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

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Appendix Tab	ble S1. Search strategy
F1 ( :	
Electronic	Detailed search strategy
databases	((((((((((((((((((((((((((((((((((((
PubMed	((((((((((((((((((((((((((((((((((()))))
	(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 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	#1 MeSH descriptor: [Genotype] explode all trees
Central	#2 genotype OR polymorphism OR pharmacogenetic OR pharmacogenomic OR genetic OR genomic OR genotyping OR variant OR variation OR cyp2c19 OR
Register of	cytochrome p450 2c19
Controlled	#3 MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees
Trials	#4 antiplatelet OR antithrombosis OR clopidogrel OR Iscover OR Plavix OR ticagrelor OR prasugrel OR thienopyridine OR P2Y12 inhibitors OR Platelet Aggregation
databases	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	(genotype OR polymorphism OR pharmacogenetic OR pharmacogenomic OR genetic OR genomic OR genotyping OR variant OR variation OR cyp2c19 OR cytochrome
Science	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)

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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., l <sup>2</sup> ) 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	or each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and forovide the citations.					
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.					
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).					
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17				
FUNDING							

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



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

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	Genot	vne	Standa	ard		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.4.1 Clopidogrel							
Al-Rubaish 2021	21	375	47	312	12.8%	0.37 [0.23, 0.61]	
Pereira 2020	113	2641	135	2635	16.9%	0.84 [0.65, 1.07]	-8-
Roberts 2012	0	91	0	96		Not estimable	
Tam 2017	1	65	2	67	1.5%	0.52 [0.05, 5.55]	
Tomaniak 2017	2	34	2	26	2.3%	0.76 [0.12, 5.07]	
Xie 2013	8	301	27	299	8.6%	0.29 [0.14, 0.64]	
Zhang 2020	9	311	23	306	8.9%	0.39 [0.18, 0.82]	
Subtotal (95% CI)		3818		3741	51.0%	0.48 [0.29, 0.79]	•
Total events	154		236				
Heterogeneity: Tau <sup>2</sup> =	0.21; Ch	i <sup>z</sup> = 14.	98, df = 5	(P = 0.	01); I <sup>z</sup> = 6	17%	
Test for overall effect:	Z = 2.86	(P = 0.0)	)04)				
1.4.2 Ticagrelor, Pras	ugrel						
Claassens 2019	34	1242	41	1246	13.5%	0.83 [0.53, 1.30]	
Subtotal (95% CI)		1242		1246	13.5%	0.83 [0.53, 1.30]	•
Total events	34		41				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.81	(P = 0.4)	12)				
1.4.3 Uncertain							_
Notarangelo 2018	58	448	94	440	16.1%	0.61 [0.45, 0.82]	-
Shi 2021	6	201	10	100	6.4%	0.30 [0.11, 0.80]	
Tuteja 2020	34	249	26	255	13.0%	1.34 [0.83, 2.16]	
Subtotal (95% CI)		898		795	35.5%	0.68 [0.34, 1.38]	
Total events	98		130				
Heterogeneity: Tau <sup>2</sup> =	0.29; Ch	i <sup>2</sup> = 10.	77, df = 2	(P = 0.	005); I² =	81%	
Test for overall effect:	Z = 1.06	(P = 0.2	29)				
Total (05% CI)		5050		5792	100.0%	0 60 10 44 0 931	•
Total avente	206	3330	407	5102	100.0%	0.00 [0.44, 0.02]	•
Hotorogonoity: Tou? -	200 0.12: Ch	iz - 07	407 00 df - 0	P = 0	001\-12-	670	
Tect for overall effect:	0.13, ON 7 = 2.24	1 = 27. (P = 0.0	00, ur≓ 9 104 \	ι(r = 0.	001), P=	0770	0.01 0.1 i 10 100
Test for cubgroup diff.	2 - 3.24   propeosi	(r ≕ 0.0 Chi≇ –	267 df-	27P-	- SI 10C N	. 22.100	Favours [Genotype] Favours [Standard]
restion suburoup dill	erences.	⊖nr=	2.37. ul =	2 (F =	0.20). (* =	- 22.1 70	

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

	Genot	ype	Stand	ard		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
1.5.1 ≥ 90%								
Al-Rubaish 2021	21	375	47	312	12.3%	0.37 [0.23, 0.61]		
Claassens 2019	34	1242	41	1246	9.8%	0.83 [0.53, 1.30]		
Notarangelo 2018	58	448	94	440	22.8%	0.61 [0.45, 0.82]		
Shi 2021	6	201	10	100	3.2%	0.30 [0.11, 0.80]		
Tam 2017	1	65	2	67	0.5%	0.52 [0.05, 5.55]		
Xie 2013	8	301	27	299	6.5%	0.29 [0.14, 0.64]		<b>_</b>
Zhang 2020	9	311	23	306	5.6%	0.39 [0.18, 0.82]		
Subtotal (95% CI)		2943		2770	<b>60.8</b> %	0.52 [0.43, 0.64]		•
Total events	137		244					
Heterogeneity: Chi <sup>2</sup> =	10.91, df	= 6 (P =	= 0.09); P	'= 45%				
Test for overall effect:	Z = 6.38	(P < 0.0	00001)					
1.5.2 < 90%								
Pereira 2020	113	2641	135	2635	32.5%	0.84 [0.65, 1.07]		
Roberts 2012	0	91	0	96		Not estimable		
Tomaniak 2017	2	34	2	26	0.5%	0.76 [0.12, 5.07]		
Tuteja 2020	34	249	26	255	6.2%	1.34 [0.83, 2.16]		
Subtotal (95% CI)		3015		3012	39.2%	0.91 [0.74, 1.13]		
Total events	149		163					
Heterogeneity: Chi <sup>2</sup> =	2.99, df=	2 (P =	0.22); l <sup>z</sup> :	= 33%				
Test for overall effect:	Z = 0.82	(P = 0.4	41)					
Total (95% CI)		5958		5782	100.0%	0.68 [0.59, 0.78]		•
Total events	286		407					-
Heterogeneity: Chi <sup>2</sup> =	27 00 df	= 9 (P :	= 0 001)·	$ ^2 = 67^{\circ}$	%		⊢	
Test for overall effect:	7 = 5.29	= 0 () · (P < ∩ f	- 0.001), 10001)	1 - 01	~~		0.01	0.1 1 10 100
Test for subaroup diff	erences:	Chi <sup>2</sup> = '	13.83. df	= 1 (P =	= 0.0002)	. I² = 92.8%		Favours [Genotype] Favours [Standard]

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

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	Genoty	/pe	Standa	ard		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
1.6.1 Caucasian								
Claassens 2019	34	1242	41	1246	16.0%	0.83 [0.53, 1.30]		
Notarangelo 2018	58	448	94	440	19.4%	0.61 [0.45, 0.82]		
Pereira 2020	113	2641	135	2635	20.5%	0.84 [0.65, 1.07]		
Roberts 2012	0	91	0	96		Not estimable		
Tuteja 2020	34	249	26	255	15.3%	1.34 [0.83, 2.16]		
Subtotal (95% CI)		4671		4672	71.1%	0.83 [0.63, 1.11]		•
Total events	239		296					
Heterogeneity: Tau <sup>2</sup> =	0.05; Chi	i <sup>2</sup> = 7.8	8, df = 3 (	P = 0.0	5); l² = 62	!%		
Test for overall effect:	Z=1.26 (	(P = 0.2)	1)					
1.6.2 Chinese								
Shi 2021	6	201	10	100	7.2%	0.30 [0.11, 0.80]		
Tam 2017	1	65	2	67	1.7%	0.52 [0.05, 5.55]		
Xie 2013	8	301	27	299	9.8%	0.29 [0.14, 0.64]		<b>_</b>
Zhang 2020	9	311	23	306	10.1%	0.39 [0.18, 0.82]		
Subtotal (95% CI)		878		772	28.9%	0.33 [0.21, 0.53]		•
Total events	24		62					
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	i <sup>2</sup> = 0.43	2, df = 3 (	P = 0.9	4); l <sup>2</sup> = 09	6		
Test for overall effect:	Z = 4.63 (	(P < 0.0	0001)					
Total (95% CI)		5549		5444	100.0%	0.65 [0.47, 0.89]		•
Total events	263		358					
Heterogeneity: Tau <sup>2</sup> =	0.11; Chi	i <sup>2</sup> = 20	47, df = 7	(P = 0.	005); l² =	66%		
Test for overall effect:	Z = 2.67 (	(P = 0.0)	108)				0.01	U.I I IU IUU Favoure [Construe] - Favoure [Standard]
Test for subaroup diff	erences:	Chi <sup>2</sup> = <sup>1</sup>	10.85. df	= 1 (P =	= 0.0010)	. I² = 90.8%		ravours (Genotype) - ravours (Standard)

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

	Genot	уре	Standa	ard		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.7.1 < 50%							
Al-Rubaish 2021	21	375	47	312	12.8%	0.37 [0.23, 0.61]	
Claassens 2019	34	1242	41	1246	13.5%	0.83 [0.53, 1.30]	
Notarangelo 2018	58	448	94	440	16.1%	0.61 [0.45, 0.82]	
Pereira 2020	113	2641	135	2635	16.9%	0.84 [0.65, 1.07]	
Roberts 2012	0	91	0	96		Not estimable	
Tomaniak 2017	2	34	2	26	2.3%	0.76 [0.12, 5.07]	
Tuteja 2020	34	249	26	255	13.0%	1.34 [0.83, 2.16]	
Subtotal (95% CI)		5080		5010	74.5%	0.73 [0.53, 1.01]	$\bullet$
Total events	262		345				
Heterogeneity: Tau <sup>2</sup> =	0.10; Ch	i² = 16.	30, df = 5	(P = 0.	006); l² =	69%	
Test for overall effect:	Z = 1.89	(P = 0.0	)6)				
1.7.2 ≥ 50%							
Shi 2021	6	201	10	100	6.4%	0.30 [0.11, 0.80]	
Tam 2017	1	65	2	67	1.5%	0.52 [0.05, 5.55]	
Xie 2013	8	301	27	299	8.6%	0.29 [0.14, 0.64]	
Zhang 2020	9	311	23	306	8.9%	0.39 [0.18, 0.82]	
Subtotal (95% CI)		878		772	25.5%	0.33 [0.21, 0.53]	•
Total events	24		62				
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Ch	i <sup>z</sup> = 0.4	2, df = 3 (	P = 0.9	4); I <sup>z</sup> = 0%	6	
Test for overall effect:	Z=4.63	(P < 0.0	00001)				
Total (95% CI)		5958		5782	100.0%	0.60 [0.44, 0.82]	•
Total events	286		407				
Heterogeneity: Tau² =	: 0.13; Ch	i² = 27.	00, df = 9	(P = 0.	001); I² =	67%	
Test for overall effect:	Z = 3.24	(P = 0.0	001)				Favours [Genotype] Favours [Standard]
Test for subaroup diff	erences:	Chi <sup>2</sup> =	7.52. df =	1 (P =	0.006). I <sup>z</sup>	= 86.7%	

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

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	Genoty	уре	Stand	ard		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.8.1 ≥ 200							
Al-Rubaish 2021	21	375	47	312	12.8%	0.37 [0.23, 0.61]	
Claassens 2019	34	1242	41	1246	13.5%	0.83 [0.53, 1.30]	
Notarangelo 2018	58	448	94	440	16.1%	0.61 [0.45, 0.82]	
Pereira 2020	113	2641	135	2635	16.9%	0.84 [0.65, 1.07]	
Shi 2021	6	201	10	100	6.4%	0.30 [0.11, 0.80]	
Tuteja 2020	34	249	26	255	13.0%	1.34 [0.83, 2.16]	+
Xie 2013	8	301	27	299	8.6%	0.29 [0.14, 0.64]	_ <b>-</b>
Zhang 2020	9	311	23	306	8.9%	0.39 [0.18, 0.82]	
Subtotal (95% CI)		5768		5593	96.1%	0.60 [0.43, 0.83]	•
Total events	283		403				
Heterogeneity: Tau <sup>2</sup> =	0.15; Ch	i² = 26.	93, df = 7	(P = 0.	0003); l² =	74%	
Test for overall effect:	Z = 3.11 (	(P = 0.0)	002)				
1.8.2 < 200							
Roberts 2012	0	91	0	96		Not estimable	
Tam 2017	1	65	2	67	1.5%	0.52 [0.05, 5.55]	
Tomaniak 2017	2	34	2	26	2.3%	0.76 [0.12, 5.07]	
Subtotal (95% Cl)		190		189	3.9%	0.66 [0.15, 2.88]	
Total events	3		4				
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	i <sup>z</sup> = 0.01	7, df = 1 (	P = 0.8	0); I <sup>z</sup> = 0%		
Test for overall effect:	Z = 0.56 (	(P = 0.5)	58)				
Total (95% CI)		5958		5782	100.0%	0.60 [0.44, 0.82]	•
Total events	286		407				
Heterogeneity: Tau <sup>2</sup> =	0.13; Ch	i² = 27.	00, df = 9	(P = 0.	001); I² = 6	37%	
Test for overall effect:	Z = 3.24 (	(P = 0.0	001)				Eavours [Genotyne] Eavours [Standard]
Test for subaroup diff	erences:	Chi² = I	0.02. df=	1 (P =	$0.90),  ^2 = 1$	0%	r avours (Genotype) in avours (Stanualu)

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

	Genotype		e Standard		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
1.9.1 Spartan Rx								
Al-Rubaish 2021	21	375	47	312	12.8%	0.37 [0.23, 0.61]		
Claassens 2019	34	1242	41	1246	13.5%	0.83 [0.53, 1.30]		
Pereira 2020	113	2641	135	2635	16.9%	0.84 [0.65, 1.07]		
Roberts 2012	0	91	0	96		Not estimable		
Tomaniak 2017	2	34	2	26	2.3%	0.76 [0.12, 5.07]		
Tuteja 2020	34	249	26	255	13.0%	1.34 [0.83, 2.16]		
Subtotal (95% CI)		4632		4570	58.5%	0.77 [0.52, 1.16]		◆
Total events	204		251					
Heterogeneity: Tau <sup>2</sup> =	0.13; Ch	i² = 13.	91, df = 4	(P = 0.	008); I² =	71%		
Test for overall effect:	Z=1.24	(P = 0.2)	2)					
1.9.2 the other syster	ns							
Notarangelo 2018	58	448	94	440	16.1%	0.61 [0.45, 0.82]		-
Shi 2021	6	201	10	100	6.4%	0.30 [0.11, 0.80]		
Tam 2017	1	65	2	67	1.5%	0.52 [0.05, 5.55]		
Xie 2013	8	301	27	299	8.6%	0.29 [0.14, 0.64]		<b>_</b>
Zhang 2020	9	311	23	306	8.9%	0.39 [0.18, 0.82]		
Subtotal (95% CI)		1326		1212	41.5%	0.46 [0.33, 0.65]		•
Total events	82		156					
Heterogeneity: Tau <sup>2</sup> =	0.03; Ch	i² = 4.9	4, df = 4 (	P = 0.2	9); I <sup>z</sup> = 19	%		
Test for overall effect:	Z=4.43	(P < 0.0	00001)					
								•
Total (95% CI)		5958		5782	<b>100.0</b> %	0.60 [0.44, 0.82]		•
Total events	286		407					
Heterogeneity: Tau <sup>2</sup> =	0.13; Ch	i² = 27.∣	00, df = 9	(P = 0.	001); I² =	67%		
Test for overall effect:	Z = 3.24	(P = 0.0	)01)				0.01	Eavours [Genotype] Eavours [Standard]
Test for subaroup differences: Chi <sup>2</sup> = 3.63, df = 1 (P = 0.06), l <sup>2</sup> = 72.5%								avours [Senotype] - avours [Standard]

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

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	Genotype		type Standard		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
1.10.1 ≥ 12 months									
Al-Rubaish 2021	0	375	4	312	2.0%	0.09 [0.00, 1.71]	•		
Claassens 2019	123	1242	159	1246	63.6%	0.78 [0.62, 0.97]			
Pereira 2020	61	2641	50	2635	20.1%	1.22 [0.84, 1.76]			
Shi 2021	8	201	3	100	1.6%	1.33 [0.36, 4.89]			
Tuteja 2020	13	249	13	255	5.1%	1.02 [0.48, 2.17]			
Zhang 2020	9	311	7	306	2.8%	1.27 [0.48, 3.35]			
Subtotal (95% CI)		5019		4854	95.2%	0.89 [0.75, 1.07]		•	
Total events	214		236						
Heterogeneity: Chi <sup>2</sup> =	7.52, df=	5 (P =	0.18); <b>i²</b> =	= 34%					
Test for overall effect:	Z = 1.26	(P = 0.2)	21)						
4.40.2 < 42 months									
1.10.2 < 12 monuns					~				
Tam 2017	2	65	1	67	0.4%	2.06 [0.19, 22.19]			
XIE 2013	4	301	11	299	4.4%	0.36 [0.12, 1.12]			
Subtotal (95% CI)		366		366	4.8%	0.50 [0.19, 1.32]			
l otal events	6		12						
Heterogeneity: Chi <sup>2</sup> =	1.68, df =	1 (P =	0.19); I <sup>2</sup> =	= 41%					
Test for overall effect:	Z=1.40	(P = 0.1	6)						
Total (95% CI)		5385		5220	100.0%	0.87 [0.73, 1.04]		•	
Total events	220		248						
Heterogeneity: Chi <sup>2</sup> =	10.41, df	= 7 (P :	= 0.17); l <sup>a</sup>	²= 33%					4
Test for overall effect:	Z=1.52	(P = 0.1	3)				0.01	Eavours [Standard] Eavours [Construe]	U
Test for subaroup differences: Chi² = 1.32. df = 1 (P = 0.25). I² = 24.5%								ravours (standard) - ravours (Genotype)	

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

	Genoty	Genotype Standard		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.11.1 Clopidogrel							
Al-Rubaish 2021	0	375	4	312	2.0%	0.09 [0.00, 1.71]	· · · · · · · · · · · · · · · · · · ·
Pereira 2020	61	2641	50	2635	20.1%	1.22 [0.84, 1.76]	
Tam 2017	2	65	1	67	0.4%	2.06 [0.19, 22.19]	
Xie 2013	4	301	11	299	4.4%	0.36 [0.12, 1.12]	
Zhang 2020	9	311	7	306	2.8%	1.27 [0.48, 3.35]	
Subtotal (95% CI)		3693		3619	<b>29.7</b> %	1.03 [0.75, 1.41]	•
Total events	76		73				
Heterogeneity: Chi <sup>2</sup> =	7.18, df=	4 (P =	0.13); I <sup>z</sup> :	= 44%			
Test for overall effect:	Z = 0.19	(P = 0.8	35)				
1.11.2 Ticagrelor, Pra	suarel						
Claassens 2019	123	1242	159	1246	63.6%	0.78 (0.62, 0.97)	
Subtotal (95% CI)		1242		1246	63.6%	0.78 [0.62, 0.97]	•
Total events	123		159				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z= 2.24	(P = 0.0	)3)				
1.11.3 Uncertain							
Shi 2021	8	201	3	100	1.6%	1.33 [0.36, 4.89]	
Tuteja 2020	13	249	13	255	5.1%	1.02 [0.48, 2.17]	
Subtotal (95% CI)		450		355	6.8%	1.10 [0.57, 2.10]	-
Total events	21		16				
Heterogeneity: Chi² =	0.11, df=	1 (P =	0.74); l² =	= 0%			
Test for overall effect:	Z = 0.28	(P = 0.7	78)				
Total (95% CI)		5385		5220	100.0%	0.87 [0.73, 1.04]	•
Total events	220		248				
Heterogeneity: Chi <sup>2</sup> =	10.41, df	= 7 (P :	= 0.17); P	²= 33%			
Test for overall effect:	Z = 1.52 (	(P = 0.1	3)				Eavoure [Standard] Eavoure [Construe]
Test for subgroup diff	erences:	Chi <sup>z</sup> =	2.61. df=	2 (P =	0.27), I <sup>2</sup> =	: 23.4%	Favours (Stanuaru) Favours (Genotype)

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

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	Genot	уре	Standard		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.12.1 ≥ 90%							
Al-Rubaish 2021	0	375	4	312	2.0%	0.09 [0.00, 1.71]	·
Claassens 2019	123	1242	159	1246	63.6%	0.78 [0.62, 0.97]	
Shi 2021	8	201	3	100	1.6%	1.33 [0.36, 4.89]	
Tam 2017	2	65	1	67	0.4%	2.06 [0.19, 22.19]	
Xie 2013	4	301	11	299	4.4%	0.36 [0.12, 1.12]	
Zhang 2020	9	311	7	306	2.8%	1.27 [0.48, 3.35]	
Subtotal (95% CI)		2495		2330	74.8%	0.77 [0.63, 0.95]	•
Total events	146		185				
Heterogeneity: Chi <sup>2</sup> =	6.07, df=	: 5 (P =	0.30); <b>I</b> ² :	= 18%			
Test for overall effect:	Z = 2.47	(P = 0.0	)1)				
1.12.2 < 90%							
Pereira 2020	61	2641	50	2635	20.1%	1.22 [0.84, 1.76]	
Tuteja 2020	13	249	13	255	5.1%	1.02 [0.48, 2.17]	
Subtotal (95% CI)		2890		2890	25.2%	1.18 [0.85, 1.64]	<b>◆</b>
Total events	74		63				
Heterogeneity: Chi <sup>2</sup> =	0.16, df=	: 1 (P =	0.69); <b>I</b> ² =	= 0%			
Test for overall effect:	Z = 0.97	(P = 0.3)	33)				
Total (95% CI)		5385		5220	<b>100.0</b> %	0.87 [0.73, 1.04]	•
Total events	220		248				
Heterogeneity: Chi <sup>2</sup> =	10.41, df	= 7 (P =	= 0.17); P	²= 33%			
Test for overall effect:	Z=1.52	(P = 0.1	3)				Eavoure [Standard] Eavoure [Gonotype]
Test for subaroup differences: Chi² = 4.53. df = 1 (P = 0.03). l² = 77.9%							Favours (Standard) Favours (Genotype)

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

	Genoty	ype	Standa	ard		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.13.1 < 50%							
Al-Rubaish 2021	0	375	4	312	1.1%	0.09 [0.00, 1.71]	· · · · · · · · · · · · · · · · · · ·
Claassens 2019	123	1242	159	1246	37.9%	0.78 [0.62, 0.97]	-
Pereira 2020	61	2641	50	2635	27.9%	1.22 [0.84, 1.76]	
Tuteja 2020	13	249	13	255	12.3%	1.02 [0.48, 2.17]	
Subtotal (95% CI)		4507		4448	79.2%	0.92 [0.63, 1.35]	♠
Total events	197		226				
Heterogeneity: Tau <sup>2</sup> =	0.07; Ch	i² = 6.6	3, df = 3 (	P = 0.0	8); I <sup>2</sup> = 559	%	
Test for overall effect:	Z = 0.41 (	(P = 0.8	68)				
1.13.2 ≥ 50%							
Shi 2021	8	201	3	100	4.9%	1.33 [0.36, 4.89]	<b>-</b>
Tam 2017	2	65	1	67	1.6%	2.06 [0.19, 22.19]	
Xie 2013	4	301	11	299	6.3%	0.36 [0.12, 1.12]	
Zhang 2020	9	311	7	306	8.1%	1.27 [0.48, 3.35]	
Subtotal (95% CI)		878		772	20.8%	0.92 [0.45, 1.88]	
Total events	23		22				
Heterogeneity: Tau <sup>2</sup> =	0.11; Ch	i² = 3.7	8, df = 3 (	P = 0.2	9); <b>I<sup>2</sup> =</b> 219	%	
Test for overall effect:	Z = 0.24 (	(P = 0.8	31)				
Total (95% CI)		5385		5220	100.0%	0.92 [0.68, 1.25]	$\bullet$
Total events	220		248				
Heterogeneity: Tau <sup>2</sup> =	0.05; Ch	i² = 10.∕	41, df = 7	(P = 0.	17); I <sup>z</sup> = 33	3%	
Test for overall effect:	Z = 0.54 (	(P = 0.5)	59)				Eavoure [Standard] Eavoure [Ganatyna]
Test for subaroup diff	erences:	Chi <sup>2</sup> = I	0.00. df=	1 (P =	0.98), I <sup>z</sup> = I	0%	ravours (standard) Favours (Senotype)

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