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

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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<br>#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))<br>#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))<br>#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<br>#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<br>#2 genotype OR polymorphism OR pharmacogenetic OR pharmacogenomic OR genetic OR genomic OR genotyping OR variant OR variation OR cyp2c19 OR cytochrome p450 2c19<br>#3 MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees<br>#4 antiplatelet OR antithrombosis OR clopidogrel OR Iscover OR Plavix OR ticagrelor OR prasugrel OR thienopyridine OR P2Y12 inhibitors OR Platelet Aggregation Inhibitors<br>#5 Acute Coronary Syndromes OR ACS OR Percutaneous Coronary Interventions OR PCI<br>#6 guide OR personalized OR guided OR guiding OR tailored OR individualized OR individualizing OR individualization OR directed OR directing<br>#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 |

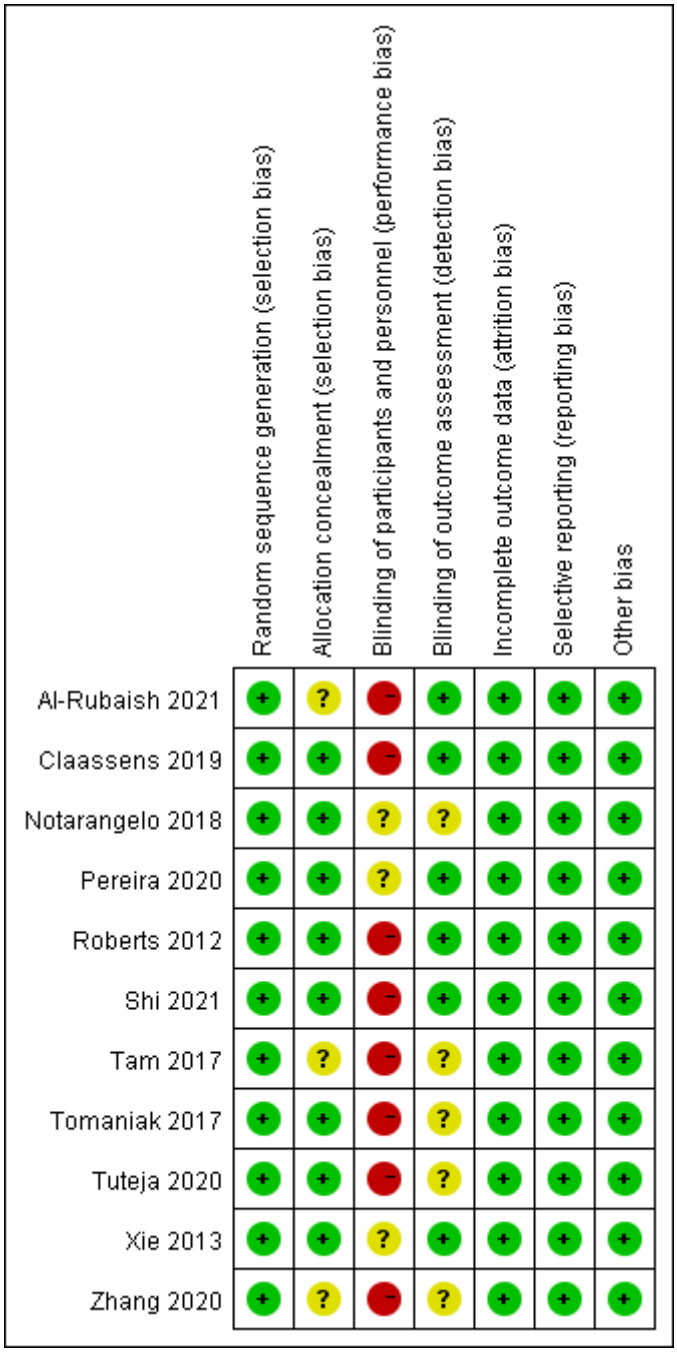


**Figure Appendix 1. The risk of bias of the included studies**

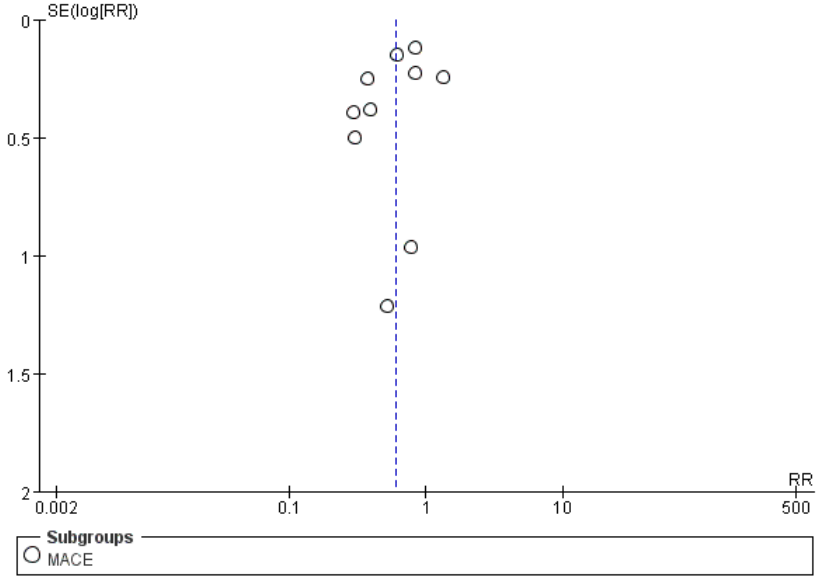


**Figure Appendix 2. Funnel plot of MACE**

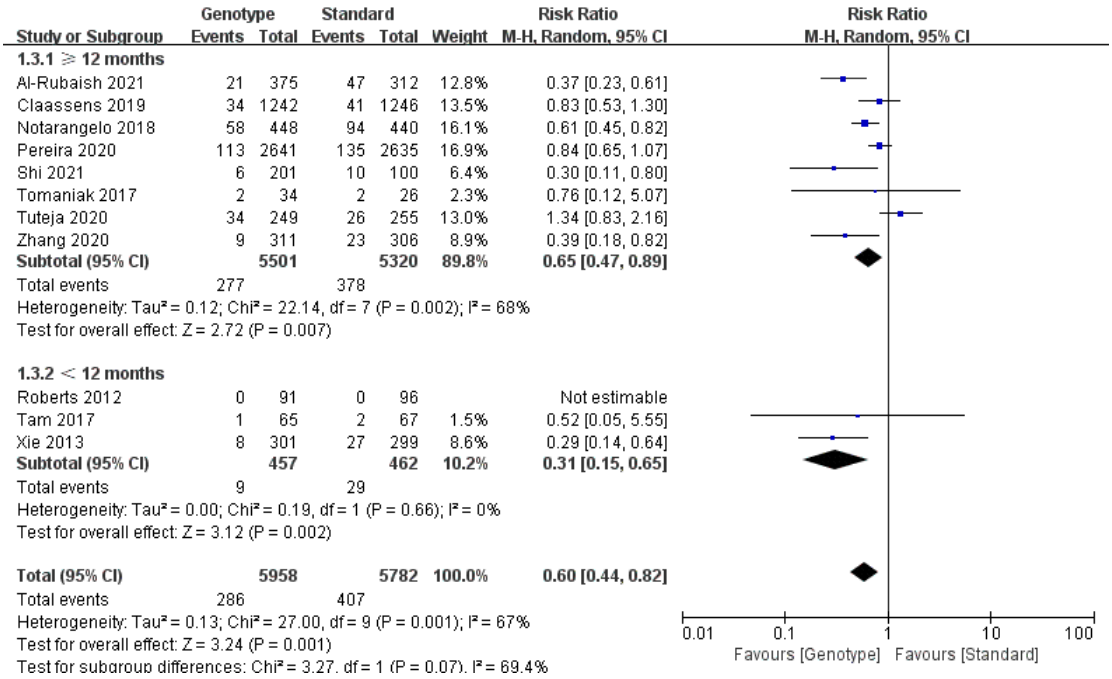


**Figure Appendix 3. Forest plot of subgroup analysis for MACE according to follow-up duration**

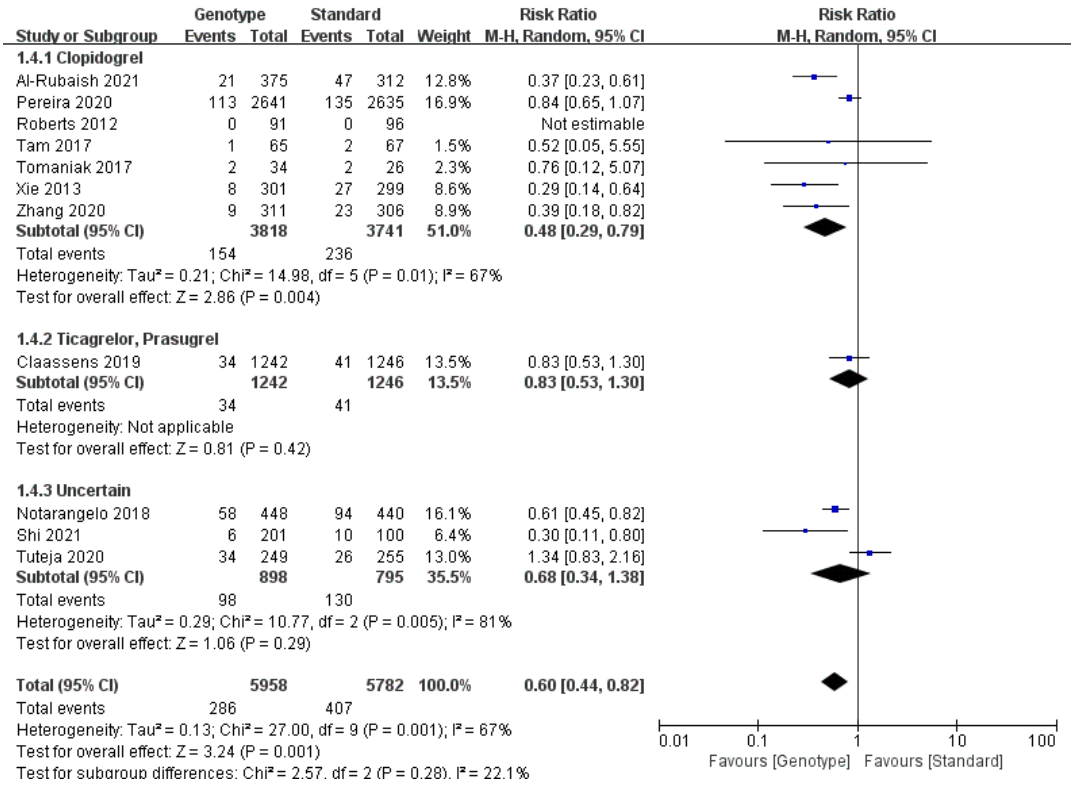


**Figure Appendix 4. Forest plot of subgroup analysis for MACE according to treatment strategy in standard treatment group**

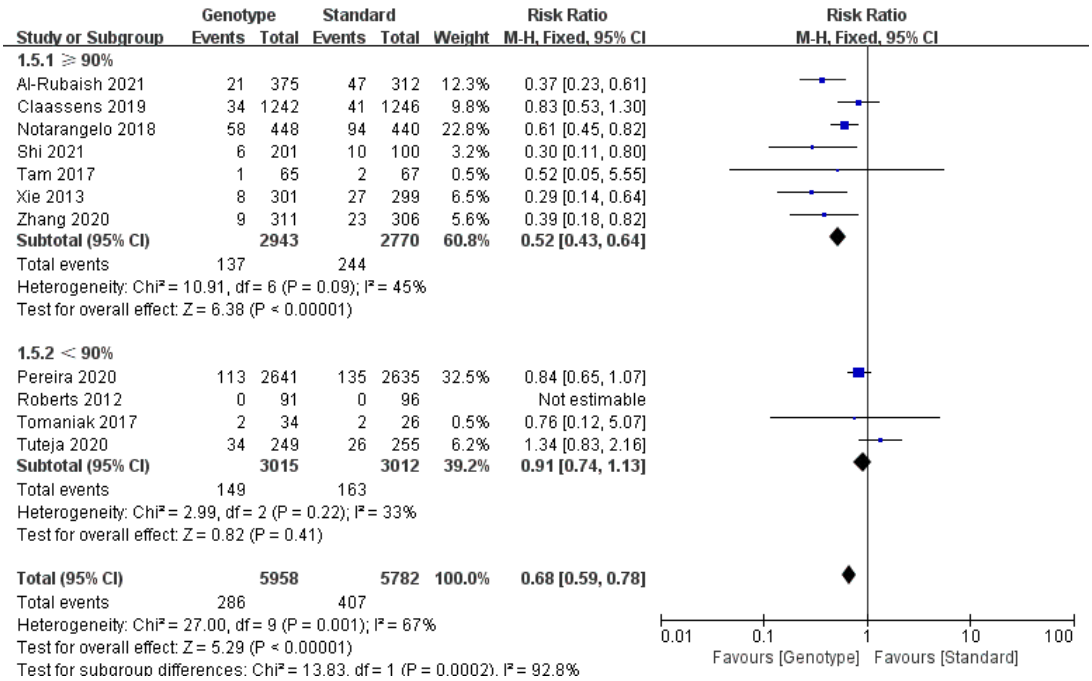


**Figure Appendix 5. Forest plot of subgroup analysis for MACE according to proportion of patients with ACS**

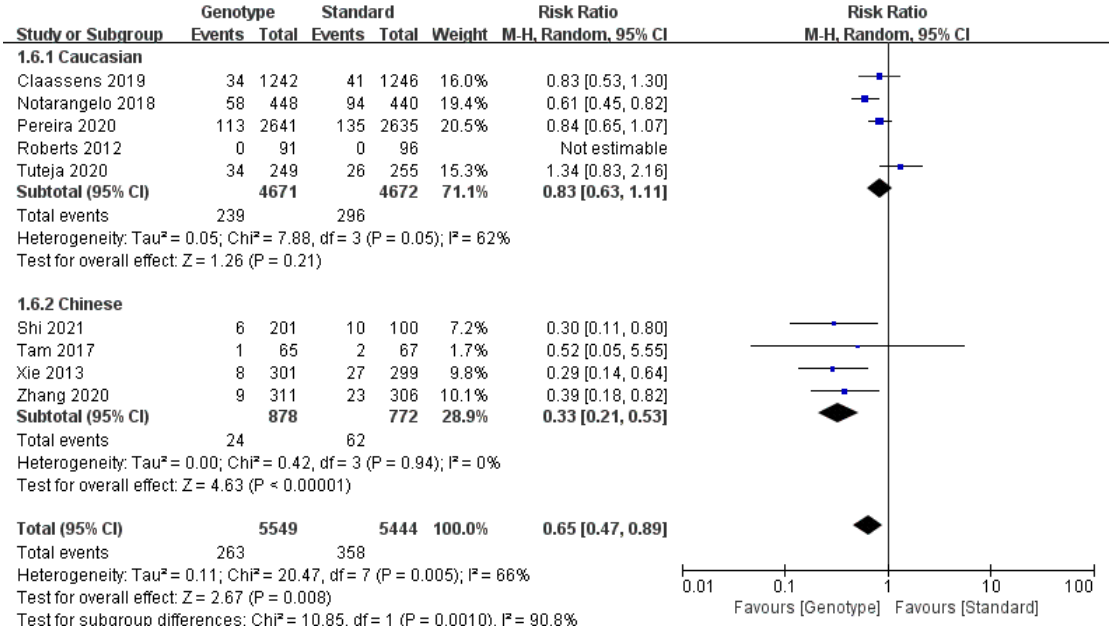


**Figure Appendix 6. Forest plot of subgroup analysis for MACE according to ethnicity**

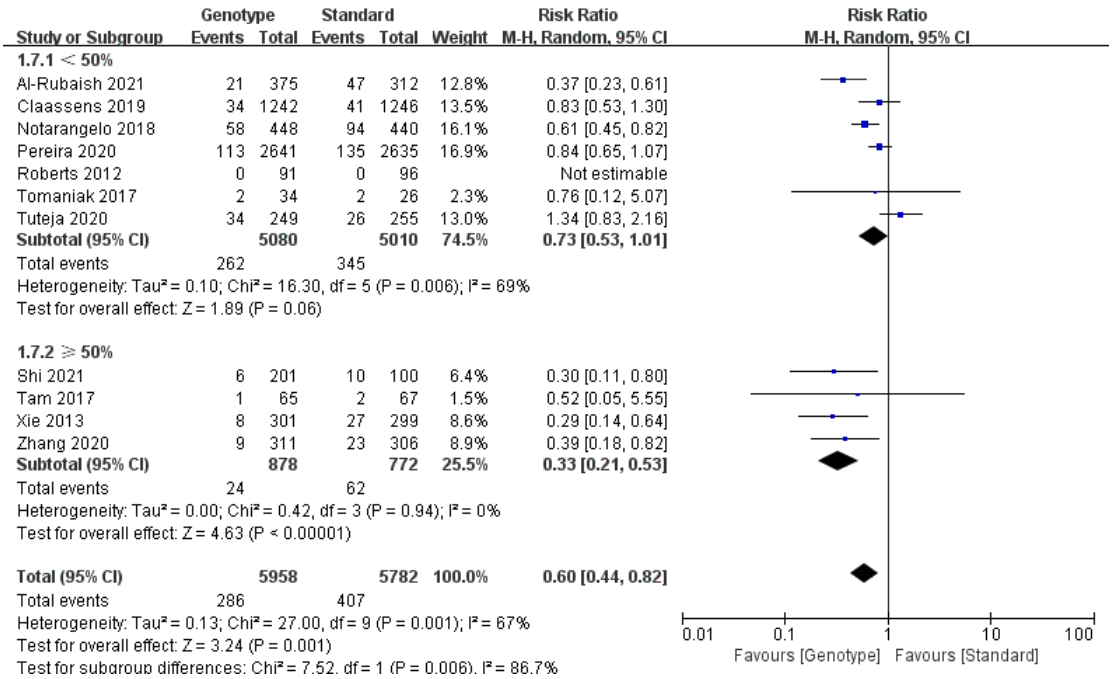


**Figure Appendix 7. Forest plot of subgroup analysis for MACE according to proportion of LOF allele carriers in genotype-guided group**

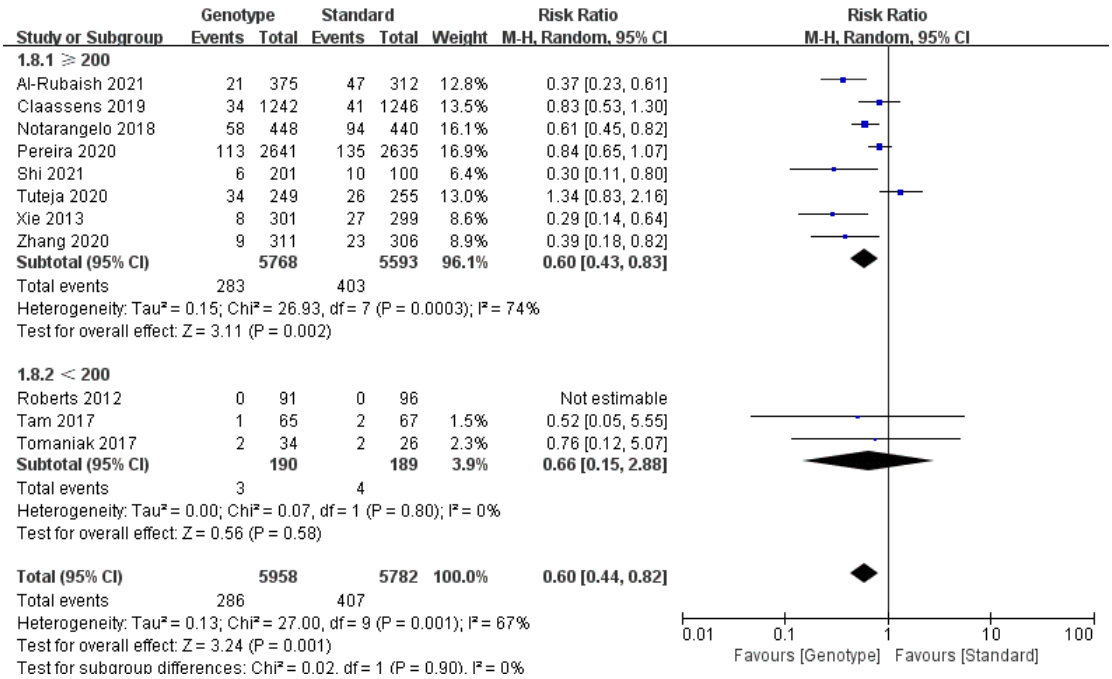


**Figure Appendix 8. Forest plot of subgroup analysis for MACE according to sample size**

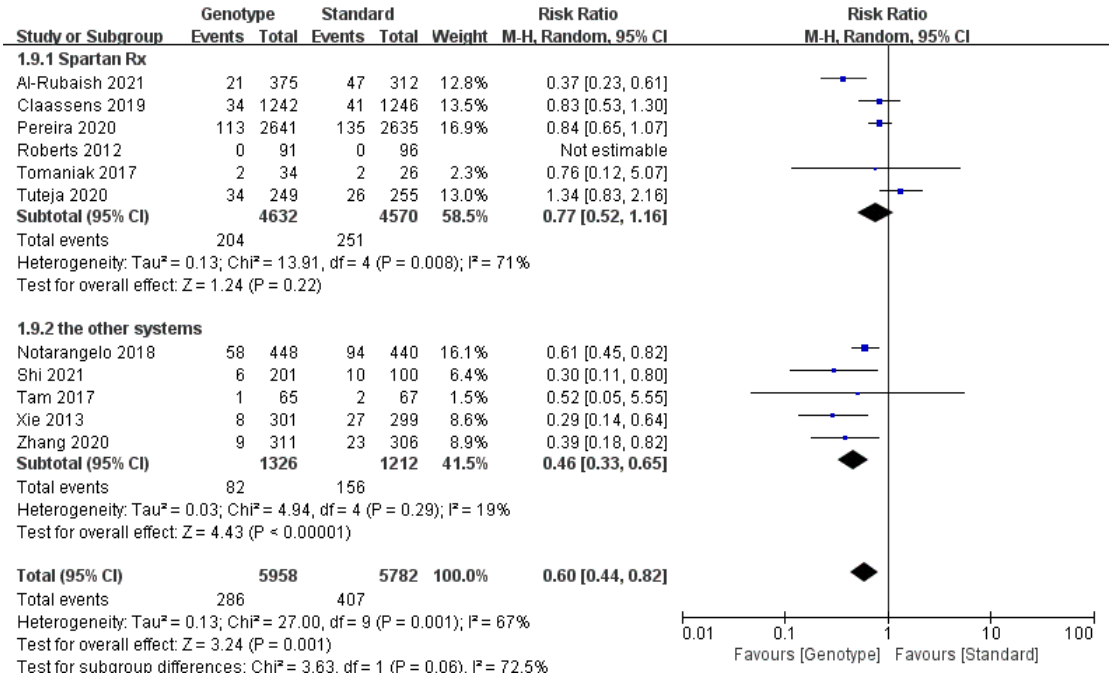


**Figure Appendix 9. Forest plot of subgroup analysis for MACE according to genotype test system**

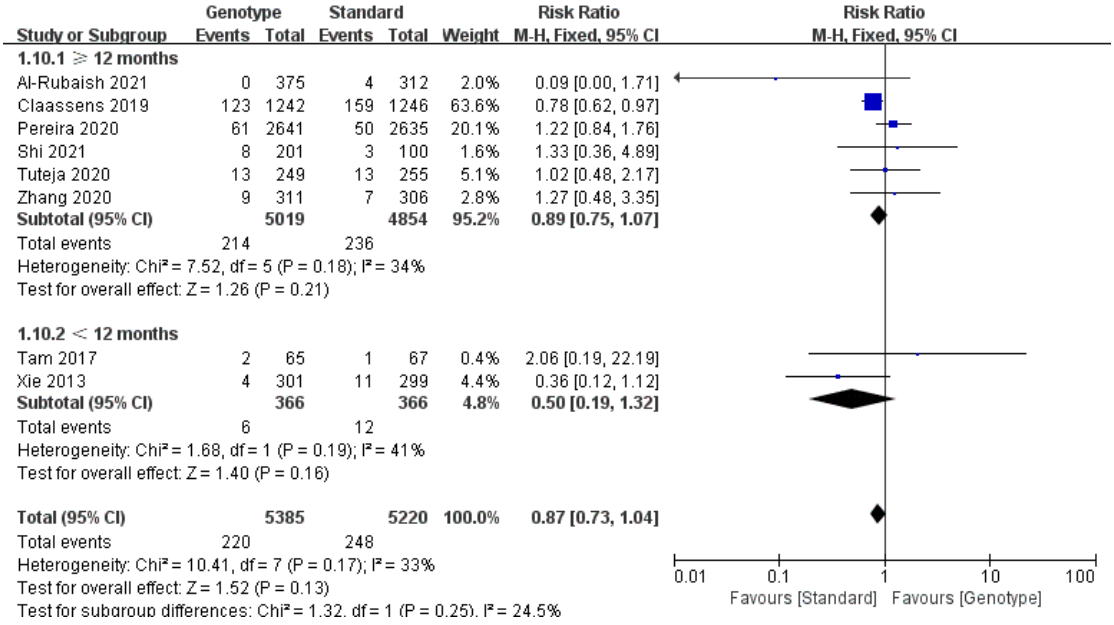


**Figure Appendix 10. Forest plot of subgroup analysis for bleeding events (BARC type 2,3,5) according to follow-up duration**

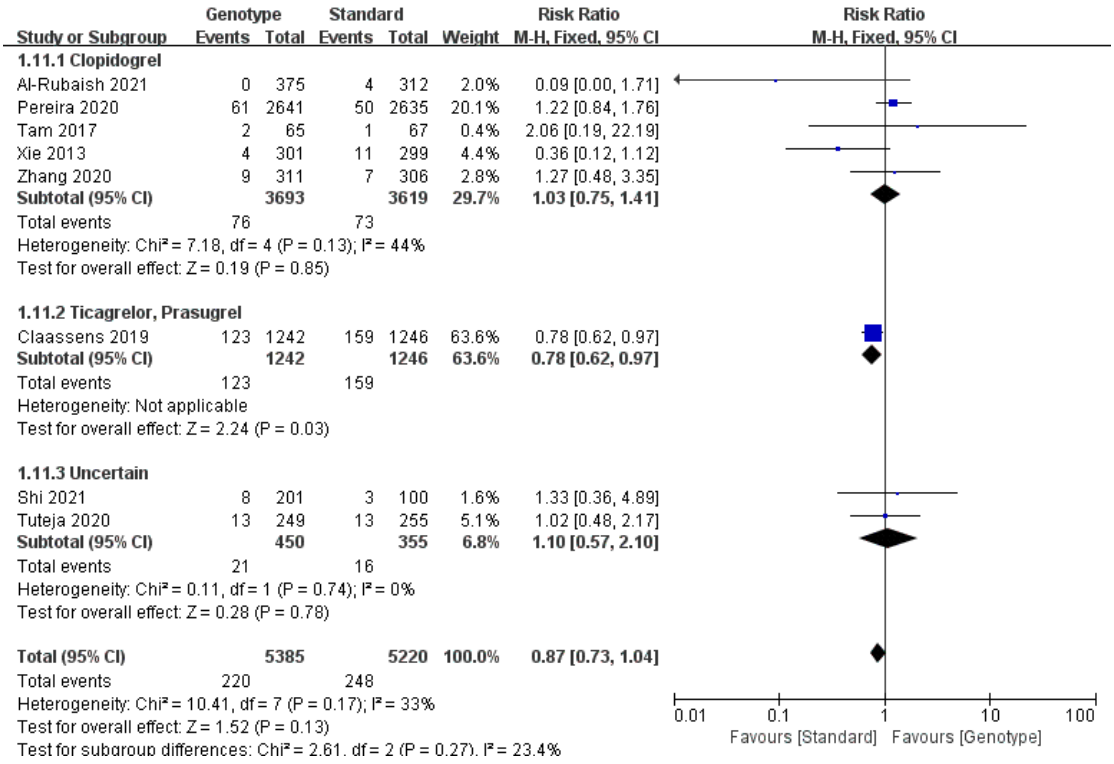


**Figure Appendix 11. Forest plot of subgroup analysis for bleeding events (BARC type 2,3,5) according to treatment strategy in standard treatment group**

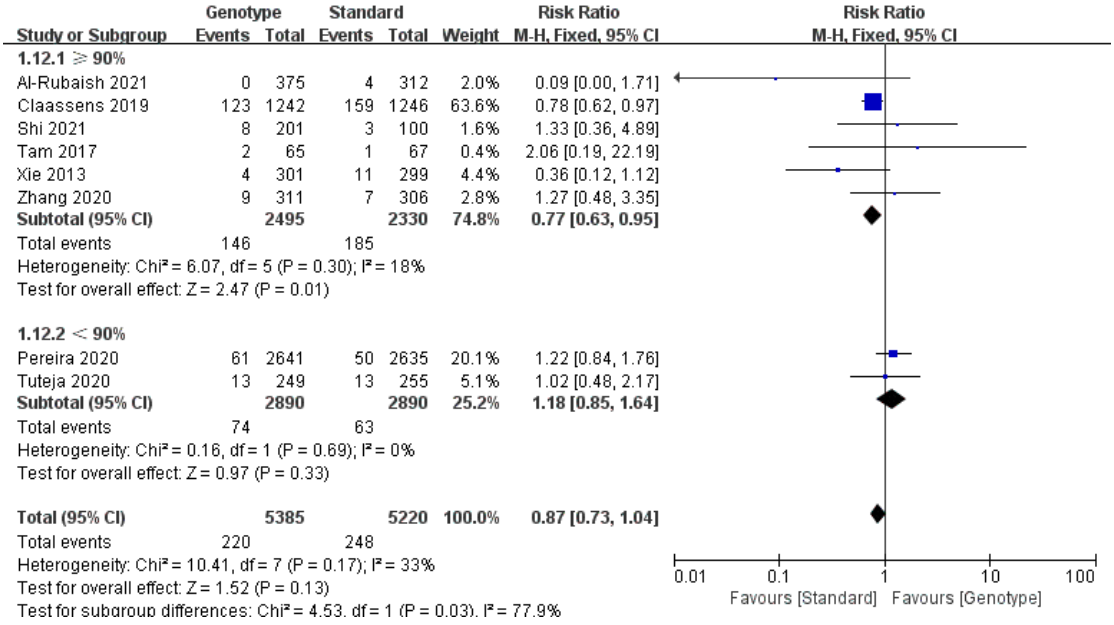


**Figure Appendix 12. Forest plot of subgroup analysis for bleeding events (BARC type 2,3,5) according to proportion of patients with ACS**

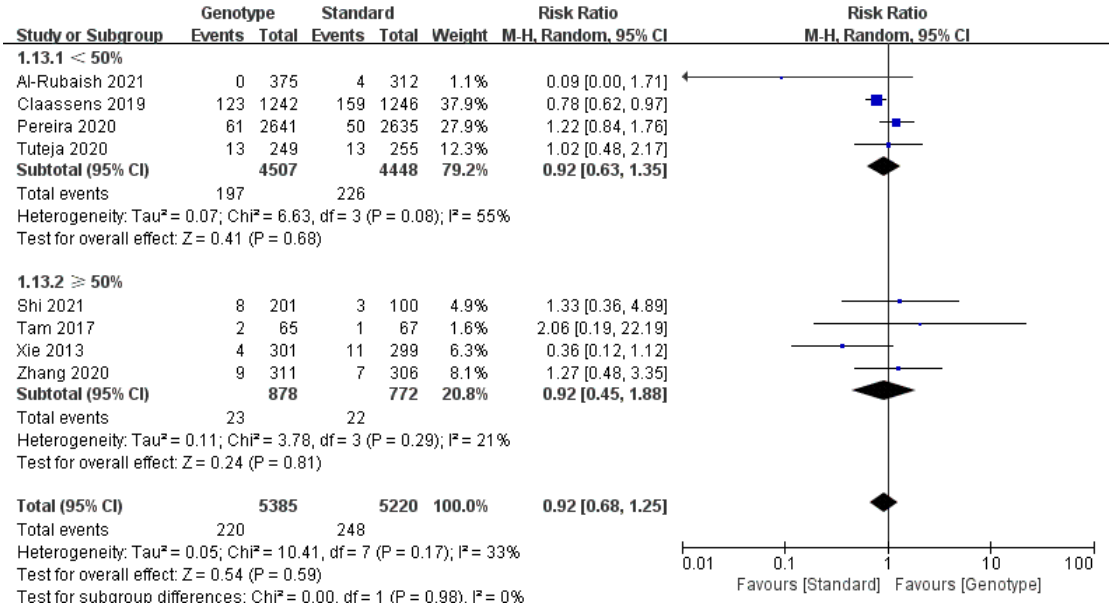


**Figure Appendix 13. Forest plot of subgroup analysis for bleeding events (BARC type 2,3,5) according to proportion of LOF allele carriers in GG group**