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SYSTEMATIC REVIEW AND META-ANALYSIS

Efficacy and Safety of Long-Term Antithrombotic Strategies in Patients With Chronic Coronary Syndrome: A Network Meta-analysis of Randomized Controlled Trials

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BACKGROUND: Long-term antithrombotic strategies for patients with chronic coronary syndrome with high-risk factors represent an important treatment dilemma in clinical practice. Our aim was to conduct a network meta-analysis to evaluate the efficacy and safety of long-term antithrombotic strategies in patients with chronic coronary syndrome.

METHODS AND RESULTS: Four randomized studies were included (n=75167; THEMIS [Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study], COMPASS [Cardiovascular Outcomes for People Using Anticoagulation Strategies], PEGASUS-TIMI 54 [Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54], and DAPT [Dual Antiplatelet Therapy]). The odds ratios (ORs) and 95% CIs) were calculated as the measure of effect size. The results of the network meta-analysis showed that, compared with aspirin monotherapy, the ORs for trial-defined major adverse cardiovascular and cerebrovascular events were 0.86; (95% CI, 0.80–0.93) for ticagrelor plus aspirin, 0.89 (95% CI, 0.78–1.02) for rivaroxaban monotherapy, 0.74 (95% CI, 0.64–0.85) for rivaroxaban plus aspirin, and 0.72 (95% CI, 0.60,–0.86) for thienopyridine plus aspirin. Compared with aspirin monotherapy, the ORs for trial-defined major bleeding were 2.15 (95% CI, 1.78–2.59]) for ticagrelor plus aspirin, 1.51 (95% CI, 1.23–1.85) for rivaroxaban monotherapy, and 1.68 (95% CI, 1.37–2.05) for rivaroxaban plus aspirin. For death from any cause, the improvement effect of rivaroxaban plus aspirin was detected versus aspirin monotherapy (OR, 0.76; 95% CI, 0.65–0.90), ticagrelor plus aspirin (OR, 0.79; 95% CI, 0.66–0.95), rivaroxaban monotherapy (OR, 0.82; 95% CI, 0.69–0.97), and thienopyridine plus aspirin (OR, 0.58; 95% CI, 0.41–0.82) regimens.

CONCLUSIONS: All antithrombotic strategies combined with aspirin significantly reduced the incidence of major adverse cardiovascular and cerebrovascular events and increased the risk of major bleeding compared with aspirin monotherapy. Considering the outcomes of all ischemic and bleeding events and all-cause mortality, rivaroxaban plus aspirin appears to be the preferred long-term antithrombotic regimen for patients with chronic coronary syndrome and high-risk factors.

Key Words: chronic coronary syndrome ■ long-term antithrombotic strategies ■ previous percutaneous coronary intervention

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CLINICAL PERSPECTIVE

What Is New?

- For all-cause mortality, the improvement effect of rivaroxaban plus aspirin was detected versus aspirin monotherapy, ticagrelor plus aspirin, rivaroxaban monotherapy, and thienopyridine plus aspirin regimens in patients with chronic coronary syndrome.

What Are the Clinical Implications?

- Rivaroxaban plus aspirin appears to be the preferred long-term antithrombotic regimen for patients with chronic coronary syndrome with high-risk factors.

Nonstandard Abbreviations and Acronyms

CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events
CCS	chronic coronary syndrome
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies trial
DAPT	Dual Anti-platelet Therapy study
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria
MACEs	major adverse cardiovascular and cerebrovascular events
PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 trial
PLATO	Platelet Inhibition and Patient Outcomes trial
POPular AGE	Clopidogrel Versus Ticagrelor or Prasugrel in Patients Aged 70 Years or Older With Non–ST-Elevation Acute Coronary Syndrome: The Randomised, Open-Label, Non-Inferiority Trial
SUCRA	surface under the cumulative ranking
THEMIS	Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study

Chronic coronary syndrome (CCS) includes patients with suspected or definite stable coronary artery disease and acute coronary syndrome (ACS) entering the chronic phase. According to the guidelines of the European Society of Cardiology published in 2019,[1] CCS is divided into 6 types, of which type 3 is defined as asymptomatic and symptomatic patients with stabilized symptoms <1 year after ACS or patients with recent revascularization; type 4 is defined as asymptomatic and symptomatic patients >1 year after the initial diagnosis or revascularization; and type 6 CCS is defined as asymptomatic subjects in whom coronary artery disease is detected at screening. Briefly, all 3 types are considered as definite coronary artery disease that is currently in a chronic or stable state. Although patients with CCS have a lower incidence of ischemic events or recurrence than patients with ACS, these patients are still at risk of myocardial infarction (MI), ischemic stroke, and cardiovascular death. For patients with stable coronary artery disease, dual antiplatelet therapy is generally administered for 6 months after percutaneous coronary intervention (PCI), and the treatment duration for patients with ACS is generally 12 months.[2] However, for patients with CCS, an important challenge in clinical practice and research is to develop strategies that will achieve fewer ischemic events without increasing bleeding events.

Aspirin irreversibly inhibits platelet cyclooxygenase-1, thereby preventing thromboxane production,[3] a question worth exploring is whether patients undergoing PCI or ACS continue to use aspirin monotherapy after the default dual antiplatelet treatment period and what treatments are considered the optimal choice. To date, many large-scale clinical studies have selected various antithrombotic strategies for patients with chronic coronary syndrome, such as P2Y12 inhibitor monotherapy,[4-6] dual antiplatelet regimens,[7-10] anticoagulant monotherapy,[11] and an anticoagulant combined with antiplatelet regimen,[12,13] all of which exhibit good efficacy in preventing ischemic events. However, these strategies increase the incidence of bleeding events to some extent compared with aspirin monotherapy, and a mutual comparison of these antithrombotic strategies has not been conducted. Therefore, the aim of this network meta-analysis is to evaluate the efficacy and safety of long-term antithrombotic strategies in patients with chronic coronary syndrome.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines (Table S1) were used in this systematic review and network meta-analysis.[14] The data that support the findings of this study are available from the corresponding author on reasonable request.

Data Sources

The Medline, EMBASE, and Cochrane database were independently searched by 2 reviewers. The search terms were "coronary artery disease," "coronary heart disease," "chronic coronary syndrome," "myocardial infarction," "acute coronary syndrome," "percutaneous coronary intervention," "coronary artery bypass grafting," "coronary stenting" paired with "aspirin," "clopidogrel," "prasugrel," "ticagrelor," "P2Y12 inhibitors," "thienopyridine," "warfarin," "vitamin K antagonists," "dabigatran," "rivaroxaban," "apixaban," "edoxaban," "factor Xa inhibitor," or "new oral anticoagulants." Searches for studies published up to August 2020 were conducted using subject heading terms, key words, and titles or abstracts, and all identified abstracts were reasonably screened (Table S2).

Study Selection

An initial eligibility screen of all retrieved titles and abstracts was conducted, and original studies were included in our network meta-analysis if they met the following criteria: (1) randomized controlled trial (RCT) accompanied by 2 or more arms; (2) subjects who experienced coronary revascularization <1 year but were asymptomatic or stable; (3) subjects analyzed >1 year after revascularization; (4) asymptomatic or stable subjects who underwent coronary angiography and showed at least one vessel with stenosis >50% but did not undergo revascularization; (5) antithrombotic therapy, including anticoagulant or antiplatelet therapy; (6) reported major cardiovascular and cerebrovascular events (MACEs) and major bleeding accompanied by follow-up events for more than 12 months.

The following exclusion criteria were used: (1) the default dual antiplatelet treatment duration was not completed, and (2) subjects who used oral anticoagulants or low molecular weight heparin for a long time before grouping.

Data Extraction

The methods of data extraction were outlined in our previous study.[15] All selected papers were reviewed by 2 reviewers who independently extracted the data. The following data were extracted: the study design, baseline characteristics, interventions, and outcomes. Following the extraction of relevant data by the 2 reviewers, data were examined for possible inconsistencies that were then resolved by discussion, and if consensus was unable to be reached, a third author was consulted. Studies were not conducted directly on humans, and ethical approval was therefore unnecessary.

Quality Assessment

Two reviewers used the 7 domains of the Cochrane risk-of-bias tool to evaluate the quality of the included studies on the basis of the following criteria: randomization sequence generation, concealment of randomization sequence, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Studies were classified as having a low, high, or unclear risk of bias for each item, as suggested in the Cochrane Handbook.[16]

Outcome Measures

The primary efficacy outcome was trial-defined MACEs, which was often defined as a combination of death from any cause or cardiovascular death, MI, and stroke; secondary efficacy outcomes were individual components of MACEs. The primary safety outcomes were trial-defined major bleeding events and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria–defined severe bleeding; secondary safety outcomes were trial-defined minor bleeding events, GUSTO-defined moderate bleeding, and intracranial hemorrhage.

Statistical Analysis

A standard paired meta-analysis was performed using the DerSimonian-Laird random-effects model. The odds ratios (ORs) and 95% CIs served as a summary statistic. Statistically significant results were those results where the 95% CI did not include 1. The heterogeneity test was completed using the χ^2-based Q-test, and a P value <0.1 was considered to indicate heterogeneous results, whereas a P value >0.1 was considered to indicate a lack of heterogeneity. If heterogeneity was observed in the results, the degree of heterogeneity was determined using the I^2 test (I^2=0–25%, no heterogeneity; I^2=25–50%, moderate heterogeneity; I^2=50–75%, substantial heterogeneity; and I^2=75–100%, extreme heterogeneity).

A network meta-analysis was performed using the frequentist approach. The OR (95% CI) served as a summary statistic. We calculated the surface under the cumulative ranking (SUCRA) value to evaluate the rankings of treatment strategies. SUCRA values

are presented as the percentage of the area under the cumulative rank probability curve and the entire plane of the plot. A smaller SUCRA value resulted in a lower incidence of adverse outcomes, indicating better efficacy of the treatment regimen. An examination of the assumption in the network meta-analysis includes homogeneity, transitivity, and consistency. The examination of the homogeneity assumption was performed through direct treatment comparisons, and thus the χ^2-based Q-test and I^2 test were used for the analysis. The transitivity assumption was assessed by comparing the distribution of clinical variables, which were considered interfering factors that might affect the outcomes. The consistency assumption was tested to verify the feasibility of mixed comparisons (ie, no inconsistency in the evidence between direct and indirect treatment comparisons). A design-by-treatment approach was used to assess inconsistency in the entire analytical network,[17] and a loop-specific approach and node-splitting approach were used to assess local inconsistency. In addition, subgroup network meta-analyses were conducted of subjects with or without a history of PCI (prespecified) or with or without a history of prior MI to assess whether the results of the study were affected by the study characteristics (effect modifiers). The verified data were analyzed using Stata software (version 15.0; Stata Corporation, College Station, TX), REVMAN software (version 5.3; Cochrane Collaboration, Oxford, UK) and Word Processing System (version 2.5; Beijing, China).

RESULTS

Literature Search

The literature search identified 945 records in Medline, 1564 records in EMBASE, and 9 records in the Cochrane database (Figure S1). After checking for duplicates, 18 unique and full-text published articles remained. A brief review of the abstract and manuscript of these 18 articles resulted in 4 studies that were appropriate for a detailed review; all 4 studies (THEMIS [Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study], COMPASS [Cardiovascular Outcomes for People Using Anticoagulation Strategies], PEGASUS-TIMI 54 [Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54], and DAPT [Dual Antiplatelet Therapy]) were included in the network meta-analysis.[7,9,10,13] The remaining 14 articles were excluded because they did not meet the inclusion criteria or met the exclusion criteria (Table S2). Briefly, 2 studies[18,19] were excluded because they described an unplanned post hoc analysis that undermined the randomization principle; 5 studies[20-24] were excluded because the end point of interest was not reported; 1 study[25] was excluded because some of the included subjects were patients without stable coronary artery disease; 5 studies[26-30] were excluded because patients with ACS were not rerandomized at follow-up after the end of default dual antiplatelet therapy, that is, the follow-up process after the nodes meeting this inclusion criterion had disrupted the randomization principle; and 1 study[31] was excluded because of noncompliance with the standard dual antiplatelet principle.

Characteristics of the Included Studies and Patients

The main characteristics of these studies are reported in Table S3. These RCTs were published between 2014 and 2019; the follow-up period ranged from 18.0 to 39.9 months, and all 4 RCTs included in this network meta-analysis were randomized, double-blind, placebo-controlled trials. In the THEMIS and PEGASUS-TIMI 54 studies, ticagrelor was used as an intervention drug. Rivaroxaban was used as the intervention in the COMPASS study. In the DAPT study, thienopyridines were used as intervention drugs, including clopidogrel and prasugrel. All patients were treated with aspirin, except for patients included in one arm of the COMPASS trial, who were treated with rivaroxaban monotherapy.

The main clinical features of the patients are shown in Table S4. A total of 75 167 patients were included in this network meta-analysis, and the sample size of a single RCT ranged from 9961 to 21 162. The overall prevalence of a history of PCI ranged from 57.8% to 100%. The mean age ranged from 61.6 to 69.0 years, 20.0% to 31.6% of patients were female, and 62.9% to 91.4% were White. With the exception of the DAPT trial, which did not report the number of vessels involved, more than 55% of patients had multiple coronary artery diseases, and most patients were at high risk of thromboembolic and bleeding events. Risk factors for atherosclerotic cardiovascular disease, such as hypertension, dyslipidemia, and diabetes mellitus, were common in the analyzed patients.

Quality of Studies

The quality assessment of the included studies is presented in Figure S2 and Table S5. All studies mentioned the use of randomized allocation, and the use of computer or network system method for randomization of the groups was considered a low risk of bias. The allocation concealment method of all studies was completed through an interactive voice response or network response system and was considered a low risk of bias. All trials were double-blind, the outcome

indicators were objective end points, a subjective evaluation was not performed, and the implementation of the blinding method would not be destroyed; thus, the performance bias and the detection bias of all trials were considered low risks. Completion rates for all trials were >90%, and missing data were adequately explained; therefore, incomplete outcome data for all trials were considered a low risk of bias. Although all trials were sponsored by pharmacists, these individuals were not involved in the analysis of the data, and thus the possible effect of the pharmacists on the results of all trials was considered a low risk of bias. All RCTs were judged to be at a low risk of bias.

Results of Homogeneity, Transitivity, and Consistency Analyses

The homogeneity assumption was $P_{heterogeneity}$=0.440 (I^2=0%) for trial-defined MACEs (Figure S3), $P_{heterogeneity}$ = 0.724 (I^2=0%) for all-cause death, $P_{heterogeneity}$=0.111 (I^2=60.6%) for cardiovascular death, $P_{heterogeneity}$=0.954 (I^2=0%) for MI, $P_{heterogeneity}$=0.824 (I^2=0%) for stroke, $P_{heterogeneity}$=0.646 (I^2=0%) for trial-defined major bleeding events, and $P_{heterogeneity}$=0.520 (I^2=0%) for intracranial hemorrhage. The results of the transitivity assessment, which are presented in a combined histogram, showed that with the exception of the proportion of PCI history, the mean age, the proportion of hypertension, the proportion of diabetes mellitus, and the proportion of multivessel coronary arteries were relatively similar across compared treatment groups (Figure S4). In this network analysis, because all arms in the included studies were directly compared and a mixed comparison was not conducted (ie, no source of inconsistency was identified), global inconsistency testing and the node-splitting approach were not necessary. In addition, only 1 loop was present in the structure of this network meta-analysis, and the loop belonged to a multiarm trial of the same study; thus, evidence inconsistency did not exist.

Structure of Network Meta-Analysis

Figure 1 shows the network of treatment regimens used in the analysis of the major efficacy outcome and major safety outcomes. We compared 5 treatment strategies: aspirin, ticagrelor plus aspirin, rivaroxaban plus aspirin, rivaroxaban, and thienopyridine plus aspirin. We used aspirin as a reference because all 5 RCTs studied this regimen.

Efficacy Outcomes

The results of the network meta-analysis showed that, with the exception of rivaroxaban monotherapy (OR, 0.89; 95% CI, 0.78–1.02), ticagrelor plus aspirin (OR, 0.86; 95% CI, 0.80–0.93), rivaroxaban plus aspirin (OR, 0.74; 95% CI, 0.64–0.85), and thienopyridine plus aspirin (OR, 0.72; 95% CI, 0.60–0.86) regimens all significantly reduced the trial-defined MACEs compared with aspirin monotherapy (Figure 2 and Table S6). In addition, rivaroxaban plus aspirin significantly reduced the incidence of MACEs compared with rivaroxaban monotherapy (OR, 0.83; 0.72–0.96) regimen. For death from any cause, the improvement effect of rivaroxaban plus aspirin was detected versus aspirin monotherapy (OR, 0.76; 95% CI, 0.65–0.90), ticagrelor plus aspirin (OR, 0.79; 95% CI, 0.66–0.95), rivaroxaban monotherapy (OR, 0.82; 95% CI, 0.69–0.97), and thienopyridine plus aspirin (OR, 0.58; 95% CI, 0.41–0.82) regimens. Rivaroxaban plus aspirin seemed to reduce the incidence of cardiovascular death compared with aspirin monotherapy (OR, 0.75; 95% CI, 0.55–1.01) and rivaroxaban monotherapy (OR, 0.78; 95% CI, 0.58–1.06) regimens, although not statistically significant.

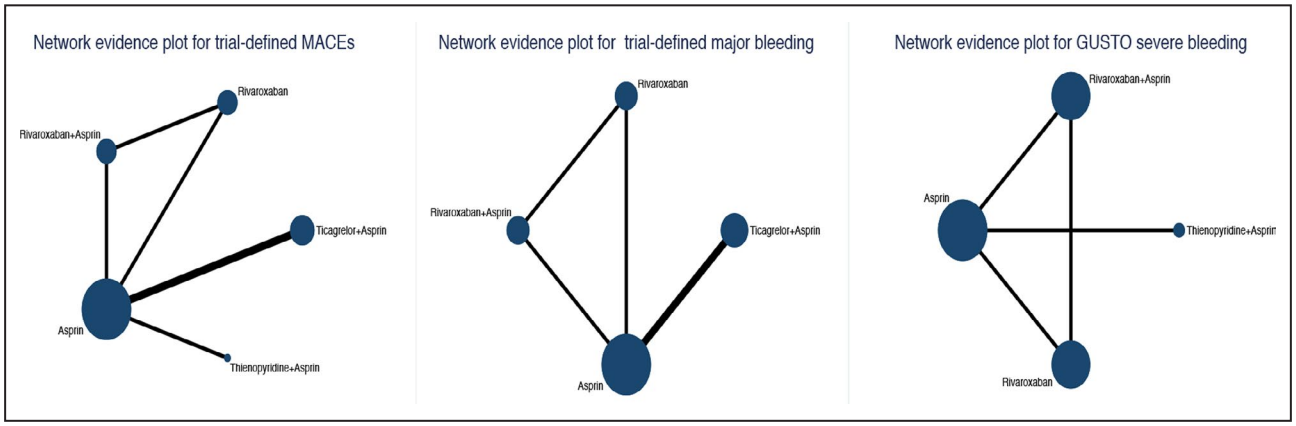

Figure 1. Evidence structure of eligible comparisons for network meta-analysis.
Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible RCTs. The width of the lines represents the cumulative number of RCTs for each pairwise comparison and the size of every node is proportional to the number of randomized participants (sample size). GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria; MACEs, major adverse cardiovascular and cerebrovascular events; and RCTs, randomized controlled trials.

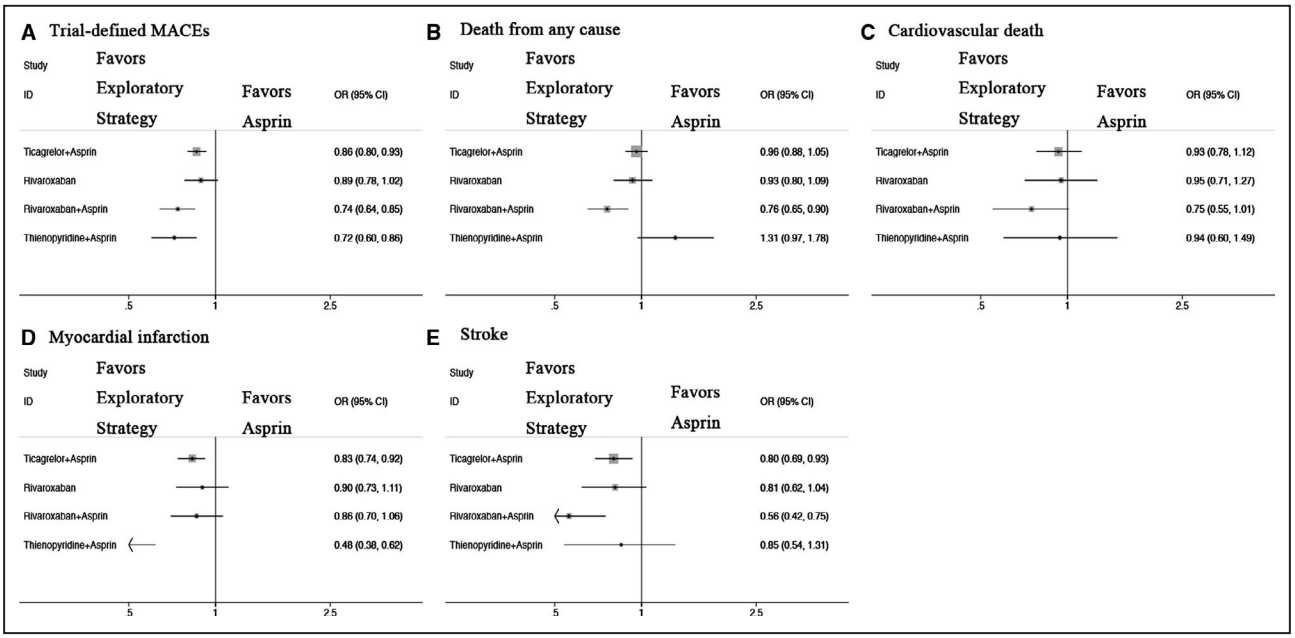

Figure 2. Forest plots for efficacy outcomes.
A, Trial-defined MACEs. **B**, Death from any cause. **C,** Cardiovascular death. **D,** Myocardial infarction. **E,** Stroke. MACEs indicates major adverse cardiovascular and cerebrovascular events; and OR, odds ratio.

Compared with aspirin monotherapy, both ticagrelor plus aspirin (OR, 0.83; 95% CI, 0.74–0.92) and thienopyridine plus aspirin (OR, 0.48; 95% CI, 0.38–0.62) regimens significantly reduce MI. Compared with aspirin monotherapy, ticagrelor plus aspirin (OR, 0.80; 95% CI, 0.69–0.93) and rivaroxaban plus aspirin (OR, 0.56; 95% CI, 0.42–0.75) regimens significantly reduced stroke, and the improvement effect of rivaroxaban plus aspirin was detected as compared with ticagrelor plus aspirin (OR, 0.70; 95% CI, 0.51–0.97) and rivaroxaban monotherapy (OR, 0.70; 95% CI, 0.52,0.94) regimens.

Safety Outcomes

The results of the network meta-analysis showed that, compared with aspirin monotherapy, all exploratory strategies including ticagrelor plus aspirin (OR, 2.15; 95% CI, 1.78–2.59]), rivaroxaban monotherapy (OR, 1.51; 95% CI, 1.23–1.85) and rivaroxaban plus aspirin (OR, 1.68; 95% CI, 1.37–2.05) increased major bleeding events (Figure 3 and Table S6). However, rivaroxaban (OR, 1.54; 95% CI, 0.95–2.50), rivaroxaban plus aspirin (OR, 1.06; 95% CI, 0.63–1.79), and thienopyridine plus aspirin (OR, 1.45; 95% CI, 0.85–2.45) regimens did not increase the incidence of GUSTO-defined severe bleeding compared with the aspirin monotherapy. Compared with aspirin monotherapy, ticagrelor plus aspirin (OR, 3.39; 95% CI, 2.07–5.57), rivaroxaban monotherapy (OR, 1.56; 95% CI, 1.38–1.77) and rivaroxaban plus aspirin (OR, 1.77; 95% CI, 1.57–2.00) regimens increased minor bleeding events. And rivaroxaban monotherapy (OR, 1.63; 95% CI, 1.07–2.49), rivaroxaban plus aspirin (OR, 2.05; 95% CI, 1.20–3.49), and thienopyridine plus aspirin (OR, 1.68; 95% CI, 1.16–2.43) regimens all increased GUSTO-defined moderate bleeding events versus aspirin monotherapy. With the exception of rivaroxaban plus aspirin (OR, 1.12; 0.64–1.97), both ticagrelor plus aspirin (OR, 1.41; 95% CI, 1.05–1.90) and rivaroxaban monotherapy (OR, 1.88; 95% CI, 1.13–3.12) regimens significantly increased the intracranial hemorrhage compared with aspirin monotherapy.

Ranking of Treatment Strategies

Table 1 shows the SUCRA values for efficacy outcomes and safety outcomes. A smaller SUCRA value indicates a lower incidence of adverse outcomes, indicating better efficacy of the treatment regimen. The rivaroxaban plus aspirin regimen achieved the greatest number of best performance rankings for all efficacy outcomes (SUCRA value, 15.9 for MACEs, 9.8 for cardiovascular death, 51.0 for MI, and 2.3 for stroke), while aspirin unexpectedly achieved the greatest number of worst performance rankings (98.8 for MACEs, 74.6 for cardiovascular death, 94.0 for MI, and 93.0 for stroke). Among all safety outcomes, aspirin was again unexpectedly the regimen with the largest number of best performance rankings (0 for major bleeding, 18.0 for severe bleeding, 0 for minor bleeding, 0.6 for moderate bleeding, and 12.0 for intracranial hemorrhage), while the ticagrelor plus aspirin regimen appeared to be the regimen with the largest number of worst performance

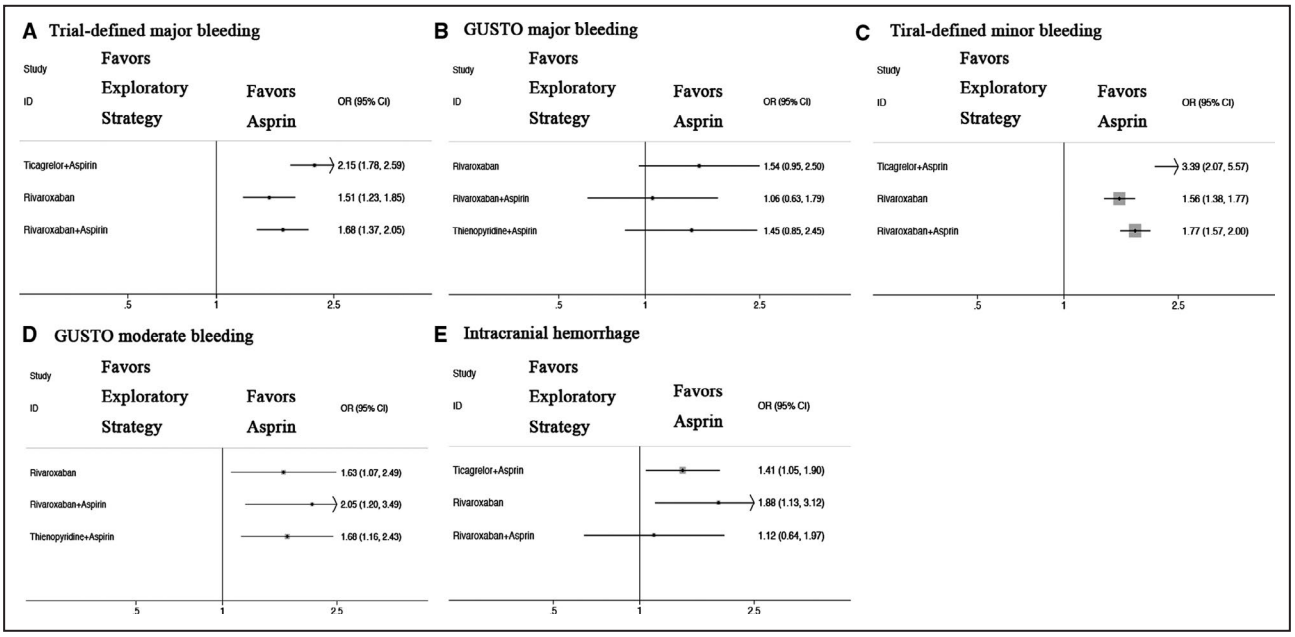

Figure 3. Forest plots for safety outcomes.
A, Trial-defined major bleeding. **B,** GUSTO major bleeding. **C,** Trial-defined minor bleeding. **D,** GUSTO moderate bleeding. **E,** Intracranial hemorrhage. GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria; and OR, odds ratio.

rankings (98.5 for major bleeding, 99.8 for minor bleeding, and 64.1 for intracranial hemorrhage). Notably, the best regimen for preventing all-cause mortality was the rivaroxaban plus aspirin regimen (0,4), while the worst regimen was the thienopyridine plus aspirin regimen (97.5). The cumulative rank probability plots showing the efficacy outcomes and safety outcomes for each treatment regimen are shown in Figure S5.

Subgroup Analysis

The subgroup analysis of whether subjects undergoing PCI (Figure S6 and Table S7) confirmed that in the PCI subgroup, ticagrelor plus aspirin (OR, 0.84; 95% CI, 0.73–0.96),[32,33] rivaroxaban plus aspirin (OR, 0.72; 95% CI, 0.60–0.87),[34] and thienopyridine plus aspirin (OR, 0.72; 95% CI, 0.60–0.86) regimens still reduced the occurrence of MACEs

Table. SUCRA Values* for Each Treatment Regimen and Outcomes

Value		Treatment Regimen									
		Aspirin		Ticagrelor + Aspirin		Rivaroxaban + Aspirin		Rivaroxaban		Thienopyridine + Aspirin	
Efficacy outcome											
Trial-defined MACEs		98.8		57.6		15.9		66.1		11.6	
Cardiovascular death		74.6		51.5		9.8		59.8		54.4	
MI		94.0		40.1		51.0		64.9		0	
Stroke		93.0		46.3		2.3		49.9		58.5	
All-cause death		66.8		45.9		0.4		39.3		97.5	
Safety outcome											
Major†	Severe bleeding‡	0	18.0	98.5	NA	63.7	28.6	37.7	81.9	NA	71.5
Minor†	Moderate bleeding‡	0	0.6	99.8	NA	66.4	85.3	33.9	52.9	NA	61.2
Intracranial hemorrhage		12.0		64.1		30.5		93.4		NA	

MACEs indicates major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; NA, not available; and SUCRA, surface under the cumulative ranking.

*SUCRA values are presented as percentage of area under the cumulative rank probability curve and the entire plane of the plot. The smaller the SUCRA value, the less incidence of adverse outcomes, which means the better the treatment regimen performance.

†Major/minor bleeding is defined by the respective trials.

‡Severe/moderate bleeding is defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria.

versus aspirin monotherapy, and the efficacy ranking based on SUCRA values was the same as the overall population. In the PCI subgroup, ticagrelor plus aspirin (OR, 1.82; 95% CI, 1.33–2.49), and rivaroxaban plus aspirin (OR, 1.73; 95% CI, 1.34–2.24) regimens still increased the incidence of major bleeding events versus aspirin monotherapy, and the efficacy rankings based on SUCRA values were also the same as the overall population. In the non-PCI subgroup, compared with aspirin monotherapy, the rivaroxaban plus aspirin (OR, 0.76; 95% CI, 0.59–0.98) regimen still reduced the occurrence of MACEs, the ticagrelor plus aspirin (OR, 0.90; 0.77–1.06) regimen did not significantly reduce the occurrence of MACEs. The safety rankings based on SUCRA values were also the same as the overall population. In the non-PCI subgroup, ticagrelor plus aspirin (OR, 2.32; 1.67–3.22) and rivaroxaban plus aspirin (OR, 1.61; 1.16–2.21) regimens still increased the incidence of major bleeding events versus aspirin monotherapy. The rankings of SUCRA values was also the same as in the overall population.

The subgroup analysis of whether subjects had a history of prior MI (Figure S7 and Table S8) confirmed that in the prior MI subgroup, both ticagrelor plus aspirin (OR, 0.84; 95% CI, 0.71–0.99), rivaroxaban plus aspirin (OR, 0.74; 95% CI, 0.60–0.91) and thienopyridine plus aspirin (OR, 0.69; 95% CI, 0.48–0.98) regimens still reduced the occurrence of MACEs versus aspirin monotherapy, and the efficacy ranking based on SUCRA values was the same as the overall population. In the prior MI subgroup, ticagrelor plus aspirin (OR, 2.27; 95% CI, 1.67–3.09), and rivaroxaban plus aspirin regimens (OR, 1.64; 95% CI, 1.27–2.11) still increased the incidence of major bleeding events versus aspirin monotherapy, and the efficacy rankings based on SUCRA values were also the same as the overall population. In the non–prior MI subgroup, compared with aspirin monotherapy, the ticagrelor plus aspirin (OR, 0.89; 95% CI, 0.68–1.16), rivaroxaban plus aspirin (OR, 0.74; 95% CI, 0.52–1.03) and thienopyridine plus aspirin (OR, 0.74; 95% CI, 0.50–1.07) regimens appeared to reduce the incidence of MACEs, although not statistically significant. The safety rankings based on SUCRA values were also similar to the overall population. In the non–prior MI subgroup, ticagrelor plus aspirin (OR, 2.08; 95% CI, 1.50–2.87) and rivaroxaban plus aspirin (OR, 1.76; 95% CI, 1.20–2.58) regimens still increased the incidence of major bleeding events versus aspirin monotherapy. The rankings of SUCRA values were also the same as in the overall population. Overall, the results of the subgroup analysis were generally consistent with the overall population.

DISCUSSION

The main findings of this network meta-analysis are listed below.

1. For regimens based on aspirin, the addition of any antithrombotic drug reduces the incidence of MACEs compared with aspirin alone.
2. In the safety evaluation, other antithrombotic regimens increase the risk of major bleeding events compared with aspirin monotherapy, and ticagrelor plus aspirin regimen appears to have low safety.
3. Considering the outcomes of all ischemic and bleeding events and all-cause mortality, rivaroxaban plus aspirin appears to be the preferred long-term antithrombotic regimen for patients with CCS and high-risk factors. However, rivaroxaban monotherapy should be avoided.

Comparison of Antithrombotic Strategies With Anticoagulants and Antiplatelet Agents

Both anticoagulants and antiplatelet drugs play an important role in antithrombotic therapy. According to a previous meta-analysis,[35] the vitamin K antagonist (warfarin) plus aspirin regimen had an additional benefit in preventing ischemic events compared with the aspirin monotherapy. However, its clinical application was limited because anticoagulant therapy increased severe bleeding events, including intracranial hemorrhage. The COMPASS study[13] published in 2017 revealed advantages of the new oral anticoagulant (rivaroxaban) plus aspirin regimen compared with the aspirin-only regimen in terms of preventing ischemic events, and although it also increased the risk of major bleeding, it did not increase intracranial hemorrhage and fatal bleeding. The results of this network meta-analysis were based on odds ratios (95% CIs) and rankings of the efficacy and safety based on SUCRA values. Of all the antithrombotic strategies, except for the outcome of MI, rivaroxaban plus aspirin seemed to be the best in terms of anti-ischemia. And it also reduced all-cause mortality, suggesting that increased bleeding does not offset the benefits of reduced ischemic events. Rivaroxaban plus aspirin significantly reduced all-cause mortality compared with all other antithrombotic regimens, which further indicated that the clinical net benefit of rivaroxaban combined with aspirin was the highest among all antithrombotic strategies. Moreover, in terms of the prevention of cerebrovascular events, the rivaroxaban plus aspirin regimen significantly reduced the incidence of ischemic events without increasing bleeding events

compared with aspirin monotherapy. Unexpectedly, both GUSTO-defined severe bleeding events and intracranial hemorrhage were more frequent with the rivaroxaban alone than with rivaroxaban plus aspirin, which is difficult to explain. This may be attributable to an imbalance in baseline levels of some factors between groups.

Antithrombotic Strategies With or Without Aspirin

Aspirin plays an important role in the secondary prevention of atherosclerotic cardiovascular disease.[3,36] However, during the long-term antithrombotic treatment of chronic coronary syndrome, controversy exists regarding whether aspirin is the first choice or whether aspirin must be included in dual antithrombotic therapy. A previous RCT (CAPRIE [Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events]) showed that the long-term use of clopidogrel in patients with atherosclerotic vascular disease was more effective at reducing the overall risk of ischemic stroke than aspirin.[5] However, a meta-analysis of clopidogrel versus aspirin alone for stable coronary artery disease showed no significant differences in ischemic and bleeding events.[37] A randomized multicenter trial[6] published in 2018 did not reveal an advantage of long-term oral administration of ticagrelor alone compared with aspirin in ischemic and bleeding events in patients after stent implantation. In our network meta-analysis, there is no direct comparison between aspirin and P2Y12 receptor inhibitors. Aspirin combined with P2Y12 receptor inhibitors improved vascular events compared with aspirin monotherapy, but the overall improvement seemed to be less effective than rivaroxaban combined with aspirin, with lower safety compared with aspirin alone and rivaroxaban combined with aspirin. The effect of rivaroxaban alone was similar to that of aspirin alone in anti-ischemic events, while rivaroxaban alone significantly increased the incidence of bleeding events. However, rivaroxaban combined with aspirin caused fewer MACEs than rivaroxaban or aspirin monotherapy. Similar results occurred in all-cause death, cardiovascular death, MI, and stroke, which suggested that combination of low-dose of rivaroxaban on an aspirin basis may be a recommended option for patients with CCS with high-risk factors. Furthermore, this prespecified subgroup analysis, based on whether or not patients undergoing PCI, suggested robustness of the overall outcome, while it revealed that rivaroxaban plus aspirin may be the recommended long-term antithrombotic regimen for patients with CCS regardless of whether they are undergoing PCI.

Antiplatelet Strategies With Thienopyridines Versus Nonthienopyridines

According to the PLATO (Platelet Inhibition and Patient Outcomes) study,[38] ticagrelor has a higher priority than clopidogrel in dual antiplatelet therapy for patients with ACS. However, a recently published RCT, the POPular AGE (Clopidogrel Versus Ticagrelor or Prasugrel in Patients Aged 70 Years or Older With Non–ST-Elevation Acute Coronary Syndrome: The Randomised, Open-Label, Non-Inferiority Trial) study, included elderly (>70 years) and nonischemic high-risk patients with ACS who had a higher risk of bleeding and a lower risk of ischemia than subjects in the PLATO study, and the results favored clopidogrel over ticagrelor.[39] In our network meta-analysis, the thienopyridine plus aspirin seemed to be more safe and even more effective than ticagrelor plus aspirin regimen, which may also suggest that some patients who need prolonged dual antiplatelet therapy are more likely to choose thienopyridine plus aspirin in the choice of antithrombotic drugs. Notably, the thienopyridine plus aspirin regimen increased the incidence of all-cause mortality compared with aspirin monotherapy, and the authors of the study explained this result as an imbalance in the cancer rates at baseline among the included patients, as the thienopyridine plus aspirin regimen group included more patients with cancer and an increased mortality rate, which the authors subsequently balanced. After correction, all-cause mortality was not significantly different between the 2 groups.

Mechanistic Insights Into Antithrombotic Regimens

The most common cause of coronary heart disease is atherosclerosis, and any external factor may induce the rupture of vulnerable plaques or subintimal hemorrhage to promote platelet aggregation[26–28]; therefore, antiplatelet therapy is essential. In addition, coronary stenosis caused by severe atherosclerotic plaques affects the velocity of intravascular blood flow, which tends to be as slow as venous flow, and thus anticoagulation is also needed.[40] This network meta-analysis suggests that the rivaroxaban plus aspirin regimen appears to have a good advantage in preventing ischemia that is even greater than the dual antiplatelet regimen, which may be attributed to the fact that approximately 60% of the patients with chronic coronary syndromes included in this analysis have multivessel coronary artery disease, which is likely to alter the coronary blood flow.

LIMITATIONS

The current analysis has some limitations. First, although clear statistical heterogeneity was not

observed in our network meta-analysis, some clinical heterogeneity was identified among the studies, with potential sources including inclusion and exclusion criteria for patients, dose and course of treatment with drugs, definition of outcomes, and follow-up time, which may affect the interpretation of our results. Second, although the sample size was sufficient for the primary efficacy and safety outcomes, the majority of included patients were White, and thus these data may not apply to other races. Additional data on the efficacy in different races must be refined. In addition, the analysis of some rare and clinically interesting end points, such as stent thrombosis, was not included because these end points were not reported in half of the included studies. Finally, fewer trials with the same exploratory treatment group were included in this analysis, and more studies with more similarities are needed in the future to provide more robust results.

CONCLUSIONS

In terms of long-term antithrombotic strategies for patients with chronic coronary syndrome and high-risk factors, all antithrombotic strategies combined with aspirin significantly reduced the incidence of MACEs and increased the risk of major bleeding events compared with aspirin monotherapy. However, compared with aspirin monotherapy, rivaroxaban plus aspirin reduced all-cause mortality and was the only strategy with a net clinical benefit in preventing cerebrovascular events. In addition, the net clinical benefit of rivaroxaban monotherapy and the ticagrelor plus aspirin regimen might be lower than other strategies. However, additional large-scale clinical trials must be conducted to further determine the appropriate long-term antithrombotic regimens for patients with CCS and high-risk factors. On the basis of the available evidence, our results tend to support the hypothesis that the rivaroxaban plus aspirin regimen has a good application prospect.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S8
Figures S1–S7
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Supplemental Material

Table S1. PRISMA checklist.

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).	6
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.	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.	8-9
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).	9
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.	10-11
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	9-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13
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).	13-16
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
Study selection	9	meta-analysis).	5-6
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.	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).	6
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.	7-8

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
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.	17

Table S2. Retrieval and filtering.

Search code

Data search	Duplicates	Total
1. Pubmed	0	+945
2. Embase	762	+802
3. Cochrane	7	+2
		1749 articles to screen

PubMed/MEDLINE search:

Name search	Search	PubMed query	Results
SCAD or ACS or PCI or CABG	#1	((((((((coronary artery disease[MeSH Major Topic]) OR (coronary artery disease[Title/Abstract])) OR (coronary heart disease[Title/Abstract])) OR (chronic coronary syndrome[Title/Abstract])) OR (myocardial infarction[Title/Abstract])) OR (acute coronary syndrome[Title/Abstract])) OR (percutaneous coronary intervention[MeSH Major Topic])) OR (percutaneous coronary intervention[Title/Abstract])) OR (coronary artery bypass grafting[Title/Abstract])	357,366
Antiplatelet therapy	#2	(((((aspirin[Title/Abstract]) OR (clopidogrel[Title/Abstract])) OR (prasugrel[Title/Abstract])) OR (ticagrelor[Title/Abstract])) OR (P2Y12 inhibitors[Title/Abstract])) OR (thienopyridine[Title/Abstract])	56,967
Anticoagulant therapy	#3	(((((((warfarin[Title/Abstract]) OR (vitamin K antagonists[Title/Abstract])) OR (dabigatran[Title/Abstract])) OR (rivaroxaban[Title/Abstract])) OR (apixaban[Title/Abstract])) OR (edoxaban[Title/Abstract])) OR (factor Xa inhibitor[Title/Abstract])) OR (new oral anticoagulants[Title/Abstract])	33,462

Combined search	#4	#1 AND #2 AND #3	945

OVID/EMBASE Search:

Name search	Search	EMBASE query	Results
SCAD or ACS or PCI or CABG	#1	'coronary artery disease':ab,ti OR 'coronary heart disease':ab,ti OR 'chronic coronary syndrome':ab,ti OR 'myocardial infarction':ab,ti OR 'acute coronary syndrome':ab,ti OR 'percutaneous coronary intervention':ab,ti OR 'coronary artery bypass graft':ab,ti OR 'coronary stenting':ab,ti	473321
Antiplatelet therapy	#2	aspirin:ab,ti OR clopidogrel:ab,ti OR prasugrel:ab,ti OR ticagrelor:ab,ti OR 'p2y12 inhibitors':ab,ti OR thienopyridine:ab,ti	88420
Anticoagulant therapy	#3	warfarin:ab,ti OR 'vitamin k antagonists':ab,ti OR dabigatran:ab,ti OR rivaroxaban:ab,ti OR apixaban:ab,ti OR edoxaban:ab,ti OR 'factor xa inhibitor':ab,ti OR 'new oral anticoagulants':ab,ti	56111
Combined search	#4	#1 AND #2 AND #3	1564

Cochrane Database search:

Name search	Search	Cochrane query	Results
SCAD or ACS or PCI or CABG	#3=#1 or #2	#1 - (coronary artery disease):ti,ab,kw OR (coronary heart disease):ti,ab,kw OR (chronic coronary syndrome):ti,ab,kw OR (myocardial infarction):ti,ab,kw OR (acute coronary syndrome):ti,ab,kw" (Word variations have been searched) #2 - (percutaneous coronary intervention):ti,ab,kw OR (coronary artery bypass grafting):ti,ab,kw OR (coronary stenting):ti,ab,kw" (Word variations have been searched)	261
Antiplatelet therapy	#6=#4 or #5	#4 - (aspirin):ti,ab,kw OR (clopidogrel):ti,ab,kw OR (prasugrel):ti,ab,kw OR (ticagrelor):ti,ab,kw OR (P2Y12 inhibitors):ti,ab,kw" (Word variations have been searched) #5 - (thienopyridine):ti,ab,kw" (Word variations have been searched)	112

Anticoagulant therapy	#9=#7 or #8	#7 - (warfarin):ti,ab,kw OR (vitamin K antagonists):ti,ab,kw OR (dabigatran):ti,ab,kw OR (rivaroxaban):ti,ab,kw OR (apixaban):ti,ab,kw" (Word variations have been searched) #8 - (edoxaban):ti,ab,kw OR (factor Xa inhibitor):ti,ab,kw OR (new oral anticoagulants):ti,ab,kw" (Word variations have been searched)	62
Combined search	#10	#3 AND #6 AND #9	9

Articles excluded after full text screening:

Number	Excluded references	Reason for exclusion
18	Berger JS, Abramson BL, Lopes RD, Heizer G, Rockhold FW, Baumgartner I, Fowkes F, Held P, Katona BG, Norgren L, et al. Ticagrelor versus clopidogrel in patients with symptomatic peripheral artery disease and prior coronary artery disease: Insights from the EUCLID trial. VASC MED. 2018;23(6):523-530.	The principle of randomization is broken by post analysis without prior plan (i.e., lack of baseline balance and interaction tests, etc)[41].
19	Eisen A, Harrington RA, Stone GW, Steg PG, Gibson CM, Hamm CW, Price MJ, Prats J, Deliargyris EN, Mahaffey KW, et al. Cangrelor compared with clopidogrel in patients with prior myocardial infarction - Insights from the CHAMPION trials. INT J CARDIOL. 2018;250:49-55.	The principle of randomization is broken by post analysis without prior plan.
20	Alexopoulos D, Despotopoulos S, Xanthopoulou I, Davlouros P. Low-Dose Ticagrelor Versus Clopidogrel in Patients With Prior Myocardial Infarction. J AM COLL CARDIOL. 2017;70(16):2091-2092.	There are no endpoints of interest.
21	Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001-2015.	There are no endpoints of interest.
22	Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, et al. Prasugrel versus clopidogrel for acute	There are no endpoints of interest.

	coronary syndromes without revascularization. N Engl J Med. 2012;367(14):1297-1309.	
23	Orme RC, Parker W, Thomas MR, Judge HM, Baster K, Sumaya W, Morgan KP, McMellon HC, Richardson JD, Grech ED, et al. Study of Two Dose Regimens of Ticagrelor Compared with Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention for Stable Coronary Artery Disease (STEEL-PCI). CIRCULATION. 2018;138(13):1290-1300.	There are no endpoints of interest.
24	Ohman EM, Roe MT, Steg PG, James SK, Povsic TJ, White J, Rockhold F, Plotnikov A, Mundl H, Strony J, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. LANCET. 2017;389(10081):1799-1808.	There are no endpoints of interest.
25	Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J AM COLL CARDIOL. 2007;49(19):1982-1988.	Non stable coronary artery disease patients are included in the included subjects.
26	Bohula EA, Aylward PE, Bonaca MP, Corbalan RL, Kiss RG, Murphy SA, Scirica BM, White H, Braunwald E, Morrow DA. Efficacy and Safety of Vorapaxar With and Without a Thienopyridine for Secondary Prevention in Patients With Previous Myocardial Infarction and No History of Stroke or Transient Ischemic Attack: Results from TRA 2°P-TIMI 50. CIRCULATION. 2015;132(20):1871-1879.	No re-randomization during follow-up after completion of dual antiplatelet therapy.
27	A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. LANCET. 1996;348(9038):1329-1339.	No re-randomization during follow-up after completion of dual antiplatelet therapy.
28	Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011;365(8):699-708.	No re-randomization during follow-up after completion of dual antiplatelet therapy.
29	Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med. 2002;347(13):969-974.	No re-randomization during follow-up after completion of dual

		antiplatelet therapy.
30	Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19.	No re-randomization during follow-up after completion of dual antiplatelet therapy.
31	Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. LANCET. 2018;392(10151):940-949.	It does not conform to the conventional dual antiplatelet principle.

Table S3. Main characteristics of trials included in the meta-analysis.

	Trial Name			
Characteristic	THEMIS	COMPASS	PEGASUS-TIMI 54	DAPT
Initiation	February 10, 2014	March 12, 2013	October, 2010	August 13, 2009
Completion	May 24, 2016	May 10, 2016	May, 2013	July 1, 2011
Publication	September 1, 2019	November 11, 2017	March 14, 2015	November 16, 2014
Design	Prospective, randomised, double-blind, placebo-controlled	Prospective, randomised, double-blind, placebo-controlled	Prospective, randomised, double-blind, placebo-controlled	Prospective, randomised, double-blind, placebo-controlled
Administration method	Patients were assigned to receive ticagrelor at a dose of 90 mg twice daily and later changed to 60 mg twice daily, or placebo alone. And all the patients also received aspirin (75 to 150 mg once daily)	Patients were assigned to receive low-dose rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily) or rivaroxaban alone (5 mg twice daily), or aspirin alone (100 mg once daily)	Patients were assigned receive ticagrelor orally at a dose of 90 mg twice daily, ticagrelor orally at a dose of 60 mg twice daily, or placebo. And all the patients also received aspirin (75 to 150 mg once daily)	Patients were assigned receive clopidogrel at a maintenance dose of 75 mg daily or prasugrel at a maintenance dose of 10 mg daily (with a dose of 5 mg daily. And all the patients also received aspirin (75 to 162mg once daily).
Main inclusion criteria	Patients had a known history of at least one vessel stenosis ≥ 50% after PCI or CABG or angiography, and a history of type 2 diabetes mellitus.	Patients had either myocardial infarction within 20 years, multivessel coronary disease with symptoms or with history of stable or unstable angina, previous multi-vessel PCI, previous multi-vessel CABG, or coronary disease with peripheral arterial disease.	Patients had a spontaneous MI 1 to 3 years.	Patients had undergoing PCI with stent deployment for 12 months and there was no MACEs and major bleeding during this period.
Main exclusion criteria	Patients had a known history of MI or stroke, or patients were receiving dual antiplatelet therapy or anticoagulant therapy.	Patients were receiving dual antiplatelet therapy or anticoagulant therapy.	Patients were receiving dual antiplatelet therapy or anticoagulant therapy.	Patients were receiving dual antiplatelet therapy or anticoagulant therapy.
Efficacy endpoints	The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or stroke. Secondary efficacy outcomes were tested hierarchically according to the following sequence: cardiovascular death, myocardial infarction, ischemic stroke, and death from any cause.	The primary efficacy outcome was a composite consisting of the frst occurrence of stroke, myocardial infarction, or cardiovascular death. These secondary outcomes were a composite of coronary heart disease death, myocardial infarction, ischaemic stroke, or acute limb ischaemia; occurrence of myocardial infarction, ischaemic stroke, cardiovascular death, or acute limb ischaemia; and overall mortality.	The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary end points were cardiovascular death and death from any cause.	The coprimary efficacy end points were the cumulative incidence of definite or probable stent thrombosis (as assessed according to the Academic Research Consortium definitions) and of major adverse cardiovascular and cerebrovascular events (defined as the composite of death, myocardial infarction, or stroke).
Safety endpoints	The primary safety outcome was major bleeding, which was defined according to the TIMI classification.	The primary safety outcome was major bleeding defned as fatal bleeding, symptomatic bleeding into a critical organ or area, surgical site bleeding leading to reoperation, or bleeding leading to hospital visit or admission.	The primary safety end point was TIMI major bleeding. Other safety end points included intracranial hemorrhage and fatal bleeding.	The primary safety end point was the incidence of moderate or severe bleeding during this same period (as assessed according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries [GUSTO] criteria).
Follow-up	39.9 months	23.4 months	33.0 months	18.0 months
Types of CCS	3 or 4	3 or 4	4	4

CABG: coronary-artery bypass grafting, CCS: chronic coronary syndromes, GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria, MACEs: major adverse cardiovascular and cerebrovascular events, MI: myocardial infarction, PCI: percutaneous coronary intervention, TIMI: Thrombolysis in Myocardial Infarction criteria.

Table S4. Main characteristics of patients enrolled among trials included in the meta-analysis.

	Treatment Regimen									
	THEMIS		COMPASS			PEGASUS-TIMI 54			DAPT	
Characteristic	Ticagrelor + Aspirin	Aspirin	Rivaroxaban + Aspirin	Rivaroxaban	Aspirin	Ticagrelor (H) +Aspirin[a]	Ticagrelor (L) + Aspirin[a]	Aspirin	Thienopyridine + Aspirin	Aspirin
No. of participants	9619	9601	8313	8250	8261	7050	7045	7067	5020	4941
Age, mean ±SD, years	66.0 ± 8.1	66.0 ± 8.1	69.0 ± 5.9	69.0 ± 5.9	69.0 ± 5.9	65.4 ± 8.4	65.2 ± 8.4	65.4 ± 8.3	61.8 ± 10.2	61.6 ± 10.1
Female sex, %	31.6	31.1	21.0	20.0	20.0	23.9	23.6	24.3	24.7	26.0
BMI, mean ±SD, kg/m²	29.0 ± 4.8	29.1 ± 5.0	28.4 ± 4.7	28.4 ± 4.6	28.5 ± 4.7	NA	NA	NA	30.5 ± 5.8	30.6 ± 5.8
Current smoker, %	11.0	10.8	20.0	20.0	20.0	16.8	17.1	16.2	24.6	24.7
White race, %	71.1	71.4	62.9	NA	63.6	86.9	86.3	86.7	91.1	91.4
Hypertension, %	92.6	92.4	76.0	76.0	75.0	77.5	77.5	77.6	75.8	74.0
Dyslipidemia, %	87.2	87.1	NA	NA	NA	76.7	76.4	77.1	NA	NA
Diabetes, %	100.0	100.0	37.0	37.0	37.0	31.8	32.8	31.9	31.1	30.1
History, %										
Peripheral artery disease	8.6	9.0	20.0	20.0	20.0	5.3	5.2	5.7	5.8	5.8
Multivessel coronary artery disease	61.9	62.3	63.0	63.0	61.0	58.9	59.5	59.6	NA	NA
PCI	57.8	58.3	60.0	60.0	59.0	83.0	83.5	82.6	100.0	100.0
CABG	22.0	21.6	33.0	31.0	31.0	NA	NA	NA	11.3	11.8

BMI: body mass index, CABG: coronary-artery bypass grafting, NA:not available, PCI: percutaneous coronary intervention, SD: standard deviation. *(L) and (H) indicate low- and high-dose schemes of ticagrelor used in the PEGASUS-TIMI 54 trial.

Table S5. Evaluation of risk of bias of included trials.

	Trial Name			
Risk bias assessment	THEMIS	COMPASS	PEGASUS-TIMI 54	DAPT
Random sequence generation	Randomization codes were generated in blocks of constant size.	A computer-generated randomisation schedule was generated by the Population Health Research Institute and used to allocate participants to treatment.	Randomization was performed with the use of a central computerized telephone or Web-based system.	A computer-generated randomization schedule stratified patients according to the type of stent they had received (drug-eluting vs. bare-metal), hospital site, type of thienopyridine drug, and presence or absence of at least one prespecified clinical or lesion-related risk factor for stent thrombosis.
Authors' judgement	Low risks of bias	Low risks of bias	Low risks of bias	Low risks of bias
Allocation concealment	Eligible patients were randomly assigned in a 1:1 ratio to the ticagrelor group or the placebo group by means of an interactive voice-response or Web-response system. Randomization codes were generated in blocks of constant size. The trial-group assignment was conducted in a double blind manner.	We used a central internet web-based randomisation for the allocation of participants to receive one of the three antithrombotic therapy treatments in a double-blind manner.	Randomization was performed with the use of a central computerized telephone or Web-based system, and assignment was double-blinded.	Randomization was performed by a central Interactive Voice Response System (IVRS) for all studies, except the Boston Scientific Liberté study, which used its own IVRS system.
Authors' judgement	Low risks of bias	Low risks of bias	Low risks of bias	Low risks of bias
Blinding of participants &personnel	The trial-group assignment was conducted in a double blind manner. And because the endpoint events are objective events, there is no subjective evaluation, so the blind method will not be destroyed.	Each treatment group was double dummy, and the patients, investigators, and central study staff were masked to treatment allocation. And because the endpoint events are objective events, there is no subjective evaluation, so the blind method will not be destroyed.	Assignment was double-blinded. And because the endpoint events are objective events, there is no subjective evaluation, so the blind method will not be destroyed.	Assignment was double-blinded. And because the endpoint events are objective events, there is no subjective evaluation, so the blind method will not be destroyed.
Authors' judgement	Low risks of bias	Low risks of bias	Low risks of bias	Low risks of bias
Blinding of outcome assessment	An academic clinical events committee adjudicated endpoint events in a blinded manner. And because the endpoint events are objective events, there is no subjective evaluation, so the blind method will not be destroyed.	Each treatment group was double dummy, and the patients, investigators, and central study staff were masked to treatment allocation. And because the endpoint events are objective events, there is no subjective evaluation, so the blind method will not be destroyed.	A central clinical-events committee, whose members were unaware of the treatment assignments, adjudicated all efficacy end points and bleeding episodes. And because the endpoint events are objective events, there is no subjective evaluation, so the blind method will not be destroyed.	A single clinical-events committee whose members were unaware of the group assignments adjudicated events, and an unblinded, independent, central data and safety monitoring committee oversaw the safety of all patients. And because the endpoint events are objective events, there is no subjective evaluation, so the blind method will not be destroyed.
Authors' judgement	Low risks of bias	Low risks of bias	Low risks of bias	Low risks of bias
Incomplete outcome data	Data regarding vital status were available for 99.9% of the patients at the end of the trial and were missing for 21 patients (13 in the ticagrelor group and 8 in the placebo group); of these patients, 10 were lost to follow-up, and 11 withdrew consent and had unknown vital status.	Mean duration of follow-up was 1.95 years, follow-up was 99.8% complete.	The median duration of follow-up was 33months (interquartile range, 28 to 37), resulting in 56,004 patient-years of follow-up. Ascertainment of the primary end point was complete for 99.2% of the potential patient-years of follow-up.	94.3% of the participants completed the follow-up

Authors' judgement	Low risks of bias	Low risks of bias	Low risks of bias	Low risks of bias
Selective reporting	It was consistent with the outcomes of the protocol.	It was consistent with the outcomes of the protocol.	It was consistent with the outcomes of the protocol.	It was consistent with the outcomes of the protocol.
Authors' judgement	Low risks of bias	Low risks of bias	Low risks of bias	Low risks of bias
Other bias (the status of pharmaceutical sponsor)	Site selection was conducted jointly by the national lead investigators and representatives of AstraZeneca, who performed site monitoring and supervision and handled the collection, storage, and analysis of the data. The Baim Clinical Research Institute independently validated all the data that are reported, with funding from AstraZeneca.	The study was designed by the Steering Committee, which included scientists from the sponsor, Bayer AG, who collaborated in study design, manuscript review and decision to publish. Site management and data collection and analysis were done at the Population Health Research Institute, Hamilton Health Sciences, and McMaster University in Hamilton, ON, Canada.	The raw database was provided to the TIMI Study Group, which conducted all the data analyses independently of the sponsor.	The stent manufacturers who funded the trial had contributing roles in the design of the trial and in the collection of the data. The Harvard Clinical Research Institute was responsible for the scientific conduct of the trial and an independent analysis of the data.
Authors' judgement	Low risks of bias	Low risks of bias	Low risks of bias	Low risks of bias

Table S6. Summary estimates for efficacy and safety outcomes from network meta-analysis.

Odds ratio (95% credible intervals) between column and row treatment regimens are reported. Odds ratio smaller than 1 means that the odds of having an event for the column treatment regimen is lower than the row treatment regimen. Statistically significant results, where the 95% credible interval does not include 1.

(1) Trial-defined major adverse cardiovascular and cerebrovascular events

Ticagrelor+Asprin	1.03 (0.88,1.20)	0.85 (0.73,1.00)	0.83 (0.68,1.01)	1.16 (1.07,1.25)
0.97 (0.83,1.14)	Rivaroxaban	0.83 (0.72,0.96)	0.81 (0.64,1.01)	1.12 (0.98,1.29)
1.17 (1.00,1.38)	1.2 (1.04,1.39)	Rivaroxaban+Asprin	0.97 (0.77,1.22)	1.35 (1.17,1.56)
1.21 (0.99,1.47)	1.24 (0.99,1.56)	1.03 (0.82,1.30)	Thienopyridine+Asprin	1.4 (1.16,1.67)
0.86 (0.80,0.93)	0.89 (0.78,1.02)	0.74 (0.64,0.85)	0.72 (0.60,0.86)	Asprin

(2) Death from any cause

Ticagrelor+Asprin	0.97 (0.81,1.16)	0.79 (0.66,0.95)	1.36 (0.99,1.87)	1.04 (0.95,1.14)
1.03 (0.86,1.24)	Rivaroxaban	0.82 (0.69,0.97)	1.41 (1.00,1.98)	1.07 (0.92,1.26)
1.26 (1.05,1.52)	1.22 (1.04,1.45)	Rivaroxaban+Asprin	1.72 (1.22,2.43)	1.31 (1.12,1.55)
0.73 (0.53,1.01)	0.71 (0.50,1.00)	0.58 (0.41,0.82)	Thienopyridine+Asprin	0.76 (0.56,1.04)
0.96 (0.88,1.05)	0.93 (0.80,1.09)	0.76 (0.65,0.90)	1.31 (0.97,1.78)	Asprin

(3) Cardiovascular death

Ticagrelor+Asprin	1.02 (0.72,1.43)	0.80 (0.56,1.14)	1.01 (0.62,1.65)	1.07 (0.89,1.29)
0.98 (0.70,1.38)	Rivaroxaban	0.78 (0.58,1.06)	0.99 (0.58,1.70)	1.05 (0.79,1.40)
1.25 (0.88,1.77)	1.27 (0.94,1.72)	Rivaroxaban+Asprin	1.26 (0.73,2.18)	1.34 (0.99,1.81)
0.99 (0.61,1.62)	1.01 (0.59,1.73)	0.79 (0.46,1.37)	Thienopyridine+Asprin	1.06 (0.67,1.68)
0.93 (0.78,1.12)	0.95 (0.71,1.27)	0.75 (0.55,1.01)	0.94 (0.60,1.49)	Asprin

(4) Myocardial infarction

Ticagrelor+Asprin	1.09 (0.87,1.38)	1.04 (0.82,1.31)	0.58 (0.45,0.76)	1.21 (1.09,1.35)
0.92 (0.73,1.15)	Rivaroxaban	0.95 (0.77,1.18)	0.53 (0.39,0.74)	1.11 (0.90,1.36)
0.96 (0.76,1.22)	1.05 (0.85,1.30)	Rivaroxaban+Asprin	0.56 (0.41,0.77)	1.17 (0.95,1.43)
1.71 (1.31,2.24)	1.87 (1.36,2.58)	1.78 (1.29,2.46)	Thienopyridine+Asprin	2.08 (1.62,2.65)
0.83 (0.74,0.92)	0.90 (0.73,1.11)	0.86 (0.70,1.06)	0.48 (0.38,0.62)	Asprin

(5) Storke

Ticagrelor+Asprin	1.01 (0.75,1.36)	0.70 (0.51,0.97)	1.06 (0.67,1.69)	1.25 (1.08,1.46)
0.99 (0.73,1.33)	Rivaroxaban	0.70 (0.52,0.94)	1.05 (0.63,1.75)	1.24 (0.96,1.61)
1.42 (1.03,1.96)	1.44 (1.06,1.94)	Rivaroxaban+Asprin	1.51 (0.89,2.55)	1.78 (1.34,2.37)
0.94 (0.59,1.50)	0.95 (0.57,1.59)	0.66 (0.39,1.12)	Thienopyridine+Asprin	1.18 (0.76,1.84)
0.80 (0.69,0.93)	0.81 (0.62,1.04)	0.56 (0.42,0.75)	0.85 (0.54,1.31)	Asprin

(6) Trial-defined major bleeding

Ticagrelor+Asprin	0.70 (0.53,0.93)	0.78 (0.59,1.02)	0.46 (0.39,0.56)
1.42 (1.08,1.88)	Rivaroxaban	1.11 (0.93,1.33)	0.66 (0.54,0.81)
1.28 (0.98,1.69)	0.90 (0.75,1.08)	Rivaroxaban+Asprin	0.60 (0.49,0.73)
2.15 (1.78,2.59)	1.51 (1.23,1.85)	1.68 (1.37,2.05)	Asprin

(7) GUSTO major bleeding

Rivaroxaban	0.69 (0.43,1.10)	0.94 (0.45,1.96)	0.65 (0.40,1.05)
1.45 (0.91,2.31)	Rivaroxaban+Asprin	1.36 (0.64,2.90)	0.94 (0.56,1.58)
1.07 (0.51,2.23)	0.74 (0.34,1.57)	Thienopyridine+Asprin	0.69 (0.41,1.17)
1.54 (0.95,2.50)	1.06 (0.63,1.79)	1.45 (0.85,2.45)	Asprin

(8) Trial-defined minor bleeding

Ticagrelor+Asprin	0.46 (0.28,0.77)	0.52 (0.31,0.87)	0.29 (0.18,0.48)
2.17 (1.30,3.62)	Rivaroxaban	1.13 (1.01,1.26)	0.64 (0.56,0.72)
1.92 (1.15,3.20)	0.88 (0.79,0.99)	Rivaroxaban+Asprin	0.57 (0.50,0.64)
3.39 (2.07,5.57)	1.56 (1.38,1.77)	1.77 (1.57,2.00)	Asprin

(9) GUSTO moderate bleeding

Rivaroxaban	1.26 (0.82,1.93)	1.03 (0.58,1.84)	0.61 (0.40,0.94)
0.79 (0.52,1.22)	Rivaroxaban+Asprin	0.82 (0.41,1.65)	0.49 (0.29,0.83)
0.97 (0.54,1.74)	1.22 (0.61,2.46)	Thienopyridine+Asprin	0.60 (0.41,0.87)
1.63 (1.07,2.49)	2.05 (1.20,3.49)	1.68 (1.16,2.43)	Asprin

(10) Intracranial hemorrhage

Ticagrelor+Asprin	1.33 (0.74,2.39)	0.80 (0.42,1.50)	0.71 (0.53,0.95)
0.75 (0.42,1.35)	Rivaroxaban	0.60 (0.37,0.98)	0.53 (0.32,0.88)
1.26 (0.67,2.37)	1.67 (1.03,2.72)	Rivaroxaban+Asprin	0.89 (0.51,1.56)
1.41 (1.05,1.90)	1.88 (1.13,3.12)	1.12 (0.64,1.97)	Asprin

Table S7. Subgroup results based on whether the subjects undergoing percutaneous coronary intervention (PCI) or not.

(1) Summary estimates for efficacy and safety outcomes from network meta-analysis

Odds ratio (95% credible intervals) between column and row treatment regimens are reported. Odds ratio smaller than 1 means that the odds of having an event for the column treatment regimen is lower than the row treatment regimen. Statistically significant results, where the 95% credible interval does not include 1.

① Trial-defined major adverse cardiovascular and cerebrovascular events in PCI subgorup

Ticagrelor+Asprin	0.87 (0.69,1.09)	0.86 (0.68,1.08)	1.20 (1.04,1.37)
1.15 (0.91,1.46)	Rivaroxaban+Asprin	0.99 (0.76,1.29)	1.38 (1.15,1.67)
1.17 (0.93,1.47)	1.01 (0.78,1.31)	Thienopyridine+Asprin	1.40 (1.16,1.68)
0.84 (0.73,0.96)	0.72 (0.60,0.87)	0.72 (0.60,0.86)	Asprin

② Trial-defined major adverse cardiovascular and cerebrovascular events in non PCI subgorup

Ticagrelor+Asprin	0.84 (0.62,1.14)	1.11 (0.94,1.30)
1.19 (0.88,1.60)	Rivaroxaban+Asprin	1.31 (1.02,1.70)
0.90 (0.77,1.06)	0.76 (0.59,0.98)	Asprin

③ Trial-defined major bleeding in PCI subgorup

Ticagrelor+Asprin	0.95 (0.64,1.43)	0.55 (0.40,0.75)
1.05 (0.70,1.57)	Rivaroxaban+Asprin	0.58 (0.45,0.75)
1.82 (1.33,2.49)	1.73 (1.34,2.24)	Asprin

④ Trial-defined major bleeding in non PCI subgorup

Ticagrelor+Asprin	0.69 (0.44,1.10)	0.43 (0.31,0.60)

1.44 (0.91,2.29)	Rivaroxaban+Asprin	0.62 (0.45,0.86)
2.32 (1.67,3.22)	1.61 (1.16,2.21)	Asprin

(2) SUCRA values[a] for each treatment regimen and outcomes in subgroup.

	Treatment Regimen				
Value	Aspirin	Ticagrelor + Aspirin	Rivaroxaban + Aspirin	Rivaroxaban	Thienopyridine + Aspirin
Efficacy outcome					
PCI subgroup					
Trial-defined MACEs	99.8	59.8	21.37	NA	18.7
Non PCI subgroup					
Trial-defined MACEs	93.5	48.9	7.6	NA	NA
Safety outcome					
PCI subgroup					
Trial-defined major bleeding	0	79.6	70.4	NA	NA
Non PCI subgroup					
Trial-defined major bleeding	0.1	96.9	53.0	NA	NA

MACEs: major adverse cardiovascular and cerebrovascular events; NA: not available, PCI: percutaneous coronary intervention. [a]The smaller the SUCRA value, the less incidence of adverse outcomes, which means the better the treatment regimen performance.

Table S8. Subgroup results based on whether the subjects undergoing prior myocardial infarction (MI) or not.

(1) Summary estimates for efficacy and safety outcomes from network meta-analysis

Odds ratio (95% credible intervals) between column and row treatment regimens are reported. Odds ratio smaller than 1 means that the odds of having an event for the column treatment regimen is lower than the row treatment regimen. Statistically significant results, where the 95% credible interval does not include 1.

① Trial-defined major adverse cardiovascular and cerebrovascular events in prior MI subgorup

Ticagrelor+Asprin	0.88 (0.68,1.15)	0.82 (0.56,1.21)	1.19 (1.01,1.40)
1.13 (0.87,1.47)	Rivaroxaban+Asprin	0.93 (0.62,1.40)	1.35 (1.09,1.66)
1.22 (0.83,1.79)	1.08 (0.72,1.62)	Thienopyridine+Asprin	1.45 (1.02,2.06)
0.84 (0.71,0.99)	0.74 (0.60,0.91)	0.69 (0.48,0.98)	Asprin

② Trial-defined major adverse cardiovascular and cerebrovascular events in non prior MI subgorup

Ticagrelor+Asprin	0.83 (0.48,1.42)	0.83 (0.45,1.51)	1.12 (0.86,1.47)
1.21 (0.70,2.07)	Rivaroxaban+Asprin	1.00 (0.70,1.43)	1.36 (0.97,1.91)
1.21 (0.66,2.21)	1.00 (0.70,1.44)	Thienopyridine+Asprin	1.36 (0.93,1.98)
0.89 (0.68,1.16)	0.74 (0.52,1.03)	0.74 (0.50,1.07)	Asprin

③ Trial-defined major bleeding in prior MI subgorup

Ticagrelor+Asprin	0.72 (0.48,1.08)	0.44 (0.32,0.60)
1.39 (0.93,2.06)	Rivaroxaban+Asprin	0.61 (0.47,0.79)
2.27 (1.67,3.09)	1.64 (1.27,2.11)	Asprin

④ Trial-defined major bleeding in non prior MI subgorup

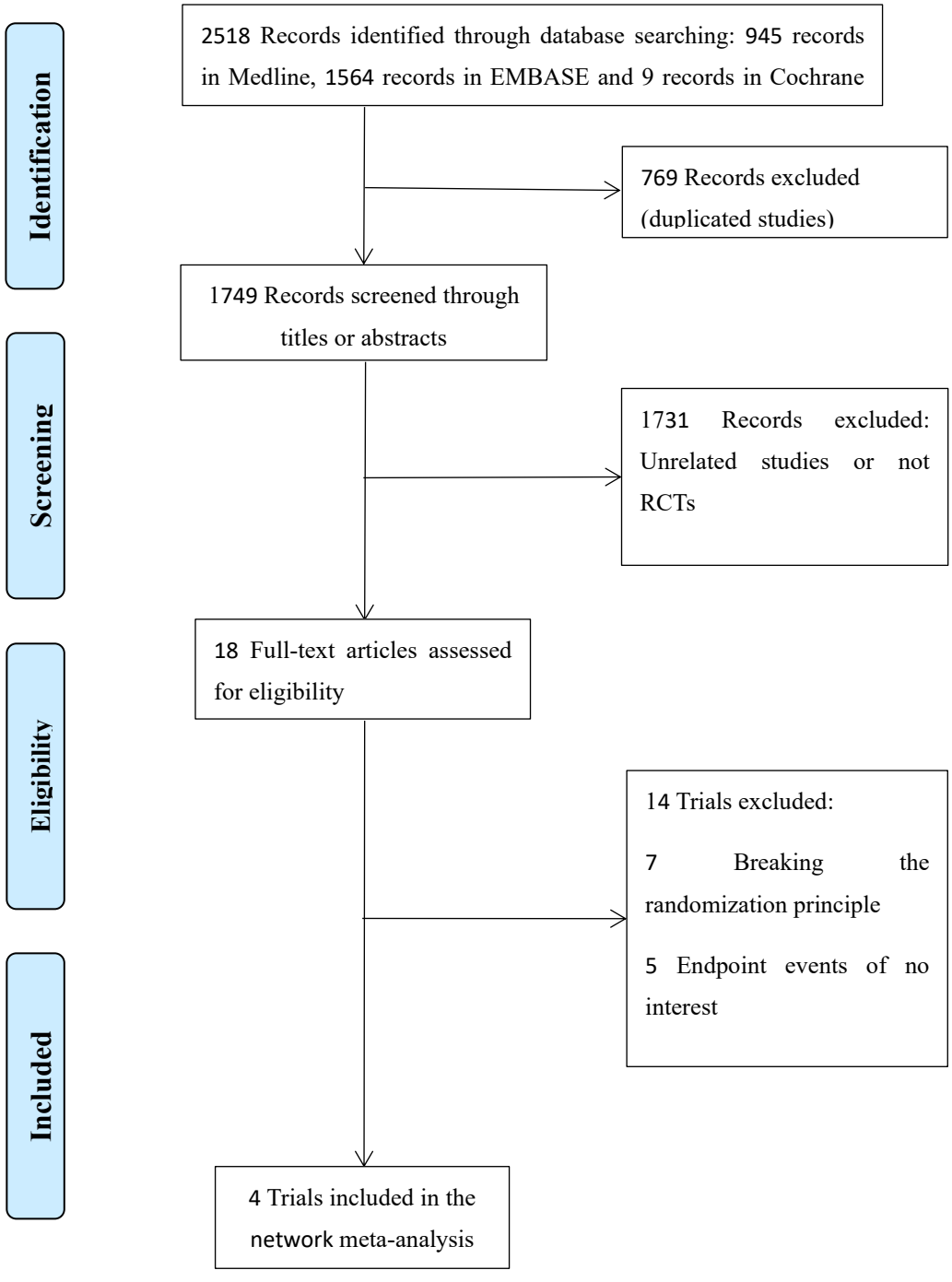
Ticagrelor+Asprin	0.85 (0.49,1.45)	0.48 (0.35,0.67)
1.18 (0.69,2.03)	Rivaroxaban+Asprin	0.57 (0.39,0.84)
2.08 (1.50,2.87)	1.76 (1.20,2.58)	Asprin

(2) SUCRA values[a] for each treatment regimen and outcomes in subgroup.

	Treatment Regimen				
Value	Aspirin	Ticagrelor + Aspirin	Rivaroxaban + Aspirin	Rivaroxaban	Thienopyridine + Aspirin
Efficacy outcome					
Prior MI subgroup					
Trial-defined MACEs	98.8	55.7	27.6	NA	17.9
Non prior MI subgroup					
Trial-defined MACEs	90.4	56.7	26.0	NA	27.0
Safety outcome					
Prior MI subgroup					
Trial-defined major bleeding	0	97.3	52.7	NA	NA
Non prior MI subgroup					
Trial-defined major bleeding	0.1	86.3	63.6	NA	NA

MACEs: major adverse cardiovascular and cerebrovascular events; NA: not available, MI: myocardial infarction. [a]The smaller the SUCRA value, the less incidence of adverse outcomes, which means the better the treatment regimen performance.

Figure S1. Flow diagram of study search and selection.



RCTs: randomized controlled trials; SCAD = stable coronary artery disease.

Figure S2. Risk of bias of included trials using the Cochrane risk assessment tool.

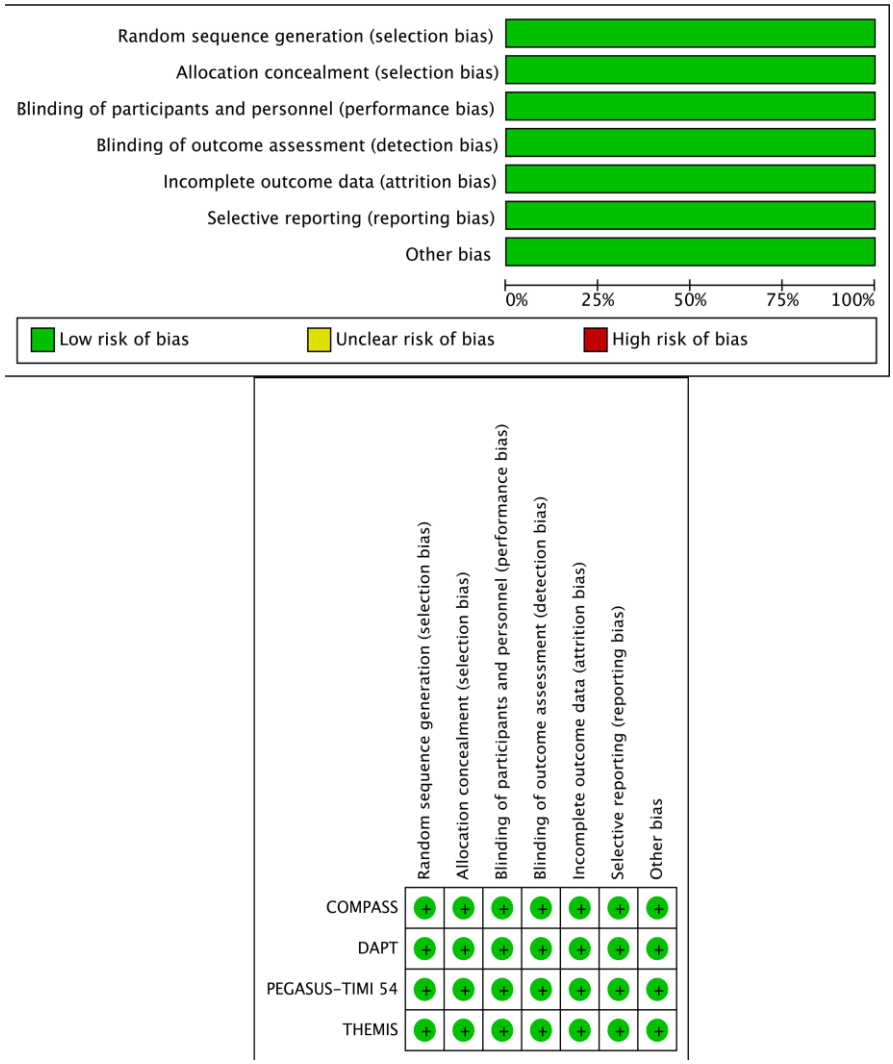
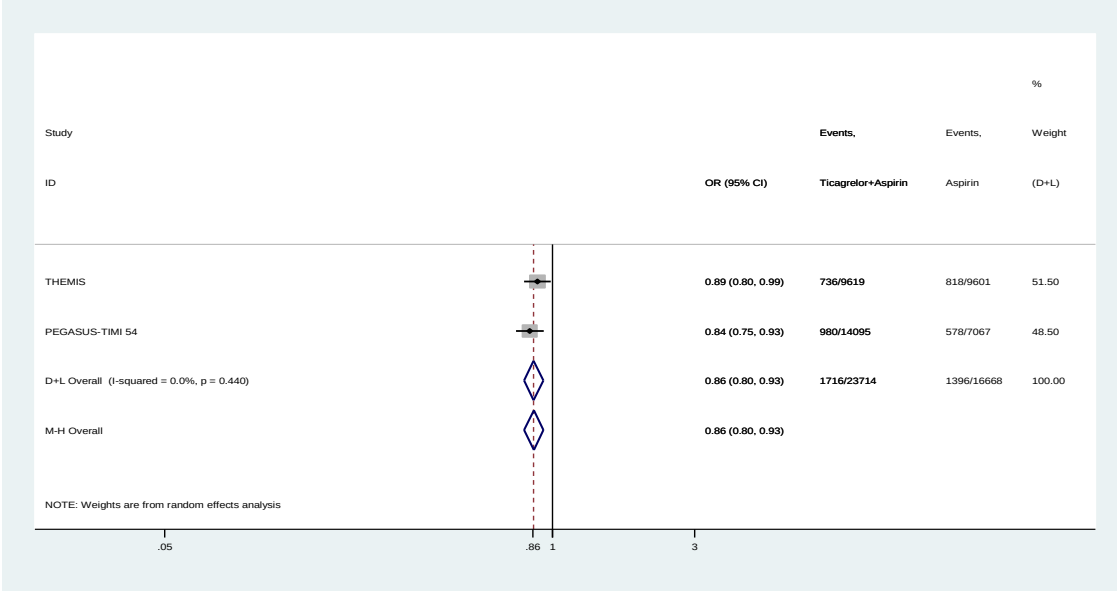


Figure S3. Homogeneity assumption in network meta-analysis.

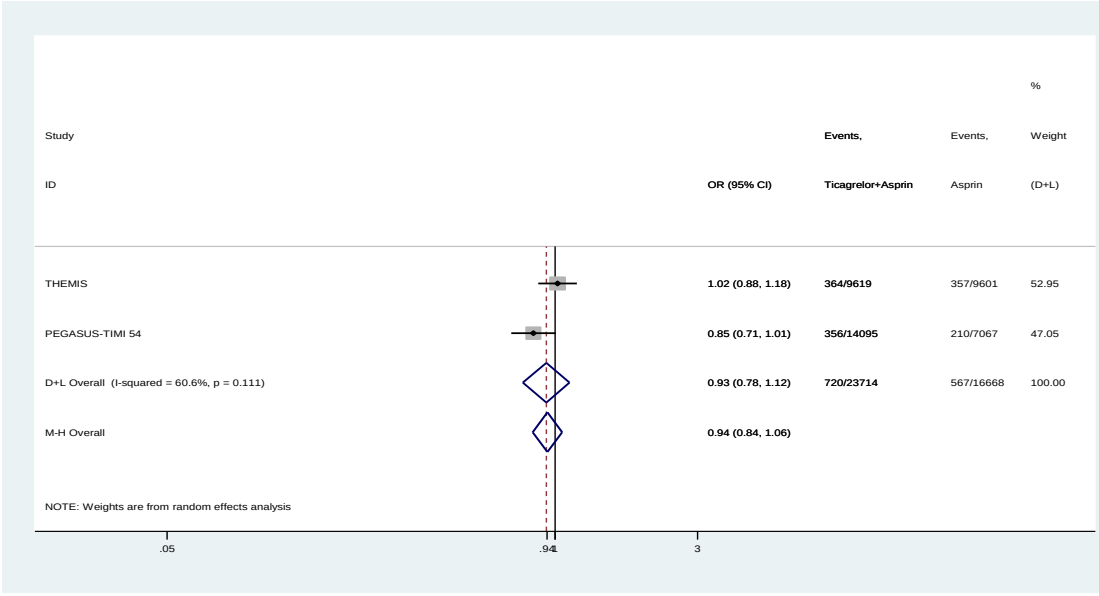
The homogeneity assumption was completed by χ^2-based Q-test, and if the p value was greater than 0.1, it was considered that the results were homogeneous, otherwise, there was heterogeneity. If the results were heterogeneous, the degree of heterogeneity was completed by I^2 test (I2= 0–25%, no heterogeneity; I^2= 25–50%, moderate heterogeneity; I^2= 50–75%, large heterogeneity; I^2= 75–100%, extreme heterogeneity).

(1) Trial-defined major adverse cardiovascular and cerebrovascular events

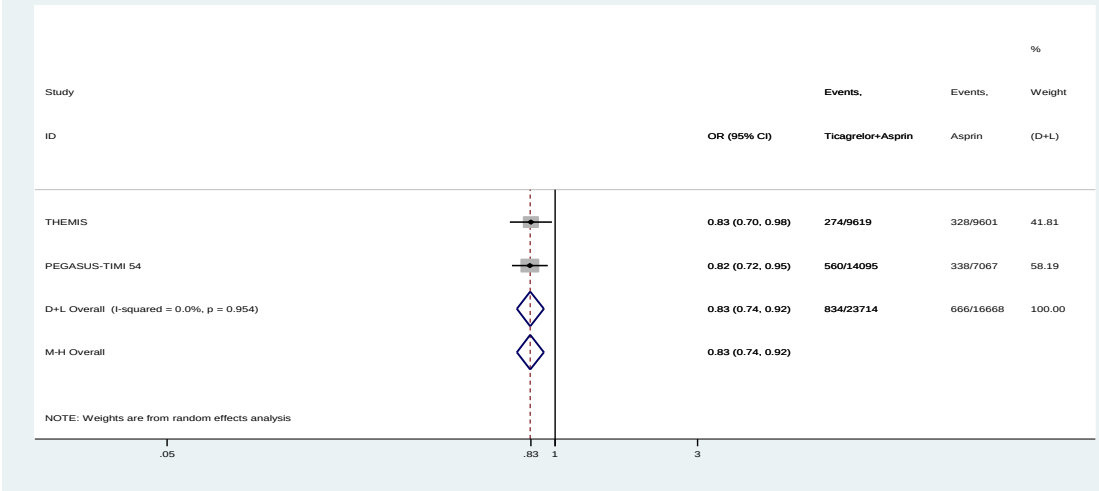


D+L: DerSimonian-Laird random effects model, M-H: Mantel-Haenszel fixed effects model.

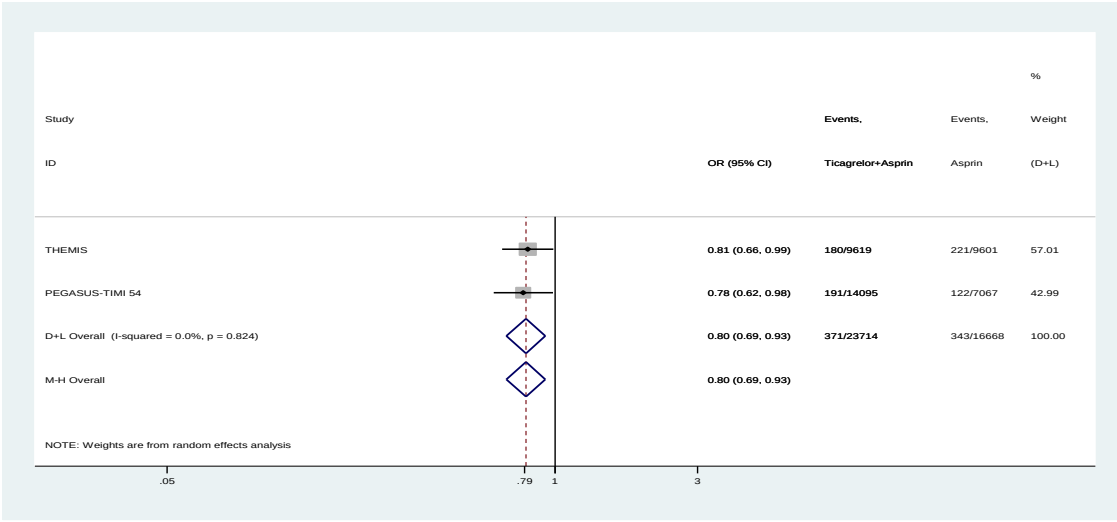
(2) Cardiovascular death



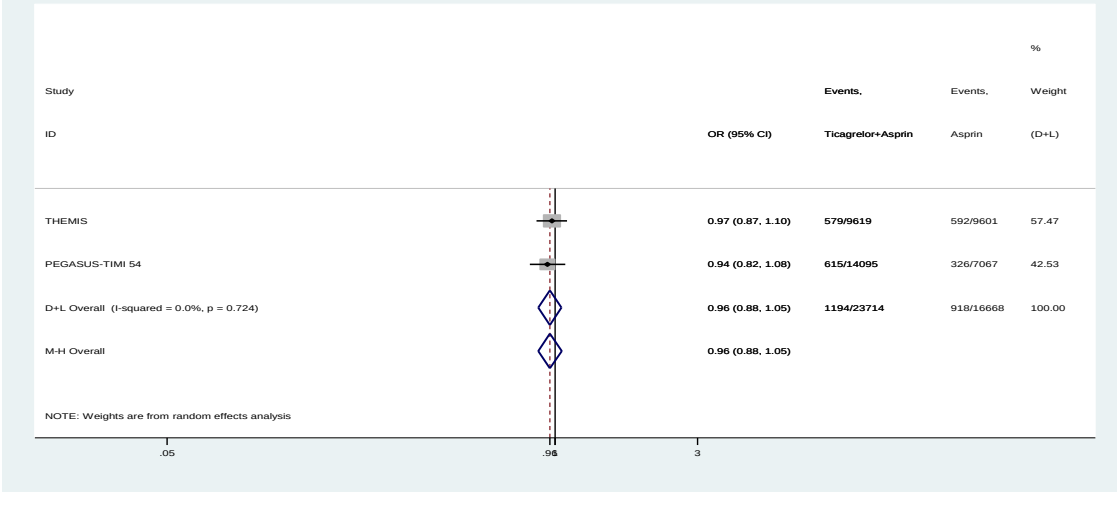
(3) Myocardial infarction



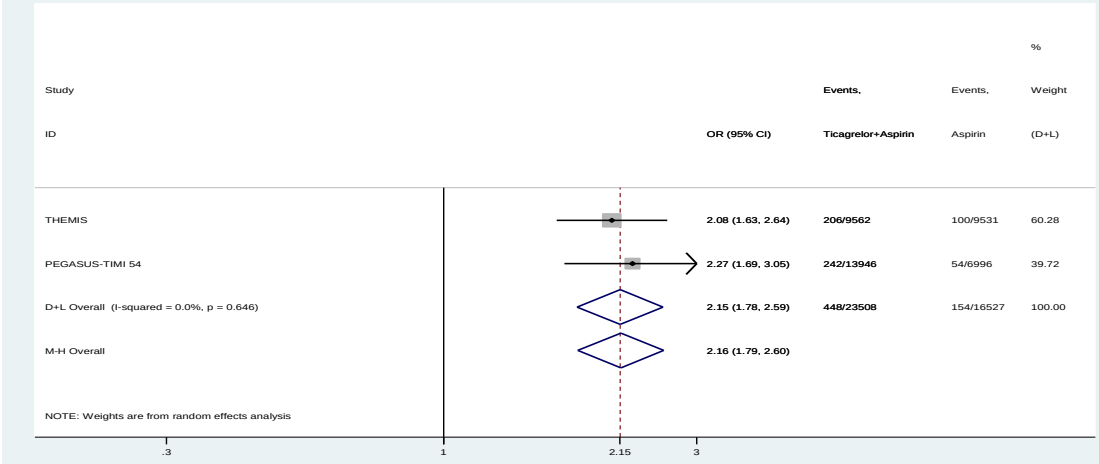
(4) Stroke



(5) Death from any cause



(6) Trial-defined major bleeding



(7) Intracranial hemorrhage

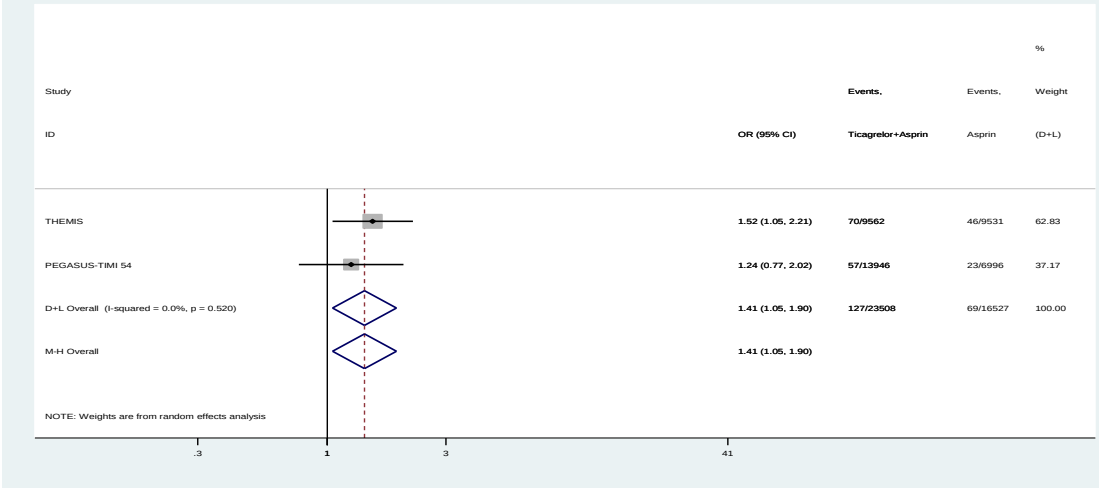
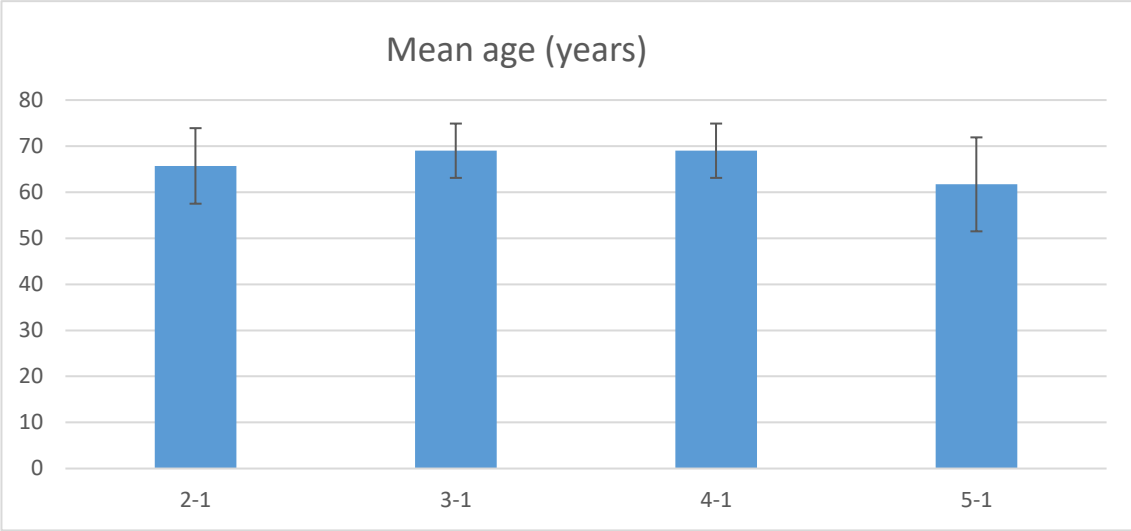


Figure S4. Transitivity assumption in network meta-analysis.

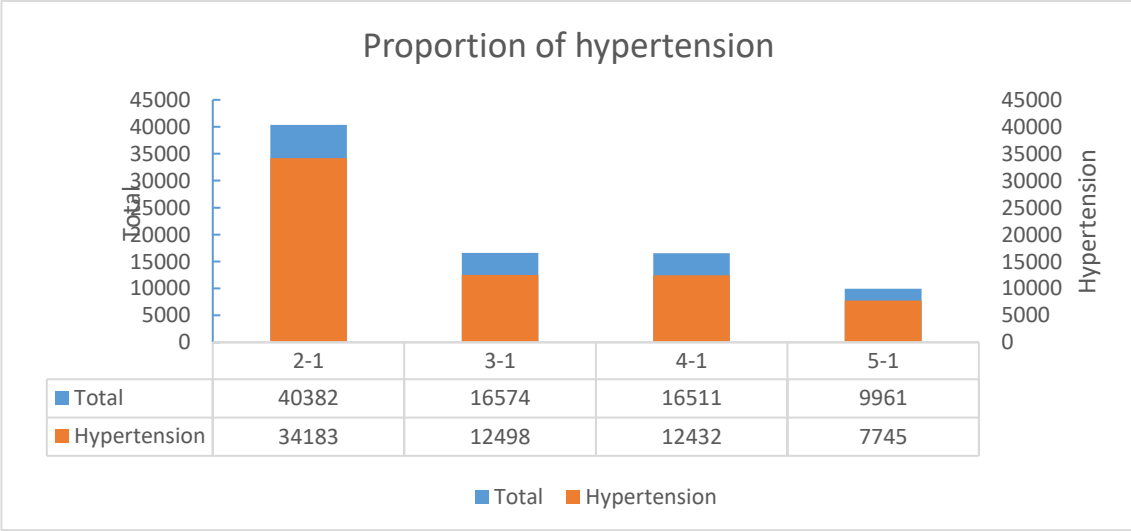
The transitivity assumption was completed by comparing the distribution of clinical variables, which were considered as interfering factors that might affect outcomes.

(1) Age

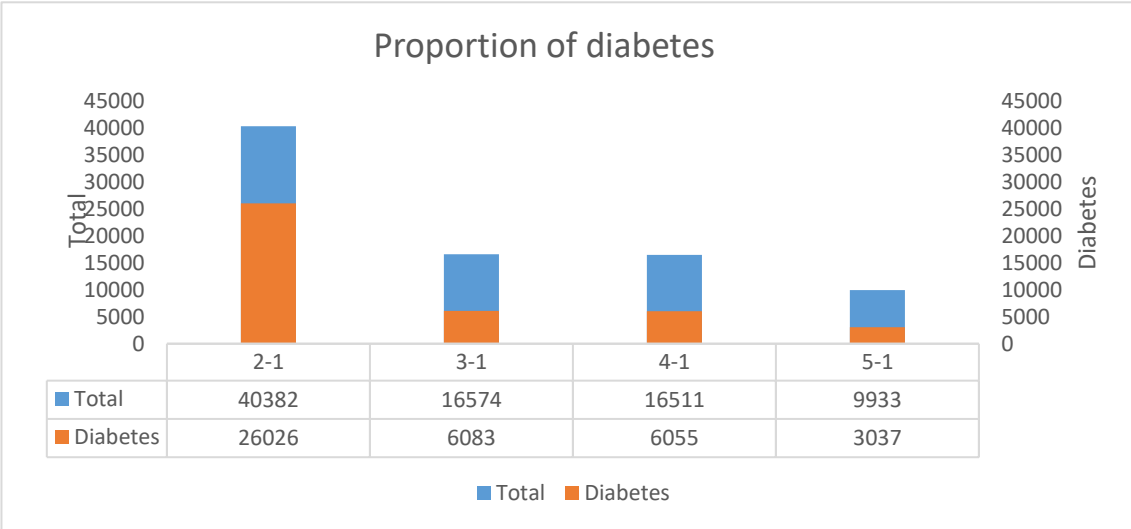


1 = Asprin; 2 = Ticagrelor+Asprin; 3 = Rivaroxaban; 4 = Rivaroxaban+Asprin; Thienopyridine+Asprin.

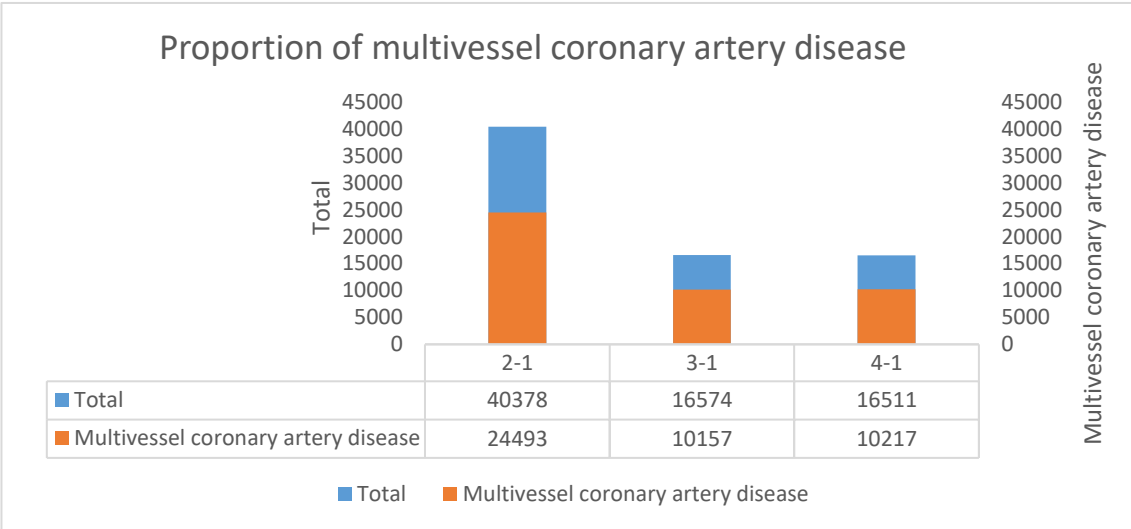
(2) Hypertension



(3) Diabetes



(4) Multivessel coronary artery disease



(5) Percutaneous coronary intervention

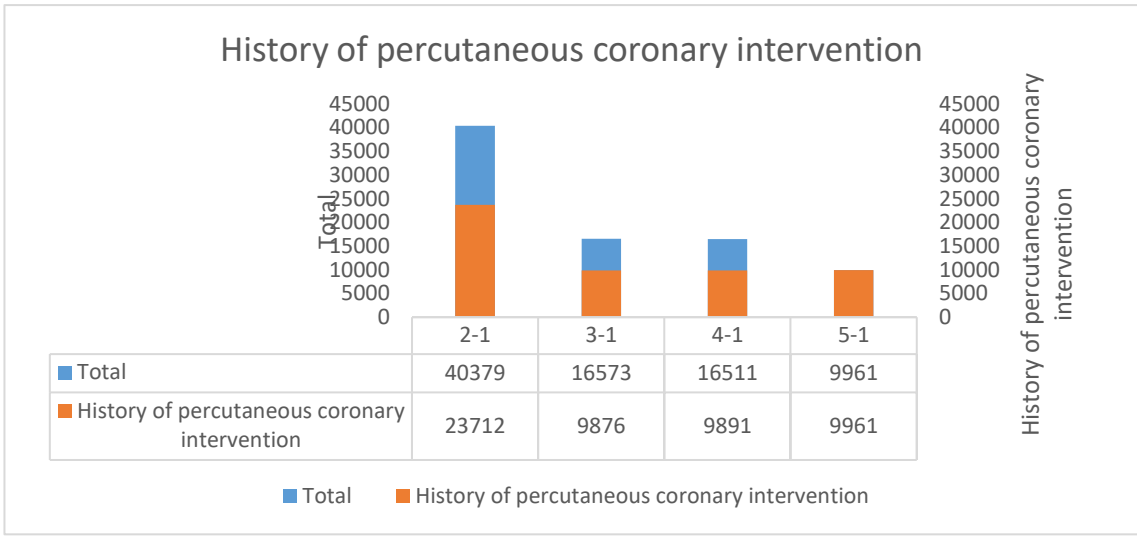
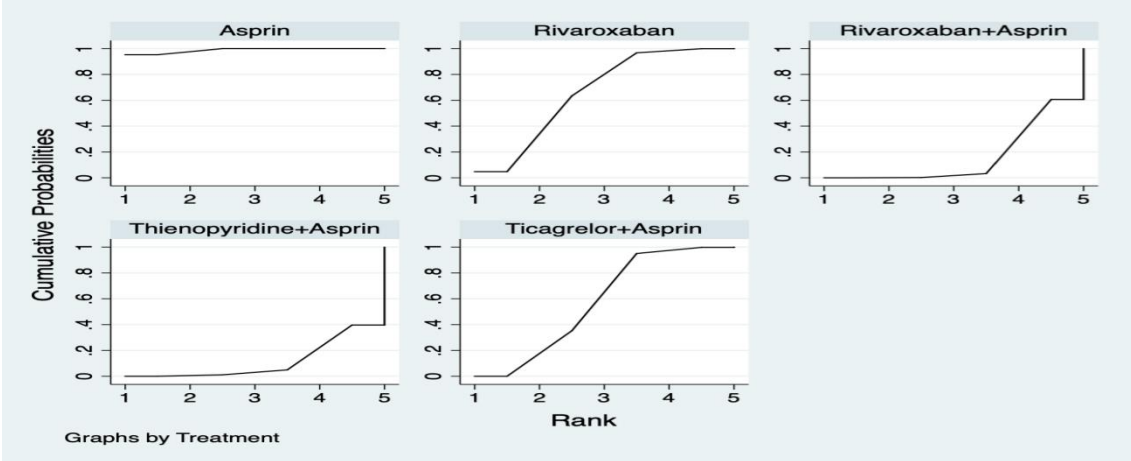

History of percutaneous coronary intervention
Total
History of percutaneous coronary intervention
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
2-1
3-1
4-1
5-1
Total
40379
16573
16511
9961
History of percutaneous coronary intervention
23712
9876
9891
9961
Total
History of percutaneous coronary intervention

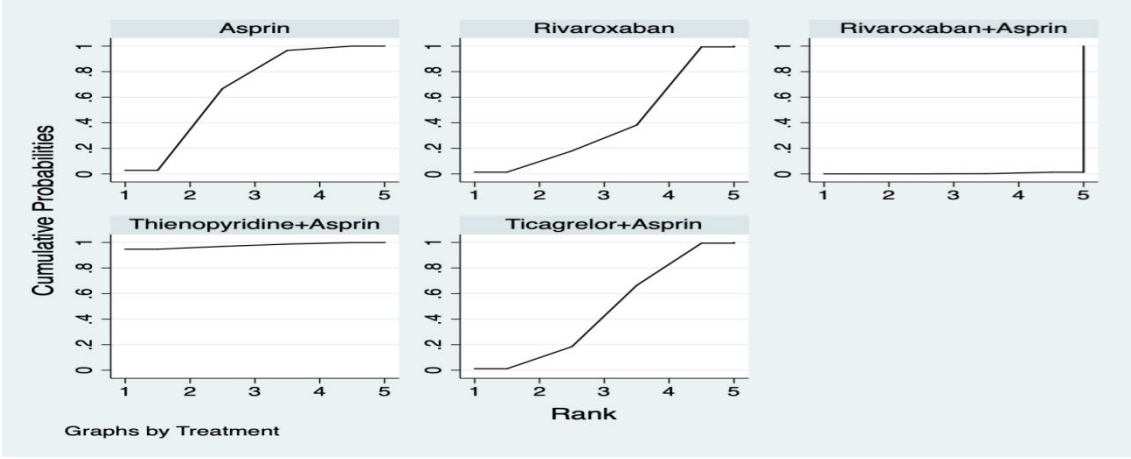
Figure S5. Cumulative rank probability plot for efficacy and safety outcomes.

The smaller the area under the curve, the lower the incidence of adverse events, which means the better treatment regimen performance.

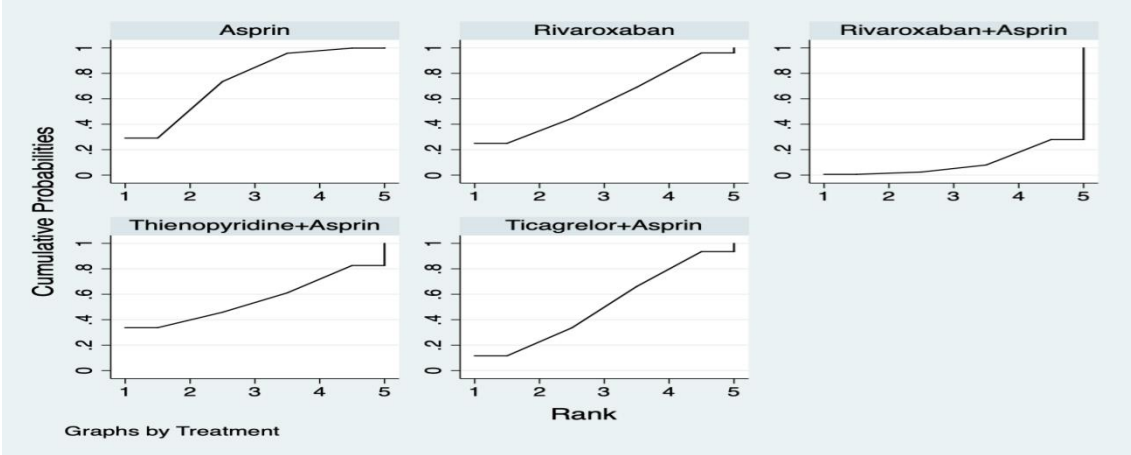
(1) Trial-defined major adverse cardiovascular and cerebrovascular events



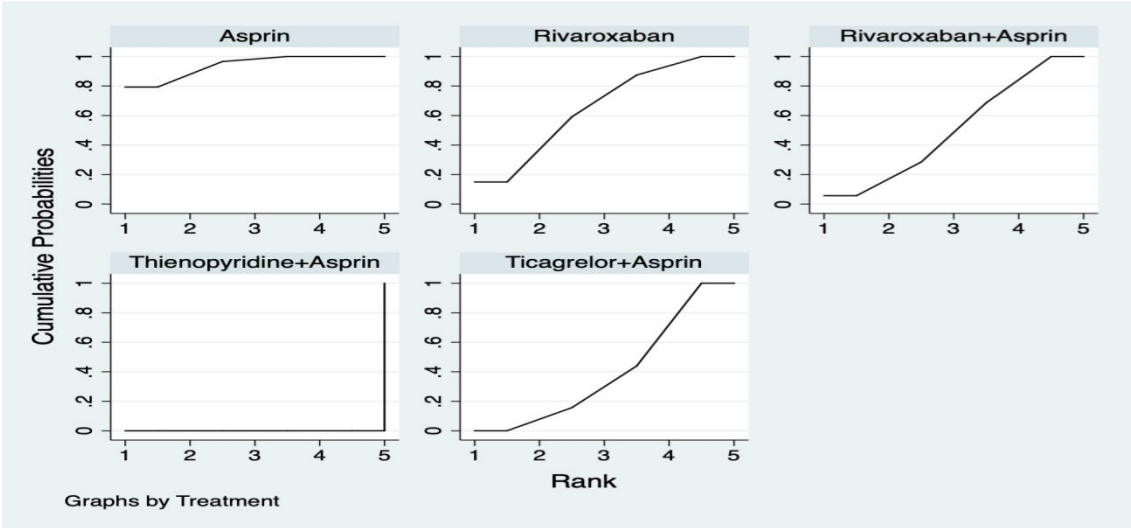
(2) Death from any cause



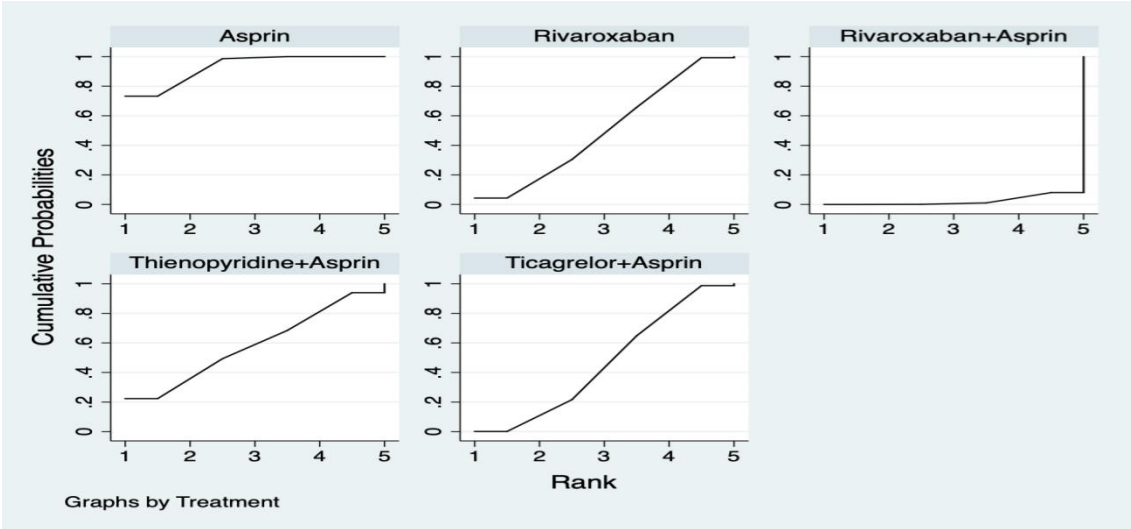
(3) Cardiovascular death



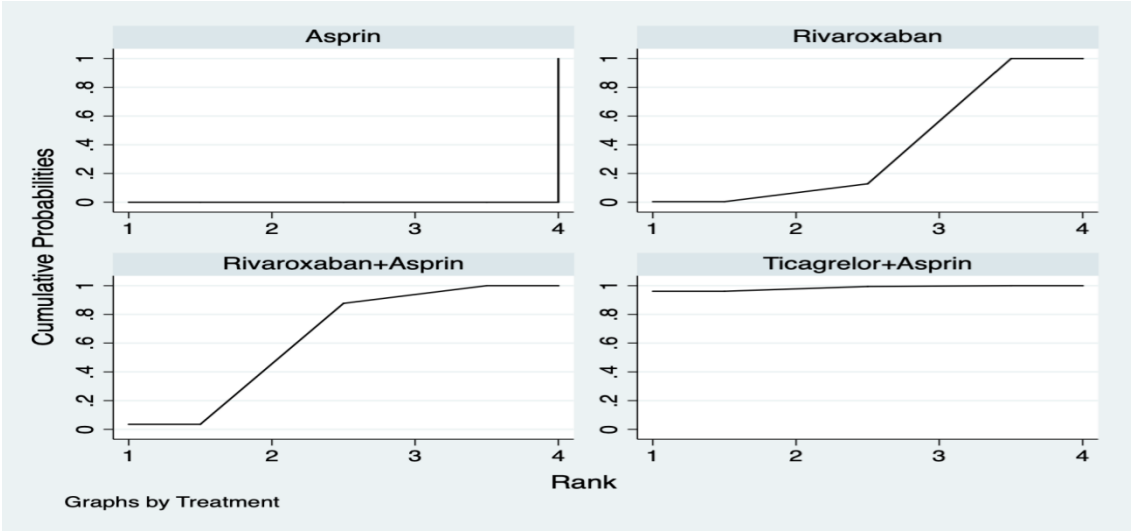
(4) Myocardial infarction



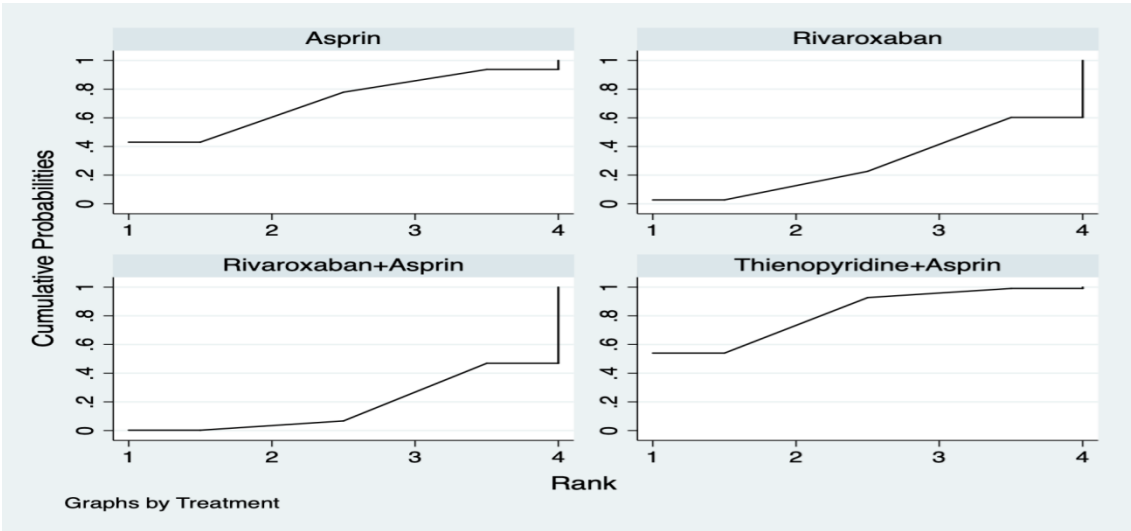
(5) Storke



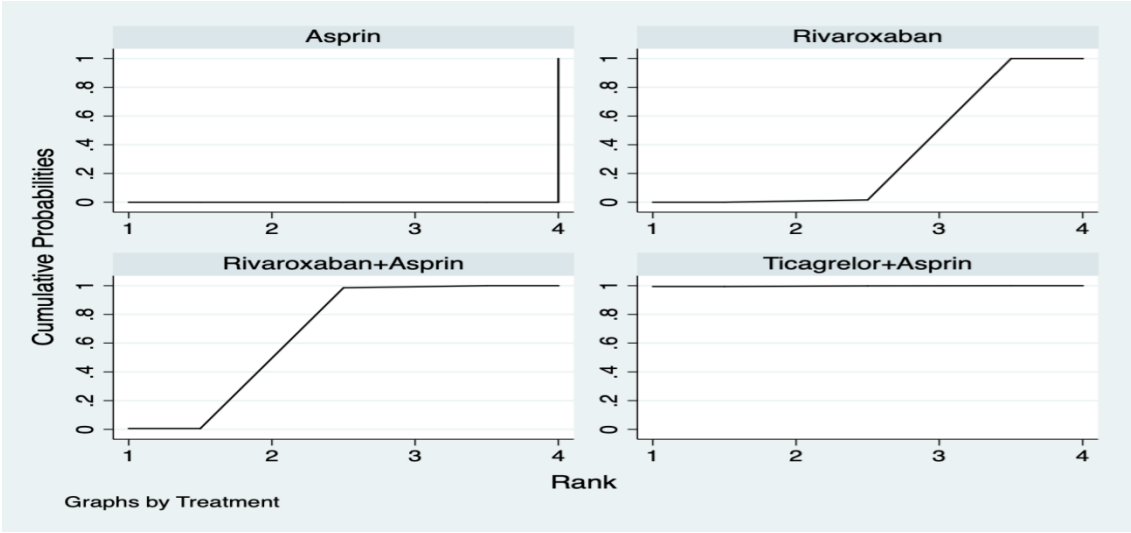
(6) Trial-defined major bleeding



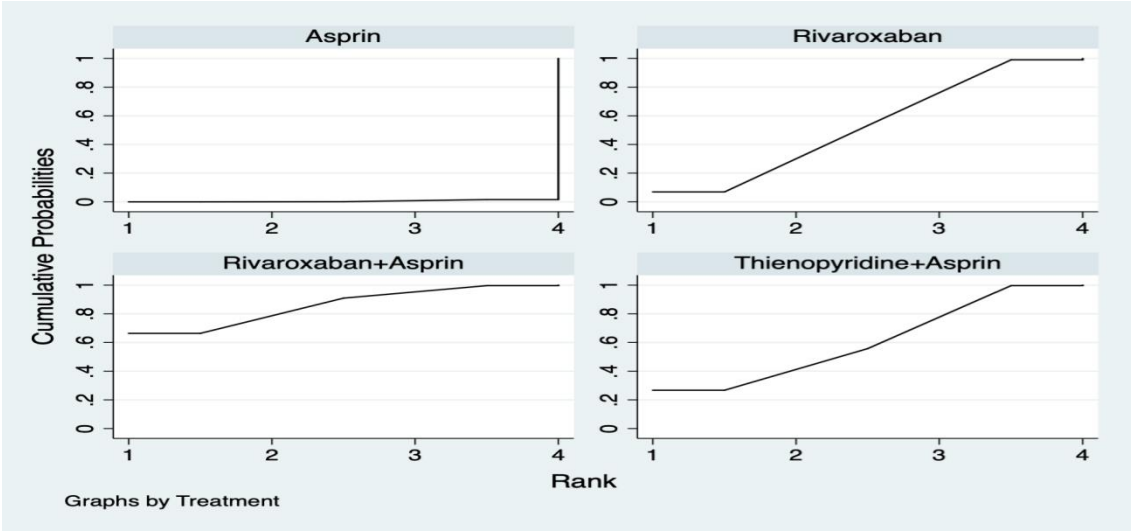
(7) GUSTO major bleeding



(8) Trial-defined minor bleeding



(9) GUSTO moderate bleeding



(10) Intracranial hemorrhage

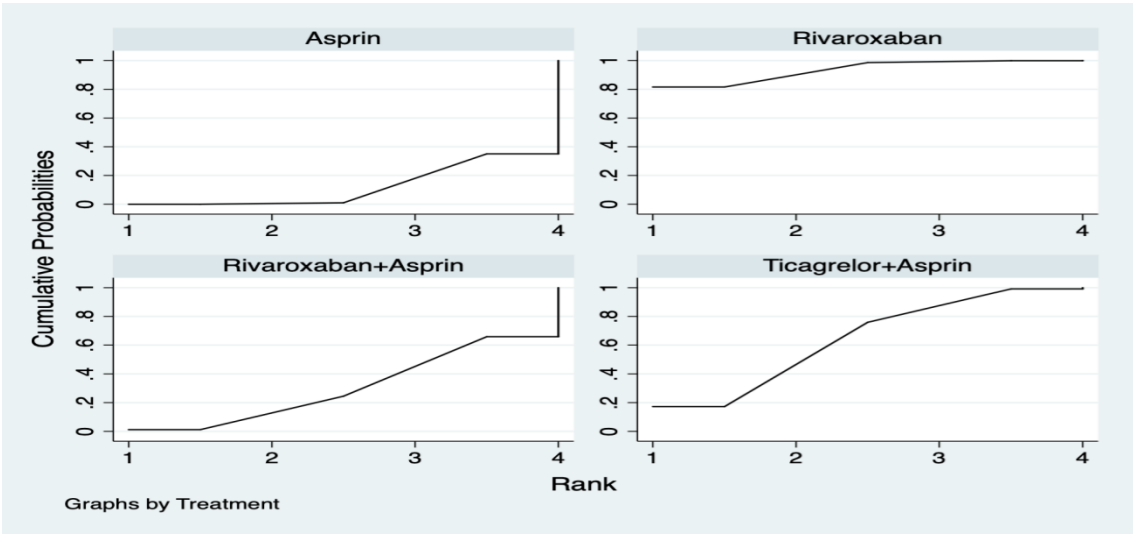
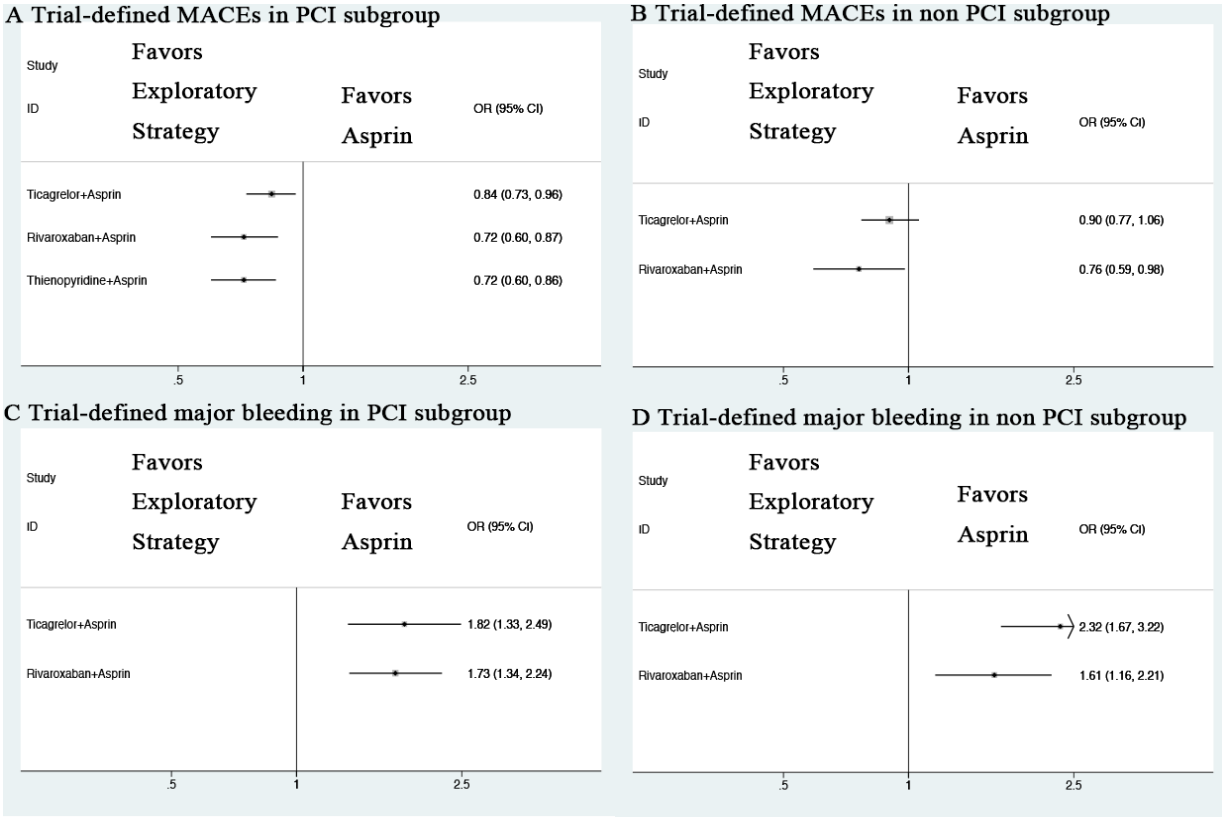

Asprin
Rivaroxaban
Rivaroxaban+Asprin
Ticagrelor+Asprin
Cumulative Probabilities
0
.2
.4
.6
.8
1
1
2
3
4
Rank
Graphs by Treatment

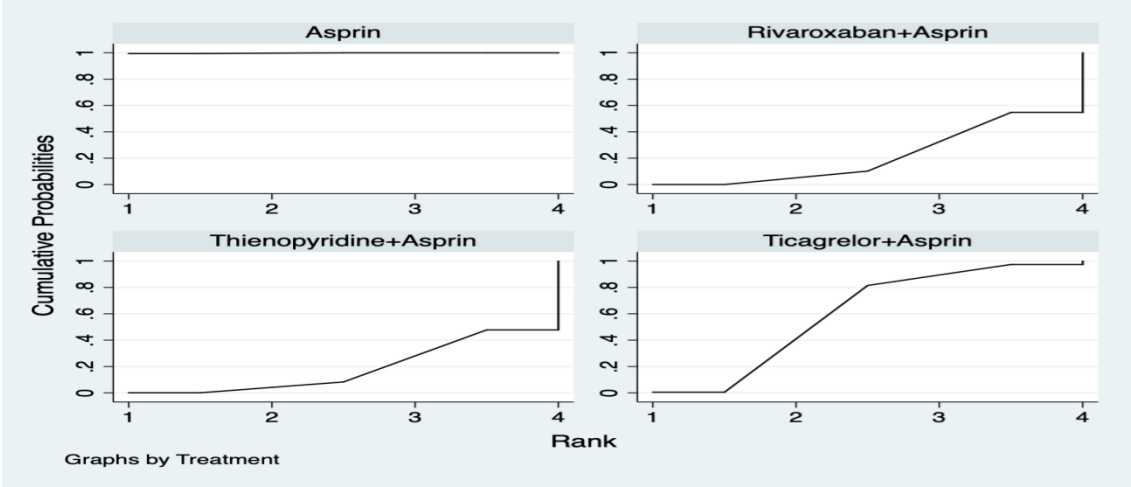
Figure S6. Subgroup results based on whether the subjects undergoing percutaneous coronary intervention (PCI) or not.

(1) Forest plots for efficacy and safety outcomes

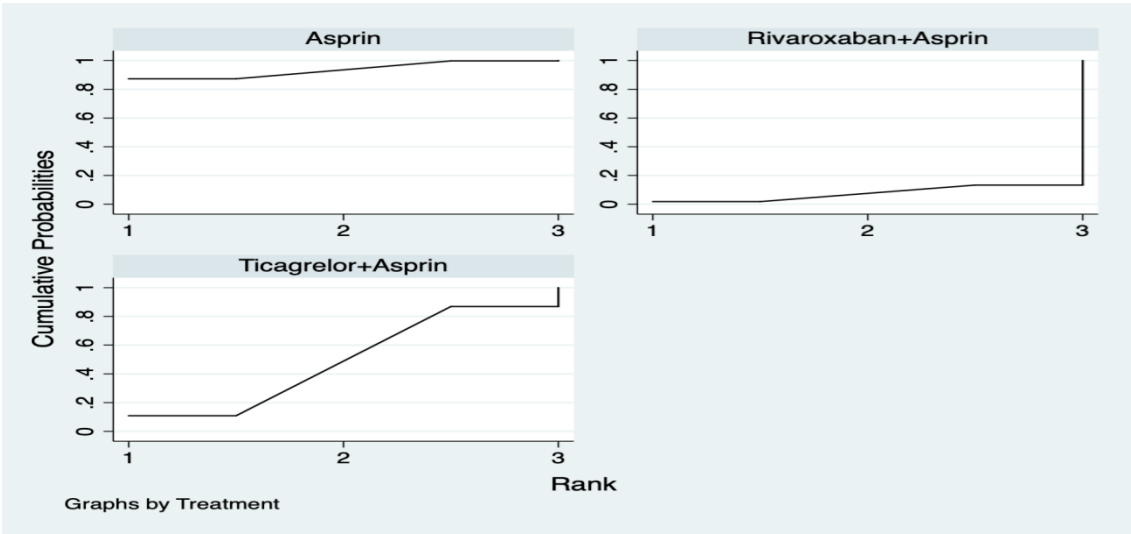


(2) Cumulative rank probability plot for efficacy and safety outcomes. The smaller the area under the curve, the lower the incidence of adverse events, which means the better treatment regimen performance.

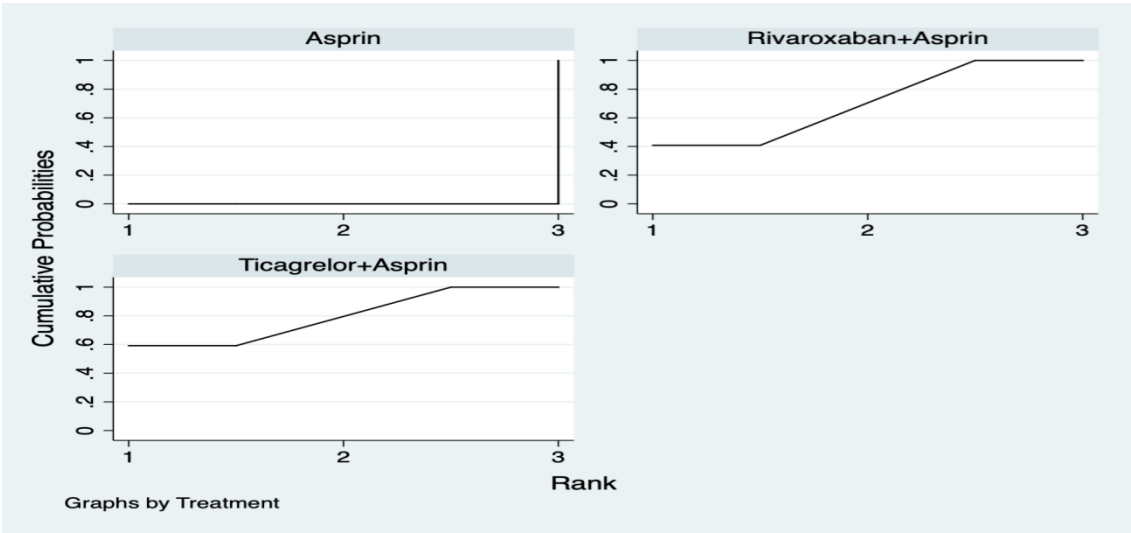
① Trial-defined major adverse cardiovascular and cerebrovascular events in PCI subgroup



② Trial-defined major adverse cardiovascular and cerebrovascular events in non PCI subgroup



③ Trial-defined major bleeding in PCI subgroup



④ Trial-defined major bleeding in non PCI subgroup

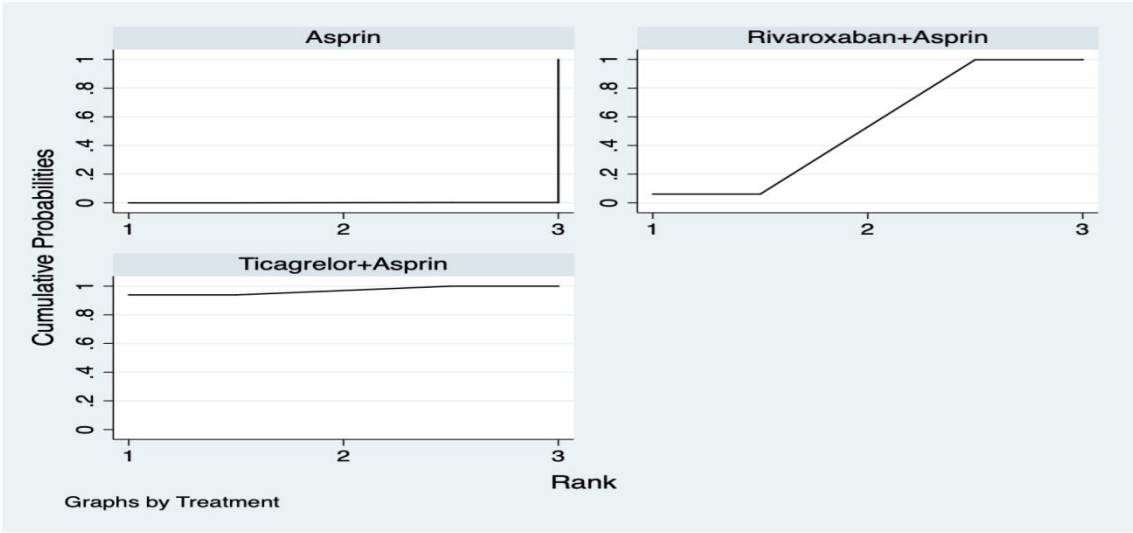
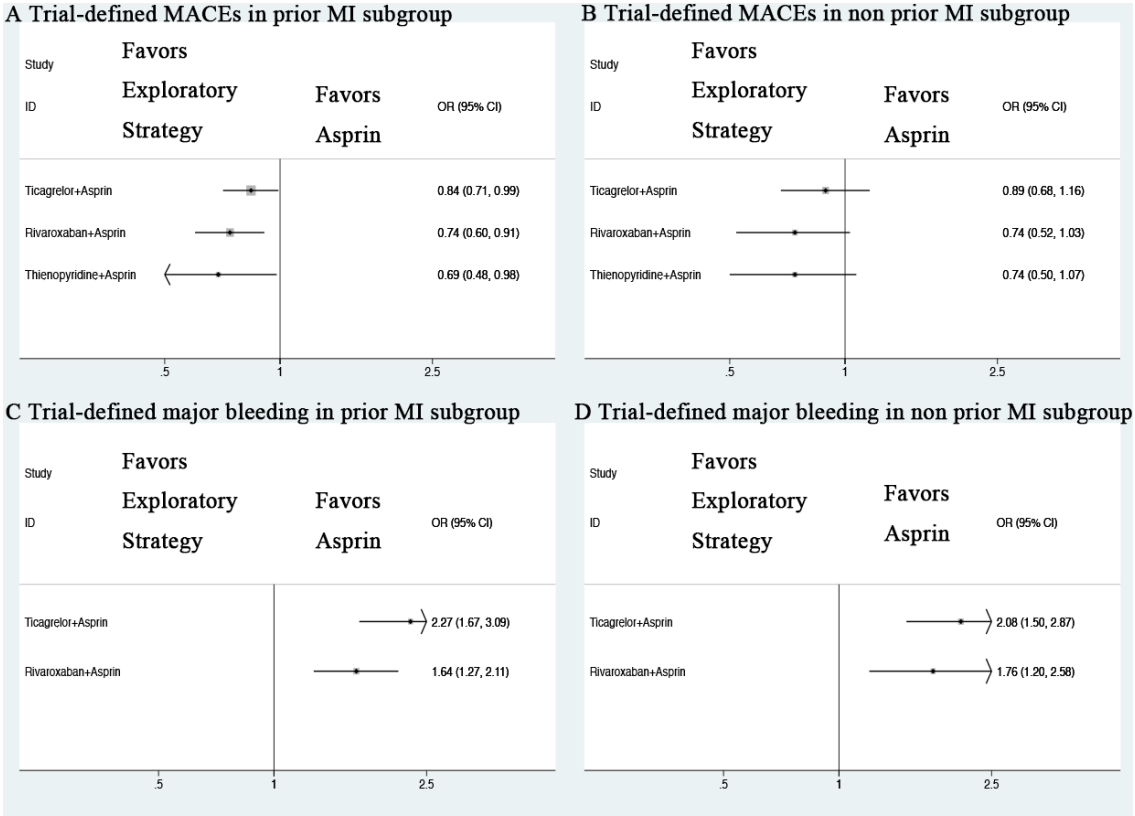


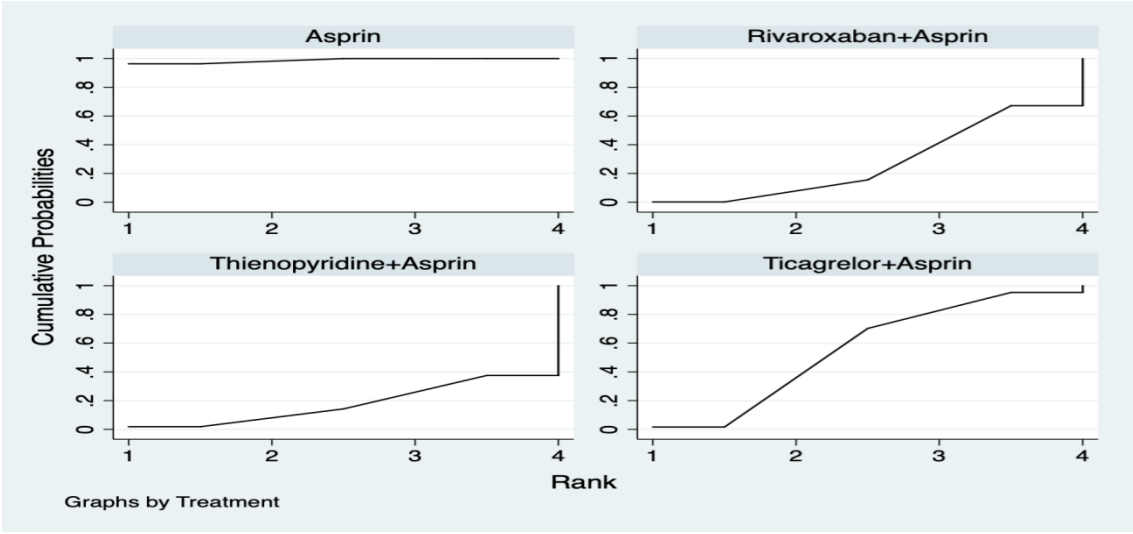
Figure S7. Subgroup results based on whether the subjects undergoing prior myocardial infarction (MI) or not.

(1) Forest plots for efficacy and safety outcomes

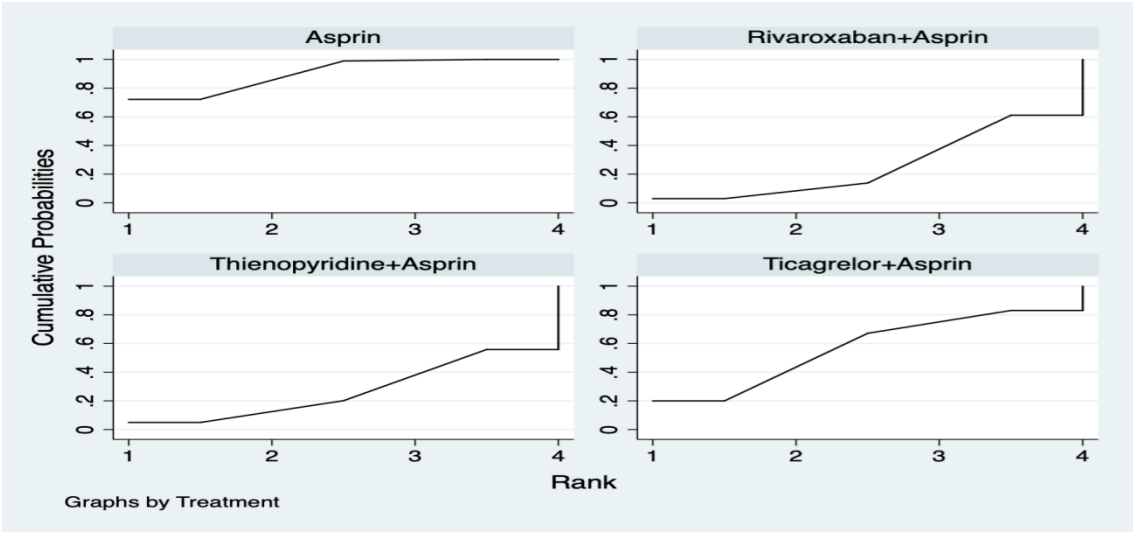


(3) Cumulative rank probability plot for efficacy and safety outcomes. The smaller the area under the curve, the lower the incidence of adverse events, which means the better treatment regimen performance.

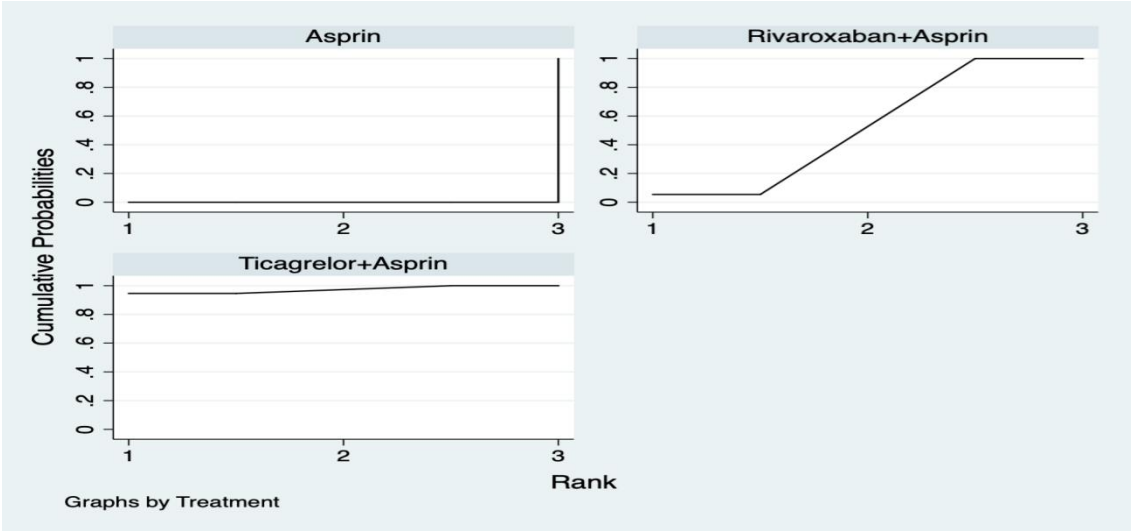
① Trial-defined major adverse cardiovascular and cerebrovascular events in prior MI subgroup



② Trial-defined major adverse cardiovascular and cerebrovascular events in non prior MI subgroup



③ Trial-defined major bleeding in prior MI subgroup



④ Trial-defined major bleeding in non prior MI subgroup