Genotype-Guided Antiplatelet Therapy Versus Standard Therapy for Patients with Coronary Artery Disease: An Updated Systematic Review and Meta-Analysis

Borui Tang[1], Xin Wang[1], Xinrui Wang[1,3], Lihong Liu[1,2], Zhuo Ma[1]

[1]Department of Pharmacy, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China; [2]Department of Pharmacy, China-Japan Friendship Hospital, Beijing, China; [3]Department of Pharmacy, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China.

Corresponding authors: Lihong Liu, Department of Pharmacy, China-Japan Friendship Hospital, Beijing, 100029, China; TEL: (+86)10 84205288; email: liulihong@bjcyh.com; Zhuo Ma, Department of Pharmacy, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, 100020, China; TEL: (+86)10 85231077; email: mazhuo2013@163.com

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ABSTRACT -- Objective: Previous studies on the efficacy and safety of genotype-guided antiplatelet therapy in patients with coronary artery disease (CAD) or undergoing percutaneous coronary intervention (PCI) have been inconclusive. **Aim:** We conducted a meta-analysis to evaluate if the genotype-guided antiplatelet strategy is superior to the standard therapy in patients with CAD or undergoing PCI. **Method:** PubMed, Web of Science, Embase, and Cochrane Central Register of Controlled Trials databases were searched up to October 1st, 2021. Studies reporting efficacy and safety outcomes in the genotype-guided treatment and standard treatment groups were included. The two groups were statistically compared. **Result:** Eleven randomized controlled trials (RCTs) involving 11740 patients were included in this meta-analysis. Compared with the standard treatment group, the genotype-guided group had significant lower risks of all efficacy outcomes, including major adverse cardiovascular events (MACEs) (RR 0.60, 95%, CI 0.44-0.82, P=0.001), all-cause death (RR 0.70, 95% CI 0.51-0.95, P=0.02), cardiovascular death (RR 0.71, 95% CI 0.53-0.95, P=0.02), myocardial infarction (RR 0.53, 95% CI 0.42-0.67, P<0.0001), stroke (RR 0.64, 95% CI 0.41-0.98, P=0.04), stent thrombosis (RR 0.63, 95% CI 0.43-0.91, P=0.01) and targeted vessel revascularization (RR 0.79, 95% CI 0.67-0.92, P=0.003). There was no significant difference in any bleeding events between the two groups. As a result of the subgroup analyses, the genotype-guided treatment was more likely to reduce the incidence of MACEs in the subgroup where the proportion of patients with ACS was ≥ 90%, and subgroup of the Chinese population. **Conclusion:** Genotype-guided antiplatelet treatment could reduce the risk of MACEs without increasing the risk of bleeding events as compared with the standard treatment in patients with CAD or those undergoing PCI. In addition, Genotype-guided antiplatelet treatment might benefit Chinese population or patients with ACS.

INTRODUCTION

Currently, clopidogrel is a classical P2Y12 receptor inhibitor which is most commonly utilized in patients with the acute coronary syndrome (ACS) or stable coronary artery disease (CAD). Dual antiplatelet therapy (DAPT), P2Y12 inhibitor combined with aspirin, is a conventional treatment in patients undergoing percutaneous coronary intervention (PCI), which effectively reduces the risk of adverse cardiovascular events (1-3). However, the clopidogrel-induced antiplatelet effects are not adequate in almost one-fourth of patients (4). Based on the latest guidelines (2,3,5), potent platelet inhibitors (ticagrelor and prasugrel) are superior in patients with myocardial infarction because of more substantial antiplatelet effects (6-8). Nonetheless, potent platelet inhibitors may increase the risk of bleeding complications compared with clopidogrel (6-9). Besides, several studies also reported more frequent discontinuation of ticagrelor due to its side effects, such as dyspnea (6,10,11).

Clopidogrel is a prodrug that is transformed into an active metabolite dependent on hepatic cytochrome P450 (CYP) enzymes and inhibits platelet aggregation by inhibiting the P2Y12 receptor (12,13). CYP2C19 is an essential determinant affecting metabolic steps of clopidogrel of the individual response variability in clopidogrel treatment (12, 13). Previous studies proposed that the loss-of-function (LOF) CYP2C19*2 and CYP2C19*3 alleles were associated with the high on-treatment platelet reactivity (HTPR) and increased ischemic complications furtherly (14-16).

It was presented that the efficacy of clopidogrel was not inferior to ticagrelor and prasugrel in patients without LOF alleles (17,18).

Several published systematic reviews and meta-analyses have summarized randomized controlled trials (RCTs) and non-RCTs evidence addressing the more substantial efficacy of CYP2C19 genotype-guided antiplatelet therapy versus standard therapy (using clopidogrel or ticagrelor all the time without selection based on genotype) (19-21). In the present work we included three new studies, including the TAILOR-PCI (22) which is the largest RCT regarding CYP2C19 genotype-guided antiplatelet therapy in which the increased bleeding risk in the genotype-guided group have been reported among the primary analysis cohort. Moreover, the latest consensus in the Asia-Pacific region stated that, despite the high prevalence of CYP2C19 polymorphisms in the Asia-Pacific region, genotype-guided DAPT was not recommended because of the lack of prospective randomized trials demonstrating a clinical benefit. We have noticed the emergence of new evidence from the Chinese population recently (23, 24). Thus, we conducted an updated meta-analysis to evaluate if the efficacy and safety of genotype-guided strategy were superior to standard therapy. In addition, we used the 2019's definitions of bleeding events as clarified by Bleeding Academic Research Consortium (BARC) and Thrombolysis in Myocardial Infarction (TIMI) standard in this systematic review and meta-analysis (25).

METHODS

Protocol and search strategy

We followed the PRISMA guideline to ensure the quality of this systematic review and meta-analysis. Two authors (B.R.T and X.W) conducted a systematical search in four electronic databases, including PubMed, EMBASE, Cochrane Central Register of Controlled Trials databases and Web of Science from inception to October 11th, 2021, without language restrictions. Reference lists of all selected articles were searched manually to identify additional studies. The search terms included 'genotype, polymorphism, pharmacogenetic, pharmacogenomic, variant, CYP2C19, guided, personalized, tailored, individualized, antiplatelet, antithrombosis, clopidogrel, ticagrelor, prasugrel, acute coronary syndromes, percutaneous coronary interventions. The full search strategy was presented in Appendix supplement.

Eligibility criteria

We used the PICOS model to select our study population. Inclusion criteria: (1) Patients: The patients with CAD or undergoing PCI planned DAPT; (2) Intervention and comparison: Studies compared genotype-guided antiplatelet treatment to standard treatment; (3) Outcomes: Studies reported clinical outcomes including MACEs, all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, targeted vessel revascularization (TVR), stent thrombosis (ST) and bleeding events; (4) Study design: RCTs. Exclusion criteria: (1) Clinical outcomes were unavailable or insufficient; (2) Study was not published in English; (3) Data duplications.

Study outcomes

The primary efficacy outcome was MACE, which was a composite endpoint with varying definitions in different studies. We followed the definition of MACE as per each study. The secondary endpoints included all-cause mortality, cardiovascular mortality, MI, stroke, ST, and TVR.

The differences in bleeding events definition could cause heterogeneity in the pooled analysis. Bleeding events (BARC type 2,3,5), an accepted definition of any bleeding events, were regarded as the primary safety outcome. The secondary endpoints were bleeding events (BARC type 3,5), major bleeding events (TIMI) and minor bleeding events (TIMI) (25,26).

Selection of studies and data extraction

Two reviewers (B.R.T and X.W) independently evaluated titles and abstracts. Duplications were removed by Endnote and manually. Any disagreement was resolved by discussion until consensus reached or by involving a third author (Z.M). Data were extracted independently from all full-text eligible articles by two reviewers. The following data were extracted: the first author, publication year, study location, study design, study period, sample size, mean age, follow-up duration, genotype test system, genotype alleles tested, treatment strategies, the proportion of LOF allele carriers, and outcomes.

Quality assessment

Two independent reviewers (B.R.T and X.W) evaluated the methodological quality of included RCTs according to the Cochrane Collaboration's tool. The risk of bias in the RCTs was evaluated based on six domains, including selection bias (random

sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. Any disagreements were resolved by a third reviewer (Z.M) until a consensus reached.

Statistical analysis

The meta-analysis was performed by the Review Manager software (Revman), version 5.4 Windows. Pooled risk ratio (RR) and 95% confidence interval (CI) were calculated for each outcome. All comparisons were based on two-tailed tests, and P-value < 0.05 were considered statistically significant. The heterogeneity was assessed using Cochran's Q test and I2 statistic. Significant statistical heterogeneity was defined by a P<0.1 or I2＞50%. When the P-value was ≥ 0.1 or I2 ≤ 50%, the fixed-effect model was used. If significant heterogeneity existed, the random-effect model was selected, and sensitivity analysis was conducted by removing the studies one by one in order to evaluate the potential influence of individual study on the pooled data. Subgroup analyses were performed according to indication, follow-up duration, ethnicity, proportion of LOF allele carriers, antiplatelet strategies in standard treatment groups and different genotype test system. Publication bias was examined with a funnel plot for the primary outcome.

RESULTS

Study selection and characteristics

A total of 2583 studies were identified. After removing duplications and excluding the ineligible records manually, 109 studies were eligible for full text assessment. Finally, a total of 11740 patients from eleven studies were included in the meta-analysis (Fig. 1) (22-24,27-34), of which 5958 patients (50.75%) received genotype-guided treatment and 5782 patients (49.25%) received standard treatment. The characteristics of the included studies were presented in Table 1a -c.

The patients in eight studies had ACS or were undergoing PCI for CAD, and the patients with elective PCI for stable CAD were enrolled in only one study. All of the included studies tested CYP2C19*2, and some of the studies tested other variants (CYP2C19*1, CYP2C19*3, CYP2C19*17 or ABCB1) by various point-of-care systems (Spartan RX, ST Q3, Verigene, etc.). The outcomes definition and specific treatment strategy in both groups were presented in Table 1c.

Study quality assessment

The risk of biases of the included studies were evaluated and were summarized in Fig. Appendix 1. Generally, high risks of performance biases were identified, owing to the open-label design of patients and personnel. However, the included studies could meet the requirement for meta-analysis.

Efficacy outcomes

All of the included studies compared the efficacy outcomes between the genotype-guided group (GENE group) and standard treatment group (STD group). The overall results of the meta-analysis were shown in Table 2 and the forest plots of efficacy outcomes were shown in Fig. 2 and Fig. 3. Eleven studies (n = 10740) reported the risk of MACE. Compared with the STD group, the meta-analysis showed that the GENE group had a significantly lower risk of MACE (RR 0.60, 95%, CI 0.44-0.82, P=0.001, I^2 = 67%). The risks of secondary outcomes were also significantly lower in the GENE group compared with the STD group, including all-cause death (RR 0.70, 95% CI 0.51-0.95, P=0.02, I^2 =46%), cardiovascular death (RR 0.71, 95% CI 0.53-0.95, P=0.02, I^2 =42%), myocardial infarction (RR 0.53, 95% CI 0.42-0.67, P<0.0001, I^2 = 0%), stroke (RR 0.64, 95% CI 0.41-0.98, P=0.04, I^2 =0%), stent thrombosis (RR 0.63, 95% CI 0.43-0.91, P=0.01, I2 =0%) and targeted vessel revascularization (RR 0.79, 95% CI 0.67-0.92, P=0.003, I^2 =62%).

Safety outcomes

Eleven studies investigated the safety outcomes between the two groups. The results of meta-analysis were shown in Table 2 and the forest plots of safety outcomes were presented in Fig. 4. The meta-analysis of eight studies (n =10605) showed no significant difference in terms of BARC 2,3,5 bleeding events (RR 0.87, 95% CI 0.73-1.04, P = 0.13, I^2 = 33%). Besides, no significant differences were observed in the risks of BARC 3,5 bleeding events, major bleeding events (TIMI) and minor bleeding events (TIMI) between GENE group and STD group (RR 1.14, 95% CI 0.82-1.58, P = 0.44, I^2 = 0%; RR 1.05, 95% CI 0.68-1.63, P = 0.81, I2 = 0%; RR 1.04, 95% CI 0.64-1.67, P = 0.88, I^2 = 0%, respectively).

Abbreviations: GENE: genotype-guided; STD: standard treatment; SD: standard deviation; PCI: percutaneous coronary intervention; ACS: acute coronary syndromes; CAD: coronary artery disease; MD: maintenance dose; LOF: loss-of-function; P: prasugrel; C: clopidogrel; T: ticagrelor; Cil: cilostazol; LD: loading dose; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; UA: unstable angina; PLATO: Platelet Inhibition and Patient Outcomes; MACEs: major adverse cardiovascular events; HTPR: high on-treatment platelet reactivity; MI: myocardial infarction; TVR: target-vessel revascularization; ST: stent thrombosis; PRU: P2Y12 reaction unit; *1: CYP2C19*1; *2: CYP2C19*2; *3: CYP2C19*3; TIMI: Thrombolysis In Myocardial Infarction; BARC: Bleeding Academic Research Consortium.

Table 1a. Characteristics of included studies

Source	Location	Ethnicity (%)	Design	Indication (proportion of patients with ACS)	Follow-up duration	Total number	
						Genotype	Standard
Shi, 2021 (23)	China	Chinese (100%)	Single center	PCI for ACS（100%）	12 months	201	100
Al-Rubaish, 2021 (34)	Saudi Arabia	Not mentioned	Multicenter	PCI for STEMI（100%）	12 months	375	312
Zhang et al, 2020 (24)	China	Chinese (100%)	Single center	PCI for ACS （100%）	12 months	311	306
Pereira, 2020, TAILOR-PCI (22)	International	White (66.4%)	Multicenter	PCI for CAD （81.6%）	12 months	2641	2635
Tuteja, 2020, ADAPT-PCI (27)	United States	White (81.3%)	Multicenter	PCI for CAD （49.9%）	24 months	249	255
Claassens, 2019, POPular (28)	Europe	White (94.3%)	Multicenter	PCI for STEMI（100%）	12 months	1242	1246
Notarangelo,2018, PHARMCLO (29)	Italy	European (100.0%)	Single center	ACS（97.2%）	12 months	448	440
Tomaniak, 2017, ONSIDE TEST (30)	Europe	Not mentioned	Multicenter	PCI for stable CAD (0%)	12 months	34	26
Tam, 2017 (31)	China	Chinese (100%)	Single center	ACS with or without PCI （100%）	1 month	65	67
Xie, 2013, IAC-PCI (32)	China	Chinese (100%)	Single center	PCI for ACS（100%）	6 months	301	299
Roberts, 2012, RAPID GENE (33)	Canada	White (85.0%)	Single center	PCI for CAD (36%)	7–30 days	91	96

Table 1b. Characteristics of included studies

Source	Age, mean (SD)		Genotype test system and alleles tested	Proportion of LOF allele carriers	
	GENE group	STD group		GENE group	STD group
Shi, 2021 (23)	59.7 (9.6)	59.8 (10.4)	Fluorescence in situ hybridization (TL988A, Xi'an TianLong)	57.20%	NA
Al-Rubaish, 2021 (34)	56.74 (11.84)	55.47 (11.22)	Spartan RX system (Spartan Bioscience Inc.)	31%	NA
Zhang et al, 2020 (24)	63.6 (10.7)	64.6 (10.7)	kit from Sinochips Bioscience Co. CYP2C19*2, *3	51.80%	NA
Pereira, 2020, TAILOR-PCI (22)	62	62	Spartan Rx & ABI TaqMan CYP2C19*1, *2, *3	34.20%	35.90%
Tuteja, 2020, ADAPT-PCI (27)	63.0 (9.7)	62.9 (10.2)	Spartan Rx. CYP2C19*1, *2, *3, *17	28%	NA
Claassens, 2019, POPular (28)	61.9 (11.1)	61.4 (11.5)	Spartan Rx. CYP2C19*1, *2, *3	31.40%	NA
Notarangelo,2018, PHARMCLO (29)	71.1 (12.3)	70.7 (12.1)	ST Q3. ABCB1, CYP2C19*2, *17	23.50%	NA
Tomaniak, 2017, ONSIDE TEST (30)	61.8 (10.6)	62.3 (7.6)	Spartan Rx. CYP2C19*2	26.50%	11.60%
Tam, 2017 (31)	61.6 (11.8)	60.3 (12.2)	Verigene. CYP2C19*2, *3, *17	61.00%	52.00%
Xie, 2013, IAC-PCI (32)	57.9 (10.7)	57.8 (10.3)	Shanghai Baiao technology. CYP2C19*1, *2, *3	52.50%	NA
Roberts, 2012, RAPID GENE (33)	59.5 (9.3)	60.8 (8.7)	Spartan Rx. CYP2C19*2	25%	24%

Table 1c. Characteristics of included studies

Source	GENE group strategy	STD group strategy	Primary outcomes	Secondary outcomes
Shi, 2021 (23)	LD: C 300 mg or T 180mg MD: *1/*2, *1/*3, *2/*2, *2/*3 or*3/*3: Recommended treatment with T 90mg/bd.	LD: C 300 mg or T 180mg MD: C 75mg/d or T 90mg/bd (Prescription of P2Y12 inhibitors was at the discretion of cardiologists).	MACCE	All-cause death, myocardial infarction, stroke, urgent coronary revascularization, stent thrombosis, bleeding events (BARC)
Al-Rubaish, 2021 (34)	MD: Carriers of *2: T 10 mg/d Noncarrier of *2: C 75 mg/d	MD: C 75 mg/d	MACE, recurrent myocardial infarction, non-fatal stroke, cardiovascular death and major bleeding (PLATO)	Stroke, stent thrombosis, target vessel revascularization, all-cause death
Zhang et al, 2020 (24)	Extensive metabolizers: C 75mg/d; intermediate metabolizers: C 150mg/d; poor metabolizers: T 180mg/d. For extensive metabolizers and intermediate metabolizers patients with HPR, the antiplatelet treatment was changed or unchanged by the clinicians according to the patient's conditions.	LD: not mentioned MD: C 75 mg/d	Safety outcome: moderate or severe hemorrhage; Efficacy outcome: MACEs, MI, ST, all-cause death	Safety outcome: mild hemorrhage
Pereira, 2020, TAILOR-PCI (22)	LD: the choice was at the discretion of the treating physician. MD: CYP2C19 LOF carriers: T; noncarriers or those with inconclusive results: C. Prasugrel was recommended as an alternative for patients who did not tolerate ticagrelor.	LD: the choice at the discretion of the treating physician. MD: C: according to drug label instructions.	Cardiovascular death, MI, stroke, ST	TIMI major or minor bleeding, TIMI major bleeding, BARC bleeding, all-cause death,
Tuteja, 2020, ADAPT-PCI (27)	Slow metabolizer status [1 or 2 LOF mutations (*2 or *3) in CYP2C19]: P or T. Normal metabolizer status (homozygous for the *1 allele in CYP2C19): C. Antiplatelet choice is ultimately decided by physician judgment incorporating all clinical factors.	Choice of antiplatelet therapy will be decided by treating physician as per usual care	Proportion of participants receiving prasugrel/ticagrelor	MACEs: cardiovascular mortality, MI, stroke, ST, and urgent revascularization; Safety outcomes: BARC bleeding
Claassens, 2019, POPular (28)	MD: Carry 1 or more CYP2C19 *2 or *3 LOF alleles: T 90mg/bd or P 10mg/d(patients ＞75 years or weighing ＜60 kg will receive 5 mg); Noncarriers: C 75mg/d.	MD：the first 100 patients: C 75mg/d. After February 2012, T 90mg/bd or P 10mg/d(patients ＞75 years or weighing ＜60 kg will receive 5 mg).	Net adverse clinical events: death, MI, ST, stroke. Safety outcomes: major bleeding (PLATO criteria)	Safety outcomes: PLATO major bleeding or minor bleeding, BARC 3 to 5 defined major bleeding
Notarangelo,2018, PHARMCLO (29)	Based on the combination of genotypes ABCB1 3435, CYP2C19*2 and *17	Based on clinical characteristics and the clinicians' preference	MACEs: death, MI, stroke, ST	Safety outcomes: BARC 3 to 5 defined major bleeding
Tomaniak, 2017, ONSIDE TEST (30)	MD: *1/*1: C 75 mg/d; *1/*2: P (60 mg) 2 h before PCI then 10 mg/d	MD:C 75 mg/d	MACEs: death, MI, stroke, ST	Safety outcomes: BARC 3 to 5 defined major bleeding
Tam, 2017 (31)	LD: *1/*1: C 300 mg. *1/*2 or *1/*3: C 600 mg *2/*2, *2/*3 or *3/*3: C 600 mg/d+Cil 200 mg MD: *1/*1: C 75 mg/d. *1/*2 or *1/*3: C 150 mg/d *2/*2, *2/*3 or *3/*3: C 150 mg/d+Cil 100 mg/bd	LD: C 600 mg (PCI for STEMI), 300 mg (PCI for NSTEMI or UA, or STEMI without PCI) MD: C 75 mg/d	HTPR: PRU > 208	MACEs: mortality, MI, and stroke
Xie, 2013, IAC-PCI (32)	LD: *1/*1: C 300 mg. *1/*2 or *1/*3: C 600 mg *2/*2, *2/*3 or *3/*3: C 600 mg/d+Cil 200 mg MD: *1/*1: C 75 mg/d. *1/*2 or*1/*3: C 150 mg/d *2/*2, *2/*3 or *3/*3: C 150 mg/d+Cil 100 mg/bd	LD: C 300 mg MD:C 75 mg/d	MACEs: mortality, MI, stroke, TVR	MACEs Safety outcomes: BARC defined all bleeding
Roberts, 2012, RAPID GENE (33)	MD: Carriers of *2: P 10 mg/d. Noncarrier of *2: C: 75 mg/d	MD: C 75 mg/d	HTPR: PRU > 208	MACEs: Mortality, MI, ST Safety outcomes: TIMI major and minor bleeding

Table 2. Results of the meta-analysis for efficiency outcomes and safety outcomes between GENE group and STD group

Event	Number of studies	Participants	Events		Pooled RR (95% CI)	P-value	Heterogeneity	
			GENE	STD			I2 (%)*	P-value
Efficiency outcomes								
MACEs	11	11740	286	407	0.60 (0.44, 0.82)	0.001	67%	0.001
All-cause mortality	10	10852	66	91	0.70 (0.51, 0.95)	0.02	46%	0.07
Cardiovascular mortality	9	11307	73	99	0.71 (0.53, 0.95)	0.02	42%	0.10
MI	11	11740	102	186	0.53 (0.42, 0.67)	<0.00001	0%	0.53
Stroke	9	11063	33	49	0.64 (0.41, 0.98)	0.04	0%	0.94
ST	10	11608	46	65	0.63 (0.43, 0.91)	0.01	0%	0.62
TVR	6	4640	197	215	0.79 (0.67, 0.92)	0.003	62%	0.03
Safety outcomes								
Bleeding events (BARC type 2,3,5)	8	10605	220	248	0.87 (0.73, 1.04)	0.13	33%	0.17
Bleeding events (BARC type 3,5)	5	8458	74	65	1.14 (0.82, 1.58)	0.44	0%	0.90
Major bleeding events (TIMI)	3	7951	41	39	1.05 (0.68, 1.63)	0.81	0%	0.80
Minor bleeding events (TIMI)	3	7951	34	33	1.04 (0.64, 1.67)	0.88	0%	0.88

CI, confidence interval; GENE, genotyping-guided treatment group; STD, standard treatment group; MACEs, major adverse cardiovascular events; MI, myocardial infarction; RR, risk ratio; ST, stent thrombosis; TVR, targeted vessel revascularization; BARC, Bleeding Academic Research Consortium; TIMI, Thrombolysis In Myocardial Infarction. *I2⩾ 50% in pooled analysis of MACEs, the random effects model was used.

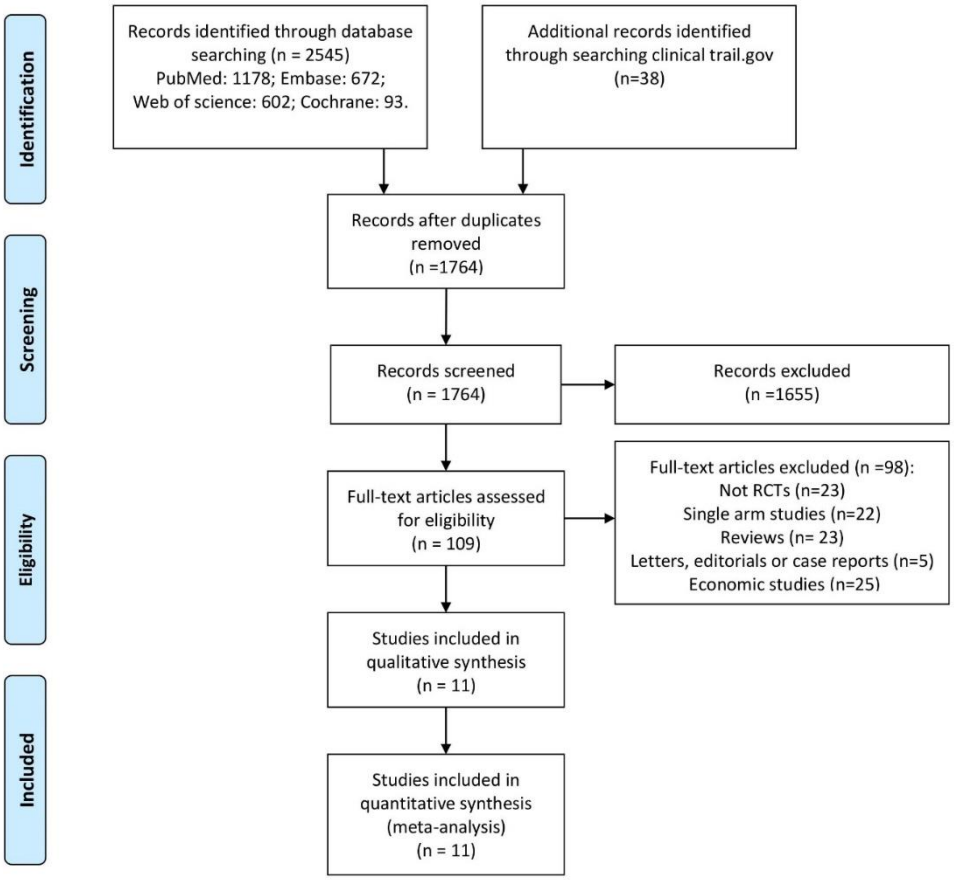

Figure 1. The flow diagram of study selection

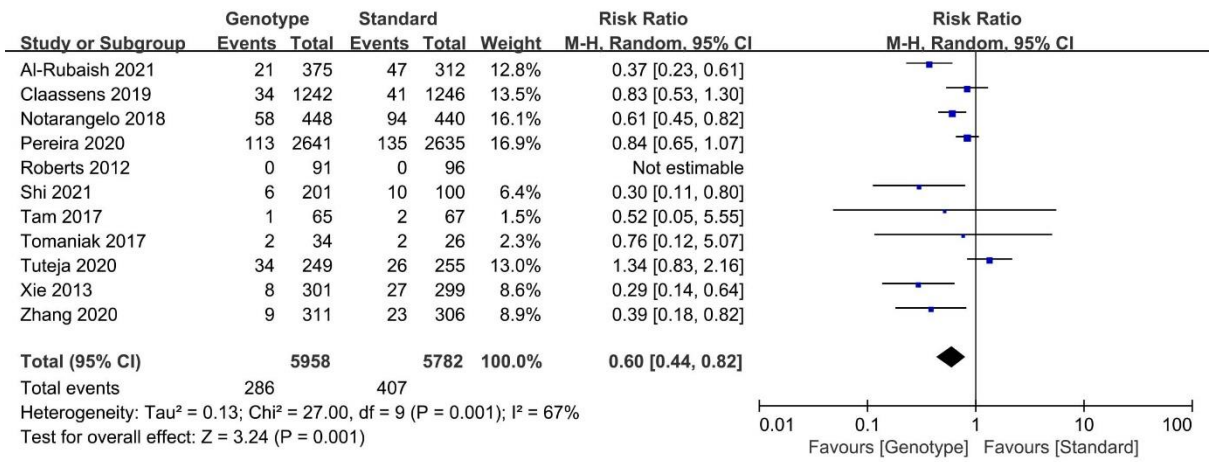

Figure 2. The forest plot of MACE

Sensitivity analysis and subgroup analysis

The sensitivity analysis was conducted in the primary efficacy outcome, which showed a significant heterogeneity in the meta-analysis (I^2= 67%, P = 0.001). The results showed that, after the removal of each single study, the heterogeneity of the remaining studies and the signification of RR did not change. Publication bias in MACEs was not detected by the funnel plot (Fig. Appendix 2) with visible symmetry in meta-analyses.

The subgroup analyses were performed for primary efficacy outcome and primary safety outcome according to the different characteristics among these included studies. The overall results of subgroup analyses for MACEs and any bleeding events were shown in Table 3 and Table 4 respectively and the forest plots of subgroup analyses were presented in Appendix supplement.

In the subgroup analyses for MACEs, when studies were classified by the proportion of patients with ACS, ethnicity, and the proportion of LOF allele carriers in GENE group, the between-subgroup heterogeneities were significant. The p-values of pooled RR were significantly lower in the subgroups with clopidogrel in STD group, ACS ≥ 90%, Chinese population, and LOF allele carriers ≥ 50% in GENE group, and sample size < 200. There were no significant differences between GENE group and STD group in the other subgroups. For any bleeding events (BARC type 2,3,5), when studies were classified by the proportion of patients with ACS, the between-subgroup heterogeneities were significant. Meanwhile, GENE group had a reduced risk of any bleeding events in the subgroups with ticagrelor, prasugrel or uncertain treatment in STD group, and ACS ≥ 90%.

DISCUSSION

DAPT has long been the standard of therapy in preventing cardiovascular and cerebrovascular ischemic events in patients with stable CAD and ACS undergoing PCI (1-3), but the choice of antiplatelet treatment composition was a considerable challenge for clinicians. Impaired conversion of clopidogrel to the active metabolite might be caused by LOF mutations, leading to HTPR commonly among patients on clopidogrel treatment while rarely in prasugrel users (14-16). HTPR has been consistently associated with an increased risk of ST and MACE (15). Thus, genotyping might be utility guidance for individualized P2Y12 inhibitor therapy, such as escalation (switch from clopidogrel to ticagrelor or prasugrel) or de-escalation treatment, to reduce the risk of ischemic and hemorrhagic (35). In recent years, point-of-care genotyping assays have become available in more medical institutions, enabling implementation in routine treatment.

However, the expert consensus statement from JACC and Asia-Pacific region showed that CYP2C19 genotype-guided antiplatelet strategy was not recommended, because of lack of data from dedicated studies (36, 37). In fact, the recent emergence of new evidence might change the results of previous meta-analyses. Therefore, the aim of the meta-analysis was to evaluate if the genotype-guided strategy was superior to standard therapy in patients with CAD or undergoing PCI. After performing the meta-analysis including eleven RCTs, we found that

Table 3. Subgroup analysis for MACEs between GENE group and STD group

Subgroup category	Number of studies	Patients	Pooled RR (95% CI)	P-value	Heterogeneity [I2(%)] In-subgroup	Heterogeneity [I2(%)] Between-subgroup
Follow-up duration						
≥ 12 months	8	10821	0.65 (0.47, 0.89)	0.007*	68%	69.4%
< 12 months	3	919	0.31 (0.15, 0.65)	0.002*	0%	
Treatment strategy in STD group						
Clopidogrel	7	7559	0.48 (0.29, 0.79)	0.004*	67%	
Ticagrelor, Prasugrel	1	2488	0.83 (0.53, 1.30)	0.42	-	22.1%
Uncertain	3	1693	0.68 (0.34, 1.38)	0.75	87%	
Proportion of patients with ACS						
≥ 90%	7	5713	0.52 (0.43, 0.64)	<0.00001*	45%	92.8%
< 90%	4	6027	0.91 (0.74, 1.13)	0.41	33%	
Ethnicity						
Caucasian	5	9343	0.83 (0.63, 1.11)	0.21	62%	90.8%
Chinese	4	1650	0.33 (0.21, 0.53)	<0.00001*	0%	
Proportion of LOF allele carriers in GENE group						
< 50%	7	10090	0.73 (0.53, 1.01)	0.06	69%	86.7%
≥ 50%	4	1650	0.33 (0.21, 0.53)	<0.00001*	0%	
Sample size						
≥ 200	8	11361	0.60 (0.43, 0.83)	0.002*	74%	0.0%
< 200	3	379	0.66 (0.15, 2.88)	0.58	0%	
Genotype test system						
Spartan Rx	6	9202	0.77 (0.52, 1.16)	0.22	71%	72.5%
the others (ST Q3, Verigene, etc)	5	2538	0.46 (0.33, 0.65)	<0.00001*	19%	

*P<0.05; ACS, acute coronary syndrome; CI, confidence interval; GENE, genotyping-guided treatment; LOF loss-of-function; RR, risk ratio; STD, standard treatment.

Table 4. Subgroup analysis for Bleeding events (BARC type 2,3,5) between GENE group and STD group

Subgroup category	Number of studies	Patients	Pooled RR (95% CI)	P-value	Heterogeneity [I2(%)] In-subgroup	Heterogeneity [I2(%)] Between-subgroup
Follow-up duration						
≥12 months	6	9873	0.89 (0.75, 1.07)	0.21	34%	24.5%
< 12 months	2	732	0.50 (0.19, 1.32)	0.16	41%	
Treatment strategy in STD group						
Clopidogrel	5	7312	1.03 (0.75, 1.41)	0.85	44%	
Ticagrelor, Prasugrel	1	2488	0.78 (0.62, 0.97)	0.03*	0%	23.4%
Uncertain	2	805	1.10 (0.57,2.10)	0.78	0%	
Proportion of patients with ACS						
≥ 90%	6	4825	0.77 (0.63, 0.95)	0.01*	18%	77.9%
< 90%	2	5780	1.18 (0.85, 1.64)	0.33	0%	
Proportion of LOF allele carriers in GENE group						
< 50%	4	8955	0.92 (0.63, 1.35)	0.68	55%	0.0%
≥ 50%	4	1650	0.92 (0.45, 1.88)	0.81	21%	

*P<0.05; ACS, acute coronary syndrome; CI, confidence interval; GENE, genotyping-guided treatment; LOF loss-of-function; RR, risk ratio; ST, standard treatment.

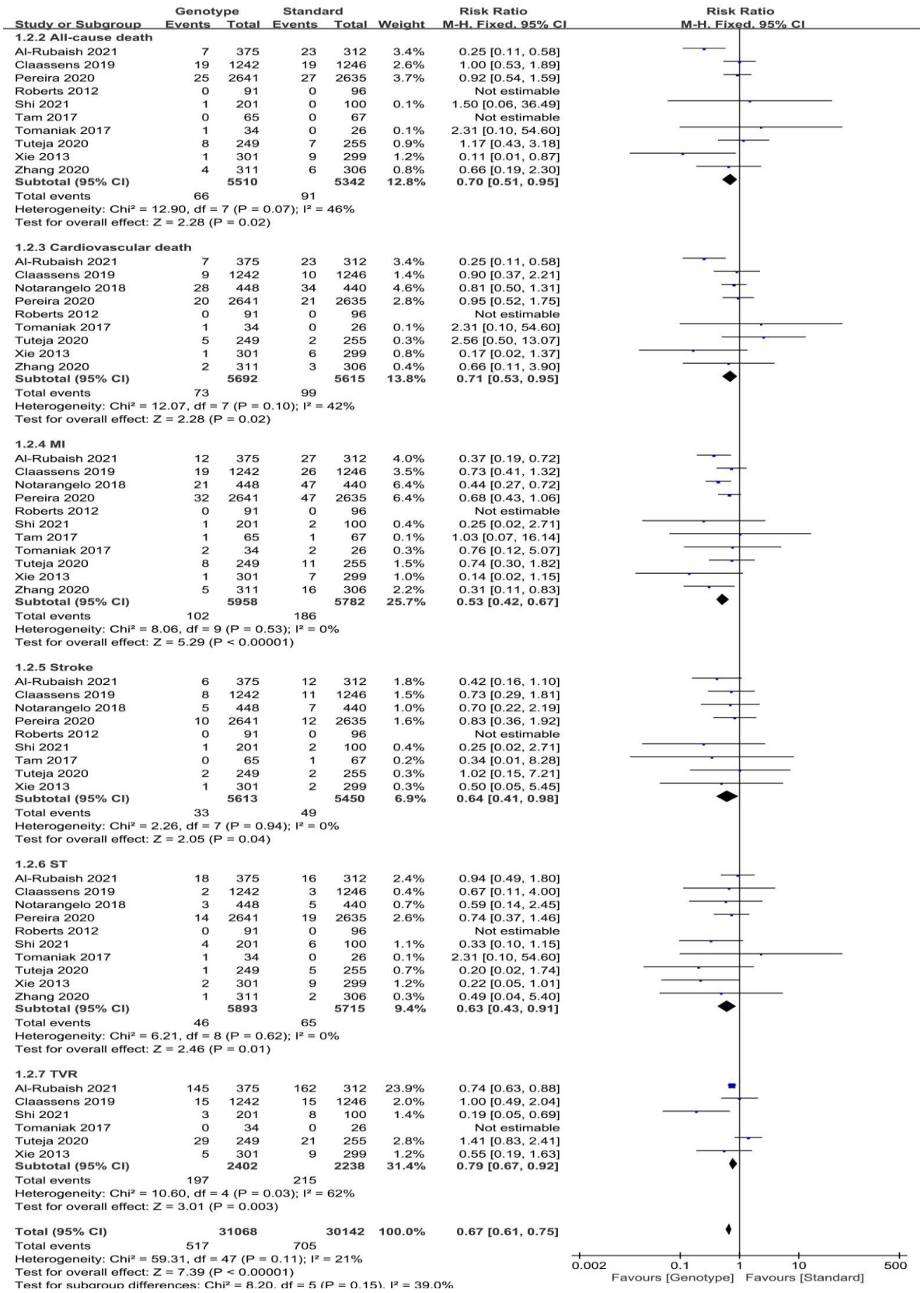

Figure 3. The forest plot of all-cause death, cardiovascular death, MI, stroke, ST, and TVR. Abbreviation: MI, myocardial infarction; TVR, targeted vessel revascularization, ST, stent thrombosis.

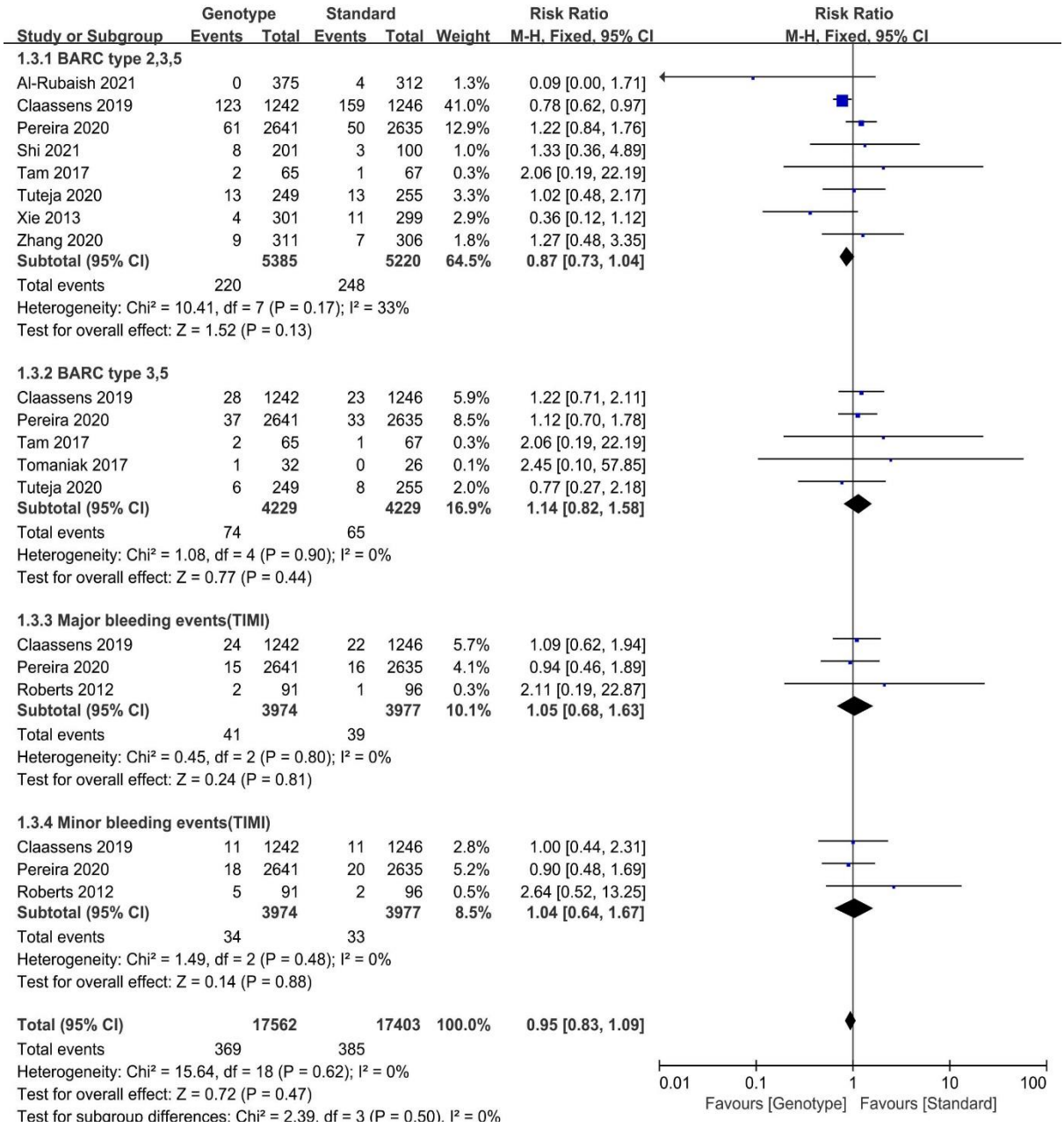

Figure 4. The forest plot of safety outcomes. Abbreviation: BARC, Bleeding Academic Research Consortium; TIMI, Thrombolysis In Myocardial Infarction.

the risk of MACEs in the GENE group was significantly lower compared with the STD group. And a significant reduction in the risk of all-cause death, cardiovascular death, MI, stroke, ST and TVR were also observed in the GENE group. Moreover, incidences of the safety endpoints were comparable between the two groups. However, the reduced risk of MACE might only occur in the Chinese patients and patients with ACS. In addition, the genotype-guided antiplatelet strategy might reduce the risk of MACE only compared with the strategy for the fixed use of clopidogrel in STD group.

Relation to prior studies and innovation

Previous meta-analyses have drawn inconsistent conclusions about whether genotype-guided antiplatelet therapy could reduce the risk of MACE which might be caused by the different inclusion of criteria (19,21,38). Our study included more trials (11 RCTs) and a substantially larger sample size

(11740 patients), particularly including the two more trials from Asian population (23,24) and the data of the whole population in the TAILOR-PCI trial (previous meta-analysis only included part of population) (20), which is the largest relevant trial and at a low risk of bias (22). The results of our study differed from previous studies in efficacy outcomes, including all-cause death, cardiovascular death, stroke, and TVR. Moreover, in previous meta-analyses, the safety outcomes, including major bleeding events and minor bleeding events, were stratified by the standard of each original study. Our study included four safety outcomes (bleeding events) classified by BARC and TIMI standard, which could avoid the bias caused by different definitions of outcomes. Additionally, subgroup analyses have been reported only for MACEs in prior meta-analyses (20,21). We performed more comprehensive and more explicable subgroup analyses for both MACEs and bleeding events to explore the impact of difference among the included studies and the reason for heterogeneity.

Heterogeneity

The pooled analysis for MACEs showed a significant heterogeneity, whereas the result of sensitivity analysis with the leave-one-out method showed no effect on the heterogeneity in the outcome of MACE, which indicated that the heterogeneity did not originate from a single study. However, the different characteristics among included studies might cause the high heterogeneity in this meta-analysis, including different follow-up duration, diagnoses of enrolled patients, ethnicity of enrolled patients and proportions of LOF allele carriers among included studies, which was also confirmed by the result of subgroup analyses.

Interpretation for the result of subgroup analyses

Treatment strategy in the STD group. We classified studies into "Clopidogrel", "Ticagrelor or prasugrel", and uncertain subgroup according to the choice of antiplatelet drug in the STD group. In the "Clopidogrel" subgroup, genotype-guided therapy reduced the risk of MACE. But the effect of genotype-guided therapy was not better than strategy of using fixed ticagrelor or prasugrel. Several studies proposed that the efficacy of potent P2Y12 inhibitors was prior to clopidogrel (6,8). Currently, ticagrelor or prasugrel was recommended for patients after PCI without bleeding risk instead of clopidogrel in European Society of Cardiology (ESC) latest guideline (2), which has gradually become the first choice for clinicians without support by precision medicine. However, there was only one RCT where patients used ticagrelor or prasugrel as a routine treatment strategy in the control group. Patients who were tested as noncarriers of the CYP2C19 LOF allele use clopidogrel rather than potent P2Y12 inhibitors in the genotype-guided group, which can be considered as de-escalation strategy (36,39). In the subgroup analysis of safety endpoints, patients who received genotype-guided therapy had a significant reduction in the risk of any bleeding events compared with the fixed ticagrelor or prasugrel group, which might be explained that genotype-guided de-escalation improved the safety of treatment. However, this result was limited by a lack of relevant studies and poor sample size. Therefore, more studies were needed to explore whether de-escalation therapy based on genotype guidance can improve the prognosis of patients.

Ethnicity. Nine studies included were divided into Caucasian and Chinese according to the ethnicity of most people. From the results of subgroup analysis, a significant reduction in the incidence of MACE was observed in Chinese subgroup between the two groups, while the Caucasian population might not benefit from genotype-guided strategy. A number of studies have shown that more Asians carried LOF allele (CYP2C19*2 and CYP2C19*3) compared with African and European populations (40-42). Nevertheless, CYP2C19*17, an increased function allele, was more likely carried in Caucasians and black populations (40-42). Diverse interracial proportion of LOF carriers could be one possible reason for the statistically difference between two subgroups.

Proportion of LOF allele carriers in GENE group. We divided studies into the "≥ 50%" subgroup and the "< 50%" subgroup according to the proportion of LOF allele carriers in the GENE group. The results of subgroup analysis showed that genotype-guided therapy could significantly reduce the incidence of MACE in the "≥ 50%" subgroup, but there was no significant difference found in the "< 50%" subgroup. For those who carrying the LOF gene, genotype-guided therapy could avoid the poor efficacy of clopidogrel, which might also interpret why Chinese population benefits more from the genotype-guided strategy. Therefore, for population with low rate of carrying LOF, fixed use of clopidogrel or choosing drugs based on clinical characteristics might be a more economical and reasonable choice, but

genotype-guided strategy still had advantages for people with high rate of carrying LOF.

Proportion of ACS patients. The enrolled patients were diagnosed with different severity of CAD among the included studies, which might cause bias in meta-analysis. Patients in some of the studies were all having ACS (23, 24, 28, 31, 32, 34), while the patients in the study ONSIDE TEST (Tomaniak,2017) were all having stable coronary heart disease (30). All studies were divided into the ">90%" subgroup and the "≤ 90%" subgroup according to the proportion of patients diagnosed with ACS. In the "> 90%" subgroup, genotype-guided therapy could reduce the risk of MACE significantly, while the difference was not significant in the "≤ 90%" subgroup between the two groups. The result might indicate that patients with ACS were more likely to benefit from genotype-guided therapy, which was reasonable for the distribution of medical resources in the real world, that is, more medical resources should be allocated to more severe patients. In latest guidelines (2), clopidogrel, instead of prasugrel or ticagrelor, was recommended for people with stable CAD after PCI. Therefore, if economic factor was considered, fixed clopidogrel treatment might be suitable as a routine DAPT strategy for patients with stable CAD. However, this result needed to be interpreted with caution due to the limitation of sample size.

Others. Various system of genotype detection may affect the results of genotyping assays. Six of the included studies used the SpartanRx system for rapid genotype detection, while five studies used other systems (ST Q3, Verigene, etc.). In TAILOR-PCI (22), the results of rapid genotyping assays by SpartanRx were verified by the TaqMan system to ensure accuracy, while results in other studies were not verified by the gold standard method (real-time polymerase chain reaction). We divided the included study into two subgroups according to the method of the gene detection system. The reduced heterogeneity indicated that the different methods of genotyping assays might be one of the sources of heterogeneity.

In terms of sample size, three of the included studies were conducted in a single center with a small sample size, and the conclusions from those might not be convincing enough. The results of subgroup analysis based on the sample size showed that genotype-guided therapy could not reduce the incidence of MACEs significantly in studies with less than 200 patients. However, a significant reduction of risk of MACEs was found in the subgroup of large sample size, and the inclusion of three small-scale studies did not change the significance of pooled RR.

Besides, as shown in the results of the subgroup analysis, genotype-guided strategy significantly reduced the risk of MACE compared to STD group in both < 12 months and ≥ 12 months subgroups. Therefore, genotype-guided strategy might not only reduce the incidence of MACE in the early stage after PCI (0-6 months), during which adverse reactions were most likely to occur, but also improve the long-term efficacy outcome.

Future research orientation

Future relevant studies may need to focus more on the study population with stable CAD rather than ACS. Moreover, studies aiming at the de-escalation treatment instead of escalation treatment after genotyping could consummate the realization of genotype-guided antiplatelet therapy. The reduced risk of MACEs in Chinese population was found in the GENE group of our meta-analysis, and the same results were observed in several cohort studies based on the Chinese population (43,44). Therefore, a relevant study in the non-Chinese population may be needed, especially in the American and African population.

Limitations

There were several limitations ineluctably in this meta-analysis. First, slight differences existed in the definitions of the MACEs, treatment strategies, and genotyping systems among included studies, which may affect the reliability of pooled RR. However, the sensitivity analysis and subgroup analysis we performed confirmed that these differences did not affect the final results. Second, most of the included studies were open-label without performing the blinding method, so that the selection biases were inevitable. However, low-risk bias was demonstrated in most aspects of the quality assessment, so the results of the meta-analysis should be significative. Third, some studies might not be included on account of the unavailable full-text.

CONCLUSIONS

The current meta-analysis results showed that genotype-guided antiplatelet treatment could reduce the risk of both composite and individual outcomes

of MACEs without increasing the risk of bleeding events as compared with the standard treatment in patients with CAD or those undergoing PCI. However, this conclusion might be more applicable to escalation treatment strategy rather than de-escalation treatment strategy. In addition, genotype-guided antiplatelet treatment might benefit Chinese population (or population with a high proportion of LOF allele carriers) or patients with ACS. In the context of the current increasing use of ticagrelor for patients after PCI, the effect of genotype-guided de-escalation treatment needs to be further verified.

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DATA AVAILABILITY. The data that support the findings of this study are available from the corresponding authors upon reasonable request.

CONFLICT OF INTEREST. The authors declare that they have no conflict of interest.

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Genotype-guided antiplatelet therapy versus standard therapy for patients with coronary artery disease: An update systematic review and meta-analysis

Borui Tang, Xin Wang, Xinrui Wang, Lihong Liu, Zhuo Ma

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Appendix Table S1. Search strategy

Electronic databases	Detailed search strategy
PubMed	((((((((((((genotype) OR (polymorphism)) OR (pharmacogenetic)) OR (pharmacogenomic)) OR (genetic)) OR (genomic)) OR (genotyping)) OR (variant)) OR (variation)) OR (cyp2c19)) OR (cytochrome p450 2c19)) AND ((((((((((guide) OR (personalized)) OR (guided)) OR (guiding)) OR (tailored)) OR (individualized)) OR (individualizing)) OR (individualization)) OR (directed)) OR (directing))) AND (((((((((antiplatelet) OR (antithrombosis)) OR (clopidogrel)) OR (Iscover)) OR (Plavix)) OR (ticagrelor)) OR (prasugrel)) OR (thienopyridine)) OR (P2Y12 inhibitors))) AND ((((((Acute Coronary Syndromes) OR (ACS)) OR (Percutaneous Coronary Interventions)) OR (PCI)) OR (Percutaneous Coronary Revascularizations)) OR (Coronary Intervention))
EMBASE	#5. #1 AND #2 AND #3 AND #4 #4. 'acute coronary syndromes'/exp OR 'acute coronary syndromes' OR (acute AND coronary AND syndromes) OR 'acs'/exp OR acs OR 'percutaneous coronar interventions' OR (percutaneous AND coronary AND ('interventions'/exp OR interventions)) OR pci OR 'percutaneous coronary revascularizations' OR (percutaneous AND coronary AND revascularizations) OR 'coronary intervention' OR (coronary AND ('intervention'/exp OR intervention)) #3. antiplatelet OR 'antithrombosis'/exp OR antithrombosis OR 'clopidogrel'/exp OR clopidogrel OR 'iscover'/exp OR iscover OR 'plavix'/exp OR plavix OR 'ticagrelor'/exp OR ticagrelor OR 'prasugrel'/exp OR prasugrel OR 'thienopyridine'/exp OR thienopyridine OR 'p2y12 inhibitors' OR (p2y12 AND ('inhibitors'/exp OR inhibitors)) #2. 'guide'/exp OR guide OR personalized OR guided OR guiding OR tailored OR individualized OR individualizing OR 'individualization'/exp OR individualization OR directed OR directing #1. 'genotype'/exp OR genotype OR 'polymorphism'/exp OR polymorphism OR pharmacogenetic OR pharmacogenomic OR 'genetic'/exp OR genetic OR genomic OR 'genotyping'/exp OR genotyping OR 'variant'/exp OR variant OR 'variation'/exp OR variation OR 'cyp2c19'/exp OR cyp2c19 OR 'cytochrome p450 2c19'/exp OR 'cytochrome p450 2c19' OR (('cytochrome'/exp OR cytochrome) AND ('p450'/exp OR p450) AND 2c19)
Cochrane Central Register of Controlled Trials databases	#1 MeSH descriptor: [Genotype] explode all trees #2 genotype OR polymorphism OR pharmacogenetic OR pharmacogenomic OR genetic OR genomic OR genotyping OR variant OR variation OR cyp2c19 OR cytochrome p450 2c19 #3 MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees #4 antiplatelet OR antithrombosis OR clopidogrel OR Iscover OR Plavix OR ticagrelor OR prasugrel OR thienopyridine OR P2Y12 inhibitors OR Platelet Aggregation Inhibitors #5 Acute Coronary Syndromes OR ACS OR Percutaneous Coronary Interventions OR PCI #6 guide OR personalized OR guided OR guiding OR tailored OR individualized OR individualizing OR individualization OR directed OR directing #7 (#1 OR #2) AND (#3 OR #4) AND #5 AND #6
Web of Science	(genotype OR polymorphism OR pharmacogenetic OR pharmacogenomic OR genetic OR genomic OR genotyping OR variant OR variation OR cyp2c19 OR cytochrome p450 2c19) AND (guide OR personalized OR guided OR guiding OR tailored OR individualized OR individualizing OR individualization OR directed OR directing) AND (antiplatelet OR antithrombosis OR clopidogrel OR Iscover OR Plavix OR ticagrelor OR prasugrel OR thienopyridine OR P2Y12 inhibitors) AND (Acute Coronary Syndromes OR ACS OR Percutaneous Coronary Interventions OR PCI OR Percutaneous Coronary Revascularizations OR Coronary Intervention)

Appendix Table S2. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not involved
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Appendix Table S2. (continue)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

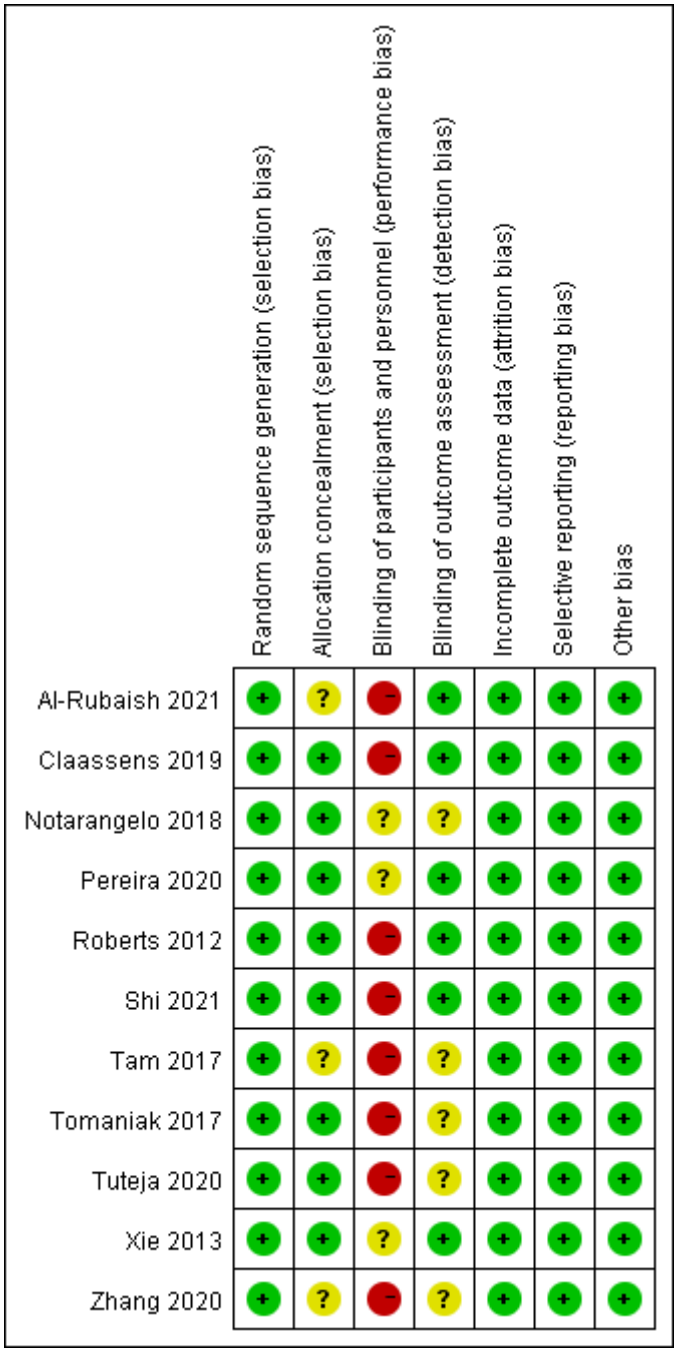

Figure Appendix 1. The risk of bias of the included studies

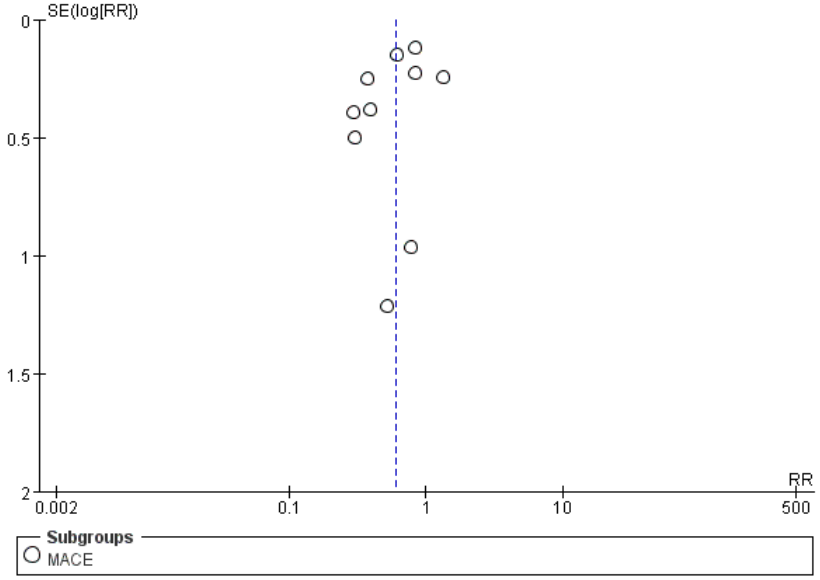

Figure Appendix 2. Funnel plot of MACE

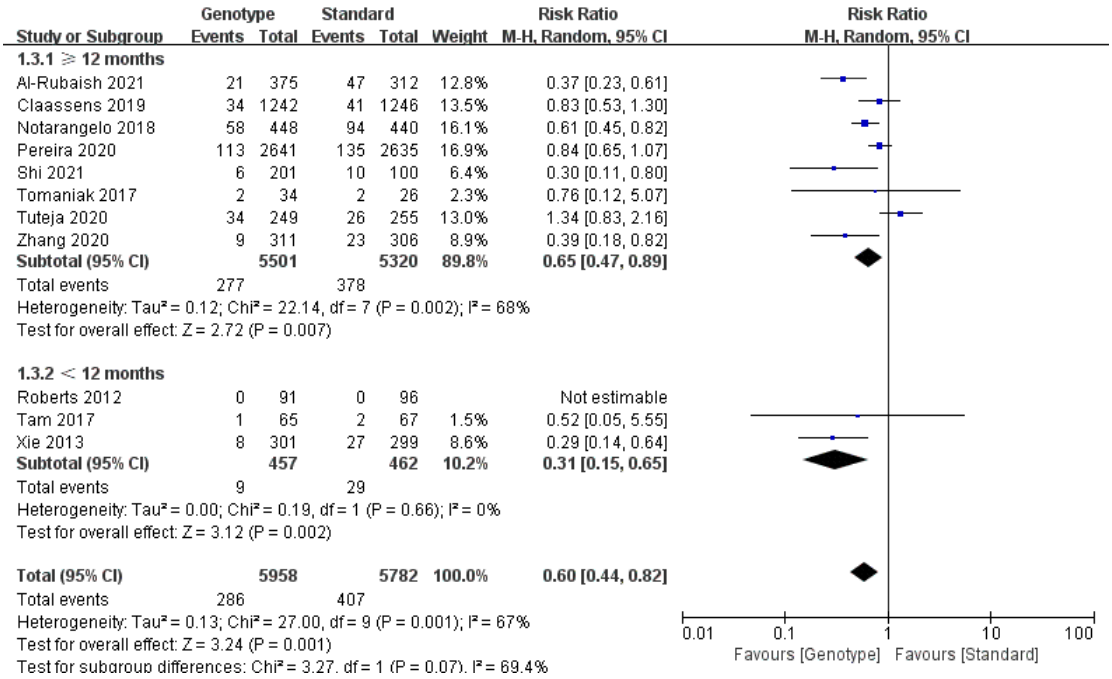

Figure Appendix 3. Forest plot of subgroup analysis for MACE according to follow-up duration

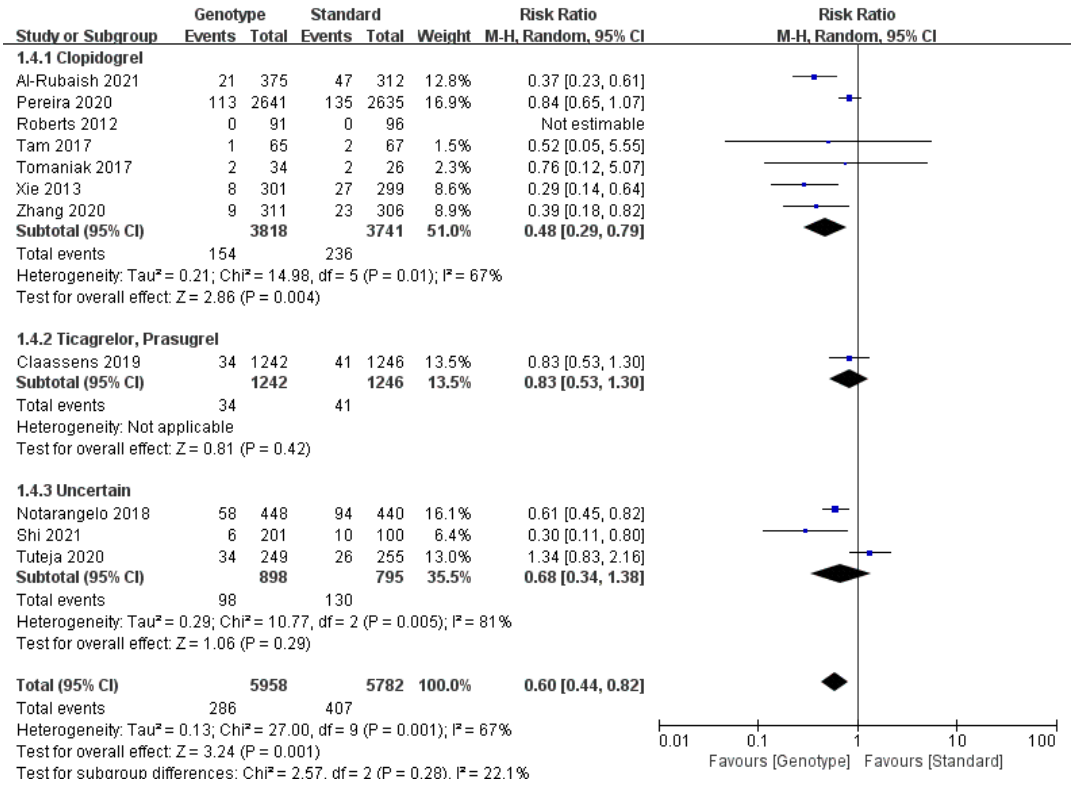

Figure Appendix 4. Forest plot of subgroup analysis for MACE according to treatment strategy in standard treatment group

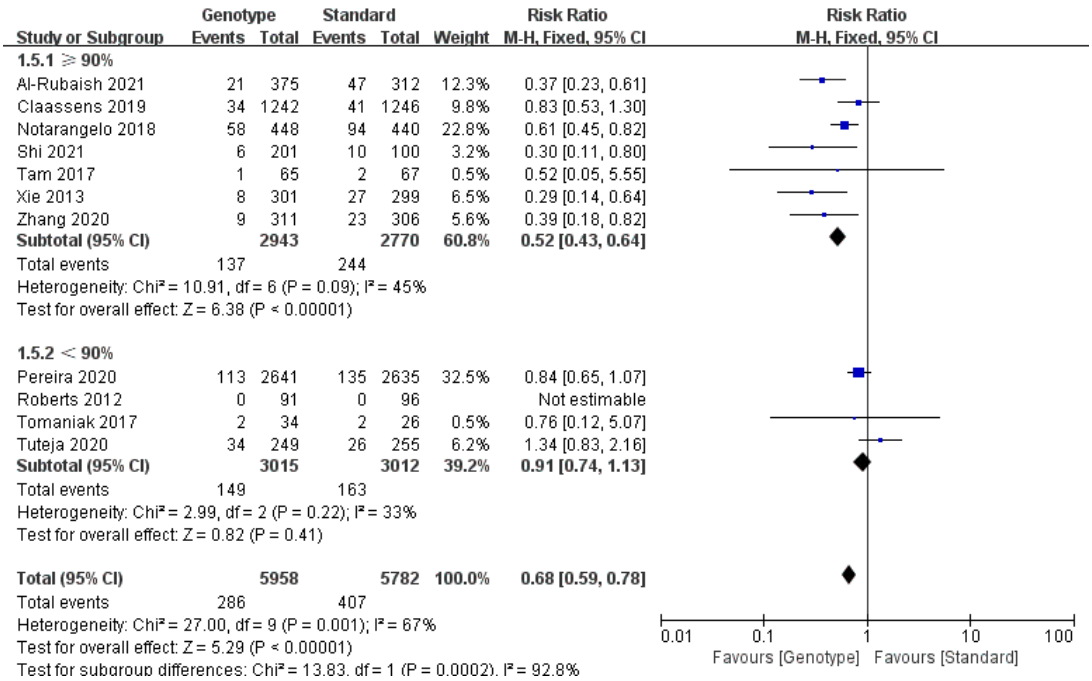

Figure Appendix 5. Forest plot of subgroup analysis for MACE according to proportion of patients with ACS

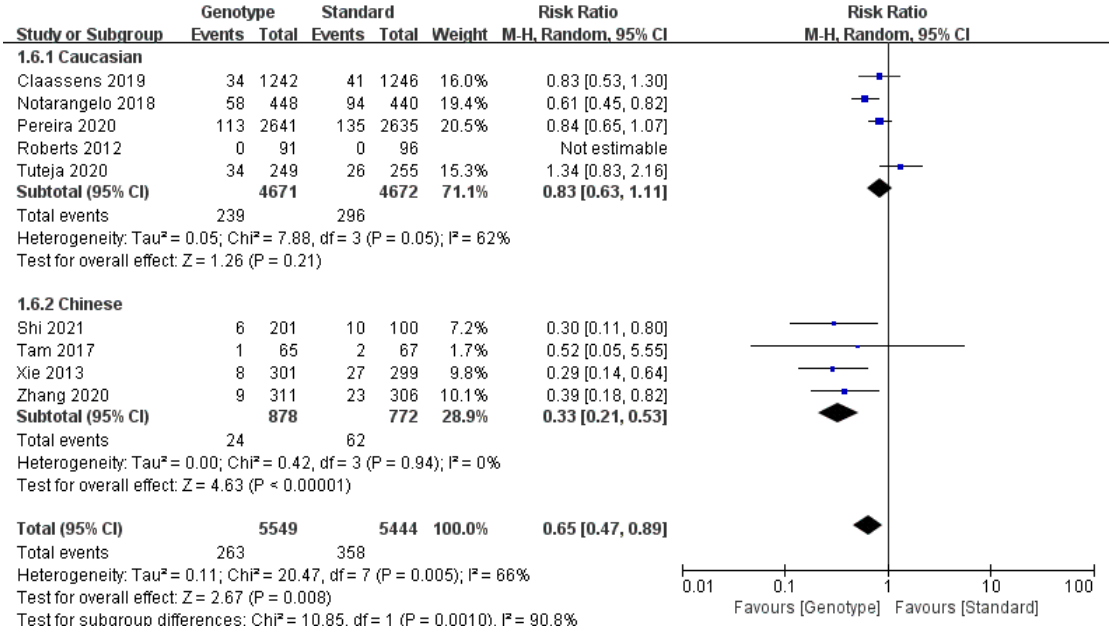

Figure Appendix 6. Forest plot of subgroup analysis for MACE according to ethnicity

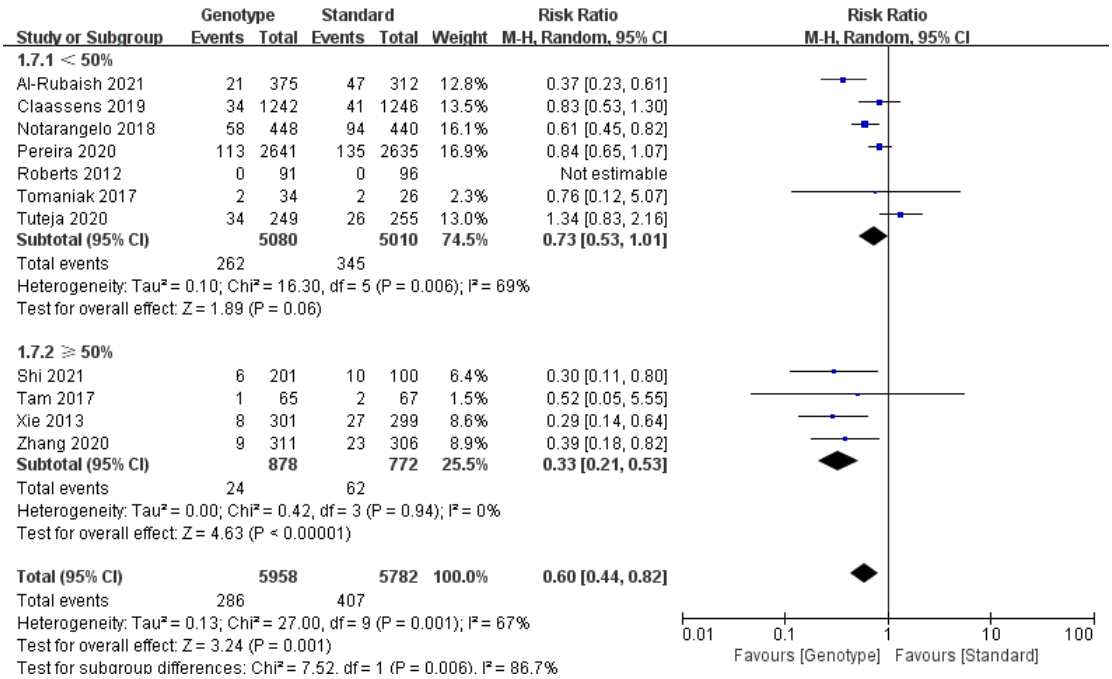

Figure Appendix 7. Forest plot of subgroup analysis for MACE according to proportion of LOF allele carriers in genotype-guided group

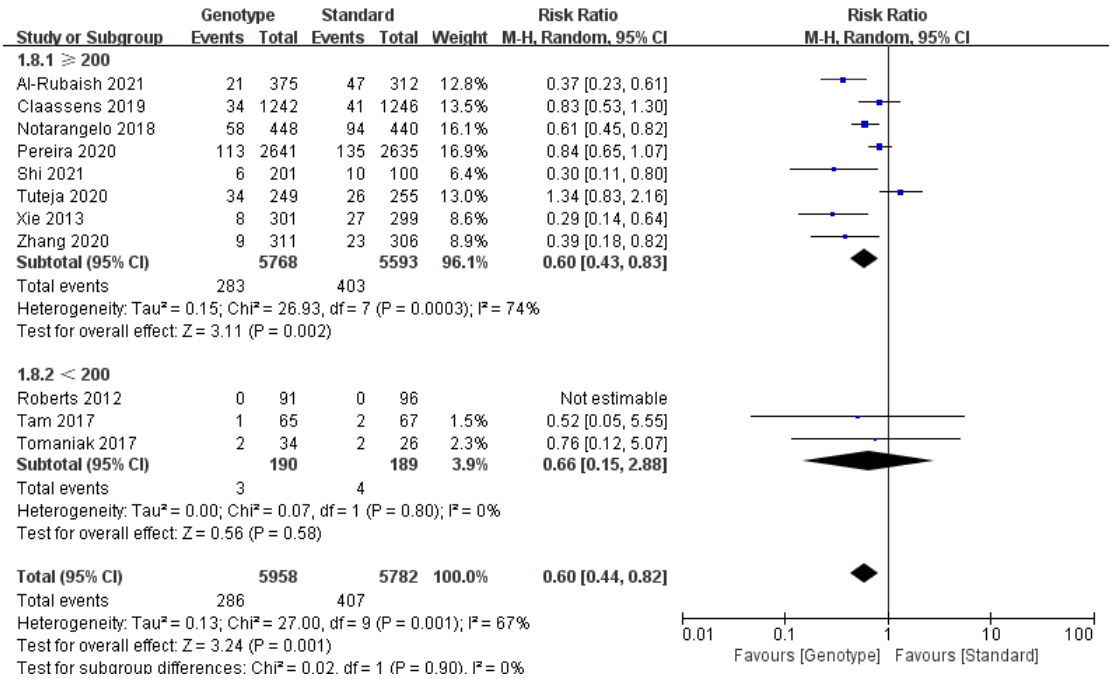

Figure Appendix 8. Forest plot of subgroup analysis for MACE according to sample size

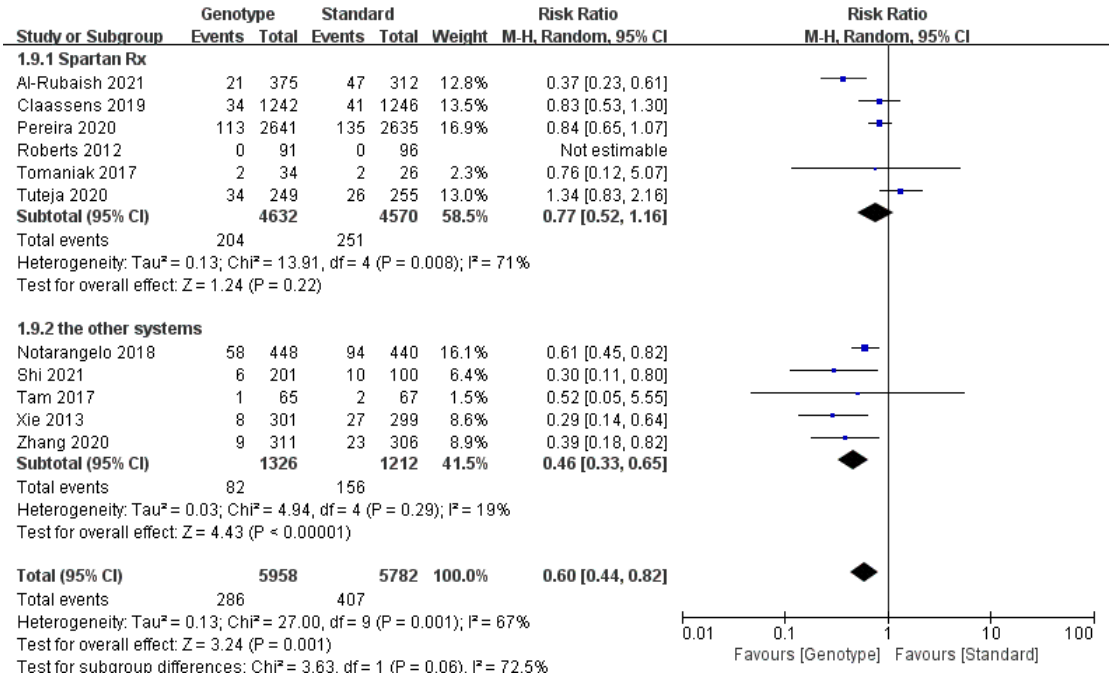

Figure Appendix 9. Forest plot of subgroup analysis for MACE according to genotype test system

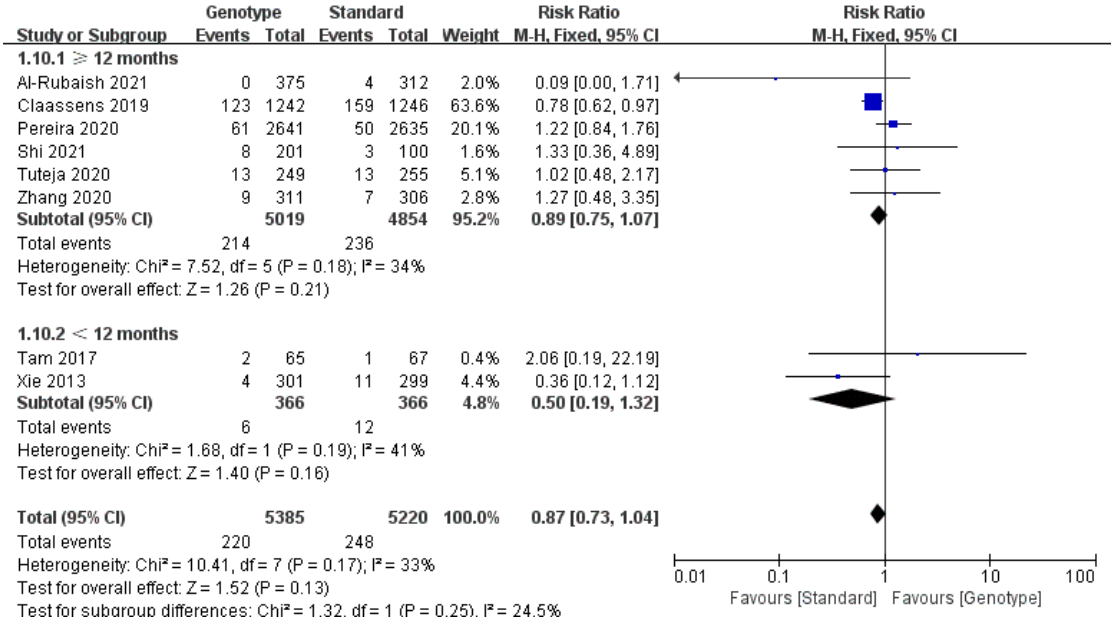

Figure Appendix 10. Forest plot of subgroup analysis for bleeding events (BARC type 2,3,5) according to follow-up duration

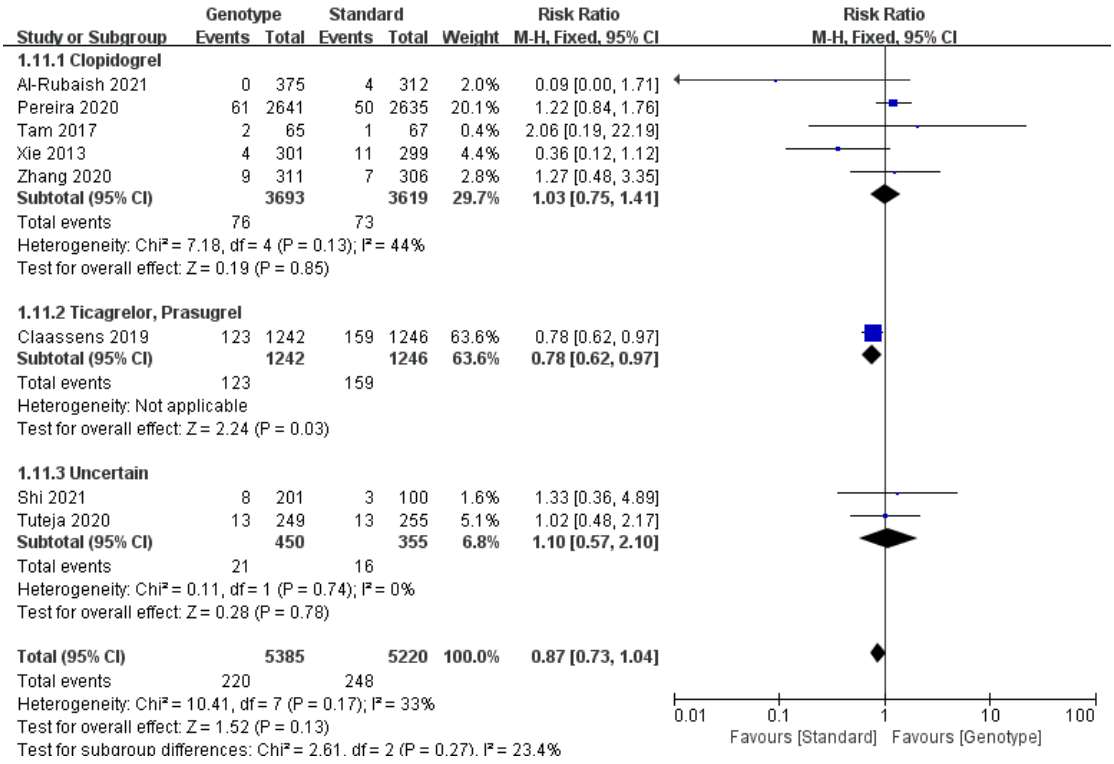

Figure Appendix 11. Forest plot of subgroup analysis for bleeding events (BARC type 2,3,5) according to treatment strategy in standard treatment group

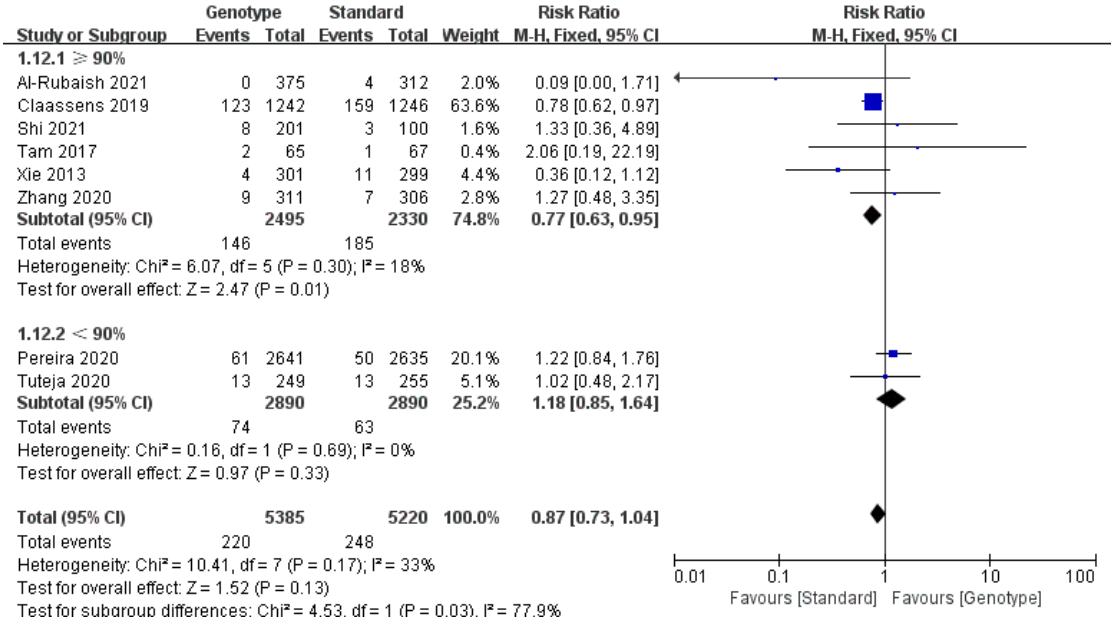

Figure Appendix 12. Forest plot of subgroup analysis for bleeding events (BARC type 2,3,5) according to proportion of patients with ACS

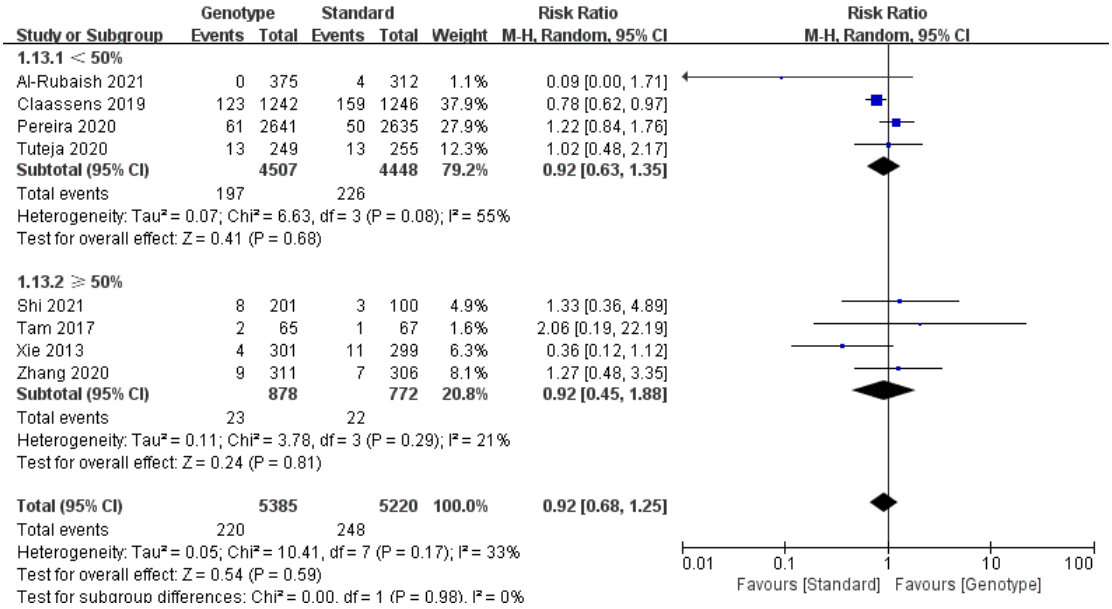

Figure Appendix 13. Forest plot of subgroup analysis for bleeding events (BARC type 2,3,5) according to proportion of LOF allele carriers in GG group