the references from all identified publications. The date range of our searches was the inception of the database to April 15, 2025. Our searches imposed no language restrictions on the results. The search strategies are shown in more detail in Supplementary Table 1 (in the online-only Data Supplement). The purpose of the search was to identify studies that have examined the relationship between genetic polymorphism in clopidogrel-treated ischemic stroke or TIA patients and assessed clopidogrel efficacy and safety in this patient population.

The study inclusion criteria were as follows: 1) Any original study about clopidogrel use in ischemic stroke or TIA patients; 2) Retrospective and prospective cohort studies, randomized clinical trials (RCTs), and post-hoc analyses of RCTs (in nested RCTs, only participants who received clopidogrel were included in our meta-analysis); 3) Outcome measures that included at least one of the two clinical endpoints of efficacy and safety. Efficacy was defined as either recurrent stroke or TIA, composite vascular events, including myocardial infarction or vascular death. Safety was defined as any other clinically significant bleeding, as defined by the Global Use of Strategies to Open Occluded Arteries (GUSTO)[14]; and 4) Studies that compared clinical outcomes between carriers and non-carriers of *CYP2C19* LoF alleles and studies about the influence of genetic polymorphism other than *CYP2C19* on clopidogrel efficacy. The study exclusion criteria were as follows: 1) Studies involving patients treated with clopidogrel for vascular conditions other than ischemic stroke or TIA; 2) Studies that included only one patient group treated with clopidogrel or alternative antiplatelets, without examining genetic polymorphism; and 3) Articles categorized as editorials, reviews, letters, or case reports.

Data extraction

Two of the authors, H.P. and Y.H.J., both stroke neurologists, conducted the initial screening of the databases for titles and abstracts to identify studies eligible for further review. A third author, T-J.S., resolved any disagreements between the reviewers by reaching a consensus. We collected data from the included studies on publication characteristics, study locations, design, participant inclusion criteria, participant demographics, sample sizes, treatment dosages and durations, genotypes, the proportions of participants included in pharmacogenetic analyses, follow-up durations and completeness, and the efficacy and safety outcomes.

Data extraction was conducted independently by two authors (H.P. and Y.H.J.) using a standardized form, with assistance and oversight from K.Y.L. and T-J.S. Any discrepancies were reviewed by a third author, T-J.S., and resolved once consensus was reached. The primary endpoint was stroke recurrence, which was categorized as either ischemic stroke (worsening of the index stroke or the onset of a new focal neurological deficit), hemorrhagic stroke, or TIA. The secondary endpoint was the occurrence of composite vascular events, which was defined as a combination of stroke, myocardial infarction, and cardiovascular death. The safety outcome was the occurrence of any bleeding. Endpoints were evaluated at the time of the longest available follow-up or death, depending on which was first. The definitions of all three of these outcomes were consistent with those used in the original studies.

Quality assessment

The Cochrane Risk-of-Bias tool (RoB 2.0) was utilized to evaluate post-hoc RCT analyses and RCTs.[15] The Risk of Bias in Non-Randomized Studies - of interventions (ROBINS-I) was employed to assess non-randomized observational studies.[16] Two reviewers (H.P. and Y.H.J.) independently conducted a risk-of-bias assessment for each study. Any disagreement was resolved through discussion. The grading of recommendations assessment, development, and evaluation (GRADE) approach was used to assess the quality of the evidence for each outcome in the included studies.[17] The design of current meta-analysis was followed the recommended guideline for meta-analysis.[18] To assess publication bias, we visually inspected funnel plots and evaluated their asymmetry using Egger's linear regression method.

Statistical analysis

We conducted a comprehensive meta-analysis to assess outcomes in clopidogrel-treated patients based on their *CYP2C19* phenotype. CYP2C19 genotyping identified alleles *1, *2, *3, *4, *5, *6, *7, *8, and *17. We classified patients with *1/*1, *1/*17, or *17/*17 as extensive metabolizers (EM). Patients carrying at least one of *2, *3, *4, *5, *6, *7, or *8 alleles were categorized as intermediate metabolizers (IM). Those who were homozygous for these alleles (e.g., *2/*2, *3/*3) were categorized as poor metabolizers (PM). Consistent with the definitions given in the contributing studies, IM and PM were categorized as carriers of *CYP2C19* LoF alleles, while EM were categorized as non-carriers.[8,9] Pooled effect estimates were calculated using a random-effects model, accounting for between study heterogeneity. The Hartung-Knapp-Sidik-Jonkman method was applied to provide a more conservative estimate.[19] Outcomes were presented as risk ratios (RRs) and 95% confidence intervals (CIs). Subgroup analyses were performed for each outcome with study design (cohort study vs. post-hoc analyses of RCT) and ethnicity. Using sample size, study quality, patient risk level, follow-up duration (<1 year vs. ≥1 year), and the presence of *CYP2C19* *17 alleles, we performed a sensitivity analysis for each study.[10] All data were analyzed using the online version of the Cochrane Review Manager software (RevMan, https://revman.cochrane.org) and R software, version 4.2.2 (R Foundation for Statistical Computing). To assess the certainty of the evidence for this meta-analysis, GRADEpro GDT (Guideline Development Tool) (McMaster University and Evidence Prime; https://www.gradepro.org) was used.

RESULTS

Study selection and characteristics

The study selection process for the meta-analysis is presented in Supplementary Fig. 1 (in the online-only Data Supplement). In total, 28 studies comprising 11,401 stroke or TIA patients (mean age 64.60±11.20 years; 68% male), were included.[8,9,11,20-44] Among these, 22 were observational cohort studies,[11,20-32,34-37,39,41,43,44] two were RCTs,[33,38] and four were post-hoc analyses of RCTs.[8,9,40,42] The duration of follow-up for outcome assessment ranged from 5 days to 54 months. In 14 of the studies, patients were treated with clopidogrel during follow-up.[20,22-25,27,28,31,33,35,37,39,41,44] In the other 14 studies, treatment during follow-up was clopidogrel and aspirin.[8,9,11,21,26,29,30,32,34,36,38,40,42,43] The key baseline characteristics of the included studies are summarized in Table 1.

The quality of the included studies and the presence of publication bias

The results of the Cochrane Risk-of-Bias 2 tool (RoB 2.0) assessments for the included RCTs are summarized in Supplementary Figs. 2 and 3 (in the online-only Data Supplement). Of the six studies, three had an unclear risk of bias due to their open-label designs, five had attrition bias due to

Table 1. Baseline characteristics of the included studies in the meta-analysis

Study	Year	Study design	Country	Participants	No. of participants	Clopidogrel dose (mg)	Age (yr)	Male (%)	Outcome measured	Follow-up	CYP2C19 LoFA carrier		CYP2C19 Non-LoFA carrier	
											Allele	*n* (%)	Allele	*n* (%)
Jia et al.[20]	2013	Observational	China	AIS	259	75	66.5±11.5	85.1	Stroke	6 months	*2, *3	160 (61.8)	*1, *17	99 (38.2)
Lin et al.[21]	2014	Retrospective	China	IS/TIA with VAS	90	75	66.8±9.6	78.6	Stroke, ICH, death	54 months	*2, *3	44 (48.9)	*1	46 (51.1)
Spokoyny et al.[22]	2014	Retrospective	USA	Stroke or TIA	53	NR	69.6±NR	53.4	IS/TIA	NR	NR	17 (32.1)	NR	36 (67.9)
Zhang et al.[23]	2014	Prospective	China	NCIS	95	75	66.0±10.0	65.3	Stroke or other ischemic vascular events	6 months	*2, *3	53 (55.8)	*1	42 (44.2)
Fang et al.[24]	2015	Retrospective	China	AIS	114	NR	66.0±10.4	75.4	Stroke	12 months	*2, *3	75 (65.8)	*1, *17	39 (34.2)
Han et al.[25]	2015	Observational	China	AIS	345	75	68.1±11.5	67.8	MACE, stroke, TIA, death, bleeding	12 months	*2, *3	201 (59.3)	*1, *17	144 (40.7)
Jeong et al.[26]	2015	Retrospective	Korea	AIS due to LAA	76	75	61.6±12.9	75	Recurrence on DWI	5 days	*2, *3	31 (40.8)	*1, *17	45 (59.2)
McDonough et al.[9]	2015	Post hoc of RCT	USA	Symptomatic small subcortical stroke/TIA	493	75	62.5±10.5	61.9	Stroke, bleeding	40 months	*2, *3	107 (21.7)	*1, *17	386 (78.3)
Sun et al.[27]	2015	Retrospective	China	AIS	625	75	61.6±12.2	74.4	IS, MI, CV death, bleeding	12.7 months	*2, *3	391 (62.5)	*1, *17	234 (37.4)
Qiu et al.[28]	2015	Observational	China	AIS	211	75	67.1±12.6	55.0	IS, MI, CV death	6 months	*2, *3	129 (61.1)	*1	82 (38.9)
Hoh et al.[29]	2016	Observational	USA	IS or TIA due to ICAS	188	75	67.0±12.3	63.3	Stroke, TIA, MI, death	12 months	*2, *3, *8	51 (27.1)	*17	137 (72.9)
Li et al.[30]	2016	Retrospective	China	Stenting for IS or TIA due to ICAS/ECAS	268	75	63.0±9.0	85.1	Stroke, TIA, MI, death	12 months	*2, *3	44 (48.9)	*1	46 (51.1)
Wang et al.[8]	2016	Post hoc of RCT	China	Minor stroke/TIA	1,463	75	62.8±10.6	67.2	Stroke, MI, death, bleeding	90 days	*2, *3	854 (58.4)	*1, *17	609 (41.6)
Yi et al.[31]	2016	Prospective	China	AIS	363	75	68.5±11.7	66.7	IS, MI, death, cerebral hemorrhage	6 months	*2, *3	215 (59.2)	*1	148 (40.8)
Zhu et al.[32]	2016	Retrospective	China	Stenting for IS	241	75	64.3±9.3	90	IS, TIA, stent thrombosis, death, hemorrhagic stroke	12 months	*2, *3	152 (63.1)	*1	89 (36.9)
Han et al.[33]	2017	RCT	Korea	NCIS	393	75	61.0±10.9	67.3	Stroke	32.4 months	*2, *3	244 (62.1)	*1, *17	149 (37.9)
Lin et al.[34]	2018	Observational	China	AIS	375	75	69.0±12.1	64.5	END, IS, MI, death, hemorrhagic stroke	8 months	*2	222 (59.2)	*1	153 (40.8)
Tomek et al.[35]	2018	Observational	Czech	IS	130	75	64.5±13.9	78	IS, TIA, MI death, bleeding	14.9 months	*1, *17	86 (66.2)	*2	44 (33.8)
Tanaka et al.[36]	2019	Prospective	Japan	IS/TIA	501	75	68.0±NR	72.7	IS, TIA, MI, death, bleeding	24 months	*2, *3	319 (63.7)	*1	182 (36.3)
Tornio et al.[37]	2018	Retrospective	UK	Stroke	94	75	74.0±NR	61.7	Stroke, MI, death	24 months	*2	67 (26.7)	*1	27 (73.3)
Wang et al.[38]	2019	RCT	China	minor stroke/TIA	329	75	60.5±9.0	73.2	Stroke, TIA, MI, death, bleeding	90 days	*2, *3	190	*1, *17	139
Liu et al.[39]	2020	Observational	China	IS	289	75	66.6±10.9	58.1	IS	6 months	*2, *3	159 (55.0)	*1	130 (45.0)

Table 1. Baseline characteristics of the included studies in the meta-analysis (continued)

Study	Year	Study design	Country	Participants	No. of participants	Clopidogrel dose (mg)	Age (yr)	Male (%)	Outcome measured	Follow-up	CYP2C19 LoFA carrier		CYP2C19 Non-LoFA carrier	
											Allele	*n* (%)	Allele	*n* (%)
Meschia et al.[40]	2020	Post hoc of RCT	USA, Australia, Finland, Mexico, Germany, New Zealand, Spain, UK	Stroke/TIA	457	75	61.7±14.4	56.7	IS, MI, death, bleeding	90 days	*2, *3	326 (71.3)	*17	131 (29.7)
Lin et al.[41]	2021	Retrospective	China	IS	89	75	65.1±13.1	57.3	IS	12 months	*2, *3	51 (57.3)	*1	38 (42.7)
Zhou et al.[42]	2020	Post hoc of RCT	China	IS	365	75	61.8±8.5	72.2	Stroke, TIA, MI, death, bleeding	90 days	*2, *3	199 (54.5)	*1, *17	166 (45.5)
Al-Rubaish et al.[43]	2022	Prospective	Saudi Arabia	IS	256	75	61.0±12.5	64.9	Stroke, MI, death	6 months	*2	54 (21.1)	*1	202 (78.9)
Lv et al.[44]	2022	Prospective	China	IS	314	75	68.1±11.5	67.8	IS, TIA, MI, death, bleeding	54 months	*2, *3	187 (59.6)	* 17	127 (40.4)
Jung et al.[11]	2025	Prospective	Korea	AIS	2,925	75	65.3±12.5	66.3	Stroke, MI, CV death, bleeding	6 months	*2, *3	1785 (61.0)	*1, *17	1,125 (38.5)

Values are presented as mean±standard deviation or numbers only unless otherwise indicated.
AIS, acute ischemic stroke; CV, cardiovascular; DWI, diffusion weighted imaging; ECAS, extracranial atherosclerotic stenosis; END, early neurological deterioration; ICAS, intracranial atherosclerotic stenosis; ICH, intracerebral hemorrhage; IS, ischemic stroke; LAA, large artery atherosclerosis; LoFA, loss of function allele; MACE, major adverse cardiovascular event; MI, myocardial infarction; NCIS, non-cardioembolic stroke; NR, not reported; RCT, randomized clinical trial; TIA, transient ischemic attack; VAS, vertebral artery stenting.

insufficient enrollment, and three had additional bias due to post hoc analyses of RCTs. The risk of bias assessment for non-randomized studies using the ROBINS-I tool was moderate (Supplementary Figs. 4 and 5 in the online-only Data Supplement). The results of the certainty-of-evidence assessments of each outcome using the GRADE guidelines are outlined in Supplementary Table 2 (in the online-only Data Supplement). Funnel plots assessing stroke or TIA recurrence, composite vascular events, and bleeding events were symmetrical, indicating no publication bias (Supplementary Fig. 6 in the online-only Data Supplement).

CYP2C19 variants and efficacy outcomes

Among the 28 studies, 25 provided data on the relationship between *CYP2C19* alleles and stroke or TIA recurrence. Carriers of *CYP2C19* LoF alleles had a significantly higher risk of recurrence than non-carriers (RR 1.89; 95% CI: 1.55–2.32; $p<0.00001$). Heterogeneity statistics were low for stroke or TIA recurrence ($I^2=6\%$, $\tau^2=0.01$, Q=28.47 [df=24, $p=0.24$]) (Fig. 1). Additionally, 13 of the 28 studies reported efficacy outcomes for recurrent ischemic stroke only. In this analysis, carriers also had a significantly higher risk of recurrence (RR 1.98; 95% CI: 1.55–2.53; $p<0.01$). Heterogeneity statistics were low for recurrent ischemic stroke only ($I^2=0\%$, $\tau^2=0.00$, Q=11.01 [df=12, $p=0.53$]) (Supplementary Fig. 7 in the online-only Data Supplement). Twenty of the 28 studies assessed composite vascular events as an outcome measure. Similar to the findings for stroke or TIA, carriers of *CYP2C19* LoF alleles had an increased risk of composite vascular events than non-carriers (RR 1.54; 95% CI: 1.16–2.04; $p=0.01$). Heterogeneity statistics indicated moderate heterogeneity for composite vascular events ($I^2=49\%$, $\tau^2=0.12$, Q=45.23 [df=19, $p<0.01$]) (Fig. 2). The certainty of evidence for stroke or TIA recurrence, recurrent ischemic stroke and composite vascular events were high, moderate and low, respectively (Supplementary Table 2 in the online-only Data Supplement).

Stroke or TIA recurrence in observational studies vs. RCTs and post-hoc analyses of RCTs

The risk of stroke or TIA recurrence was significantly higher in carriers of *CYP2C19* LoF alleles than in non-carriers in both the 19 observational studies (RR 2.20; 95% CI: 1.74–2.79; $p<0.01$) and the six RCTs and post-hoc analyses of RCTs (RR 1.44; 95% CI: 1.04–1.99; $p=0.03$). Heterogeneity statistics indicated low ($I^2=6\%$, $\tau^2=0.01$, Q=28.47 [df=24, $p=0.24$]) (Fig. 3). Although the pooled risk was numerically higher in observational studies than in RCTs (RR 2.20 vs. RR 1.44), a meta-analysis of variance (ANOVA) found no significant difference by study design (β=0.12 on the log RR scale, standard error=1.88, $p=0.95$; ratio of RRs=1.13). In observa-

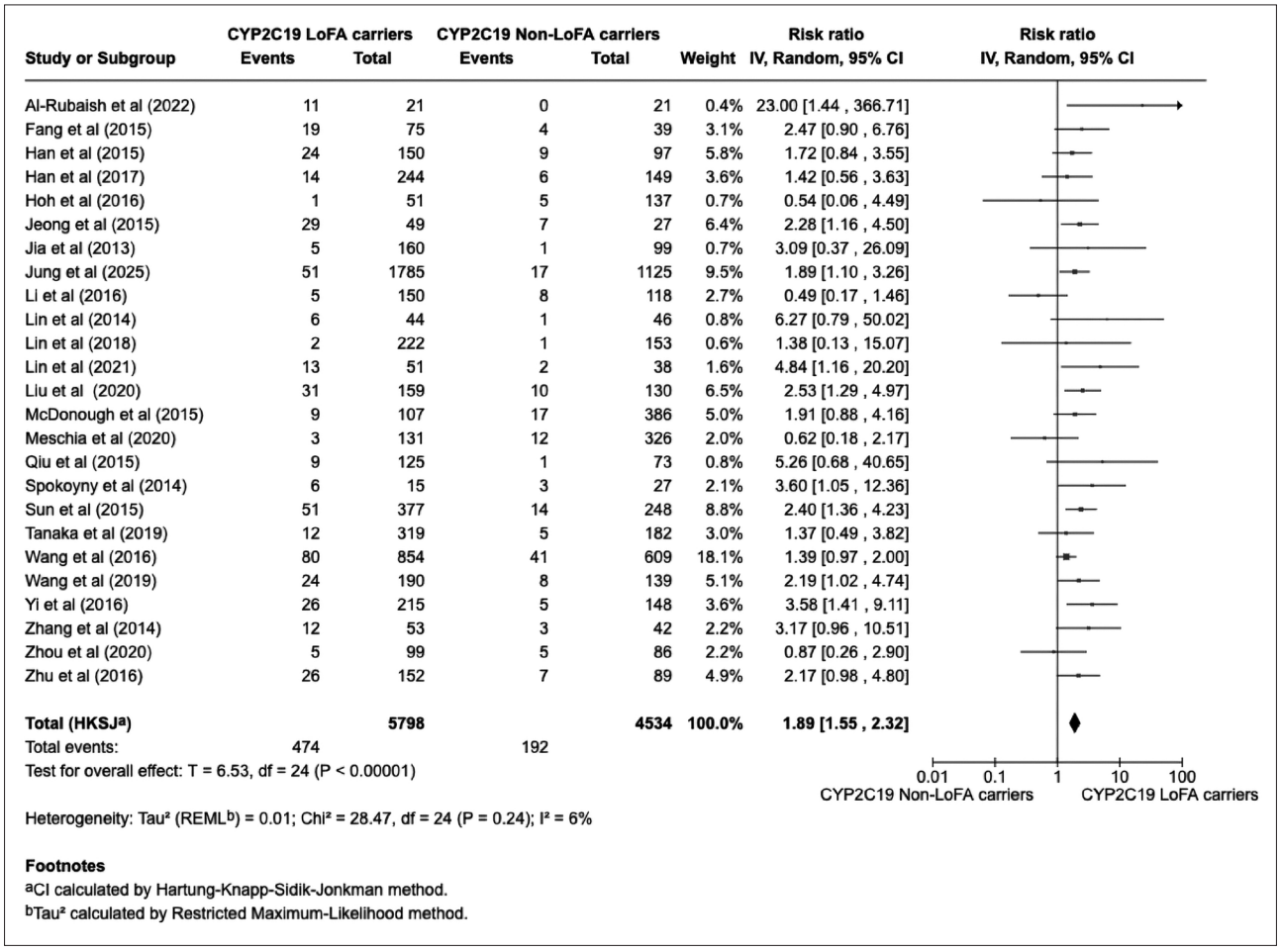

Fig. 1. Forest plot of the relationship between the presence of *CYP2C19* loss-of-function alleles and the risk of stroke or transient ischemic attack recurrence in patients treated with clopidogrel for secondary prevention. CI, confidence interval; IV, inverse variance; LoFA, loss of function allele.

tional studies and RCTs with post-hoc analyses of RCTs, the certainty of evidence for stroke or TIA recurrence was moderate and high, respectively (Supplementary Table 2 in the online-only Data Supplement).

Stroke or TIA recurrence with *CYP2C19* LoF alleles and clopidogrel in Asian patients vs. those of other ethnicities

We compared the effects of *CYP2C19* LoF alleles on Asian patients with their effects on patients of other ethnicities. The risk of recurrent stroke or TIA was significantly elevated only in patients of Asian ancestry (RR 1.97; 95% CI: 1.60−2.43; $p<0.00001$), while no significant difference was found in patients of other ethnicities (Europeans/American/Oceania ancestry: RR 1.64, 95% CI: 0.34−7.93, $p=0.39$; African ancestry: RR 1.78, 95% CI: 0.09−35.76, $p=0.25$) of *CYP2C19* LoF alleles. Additionally, other ethnicities showed a significantly lower incidence of stroke or TIA recurrence among non-carriers (RR 0.26; 95% CI: 0.19−0.35; $p=0.01$). Heterogeneity statistics was low ($I^2=6\%$, $\tau^2=0.02$, Q=33.67 [df=29, $p=0.25$]) (Fig. 4). In Asian ancestry, the certainty of evidence for stroke or TIA was moderate, whereas it was very low in all groups other than Asian (Supplementary Table 2 in the online-only Data Supplement).

Stroke or TIA recurrence in IM vs. PM of clopidogrel

A total of 22 studies compared the incidence of stroke or TIA recurrence in IM and PM groups according to the presence of the *CYP2C19* genotype. Among those with *CYP2C19* LoF alleles, those in the PM group had a significantly higher risk of stroke or TIA recurrence than those in the IM group (RR 1.88; 95% CI: 1.42−2.50; $p<0.01$). Heterogeneity statistics indicated moderate ($I^2=34\%$, $\tau^2=0.15$, Q=28.67 [df=21, $p=0.12$]) (Fig. 5). The certainty of evidence comparing IM and PM groups was moderate (Supplementary Table 2 in the online-only Data Supplement).

Bleeding events

Among the 28 studies included, 14 used the occurrence of bleeding as a safety outcome. The definition of bleeding used

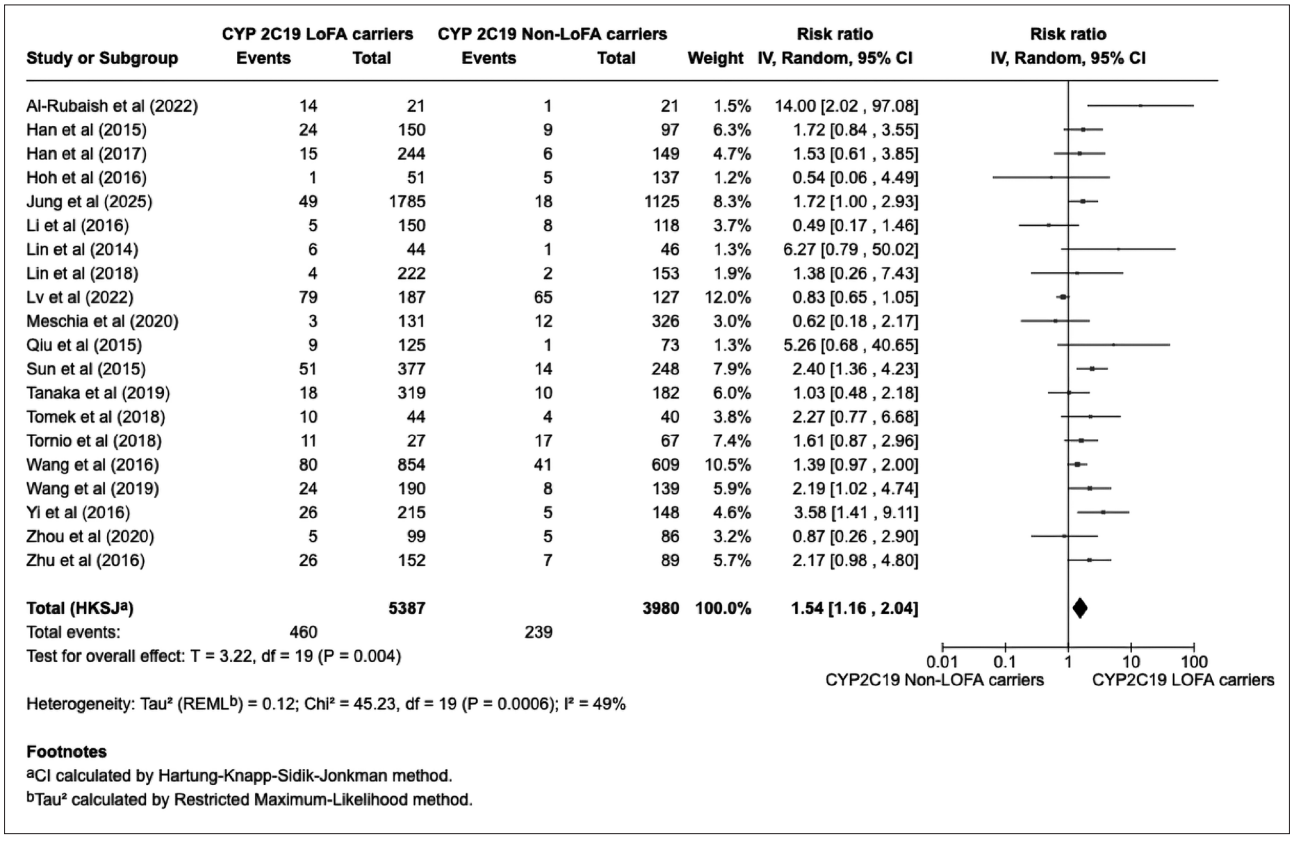

Fig. 2. Forest plot of the relationship between the presence of *CYP2C19* loss-of-function alleles and the risk of composite vascular events (stroke, myocardial infarction, vascular death) in patients treated with clopidogrel for secondary prevention. CI, confidence interval; IV, inverse variance; LoFA, loss of function allele.

in these studies was summarized in Supplementary Table 3 (in the online-only Data Supplement). The combined findings of these 14 studies reported bleeding events in 3.0% of *CYP2C19* LoF allele carriers and 3.3% of non-carriers. The bleeding rate was not significantly different between carriers and non-carriers of *CYP2C19* LoF alleles (RR 0.98; 95% CI: 0.81−1.18; p=0.82). Heterogeneity statistics indicated low for bleeding events (I^2=0%, τ^2=0.00, Q=4.46 [df=13, p=0.99]) (Fig. 6). No significant difference in bleeding events between carriers and non-carriers was observed in either Asian or non-Asian populations (Supplementary Fig. 8 in the online-only Data Supplement). The certainty of evidence of bleeding events was moderate (Supplementary Table 2 in the online-only Data Supplement).

Sensitivity analysis

We performed a sensitivity analysis to assess whether the association varied by the study design (RCT vs. observational study), sample size (≥200 vs. <200), patients' baseline risk levels (high vs. low), follow-up duration (≥1 year vs. <1 year), the presence or absence of *CYP2C19**17 LoF alleles on recurrent stroke or TIA, ischemic stroke subtypes (large artery atherosclerosis [LAA] vs. non-LAA), index event type (ischemic stroke vs. ischemic stroke or TIA), and antiplatelet regimen (dual antiplatelet therapy vs. mono antiplatelet therapy). In sensitivity analysis, across strata, carriers of *CYP2C19* LoF alleles consistently had a higher risk of recurrent stroke or TIA than non-carriers, except in the ischemic stroke subtypes, where the point estimates trended higher but did not reach statistical significance (Supplementary Fig. 9 in the online-only Data Supplement).

Genetic polymorphisms other than *CYP2C19* and their impact on outcomes in stroke and TIA patients following clopidogrel treatment

The effects of genetic polymorphisms other than *CYP2C19* on clopidogrel efficacy in ischemic stroke and TIA patients are detailed in Supplementary Table 4 (in the online-only Data Supplement). A total of 11 studies were included.[20,21,23,25,28-31,45-47] Among these, variants in the *ABCB1* (homozygous for the T allele of rs4148727 and the C allele of rs1045642), *P2Y12*, *PON1*, and *CES1A2* genes, were associated with increased risk of ischemic stroke or composite vascular events following stroke or stenting.[30,45,47] No associations were found be-

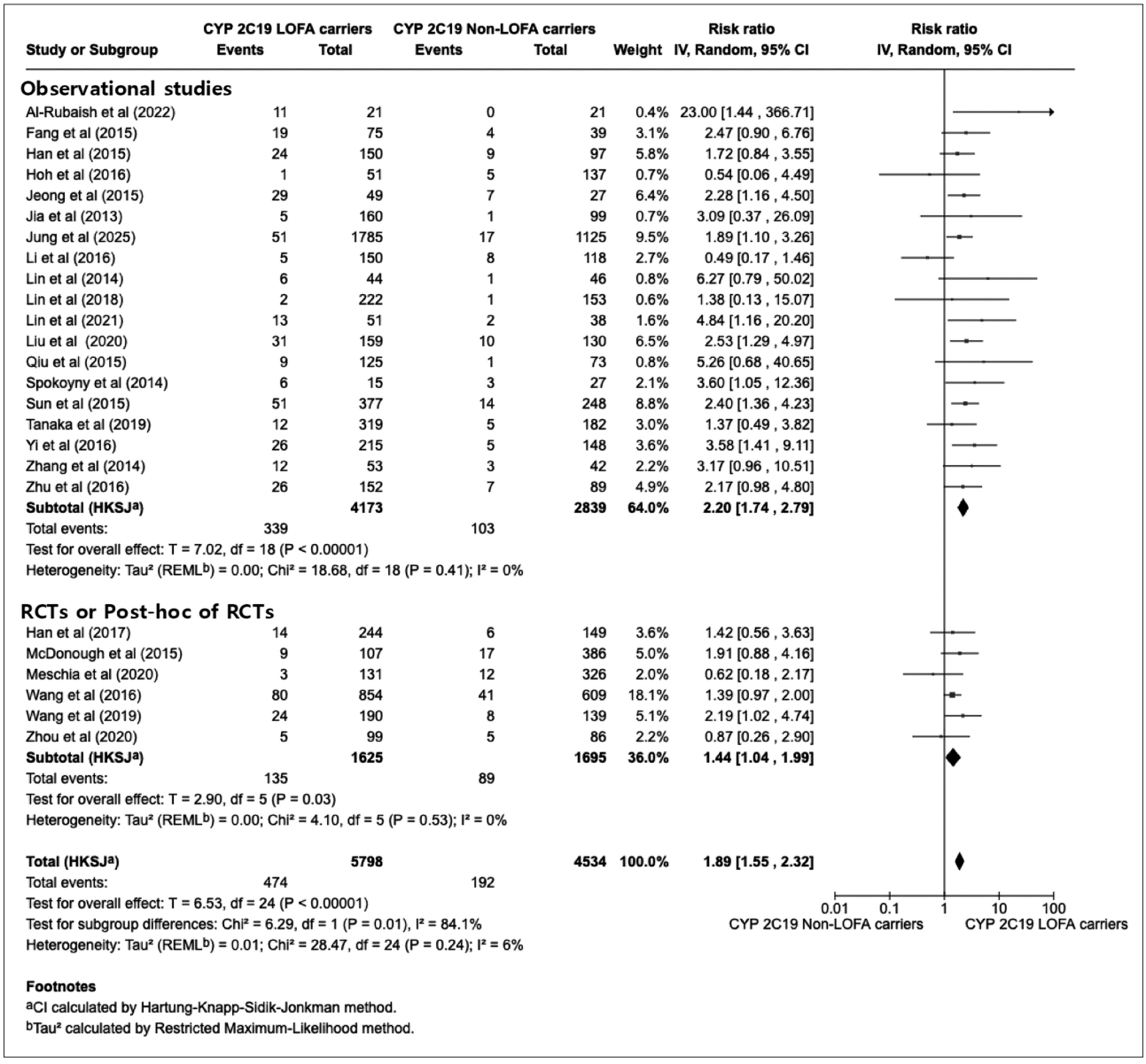

Fig. 3. Forest plot of the relationship between the presence of *CYP2C19* loss-of-function alleles on stroke or transient ischemic attack recurrence in patients treated with clopidogrel for secondary prevention in observational studies and RCTs or post-hoc analyses of RCTs. CI, confidence interval; IV, inverse variance; LOFA, loss of function allele; RCT, randomized clinical trial.

tween other genes and stroke recurrence or vascular events in patients treated with clopidogrel following stroke or TIA.

DISCUSSION

In this systematic review and meta-analysis of 28 studies, comprising a total of 11,401 ischemic stroke or TIA patients treated with clopidogrel, we found that carriers of *CYP2C19* LoF alleles had higher risks of stroke or TIA recurrence and composite vascular events than non-carriers but no increase in the risk of bleeding events. Additionally, the elevated risk of stroke or TIA recurrence was consistent across both observational and RCTs or post-hoc analyses of RCTs. However, when the total sample was sub-grouped by ethnicity, the elevated risk was only significant among Asian participants. A sensitivity analysis using various strata also supported our findings. In addition to *CYP2C19*, the *ABCB1*, *P2Y12*, *PON1*, and *CES1A2* genes were also associated with higher risks of ischemic stroke recurrence or composite vascular events in patients treated with clopidogrel for secondary prevention in some of the studies.[30,45,47]

Clopidogrel is a prodrug that requires hepatic metabolism to convert it into its active form. This metabolic process can be influenced by various genetic polymorphisms. Although

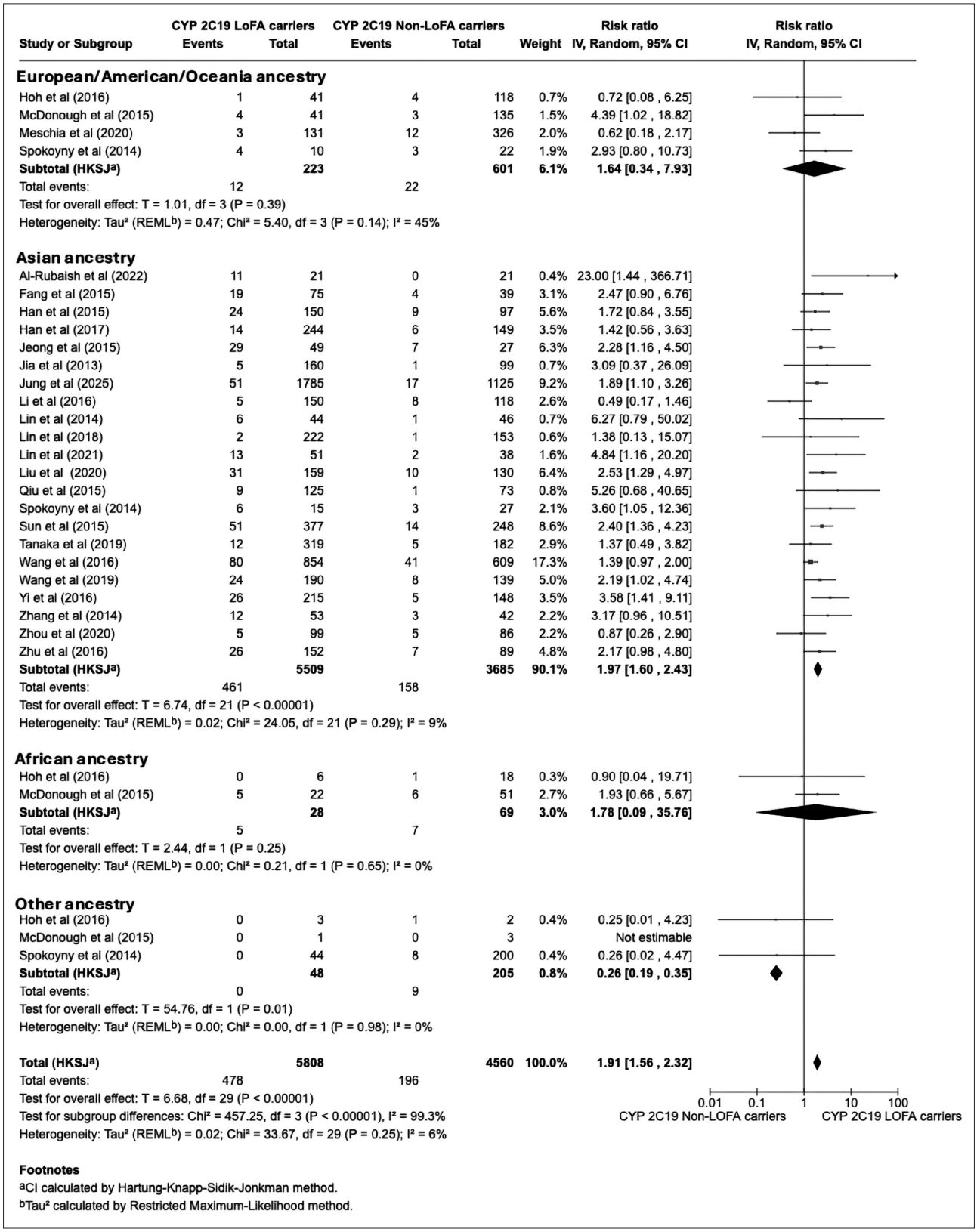

Fig. 4. Forest plot of the relationship between the presence of *CYP2C19* loss-of-function alleles in different ethnicities on the recurrence of stroke or transient ischemic attack in patients treated with clopidogrel for secondary prevention. CI, confidence interval; IV, inverse variance; LoFA, loss of function allele.

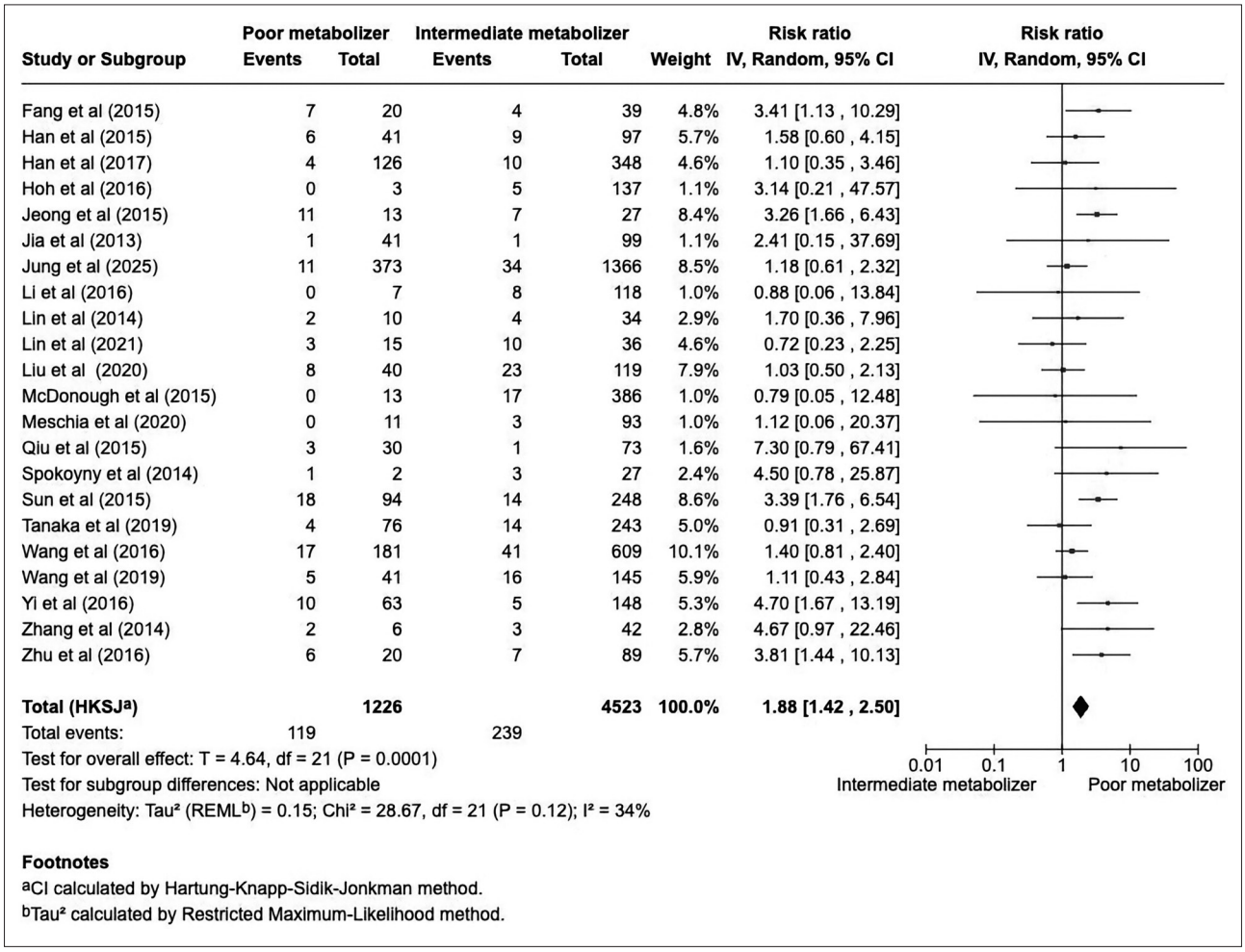

Fig. 5. Forest plot of the relationship between the presence of *CYP2C19* loss-of-function alleles and the risk of stroke or TIA in intermediate versus poor metabolizers treated with clopidogrel for secondary prevention. CI, confidence interval; IV, inverse variance; TIA, transient ischemic attack.

previous meta-analyses have investigated the impact of genetic polymorphisms on clopidogrel efficacy in patients with CAD, the findings have been inconsistent.[48,49] Notably platelet activation plays a less significant role in the pathophysiology of stroke than that of CAD. Moreover, the use of antiplatelet therapy for ischemic stroke patients carries a higher risk of intracranial hemorrhage than in those with CAD.[7] Therefore, the findings from studies on CAD cannot be generalized to stroke patients, as the underlying mechanisms and risk factors differ between the two conditions. In the present meta-analysis, we focus specifically on stroke and TIA patients. We provide evidence of the importance of genetic polymorphisms when treating patients with clopidogrel for the secondary prevention of stroke or TIA.

Our meta-analysis demonstrated that the risk of recurrent ischemic stroke or TIA was higher in observational studies than in post-hoc analyses of RCTs, despite showing consistently and significantly higher risk among carriers of *CYP2C19* LoF alleles (RR, 2.20 vs. 1.44). Although the pooled RR appeared higher in observational studies than in post hoc RCT analyses (2.20 vs. 1.44), an ANOVA-style moderator analysis using randomeffects metaregression found no significant effect modification by study design. Apparent differences may reflect residual confounding and confounding by indication, differences in outcome ascertainment and adjustment sets, and the small number of post hoc RCT analyses. We therefore interpret the observed discrepancy cautiously.

Carriers of *CYP2C19* LoF alleles represent approximately 30% of the Caucasian population and up to 60% of the Asian population.[10,11,27] Our analysis verified these proportions, with 27.1% in Caucasian populations versus 59.9% in Asian populations. Considering the high percentage of *CYP2C19* LoF allele carriers among Asian populations, it is particularly important to assess the impact of genetic polymorphism on the effectiveness of clopidogrel and its clinical outcomes among Asian patients. Consistent with previous findings, our study showed a higher risk of stroke or TIA recurrence in carriers of *CYP2C19* LoF alleles, specifically within Asian

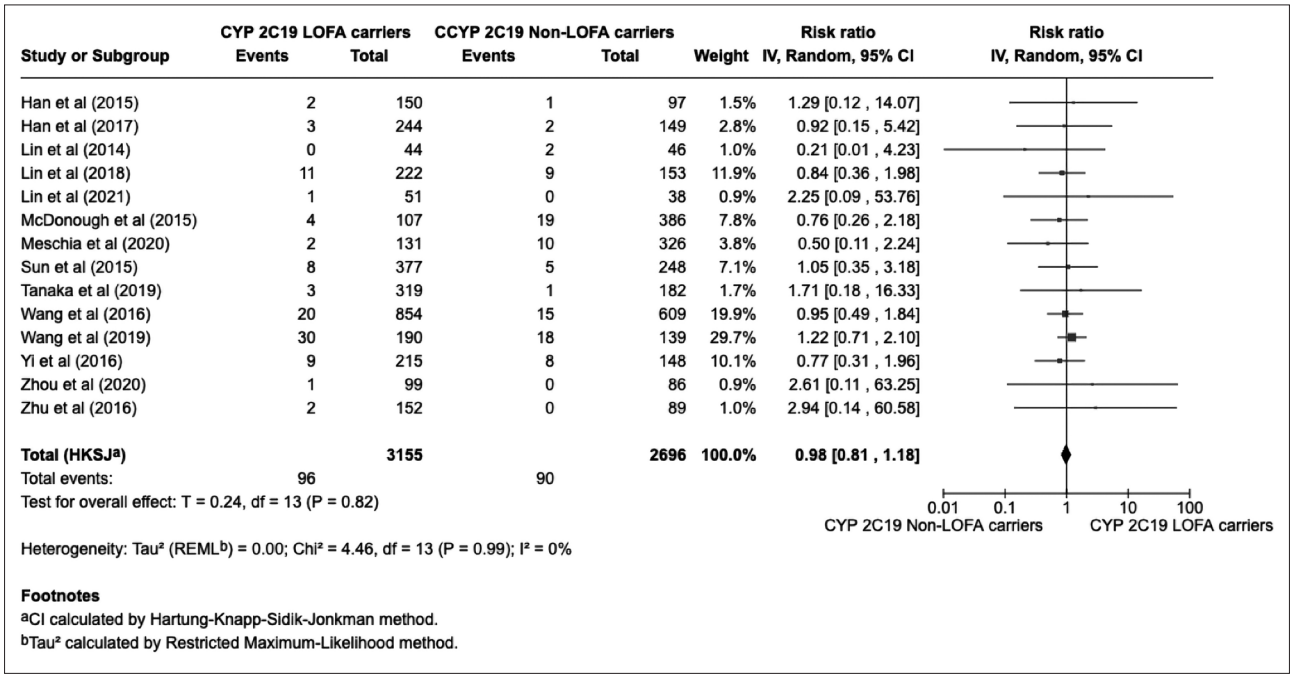

Fig. 6. Forest plot of the relationship between the presence of *CYP2C19* loss-of-function alleles and bleeding events in patients treated with clopidogrel for secondary prevention of stroke or transient ischemic attack. CI, confidence interval; IV, inverse variance; LOFA, loss of function allele.

populations.

The CHANCE-2 RCT demonstrated that ticagrelor, a potent antiplatelet agent unaffected by the *CYP2C19* genotype, is more effective than clopidogrel for secondary stroke prevention in carriers of *CYP2C19* LoF alleles.[50] In addition, we found a significantly higher risk of stroke or TIA recurrence in the PM group than in the IM group. Based on our findings and the results of the CHANCE-2 study, we suggest that genetic testing and tailored antiplatelet therapy for secondary prevention in Asian patients following stroke or TIA.

When the population of this meta-analysis was sub-grouped by ethnicity, only the Asian group exhibited significantly increased risks among carriers of *CYP2C19* LoF alleles. This was likely due to the limited number of relevant studies that included other ethnic groups. In particular, the small sample sizes of African patients in the included studies made it difficult to draw any statistically significant conclusions. This highlights the need for larger, more comprehensive studies to better understand the impact of *CYP2C19* LoF alleles on the recurrence of stroke or TIA in patients treated with clopidogrel.

Our study has several limitations. First, the included studies differed in several key factors, including study populations, the timing of treatment after symptom onset, the duration of clopidogrel use, and the length of follow-up. These differences could influence the overall effects observed. Second, in addition to genotype, other factors, including smoking and being overweight or obese, have been reported to influence the efficacy of clopidogrel. These were not considered in this meta-analysis. Third, the presence of the *17 allele could have influenced the relationship between LoF alleles and patient outcomes. Specifically, 11 of the included studies did not account for the *17 allele. In the other 13 studies, participants who carried both a LoF allele (such as *2, *3, or *8) and a *17 allele, were classified as carriers of *CYP2C19* LoF alleles. Furthermore, sensitivity analyses revealed consistent results regardless of whether studies accounted for the *17 allele. Fourth, the presence of *CYP2C19* LoF alleles was associated with a significantly increased risk of recurrent stroke or TIA among Asian populations, whereas no such association was observed in non-Asian populations. However, because the non-Asian subgroup was relatively small and underpowered, definitive conclusions cannot be drawn. Fifth, only 14 studies reported bleeding outcomes, and the definitions of bleeding events were inconsistent across studies. Given the central importance of bleeding as a safety endpoint in antiplatelet therapy, future investigations should employ standardized and detailed definitions to enable more robust and generalizable conclusions.

In conclusion, among ischemic stroke and TIA patients who receive clopidogrel for secondary prevention, those carrying *CYP2C19* LoF alleles have significantly higher risks of ischemic stroke or TIA recurrence and composite vascular events than non-carriers. This risk is particularly pro-

nounced in Asian populations. These findings highlight the potential benefits of *CYP2C19* genetic testing when considering clopidogrel therapy for secondary prevention of stroke. For Asian patients, alternative antiplatelet therapies that are unaffected by the *CYP2C19* LoF genotype may improve treatment outcomes and support precision medicine.

Supplementary Materials

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Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

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Conflicts of Interest

Tae-Jin Song, a contributing editor of the *Journal of Clinical Neurology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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