Antiplatelet regimens for Asian patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis

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Background: The optimal antiplatelet treatment for the secondary prevention of non-cardioembolic stroke or transient ischemic attack (TIA) remains uncertain in Asians.

Methods: We searched for eligible randomized control trials in Medline, Embase, and the Cochrane Library. A Bayesian network meta-analysis (NMA) was performed to assess the efficacy and safety of antiplatelet regimens with placebo as the control. Each therapy was compared using relative risk ratios (RR) and 95% credible intervals (CrI), and ranked according to the value of the surface under the cumulative ranking curve.

Results: A total of 84,103 patients from 32 studies were included: patients in used aspirin (n=26,834); cilostazol (n=3,303); clopidogrel (n=12,406); prasugrel (n=1,885); sarpogrelate (n=752); ticagrelor (n=1,933); ticlopidine (n=1,644); triflusal (n=391); aspirin plus cilostazol (n=1,120), aspirin plus clopidogrel (n=4,623); aspirin plus dipyridamole (n=10,853); aspirin plus ticagrelor (n=5,859); aspirin plus ticlopidine (n=132). Patients who used aspirin plus clopidogrel and cilostazol had a lower risk of recurrent stroke than those who used placebo. Patients administered with aspirin plus ticagrelor, aspirin plus clopidogrel, and cilostazol had a lower risk of composite vascular events than those administered placebo. Patients administered aspirin plus ticagrelor had a higher risk of major bleeding than those administered placebo. Clustered three-dimensional rank plots of recurrent stroke, major bleeding, and composite vascular events demonstrated that cilostazol had higher values of the surface under the cumulative ranking curve than other treatments.

Conclusions: Of the antiplatelet regimens, cilostazol showed the best net clinical benefits than other antiplatelet regimens in Asians with non-cardioembolic stroke or TIA.

Keywords: Antiplatelet agents; network meta-analysis (NMA); secondary prevention; Asian; stroke

Submitted Dec 12, 2020. Accepted for publication Mar 10, 2021.
doi: 10.21037/atm-20-7951
View this article at: http://dx.doi.org/10.21037/atm-20-7951

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Introduction

Antiplatelet treatment is the main strategy for the secondary prevention of vascular events in patients with non-cardioembolic stroke or transient ischemic attack (TIA) (1,2). Previous guidelines have recommended aspirin, clopidogrel, aspirin plus clopidogrel, and aspirin plus dipyridamole for secondary prevention (3). However, these are mostly based on clinical trial results from Western populations.

Several characteristics of ischemic stroke (IS) in Asian populations differ from those in Western populations. The stroke mortality and incidence rates are higher (4), and IS due to intracranial atherosclerotic stenosis and small-vessel occlusion is more frequent in Asian than in Western populations (5). The high prevalence of small-vessel disease is associated with an increased risk of cerebral hemorrhage. The risk of bleeding, including gastrointestinal bleeding, is also higher in Asians than in Westerners (6). This may be partially attributed to the high prevalence of *Helicobacter pylori* infection and genetic differences (7). The metabolisms of specific antiplatelet agents are also affected by genetic variance, which may also affect the efficacy and safety in patients with specific phenotypes more frequently observed in Asians.

Based on these findings, antiplatelet agents with reduced risks of bleeding may be potentially beneficial in Asian populations. However, no meta-analysis on the optimal antiplatelet agent for Asians has been conducted. Here, we performed a systematic review and network meta-analysis (NMA) to assess the comparative efficacy and safety of antiplatelet regimens for secondary prevention after non-cardioembolic IS or TIA in Asians.

We describe the contents in accordance with the PRISMA NMA reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7951).

Methods

This systematic review follows the principles in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (8).

Search strategy

We used multiple comprehensive databases (Medline, Embase, and Cochrane Library) to identify relevant studies from inception to May 26, 2020. The search terms included "ischemic stroke", "transient ischemic attack", "secondary prevention", and "antiplatelet agents". No restrictions on language were set. The detailed search strategies are presented in Table S1. The searched articles were reviewed in two steps by two independent reviewers (SJ Jung and JM Jung). An initial search was performed using the titles and abstracts, after which a further full-text review was performed. A manual search using additional sources, such as reference lists, was also performed. We contacted the relevant authors to obtain more information, if necessary.

Study selection

Studies were included if they were randomized and head-to-head trials that compared the efficacy and safety of antiplatelet regimens for the secondary prevention of non-cardioembolic stroke and/or TIA. Studies were excluded if they (I) investigated diseases other than IS or TIA, such as coronary artery disease or peripheral vascular disease, (II) compared anti-coagulant drugs or aspirin doses beyond the range of 50–330 mg, and (III) included only non-Asian populations. However, if we could find and extract the Asian population results of the global trials conducted on two or more continents, we included the results from the subgroup analysis. For international trials without a subgroup analysis based on ethnicity, only trials with more than 30% of Asian patients were included. For the trials with an extended follow-up, only those with follow-up periods according to the original study design were included. Different opinions of the two independent reviewers were resolved through consensus.

Data extraction and quality assessment

Two independent reviewers extracted the data using a predefined data extraction template. The data from the eligible trials included the following: basal characteristics (ethnicity, sex, age, stroke subtype, and underlying diseases such as hypertension and diabetes), detailed characteristics of the study (design, type of intervention drug, dosage, sample size, onset-to-treatment time, duration of total treatment, combination treatment, and follow-up), and indicators of the treatment effect such as the frequencies of recurrent strokes, recurrent IS, composite vascular events (stroke, myocardial infarction, and vascular death), all forms of bleeding, and major bleeding. The primary efficacy outcome was a recurrent stroke, and the primary safety outcome was major bleeding. The secondary efficacy outcomes were recurrent IS and composite vascular events, and the secondary safety outcome was all bleeding. For the

trials that did not report on the outcomes of interest, the value obtained by adding or subtracting the values from other resources, including relevant articles and previous meta-analyses, was used. For multi-arm trials involving antiplatelet agents and other drugs, we extracted two or more interesting comparison arms and ignored the others.

The risk of bias for each study was assessed using the Cochrane risk of bias assessment tool (9). The risks of bias for the domains were categorized as low risk, unclear risk, or high risk. The risk of bias was assessed by two independent reviewers, and any disagreements were resolved through a discussion.

Statistical analysis

We performed a Bayesian NMA, using the R version 3.6 "gemtc" package. The analysis pooled the relative risk ratios (RR) and 95% credible intervals (CrI) using the number of patients experiencing index events and the total number of patients in an intention-to-treat population. A two-sided P value of <0.05 was considered statistically significant. Placebo or aspirin was used as a common comparator. For the inconsistency test, we performed node-splitting assessments to determine the association between the direct and indirect evidence. If no statistical significance was observed, the evidence was presumed to be consistent for the direct and indirect comparisons. Publication bias was examined using funnel plots. The antiplatelet regimens were ranked based on the surface under the cumulative ranking curve (SUCRA) probabilities and the rankograms. The SUCRA is expressed as a percentage ranging from 0–100%. A higher SUCRA value indicates a higher ranking of a specific treatment; a top rank or one of the top ranks. Finally, the net clinical benefit (NCB) was determined using three-dimensional clustered rank plots and SUCRA ranking probabilities and used to assess the primary efficacy, safety, and composite vascular outcomes.

Subgroup analyses based on the symptom onset-to-treatment duration of the antiplatelet agents (≤72 *vs.* >72 hours) were used to discriminate against the effect according to the period with a higher ischemic burden than bleeding risk.

Results

Literature search results

According to our search strategies, 1,571 relevant publications (460 from Medline, 768 from Embase, and 343 from Cochrane Library) were initially identified, and 49 additional records were found from other sources. Of them, 32 eligible articles were finally included in this NMA (*Figure 1*). The symptom onset-to-treatment duration of fourteen trials (10-23) was within 72 hours, and that of eighteen trials (24-41) was after 72 hours.

Study characteristics and network formation

The 32 included trials tested 13 antiplatelet regimens, including aspirin, cilostazol, clopidogrel, prasugrel, sarpogrelate, ticagrelor, ticlopidine, triflusal, aspirin plus cilostazol, aspirin plus clopidogrel, aspirin plus dipyridamole, aspirin plus ticagrelor, and aspirin plus ticlopidine. Thirty trials included only Asians. The proportions of the Asian population in the PRoFESS (29) and THALES (23) global trials were 32% and 42%, respectively. Detailed characteristics of the included trials are presented in Table S2. Of the 32 eligible trials, 31 had two intervention arms. One trial (39) compared three intervention arms, but it compared different doses of clopidogrel plus aspirin (aspirin 100 mg plus clopidogrel 50 mg once daily *vs.* aspirin 100 mg plus clopidogrel 75 mg once daily) with that of aspirin. Two different doses of clopidogrel were grouped and analyzed as two treatment arms. The mean age of the patients was 64 years. The mean incidence of hypertension and diabetes at baseline were 62% and 28%, respectively. The mean duration of follow-up was 19 months, and the duration of follow-up was one month (10,16,19,23) or less (12,17), in six trials. *Figure 2* shows the network plots of antiplatelet regimens.

Risk of bias

Of the 32 eligible trials, some showed indicators of a high or unclear risk of bias: random sequence generation (n=5, 15.6%), allocation concealment (n=4, 12.5%), blinding of participants and personnel (n=13, 40.6%), blinding of outcome assessment (n=10, 31.2%), and other bias (n=2, 6.2%). The detailed characteristics of the risk of bias in the included trials are provided in Figures S1 and S2.

Outcomes of interest

Recurrent stroke

Thirty-one trials, with a sample size of 84,113, reported recurrent stroke events. *Figure 3* shows the results of the NMA. Aspirin plus clopidogrel (RR =0.53, 95% CrI: 0.27–

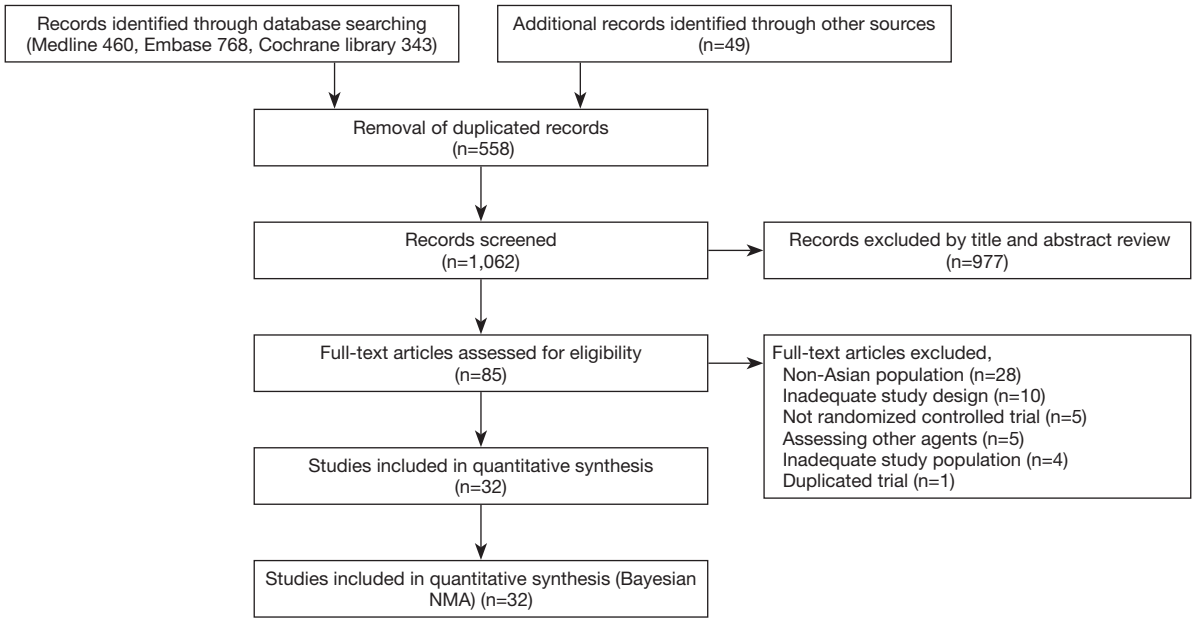

Figure 1 PRISMA flow chart.

0.83) and cilostazol (RR =0.58, 95% CrI: 0.36–0.91) were associated with significantly lower risks of recurrent stroke than placebo. They were also associated with a lower risk of recurrent stroke than aspirin [RR, 95% CrI; 0.57 (0.39–0.75) and 0.64 (0.46–0.88), respectively; Table S3]. Other antiplatelet regimens were not significantly more effective than placebo in preventing recurrent stroke. Based on the SUCRA values and the rankogram, aspirin plus clopidogrel ranked first, followed by cilostazol (Table S4 and Figure S3).

Recurrent IS

Thirty-two trials reported recurrent IS with a sample size of 85,982. As shown in *Figure 3*, aspirin plus clopidogrel (RR =0.41, 95% CrI: 0.20–0.67), aspirin plus ticagrelor (RR =0.48, 95% CrI: 0.21–0.84), and cilostazol (RR =0.56, 95% CrI: 0.34–0.90) were associated with significantly lower risks of recurrent IS than placebo. The other antiplatelet regimens were not more effective than placebo. Aspirin plus clopidogrel (RR =0.54, 95% CrI: 0.35–0.72) and aspirin plus ticagrelor (RR =0.65, 95% CrI: 0.34–0.94) were also associated with a lower risk of recurrent IS than aspirin (Table S3). Aspirin plus ticagrelor ranked first, followed by aspirin plus clopidogrel, aspirin plus cilostazol, and cilostazol (Table S4 and Figure S3). The efficacy of aspirin plus cilostazol was not significant although it ranked third (RR =0.54, 95% CrI: 0.24–1.15).

Composite vascular events

Twenty-one trials, with a sample size of 74,728, reported composite vascular events. Aspirin plus ticagrelor (RR =0.38, 95% CrI: 0.19–0.77), aspirin plus clopidogrel (RR =0.56, 95% CrI: 0.37–0.74), and cilostazol (RR =0.61, 95% CrI: 0.45–0.80) were associated with significantly lower risks of composite vascular events than placebo (*Figure 3*); they were also associated with a lower risk of composite vascular events than aspirin [RR, 95% CrI: 0.44 (0.23–0.87) for aspirin plus ticagrelor, 0.65 (0.49–0.79) for aspirin plus clopidogrel, and 0.71 (0.57–0.88) for cilostazol]. The other antiplatelet regimens were not more effective than placebo in preventing composite vascular events; aspirin plus ticagrelor ranked first, aspirin plus clopidogrel second, and cilostazol ranked third (Table S4 and Figure S3).

Major bleeding

Twenty-eight trials, with a sample size of 81,087, reported major bleeding. Most antiplatelet regimens, except aspirin plus ticagrelor (RR =3.74, 95% CrI: 1.24–10.17), were not associated with a higher risk of major bleeding than placebo (*Figure 3*). Compared with aspirin, aspirin plus ticagrelor (RR =2.82, 95% CrI: 1.24–6.04) was associated with a higher risk of major bleeding, whereas cilostazol

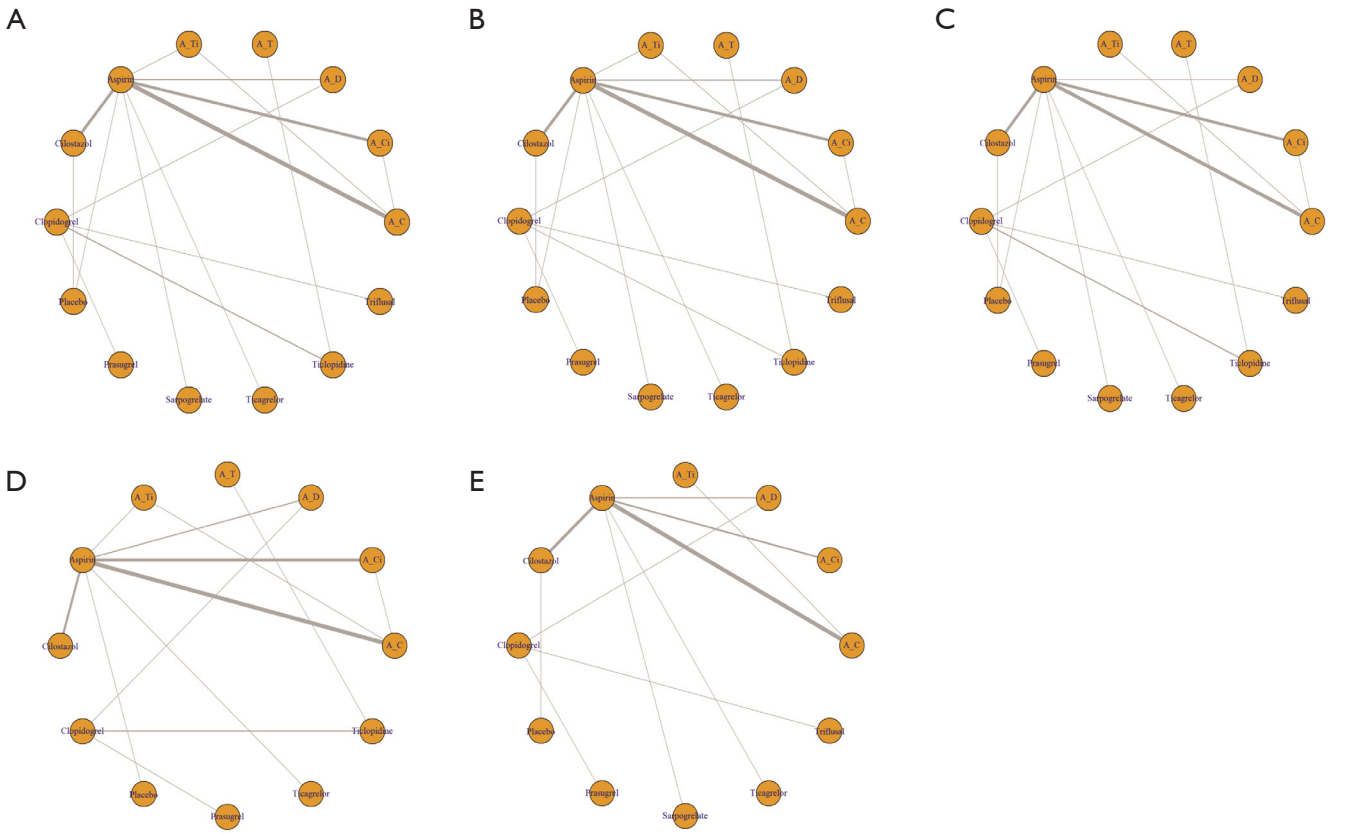

Figure 2 Network plots for the antiplatelet regimens. (A) Recurrent stroke; (B) recurrent ischemic stroke; (C) composite vascular events; (D) major bleeding; (E) all bleeding. A_Ti, aspirin plus ticagrelor; A_T, aspirin plus ticlopidine; A_D, aspirin plus dipyridamole; A_C, aspirin plus clopidogrel; A_Ci, aspirin plus cilostazol.

(RR =0.37, 95% CrI: 0.18–0.69) was associated with a lower risk of major bleeding (Table S3); cilostazol was the first, and aspirin plus ticagrelor was the last (Table S4 and Figure S3).

All bleeding

Twenty-four trials, with a sample size of 50,325, reported all forms of bleeding. In *Figure 3*, most antiplatelet regimens were not associated with a significantly higher risk of all bleeding than the placebo, excluding aspirin plus ticagrelor (RR =3.89, 95% CrI: 1.54–10.59) and aspirin plus clopidogrel (RR =2.48, 95% CrI: 1.10–5.81). When compared with aspirin, aspirin plus ticagrelor (RR =2.41, 95% CrI: 1.38–4.43) and aspirin plus clopidogrel (RR =1.52, 95% CrI: 1.12–2.13) were associated with a higher risk of all bleeding, whereas cilostazol (RR =0.64, 95% CrI: 0.47–0.80) was associated with a lower risk (Table S3); cilostazol was ranked first, and aspirin plus ticagrelor was ranked last (Table S4 and Figure S3).

Ranking and NCB

A clustered three-dimensional rank plot demonstrated that cilostazol was the best antiplatelet therapy based on the NCB in relation to recurrent strokes, major bleeding, and composite vascular events (*Figure 4A*).

Inconsistency assessment and publication bias

Figure S4 shows the inconsistencies between the direct and indirect comparisons. There was no evidence of inconsistencies between the effect estimates of the direct and indirect evidence, except for those for recurrent IS in the aspirin *vs.* aspirin plus ticagrelor group (P=0.046). This assessment could not be performed for all bleeding due to a lack of outcome data. Symmetric funnel plots showed that there was no evidence of

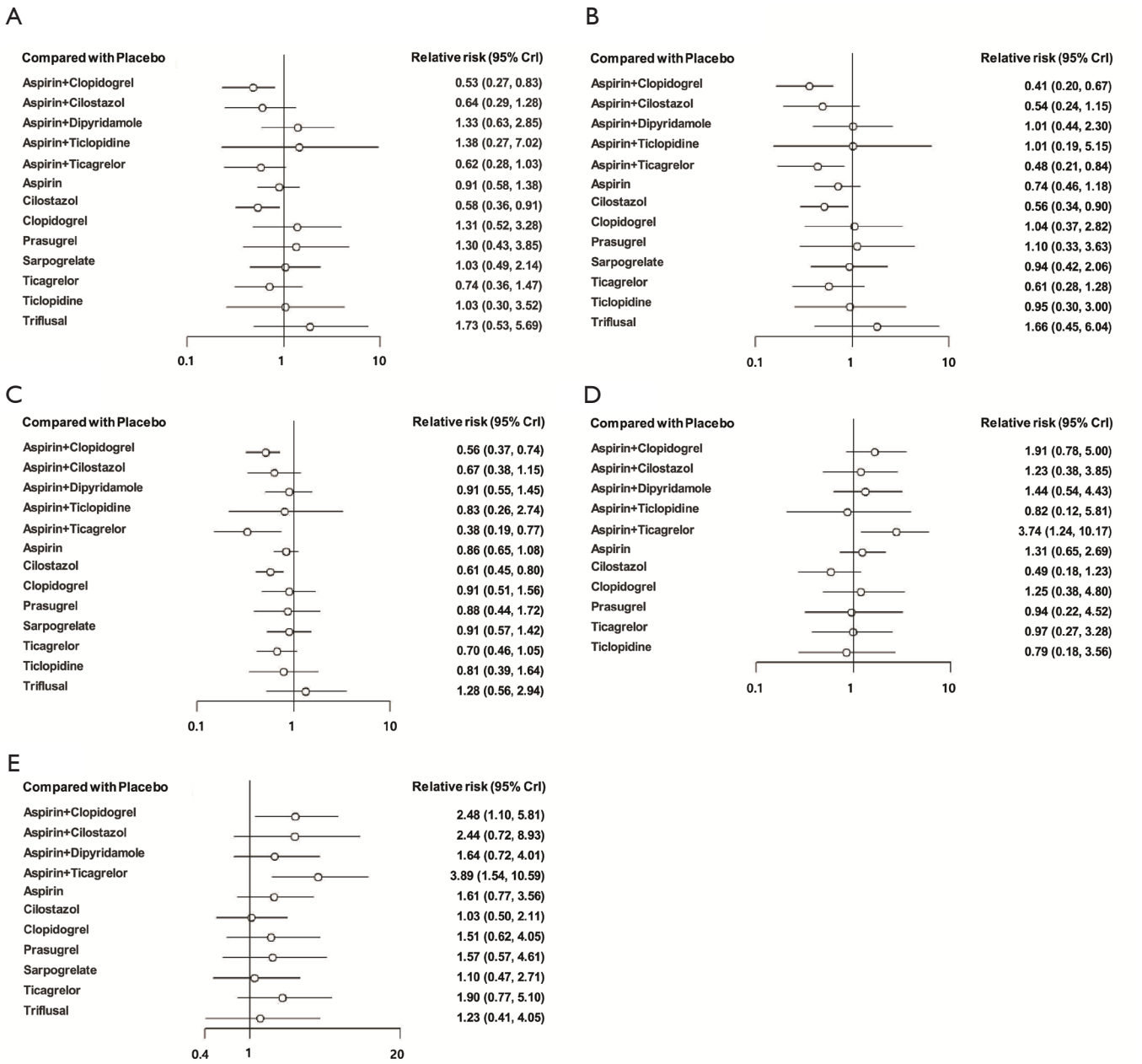

Figure 3 Forrest plots for the antiplatelet regimens and placebo. (A) Recurrent stroke; (B) recurrent ischemic stroke; (C) composite vascular events; (D) major bleeding; (E) all bleeding.

publication bias in this NMA (Figure S5).

Subgroup analysis

Before 72 hours from stroke onset

Fourteen trials were included in this analysis. Most of the studies compared dual antiplatelet therapy (DAPT) and monotherapy, and the studies on monotherapy were Chen (10) for aspirin *vs.* placebo, Lee *et al.* (13) for cilostazol and aspirin, and Wang *et al.* (20) for ticagrelor and aspirin. The durations of treatment with aspirin plus dipyridamole and aspirin plus cilostazol were not limited. The durations

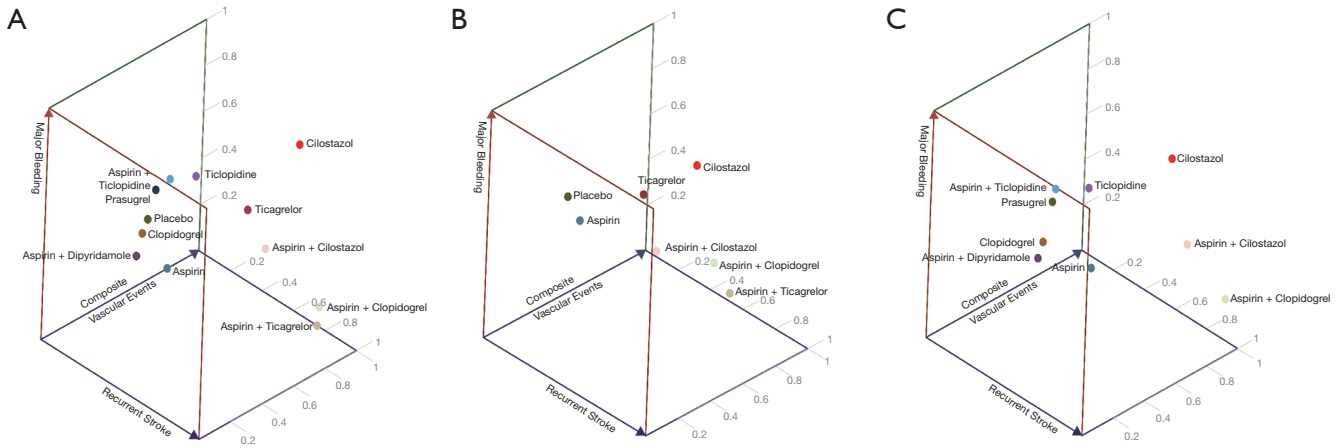

Figure 4 Three-dimensional clustered ranking plots. The x, y, and z-axes show the surface under the cumulative ranking curve (SUCRA) values for recurrent stroke, composite vascular events, and major bleeding, respectively. The point in the upper right is a hypothetical point with 100% SUCRA values for recurrent stroke, composite vascular events, and major bleeding. The antiplatelet regimen with ranking closest to this hypothetical point can be considered to have the greatest net clinical benefit. (A) Entire population; (B) seventy-two hours before stroke onset; (C) seventy-two hours after stroke onset.

of treatment with aspirin plus clopidogrel and aspirin plus ticagrelor were limited to three weeks and one month.

The antiplatelet regimens showed no significant differences in the risks of all outcomes compared with placebo (Figure S6). However, the aspirin plus clopidogrel combination was associated with lower risks of recurrent stroke, composite vascular events, and recurrent IS than aspirin [RR =0.59, 95% CrI: (0.30–0.93), 0.63 (0.36–0.89), and 0.54 (0.25–0.90)]. Conversely, aspirin plus ticagrelor and aspirin plus clopidogrel were associated with a higher risk of all bleeding than aspirin (RR =2.41, 95% CrI: 1.01–6.17; RR =1.52, 95% CrI: 1.01–2.47), although these two DAPTs were not associated with a significantly higher risk of major bleeding than placebo or aspirin. Although cilostazol did not show significantly different safety and efficacy from placebo or aspirin, its SUCRA rankings were first, second, and third for major bleeding, recurrent stroke, and composite vascular events, respectively, and it had the high NCB (Figure S7 and *Figure 4B*).

After 72 hours from stroke onset

Eighteen trials were included. None of the included trials excluded patients with index events within 72 hours from the symptom onset to the treatment. Nevertheless, most of the index events developed 72 hours after symptom onset, and most studies had follow-ups lasting for three or more months, which reflected the secondary prevention of the chronic and stable stages compared with other subgroups.

The aspirin plus clopidogrel combination was associated with lower risks of recurrent stroke and recurrent IS than the placebo in the subgroup analysis 72 hours after stroke onset (RR =0.26, 95% CrI: 0.09–0.75; RR =0.23, 95% CrI: 0.08–0.66). Cilostazol was also associated with a lower risk of recurrent stroke than placebo (RR =0.52, 95% CrI: 0.28–0.99). The outcomes of the aspirin plus cilostazol combination treatment were not significantly different from those of the aspirin or placebo treatment, but its SUCRA rankings were second for recurrent stroke, recurrent IS, and composite vascular events. The detailed relative risks, 95% CrI, and SUCRA rankings for all the outcomes are provided in Figure S8 and Figure S9.

Regarding safety, cilostazol was associated with lower risks of major and all bleeding than aspirin (RR =0.36, 95% CrI: 0.10–0.95; RR =0.59, 95% CrI: 0.23–0.97, respectively). As with NMA, cilostazol had the highest NCB (*Figure 4C*).

Discussion

This was the first systematic review and NMA to comparatively assess the efficacy and safety of antiplatelet regimens for the secondary prevention of non-cardioembolic IS or TIA in Asian populations, and it enrolled 84,103 patients from 32 trials. Based on the primary efficacy

outcome, aspirin plus clopidogrel and cilostazol were associated with a lower risk of recurrent stroke than placebo. Based on the primary safety outcome, most antiplatelet regimens, excluding aspirin plus ticagrelor, were not associated with a higher risk of major bleeding; only cilostazol was associated with a lower risk of major bleeding than aspirin. Finally, the clustered three-dimensional rank plot demonstrated that cilostazol, among the antiplatelet regimens, had the highest NCB for all the main outcomes.

The risk of recurrent stroke is higher during the acute than the chronic period. To reduce the risk of recurrent stroke, potent antiplatelet agents were administered as early as possible. Similar to the results of major clinical trials, our subgroup analysis (symptom onset-to-treatment <72 hours) showed that aspirin plus clopidogrel and aspirin plus ticagrelor had the highest ranking for recurrent stroke, composite vascular outcomes, and recurrent IS based on the SUCRA. Although the treatment durations for these two DAPTs were within one month in all the included trials, the risks of bleeding of all forms, as well as major bleeding, were also higher; this can be partially attributed to the higher bleeding risk in Asians. In the main analysis, these two DAPTs were associated with increased risks of all bleeding; aspirin plus ticagrelor, especially, increased the risk of major bleeding, which should be considered when determining a long-term secondary prevention strategy.

For long-term secondary prevention of stroke, aspirin is considered the standard drug, and most guidelines recommend it (3,42). However, aspirin has been investigated mainly in Western countries, and several meta-analyses have been performed based on results from Western populations (1,43). The effect of aspirin has not been thoroughly investigated in the Asian population. Therefore, several Western trials that reported a good efficacy of aspirin were excluded from our NMA. This seems to be the main reason why the efficacy of aspirin was not better than that of placebo in our NMA. In addition, a lower dose of aspirin was mainly used in contrast with the moderate- to high-dose aspirin used in Asian populations with concerns of bleeding (44). Clopidogrel did not also show a significantly better efficacy than placebo in our NMA. Clopidogrel is a prodrug, which has to be converted into an active metabolite by CYP2C19 to inhibit platelet function. Because of the high prevalence of CYP2C19 polymorphism (poor metabolizer) in Asian populations (45), clopidogrel does not seem to show efficacy comparable to that in Western populations.

Cilostazol has multiple actions that affect various factors associated with thrombus formation and vascular occlusion, such as increasing nitric oxide (an endogenous vasodilatation factor), decreasing intracellular calcium concentration, and inhibiting the proliferation of smooth muscle cells (46). Therefore, cilostazol can reduce the risk of stroke in those with small-vessel disease prone to intracerebral hemorrhage and decrease the atherosclerotic burden in patients with intracranial atherosclerosis. Cilostazol protects all components of the blood-brain barrier, including the endothelial cells, pericytes, tight junction proteins, adherence junction proteins, and the basement membrane, suggesting that it also reduces hemorrhagic stroke (47). Furthermore, the reversible platelet inhibition mechanism enables a relatively rapid recovery time of platelet function and low bleeding risk (48). Genetic polymorphisms of CYP450 also affect cilostazol metabolism (49), but the influence on cilostazol is limited in Asia because of the low incidence of polymorphisms related to poor-metabolizers (50). These findings are consistent with our finding that cilostazol was associated with lower infarction and bleeding risks than other antiplatelet agents, given the prevalence of stroke and the high risk of bleeding in Asians. Interestingly, a recent study reported that a cilostazol-based combination with aspirin or clopidogrel was more efficacious in reducing IS than a single antiplatelet agent (aspirin or clopidogrel) without increasing the risk of hemorrhage (51). However, due to a lack of data on the separate outcomes, our NMA did not include this recent study, and we could have underestimated the efficacy and safety of the aspirin plus cilostazol combination (52). Further large-sample randomized trials of DAPT based on cilostazol are warranted.

This systematic review has several limitations. First, most of the antiplatelet agents did not show significantly better efficacies than placebo in our NMA. As mentioned above, the most important trials that tested aspirin's efficacy were excluded because they were conducted in Western countries. Therefore, aspirin was not significantly more efficacious than placebo in our NMA. Second, this is a study-level meta-analysis that lacked individual patient data. Although this NMA included trials with various durations of follow-up, we used relative RRs rather than hazard ratios, due to the deficient individual patient data. However, because all studies with follow-up durations within one month were included in the "before 72 hours from stroke onset" subgroup, the effect of the follow-up duration diversity may have been restricted to an extent during the subgroup analyses. Third, there was an inconsistency

between the direct and indirect evidence for the effects of aspirin and aspirin plus ticagrelor on recurrent IS. This inconsistency resolved during the subgroup analysis. Therefore, the increased heterogeneity was thought to originate from the differences in the durations from the symptom onset to treatment. Considering that there were no differences between the outcomes of the primary and subgroup analyses, the overall consistency is thought to have been satisfactory, meaning that our network model selection was appropriate. Fourth, although most included trials included Asian populations, two global trials (23,29) only involved 32% and 42% of Asians, respectively; one trial (20) used a subgroup analysis from a global trial, which is SOCRATES (53). All the populations used for our NMA were not purely Asian, and the subgroup analysis has a risk of randomization error. Finally, the mechanism of IS and the duration of treatment with DAPT were not considered, although they can influence the antiplatelet treatment strategy for secondary prevention.

In conclusion, this Bayesian NMA indicates that cilostazol is a better choice than other antiplatelet regimens for Asians with non-cardioembolic stroke or TIA, based on the efficacy and safety outcomes. The selection of appropriate antiplatelet agents may differ with the risk-benefit assessment outcome and the duration between symptom onset and treatment. Due to the limitations of this NMA, further head-to-head randomized trials are needed to determine the appropriate antiplatelet regimens for various clinical situations.

Acknowledgments

The authors would like to thank Eun-Ji Kang from the Medical Library of Korea University for searching abstracts and articles related to this study and Editage (www.editage.co.kr) for the English language editing.

Funding: This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (NRF-2020R1C1C1009294).

Footnote

Reporting Checklist: The authors have completed the PRISMA NMA reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-7951

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-7951). JMJ serves as an unpaid editorial board member of *Annals of Translational Medicine* from Nov 2019 to Oct 2021. JMJ currently serves on the Editorial Board of Neurology for this journal, JMJ reports other from Pfizer Pharmaceutical Company, other from Sanofi-Aventis Pharmaceutical Company, other from Daewoong Pharmaceutical Company, other from Otuska, other from Hanmi Pharmaceutical Company, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Jung SJ, Shim SR, Kim BJ, Jung JM. Antiplatelet regimens for Asian patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis. Ann Transl Med 2021;9(9):753. doi: 10.21037/atm-20-7951

Supplementary

Antiplatelet Regimens for Asian Patients with Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Network Meta-analysis

Table S1 Search strategy

Search No.	Medline	Embase	Cochrane Trials
#1	Stroke, Lacunar[mh] OR lacunar stroke*[tiab] OR lacunar infarct*[tiab] OR lacunar syndrome*[tiab] OR ischemic stroke*[tiab] OR ischaemic stroke*[tiab] OR ischemic brain stroke*[tiab] OR ischaemic brain stroke*[tiab] OR brain ischemia*[tiab] OR brain ischaemia*[tiab] OR cerebral ischemia*[tiab] OR cerebral ischaemia*[tiab] OR cerebrovascular ischemia*[tiab] OR cerebrovascular ischaemia*[tiab] OR ischemic brain[tiab] OR ischaemic brain[tiab] OR ischemic encephalopath*[tiab] OR ischaemicencephalopath*[tiab]	('lacunar stroke'/de OR (lacunar NEXT/1 (stroke* OR infarct* OR syndrome*)):ti,ab OR (isch*mic NEAR/3 stroke*):ti,ab OR (brain NEAR/3 isch*mi*):ti,ab OR (cerebral NEAR/3 isch*mia*):ti,ab OR (cerebrovascular NEAR/3 isch*mia*):ti,ab OR (isch*mic NEAR/3 encephalopath*):ti,ab)	[mh "Stroke, Lacunar"] OR (lacunar NEXT (stroke* OR infarct* OR syndrome*)):ti,ab OR (isch*mic NEAR/3 stroke*):ti,ab OR (brain NEAR/3 isch*mi*):ti,ab OR (cerebral NEAR/3 isch*mia*):ti,ab OR (cerebrovascular NEAR/3 isch*mia*):ti,ab OR (isch*mic NEAR/3 encephalopath*):ti,ab
#2	Cerebral Infarction[mh] OR brain infarct*[tiab] OR brain stem infarct*[tiab] OR cerebral infarct*[tiab] OR cerebrovascular infarct*[tiab] OR cortical infarct*[tiab] OR hemisphere infarct*[tiab] OR hemispheric infarct*[tiab]	('brain infarction'/exp OR ((brain OR cerebral OR cerebrovascular OR cortical OR hemispher*) NEXT/2 infarct*):ti,ab)	[mh "Cerebral Infarction"] OR ((brain OR cerebral OR cerebrovascular OR cortical OR hemispher*) NEXT/2 infarct*):ti,ab
#3	Ischemic Attack, Transient[mh] OR transient ischemic attack*[tiab] OR transient ischaemic attack*[tiab] OR transient brain ischemia*[tiab] OR transient brain ischaemia*[tiab] OR transient cerebral ischemia*[tiab] OR transient cerebral ischaemia*[tiab] OR (brain[tiab] AND (TIA[tiab] OR TIAs[tiab]))	('transient ischemic attack'/exp OR (transient NEAR/2 isch*mic NEAR/2 attack*):ti,ab OR (transient NEAR/2 (brain OR cerebral) NEAR/2 isch*mia*):ti,ab OR (brain NEAR/5 (TIA OR TIAs)):ti,ab)	[mh "Ischemic Attack, Transient"] OR (transient NEAR/2 isch*mic NEAR/2 attack*):ti,ab OR (transient NEAR/2 (brain OR cerebral) NEAR/2 isch*mia*):ti,ab OR (brain NEAR/5 (TIA OR TIAs)):ti,ab
#4	#1 OR #2 OR #3	#1 OR #2 OR #3	#1 OR #2 OR #3
#5	Platelet Aggregation Inhibitors[mh] OR platelet aggregation inhibitor*[tiab] OR platelet antiaggregant*[tiab] OR platelet anti-aggregant*[tiab] OR platelet inhibitor*[tiab] OR antiplatelet agent*[tiab] OR antiplatelet drug*[tiab] OR anti-platelet agent*[tiab] OR anti-platelet drug*[tiab] OR platelet antagonist*[tiab] OR antithrombotic agent*[tiab] OR anti-thrombotic agent*[tiab] OR thrombocyte aggregation inhibitor*[tiab]	('antithrombotic agent'/de OR ((platelet OR thrombocyte) NEXT/2 (inhibitor* OR antiaggregant* OR anti-aggregant* OR antagonist*)):ti,ab OR ((antiplatelet OR anti-platelet OR antithrombotic OR anti-thrombotic) NEXT/2 (drug* OR agent*)):ti,ab)	[mh "Platelet Aggregation Inhibitors"] OR ((platelet OR thrombocyte) NEXT/2 (inhibitor* OR antiaggregant* OR anti-aggregant* OR antagonist*)):ti,ab OR ((antiplatelet OR anti-platelet OR antithrombotic OR anti-thrombocytic) NEXT/2 (drug* OR agent*)):ti,ab
#6	Aspirin[mh] OR aspirin[tw] OR acetylsalicylic acid[tw] OR acetyl salicylic acid[tw] OR acetosalicylic acid[tw] OR Acylpyrin[tw] OR Colfarit[tw] OR Ecotrin[tw] OR Endosprin[tw] OR Magnecyl[tw] OR Micristin[tw] OR Polopirin[tw] OR Polopiryna[tw] OR Solupsan[tw] OR Zorprin[tw] OR Acetysal[tw] OR Aloxiprimum[tw] OR Dispril[tw] OR Easprin[tw] OR Solprin[tw]	('acetylsalicylic acid'/de OR (aspirin OR 'acetylsalicylic acid' OR 'acetyl salicylic acid' OR 'acetosalicylic acid' OR Acylpyrin OR Colfarit OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solupsan OR Zorprin OR Acetysal OR Aloxiprimum OR Dispril OR Easprin OR Solprin):ti,ab)	[mh Aspirin] OR (aspirin OR "acetylsalicylic acid" OR "acetyl salicylic acid" OR "acetosalicylic acid" OR Acylpyrin OR Colfarit OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solupsan OR Zorprin OR Acetysal OR Aloxiprimum OR Dispril OR Easprin OR Solprin):ti,ab
#7	Clopidogrel[mh] OR Clopidogrel[tw] OR SC 25989C[tw] OR SC 25990C[tw] OR SR 25989[tw] OR Iscover[tw] OR PCR-4099[tw] OR Plavix[tw]	clopidogrel/de OR (Clopidogrel OR SC-25989C OR SC-25990C OR SR-25989 OR Iscover OR PCR-4099 OR Plavix):ti,ab	[mh Clopidogrel] OR (Clopidogrel OR SC-25989C OR SC-25990C OR SR-25989 OR Iscover OR PCR-4099 OR Plavix):ti,ab
#8	Cilostazol[mh] OR Cilostazol[tw] OR OPC-13013[tw] OR Pletal[tw] OR pletaal[tw]	cilostazol/de OR (Cilostazol OR OPC-13013 OR Pletal OR pletaal):ti,ab	[mh Cilostazol] OR (Cilostazol OR OPC-13013 OR Pletal OR pletaal):ti,ab
#9	Ticagrelor[mh] OR Ticagrelor[tw] OR Brilique[tw] OR AZD 6140[tw] OR Brilinta[tw]	ticagrelor/de OR (Ticagrelor OR Brilique OR AZD-6140 OR Brilinta):ti,ab	[mh Ticagrelor] OR (Ticagrelor OR Brilique OR AZD-6140 OR Brilinta):ti,ab
#10	Prasugrel Hydrochloride[mh] OR Prasugrel[tw] OR CS 747[tw] OR Efient[tw] OR Effient[tw] OR LY 640315[tw]	prasugrel/de OR (Prasugrel OR CS-747 OR Efient OR Effient OR LY-640315):ti,ab	[mh "Prasugrel Hydrochloride"] OR (Prasugrel OR CS-747 OR Efient OR Effient OR LY-640315):ti,ab
#11	triflusal[tw] OR 2-acetoxy-4-trifluoromethylbenzoic acid[tw] OR Disgren[tw] OR tecnosal[tw] OR triflux[tw] OR aflen[tw]	triflusal/de OR (triflusal OR '2-acetoxy-4-trifluoromethylbenzoic acid' OR Disgren OR tecnosal OR triflux OR aflen):ti,ab	(triflusal OR "2-acetoxy-4-trifluoromethylbenzoic acid" OR Disgren OR tecnosal OR triflux OR aflen):ti,ab
#12	Dipyridamole[mh] OR Dipyridamole[tw] OR Dipyramidole[tw] OR Cerebrovase[tw] OR Persantine[tw] OR Persantin[tw] OR Curantil[tw] OR Curantyl[tw] OR Kurantil[tw] OR Miosen[tw] OR Novo-Dipiradol[tw] OR Antistenocardin[tw] OR Cléridium[tw] OR Cleridium[tw]	dipyridamole/de OR (Dipyridamole OR Dipyramidole OR Cerebrovase OR Persantine OR Persantin OR Curantil OR Curantyl OR Kurantil OR Miosen OR Novo-Dipiradol OR Antistenocardin OR Cléridium OR Cleridium):ti,ab	[mh Dipyridamole] OR (Dipyridamole OR Dipyramidole OR Cerebrovase OR Persantine OR Persantin OR Curantil OR Curantyl OR Kurantil OR Miosen OR Novo-Dipiradol OR Antistenocardin OR Cléridium OR Cleridium):ti,ab
#13	OR #5 to #12	OR #5 to #12	OR #5 to #12
#14	Secondary Prevention[mh] OR secondary prevention*[tw] OR secondary disease prevention*[tw] OR relapse prevention*[tw] OR recurrence prevention*[tw]	('secondary prevention'/de OR ((secondary OR relapse OR recurrence) NEXT/2 prevention*):ti,ab)	[mh "Secondary Prevention"] OR ((secondary OR relapse OR recurrence) NEXT/2 prevention*):ti,ab
#15	#4 AND #13 AND #14	#4 AND #13 AND #14	#4 AND #13 AND #14
#16	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])	('randomized controlled trial'/de OR 'controlled clinical trial'/de OR randomi?ed:ti,ab OR placebo:ti,ab OR 'clinical trial (topic)'/de OR randomly:ti,ab OR trial:ti) NOT (animal/exp NOT human/exp)	Cochrane Reviews 10 Trials 343
#17	#15 AND #16	#15 AND #16	
#18		('conference paper'/exp OR 'conference paper'/it OR 'conference proceeding':pt OR 'conference review'/it OR 'conference abstract':it OR 'abstract report'/exp)	
#19		#17 NOT #18	Trials

http://dx.doi.org/10.21037/atm-20-7951

Table S2 Characteristics of the enrolled trials

Trial	Antiplatelet regimens	Asian	F/U	Tx	Study	N	T	C	Male	Age	HTN	DM
1997 CAST, Chen[10]	Aspirin *vs.* Placebo	100%	1M	<48h	IS	20655	10335	10320	64%	63	25%	NC
2000 CSPS, Gotoh[11]	Cilostazol *vs.* Placebo	100%	22M		IS	1067	533	534	66%	65	61%	25%
2003 TOPALS, Ito[12]	A_T *vs.* Ticlopidine	100%	19M		IS/TIA	270	132	138	65%	67	47%	23%
2005 Chairangsarit[13]	A_D *vs.* Aspirin	100%	6M	<48h	IS	38	20	18	53%	64	50%	32%
2005 TOSS, Kwon[14]	A_Ci *vs.* Aspirin	100%	6M		IS	135	67	68	61%	62	58%	40%
2008 CASISP, Huang[15]	Cilostazol *vs.* Aspirin	100%	15M		IS	719	360	359	69%	60	79%	18%
2008 Fukuuchi[16]	Clopidogrel *vs.* Ticlopidine	100%	12M		IS	1151	573	578	73%	65	68%	19%
2008 PRoFESS, Sacco[17]	A_D *vs.* Clopidogrel	32%	30M		IS	20332	10181	10151	64%	66	74%	29%
2008 S-ACCESS, Shinohara[18]	Sarpogrelate *vs.* Aspirin	100%	19M		IS	1510	752	758	72%	65	70%	28%
2009 Guo[19]	Cilostazol *vs.* Aspirin	100%	12M		IS	68	34	34	35%	60	NC	NC
2009 Uchiyama[20]	Clopidogrel *vs.* Ticlopidine	100%	12M		IS	1869	941	928	72%	64	70%	22%
2010 CLAIR, Wong[21]	A_C *vs.* Aspirin	100%	1W	<72h	IS/TIA	98	46	52	78%	59	64%	38%
2010 CSPS2, Shinohara[22]	Cilostazol *vs.* Aspirin	100%	29M		IS	2757	1379	1378	72%	63	74%	29%
2011 CAIST, Lee[23]	Cilostazol *vs.* Aspirin	100%	3M	<48h	IS	458	231	227	62%	63	65%	35%
2011 JASAP, Uchiyama[24]	A_D *vs.* Aspirin	100%	15.3M		IS	1291	652	639	72%	66	89%	41%
2011 TOSS2, Kwon[25]	A_Ci *vs.* A_C	100%	7M		IS	457	232	225	52%	65	72%	43%
2012 ECLIPse, Han[26]	A_Ci *vs.* Aspirin	100%	3M		IS	203	100	103	75%	65	57%	29%
2012 Nakamura[27]	A_Ci *vs.* Aspirin	100%	6M	<48h	IS	76	38	38	74%	66	82%	35%
2013 CHANCE, Wang[28]	A_C *vs.* Aspirin	100%	3M	<24h	IS/TIA	5170	2584	2586	67%	63	66%	22%
2014 Yi[29]	A_C *vs.* Aspirin	100%	1M	<48h	IS	574	286	288	55%	69	73%	38%
2015 CATHARSIS, Uchiyama[30]	A_Ci *vs.* Aspirin	100%	24M		IS	163	83	80	66%	68	77%	37%
2015 He[31]	A_C *vs.* Aspirin	100%	2W	<72h	IS/TIA	690	343	347	57%	62	68%	42%
2015 Yi[32]	A_C *vs.* Aspirin	100%	6M	<48h	IS	979	490	489	56%	69	71%	34%
2016 COMPRESS, Hong[33]	A_C *vs.* Aspirin	100%	1M	<48h	IS	358	178	180	64%	67	67%	33%
2016 SOCRATES(A), Wang[34]	Ticagrelor *vs.* Aspirin	100%	3M	<24h	IS/TIA	3858	1933	1925	63%	64	69%	25%
2017 MAESTRO, Han[35]	Triflusal *vs.* Clopidogrel	100%	32M		IS	784	391	393	68%	61	61%	29%
2017 Zuo[36]	A_C *vs.* Aspirin	100%	3M		IS/TIA	200	66/66	68	61%	61	65%	32%
2018 PICASSO, Kim[37]	Cilostazol *vs.* Aspirin	100%	23M		IS/TIA	1534	766	768	62%	65	89%	33%
2019 ADS, Aoki[38]	A_Ci *vs.* Aspirin	100%	3M	<48h	IS	1201	600	601	66%	69	76%	32%
2019 PRASTRO-I, Ogawa[39]	Prasugrel *vs.* Clopidogrel	100%	25M		IS	3747	1885	1862	79%	62	80%	33%
2019 PRINCE, Wang[40]	A_Ti *vs.* A_C	100%	3M	<24h	IS/TIA	675	336	339	74%	60	61%	25%
2020 THALES, Johnston[41]	A_Ti *vs.* Aspirin	42%	1M	<24h	IS/TIA	11016	5523	5493	62%	65	78%	29%

A_C, aspirin plus clopidogrel; A_Ci, aspirin plus cilostazol; A_D, aspirin plus dipyridamole; A_T, aspirin plus ticlopidine; A_Ti, aspirin plus ticagrelor; C, number of comparator group; F/U, follow-up period; IS, ischemic stroke; N, number of total participants; Study, study population; T, number of treatment group; TIA, transient ischemic stroke; Tx, time from symptom onset to treatment.

http://dx.doi.org/10.21037/atm-20-7951

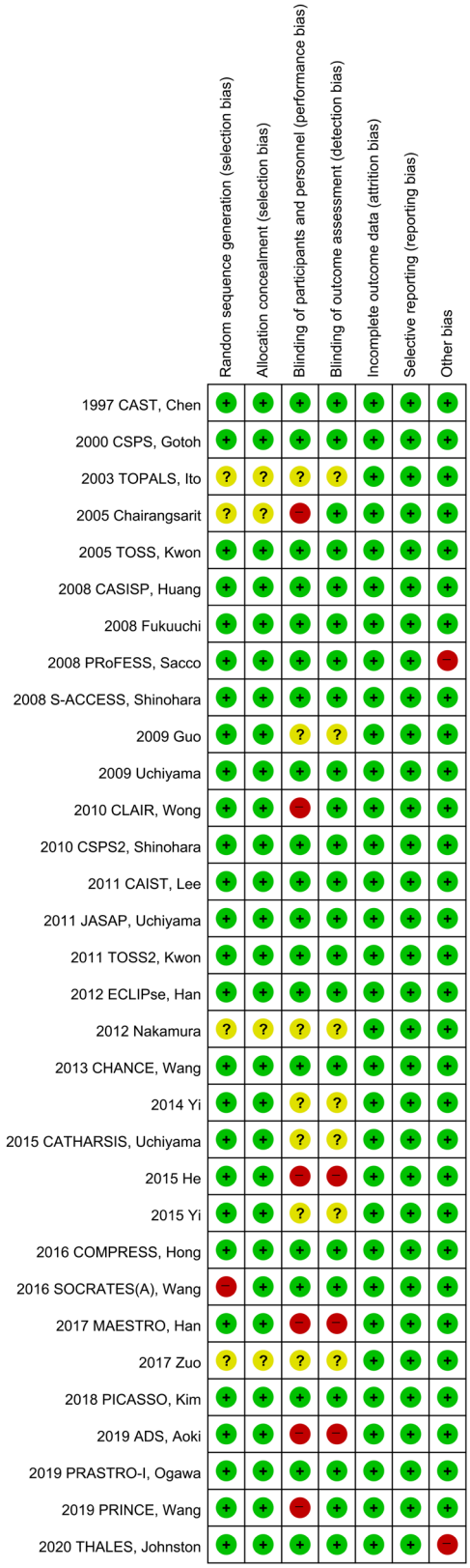

Figure S1 The risk of bias depicted as colors (red: high-risk; green: low-risk; yellow: unclear).

http://dx.doi.org/10.21037/atm-20-7951

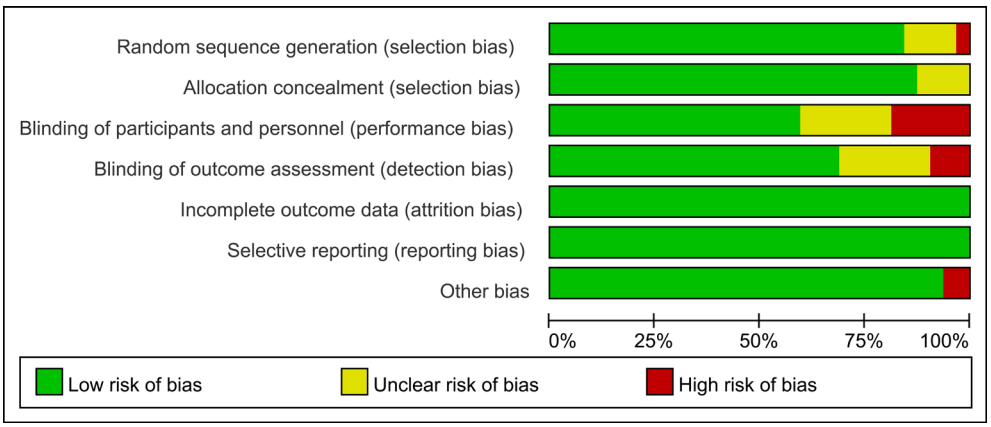

Figure S2 Total graph of the risk of bias of the entire network meta-analysis. Random sequence generation: TOPALS[12], Chairangsarit[13], Nakamura[27], and Zuo[36] did not describe their detailed randomization methods; Wang[34] is the sub-analysis of the Asian population in the SOCRATES[52] trial. Blinding of the participants, personnel, and outcome assessment: TOPALS[12], Guo[19], Nakamura[27], Yi2014[29], CATHARSIS[30], Yi2015[32], and Zuo[36]did not describe the methods they used to blind the participants and personnel, or to blind the outcome assessments; He[31], MAESTRO[35], and ADS[38] were open-label trials. Other types of bias: PRoFESS[17] and THALES[41] were worldwide trials and did not contain only an Asian population.

http://dx.doi.org/10.21037/atm-20-7951

Table S3 League tables of the relative risks and 95% credible intervals for (A) recurrent stroke, (B) recurrent ischemic stroke, (C) composite vascular events, (D) major bleeding, and (E) all bleeding

(A) Recurrent stroke

	A_C	Cilostazol	A_Ti	A_Ci	Ticagrelor	Aspirin	Ticlopidine	Placebo	Sarpogrelate	A_T	Prasugrel	Clopidogrel	A_D	Triflusal
A_C														
Cilostazol	0.91 0.53-1.34													
A_Ti	0.85 0.54-1.38	0.92 0.58-1.80												
A_Ci	0.83 0.44-1.50	0.91 0.47-1.81	0.97 0.45-1.91											
Ticagrelor	0.73 0.34-1.22	0.78 0.42-1.48	0.85 0.37-1.52	0.85 0.38-1.83										
Aspirin	0.57 0.39-0.75	0.64 0.46-0.88	0.68 0.38-0.97	0.70 0.37-1.24	0.81 0.46-1.41									
Ticlopidine	0.52 0.14-1.53	0.56 0.17-1.80	0.61 0.16-1.84	0.62 0.16-2.11	0.72 0.20-2.48	0.89 0.28-2.68								
Placebo	0.53 0.27-0.83	0.58 0.36-0.91	0.62 0.28-1.03	0.64 0.29-1.28	0.74 0.36-1.47	0.91 0.58-1.38	1.03 0.30-3.52							
Sarpogrelate	0.51 0.23-0.91	0.56 0.29-1.07	0.61 0.25-1.12	0.61 0.26-1.35	0.71 0.31-1.57	0.87 0.48-1.56	0.98 0.28-3.59	0.96 0.47-1.98						
A_T	0.38 0.07-1.77	0.42 0.09-2.06	0.45 0.08-2.10	0.46 0.08-2.34	0.54 0.10-2.77	0.66 0.14-3.09	0.74 0.26-2.20	0.72 0.14-3.59	0.75 0.14-3.89					
Prasugrel	0.41 0.13-1.06	0.44 0.16-1.26	0.48 0.14-1.29	0.49 0.15-1.47	0.56 0.18-1.77	0.69 0.26-1.88	0.79 0.29-2.17	0.75 0.26-2.27	0.79 0.25-2.51	1.05 0.24-4.39				
Clopidogrel	0.41 0.15-0.87	0.44 0.18-1.05	0.48 0.16-1.07	0.49 0.17-1.25	0.56 0.21-1.46	0.69 0.31-1.53	0.77 0.35-1.74	0.75 0.30-1.88	0.79 0.29-2.11	1.05 0.26-3.85	0.98 0.54-1.78			
A_D	0.40 0.18-0.73	0.43 0.21-0.86	0.47 0.19-0.92	0.47 0.20-1.08	0.55 0.24-1.24	0.67 0.36-1.25	0.76 0.30-1.99	0.74 0.35-1.58	0.77 0.33-1.79	1.03 0.24-4.09	0.97 0.44-2.11	0.98 0.58-1.65		
Triflusal	0.30 0.09-0.90	0.33 0.11-1.05	0.36 0.10-1.08	0.36 0.10-1.25	0.42 0.12-1.45	0.52 0.17-1.57	0.58 0.20-1.78	0.57 0.17-1.88	0.59 0.17-2.08	0.81 0.17-3.59	0.75 0.29-1.93	0.75 0.36-1.59	0.76 0.32-1.89	

(B) Recurrent ischemic stroke

	A_C	A_Ti	A_Ci	Cilostazol	Ticagrelor	Aspirin	Ticlopidine	A_T	Sarpogrelate	A_D	Clopidogrel	Placebo	Prasugrel	Triflusal
A_C														
A_Ti	0.85 0.52-1.43													
A_Ci	0.73 0.37-1.41	0.85 0.38-1.82												
Cilostazol	0.74 0.41-1.12	0.86 0.42-1.41	0.98 0.46-1.99											
Ticagrelor	0.67 0.31-1.19	0.79 0.32-1.48	0.90 0.37-2.02	0.90 0.46-1.75										
Aspirin	0.54 0.35-0.72	0.65 0.34-0.94	0.72 0.37-1.34	0.74 0.53-1.07	0.82 0.45-1.47									
Ticlopidine	0.42 0.13-1.18	0.49 0.14-1.42	0.57 0.16-1.89	0.57 0.19-1.74	0.62 0.19-2.08	0.76 0.27-2.21								
A_T	0.40 0.07-1.85	0.47 0.07-2.21	0.55 0.09-2.82	0.56 0.10-2.68	0.61 0.10-3.12	0.74 0.14-3.42	0.97 0.28-3.00							
Sarpogrelate	0.44 0.19-0.83	0.51 0.20-1.03	0.59 0.23-1.40	0.59 0.29-1.22	0.65 0.28-1.53	0.79 0.42-1.49	1.04 0.30-3.45	1.06 0.21-6.35						
A_D	0.40 0.17-0.81	0.47 0.18-0.99	0.54 0.21-1.34	0.54 0.26-1.19	0.60 0.25-1.50	0.73 0.37-1.46	0.96 0.42-2.08	0.98 0.24-4.43	0.91 0.37-2.31					
Clopidogrel	0.39 0.14-0.93	0.46 0.15-1.13	0.5 0.17-1.51	0.53 0.21-1.39	0.58 0.21-1.68	0.71 0.30-1.73	0.93 0.52-1.64	0.96 0.26-3.81	0.89 0.31-2.65	0.97 0.56-1.70				
Placebo	0.41 0.20-0.67	0.48 0.21-0.84	0.54 0.24-1.15	0.56 0.34-0.9	0.61 0.28-1.28	0.74 0.46-1.18	0.95 0.30-3.00	1.01 0.19-5.15	0.94 0.42-2.06	1.01 0.44-2.30	1.04 0.37-2.82			
Prasugrel	0.37 0.11-1.06	0.43 0.12-1.27	0.49 0.13-1.71	0.49 0.16-1.59	0.54 0.16-1.90	0.66 0.22-1.98	0.87 0.37-2.04	0.90 0.22-4.17	0.83 0.24-2.94	0.91 0.39-2.13	0.93 0.49-1.77	0.89 0.28-2.94		
Triflusal	0.24 0.06-0.81	0.28 0.07-0.98	0.33 0.08-1.24	0.33 0.10-1.17	0.36 0.10-1.40	0.44 0.13-1.50	0.57 0.21-1.61	0.59 0.13-3.09	0.55 0.14-2.19	0.60 0.22-1.63	0.62 0.27-1.42	0.59 0.17-2.20	0.66 0.23-1.84	

(C) Composite vascular events

	A_Ti	A_C	Cilostazol	A_Ci	Ticagrelor	Ticlopidine	A_T	Aspirin	Prasugrel	Clopidogrel	A_D	Sarpogrelate	Placebo	Triflusal
A_Ti														
A_C	0.69 0.38-1.24													
Cilostazol	0.62 0.31-1.20	0.90 0.63-1.20												
A_Ci	0.55 0.25-1.21	0.79 0.48-1.37	0.89 0.53-1.60											
Ticagrelor	0.54 0.26-1.07	0.77 0.50-1.12	0.86 0.58-1.26	0.97 0.51-1.70										
Ticlopidine	0.47 0.18-1.21	0.68 0.32-1.38	0.76 0.37-1.55	0.85 0.35-1.96	0.88 0.41-1.87									
A_T	0.42 0.12-1.52	0.61 0.20-1.92	0.68 0.22-2.19	0.76 0.22-2.62	0.78 0.25-2.60	0.89 0.37-2.27								
Aspirin	0.44 0.23-0.87	0.65 0.49-0.79	0.71 0.57-0.88	0.78 0.47-1.26	0.81 0.59-1.15	0.94 0.48-1.84	0.96 0.31-3.12							
Prasugrel	0.43 0.16-1.04	0.62 0.29-1.19	0.69 0.34-1.33	0.77 0.33-1.72	0.79 0.38-1.63	0.90 0.49-1.65	1.00 0.33-2.88	0.96 0.51-1.82						
Clopidogrel	0.42 0.18-0.91	0.60 0.33-1.01	0.67 0.38-1.14	0.76 0.36-1.47	0.81 0.43-1.40	0.88 0.56-1.40	0.96 0.36-2.56	0.94 0.58-1.54	0.97 0.65-1.45					
A_D	0.42 0.19-0.87	0.60 0.36-0.95	0.67 0.42-1.07	0.76 0.39-1.42	0.78 0.46-1.32	0.88 0.52-1.51	0.97 0.34-2.66	0.94 0.63-1.43	0.97 0.60-1.59	1.00 0.75-1.33				
Sarpogrelate	0.41 0.19-0.83	0.60 0.37-0.90	0.67 0.43-1.02	0.75 0.38-1.37	0.78 0.46-1.26	0.88 0.40-1.87	0.98 0.29-3.00	0.94 0.64-1.35	0.97 0.46-2.01	0.99 0.53-1.81	0.99 0.56-1.70			
Placebo	0.38 0.19-0.77	0.56 0.37-0.74	0.61 0.45-0.80	0.67 0.38-1.15	0.70 0.46-1.05	0.81 0.39-1.64	0.83 0.26-2.74	0.86 0.65-1.08	0.88 0.44-1.72	0.91 0.51-1.56	0.91 0.55-1.45	0.91 0.57-1.42		
Triflusal	0.28 0.10-0.78	0.41 0.18-0.92	0.46 0.21-1.03	0.51 0.20-1.29	0.53 0.23-1.24	0.60 0.28-1.32	0.64 0.21-2.19	0.64 0.30-1.41	0.67 0.32-1.38	0.69 0.37-1.25	0.68 0.35-1.32	0.68 0.30-1.65	0.74 0.34-1.73	

(D) Major bleeding

	Cilostazol	Ticlopidine	A_T	Prasugrel	Placebo	Ticagrelor	A_Ci	Clopidogrel	Aspirin	A_D	A_C	A_Ti
Cilostazol												
Ticlopidine	0.61 0.13-2.58											
A_T	0.59 0.08-3.97	0.96 0.26-3.49										
Prasugrel	0.51 0.10-2.16	0.82 0.24-2.69	0.85 0.14-4.85									
Placebo	0.49 0.18-1.23	0.79 0.18-3.56	0.82 0.12-5.81	0.94 0.22-4.52								
Ticagrelor	0.50 0.15-1.55	0.82 0.15-4.22	0.83 0.10-6.68	0.99 0.18-5.25	1.02 0.30-3.18							
A_Ci	0.38 0.12-1.14	0.61 0.13-3.22	1.55 0.09-5.00	0.76 0.15-3.85	0.77 0.26-2.42	0.76 0.20-3.06						
Clopidogrel	0.37 0.10-1.22	0.60 0.26-1.37	0.62 0.13-2.97	0.73 0.31-1.72	0.76 0.20-2.54	0.73 0.18-3.12	0.98 0.23-3.66					
Aspirin	0.37 0.18-0.69	0.60 0.16-2.29	0.63 0.10-3.81	0.70 0.19-2.91	0.76 0.37-1.52	0.74 0.25-1.99	0.93 0.36-2.28	0.95 0.36-2.94				
A_D	0.32 0.11-0.88	0.53 0.17-1.52	0.54 0.10-2.91	0.64 0.21-1.92	0.66 0.22-1.84	0.64 0.18-2.33	0.86 0.24-2.67	0.87 0.43-1.75	0.88 0.38-1.93			
A_C	0.24 0.09-0.59	0.40 0.08-1.74	0.41 0.05-2.94	0.48 0.10-2.22	0.52 0.20-1.28	0.49 0.15-1.60	0.63 0.22-1.66	0.66 0.18-2.30	0.68 0.34-1.24	0.75 0.25-2.10		
A_Ti	0.13 0.04-0.36	0.21 0.04-1.03	0.21 0.03-1.68	0.25 0.05-1.31	0.26 0.09-0.78	0.26 0.07-0.97	0.33 0.10-1.15	0.34 0.10-1.37	0.35 0.16-0.80	0.40 0.13-1.30	0.53 0.21-1.33	

(E) All bleeding

	Cilostazol	Placebo	Sarpogrelate	Triflusal	Clopidogrel	Prasugrel	Aspirin	A_D	Ticagrelor	A_Ci	A_C	A_Ti
Cilostazol												
Placebo	1.03 0.50-2.11											
Sarpogrelate	0.93 0.55-1.49	0.88 0.37-2.09										
Triflusal	0.84 0.33-1.88	0.79 0.25-2.32	0.90 0.34-2.21									
Clopidogrel	0.68 0.34-1.16	0.64 0.25-1.57	0.73 0.35-1.40	0.80 0.43-1.55								
Prasugrel	0.66 0.29-1.28	0.62 0.22-1.66	0.70 0.30-1.53	0.77 0.34-1.71	0.96 0.63-1.48							
Aspirin	0.64 0.47-0.80	0.61 0.28-1.29	0.68 0.44-1.05	0.76 0.33-1.83	0.93 0.54-1.68	0.97 0.47-2.02						
A_D	0.63 0.37-0.95	0.59 0.25-1.36	0.68 0.37-1.16	0.75 0.37-1.59	0.92 0.64-1.35	0.95 0.54-1.70	0.98 0.65-1.40					
Ticagrelor	0.53 0.28-0.96	0.50 0.19-1.26	0.57 0.28-1.15	0.63 0.24-1.78	0.78 0.37-1.75	0.81 0.34-2.01	0.83 0.48-1.45	0.85 0.44-1.70				
A_Ci	0.43 0.12-1.25	0.40 0.10-1.47	0.46 0.13-1.46	0.52 0.12-1.96	0.64 0.17-2.04	0.66 0.17-2.35	0.67 0.20-1.93	0.69 0.19-2.09	0.81 0.21-2.65			
A_C	0.41 0.26-0.61	0.40 0.17-0.90	0.44 0.26-0.75	0.49 0.20-1.22	0.61 0.33-1.16	0.63 0.30-1.37	0.65 0.46-0.89	0.66 0.40-1.10	0.78 0.40-1.47	0.95 0.31-3.35		
A_Ti	0.26 0.13-0.48	0.25 0.09-0.63	0.28 0.13-0.57	0.31 0.11-0.88	0.39 0.18-0.87	0.40 0.16-1.01	0.41 0.23-0.72	0.42 0.21-0.84	0.49 0.22-1.08	0.60 0.18-2.30	0.63 0.39-1.02	

http://dx.doi.org/10.21037/atm-20-7951

Table S4 Surface under the cumulative ranking curve (SUCRA) values and ranks

Antiplatelet Regimens	Recurrent stroke		Recurrent ischemic stroke		Composite vascular events		Major bleeding		All bleeding	
	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
Aspirin	0.4986558	6	0.5261077	6	0.2819797	8	0.41287955	9	0.47955682	7
Cilostazol	0.8349288	2	0.7444500	4	0.7612962	3	0.91107045	1	0.86606136	1
Clopidogrel	0.2695135	12	0.3274346	11	0.3518019	10	0.43967727	8	0.55560682	5
Placebo	0.4196519	8	0.3137692	12	0.2276981	13	0.61278409	5	0.81932727	2
Prasugrel	0.2947077	11	0.2967981	13	0.4026769	9	0.61795227	4	0.50163182	6
Sarpogrelate	0.4045115	9	0.3679038	9	0.3468173	12	-	-	0.80729773	3
Ticagrelor	0.6566538	5	0.6720212	5	0.6247096	5	0.60345227	6	0.34960455	9
Ticlopidine	0.4582615	7	0.3974577	7	0.4912962	6	0.71462500	2	-	-
Triflusal	0.1497942	14	0.1176423	14	0.1153077	14	-	-	0.70073409	4
Aspirin + Cilostazol	0.7525500	4	0.7457423	3	0.6477731	4	0.46839318	7	0.25909091	10
Aspirin + Clopidogrel	0.9085288	1	0.9366154	1	0.8468385	2	0.20552500	11	0.17658409	11
Aspirin + Dipyridamole	0.2407692	13	0.3317865	10	0.3479500	11	0.32975909	10	0.45227273	8
Aspirin + Ticagrelor	0.7950154	3	0.8417442	2	0.9534019	1	0.03577273	12	0.03223182	12
Aspirin + Ticlopidine	0.3164577	10	0.3805269	8	0.4718558	7	0.64810909	3	-	-

http://dx.doi.org/10.21037/atm-20-7951

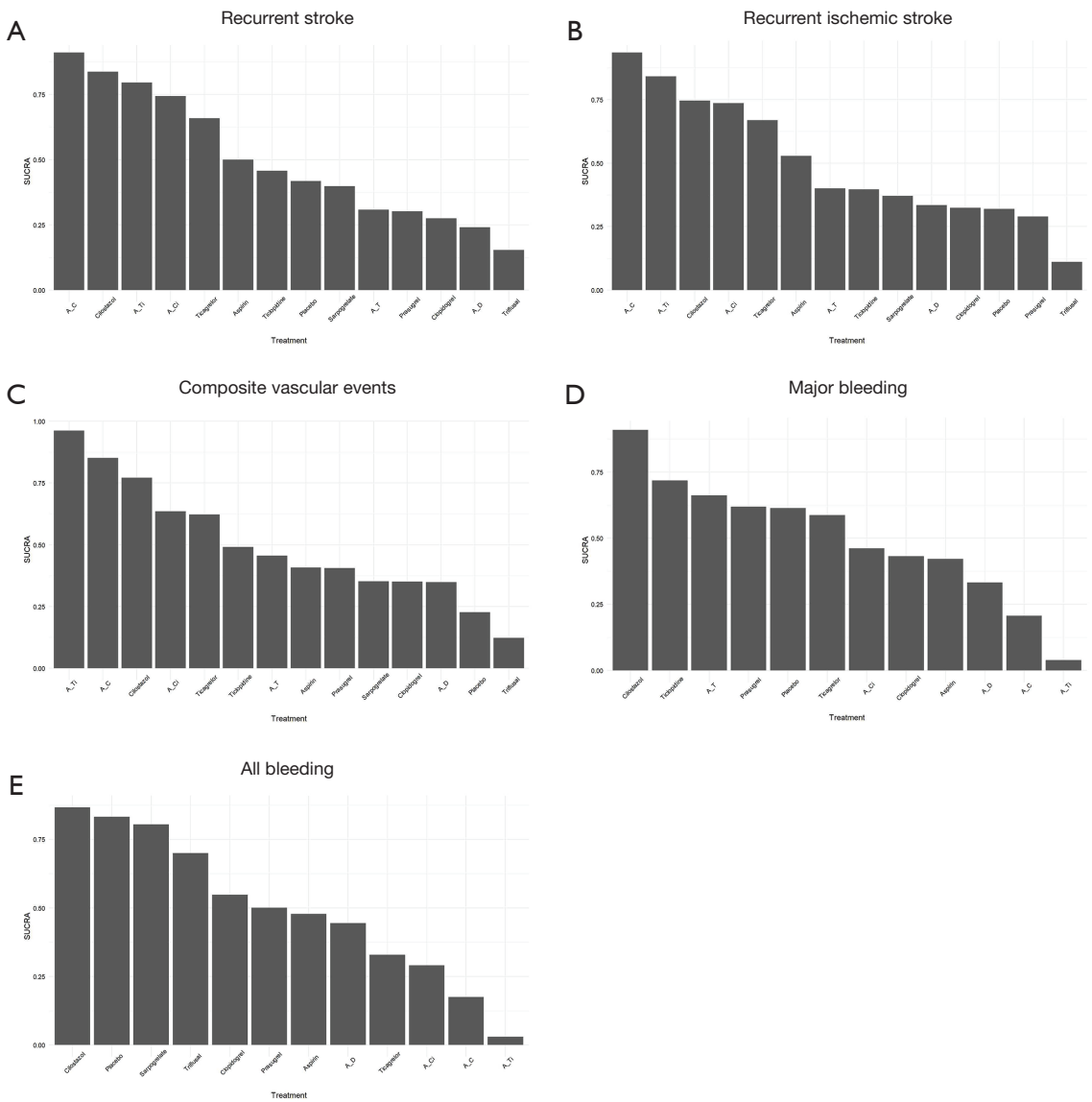

Figure S3 Surface under the cumulative ranking curve (SUCRA) rankograms of the antiplatelet regimens. (A) SUCRA rankogram of the antiplatelet regimens for the recurrent stroke. Aspirin plus clopidogrel ranked first, followed by cilostazol. (B) SUCRA rankogram of the antiplatelet regimens for the recurrent ischemic stroke. Aspirin plus ticagrelor ranked first, aspirin plus clopidogrel second, and cilostazol ranked fourth. (C) SUCRA rankogram of the antiplatelet regimens for the composite vascular events. Aspirin plus ticagrelor ranked first, aspirin plus clopidogrel second, and cilostazol ranked third. (D) SUCRA rankogram of the antiplatelet regimens for the major bleeding. Cilostazol ranked first, and aspirin plus ticagrelor ranked the last. (E) SUCRA rankogram of the antiplatelet regimens for the all bleeding. Cilostazol ranked first, and aspirin plus ticagrelor ranked the last.

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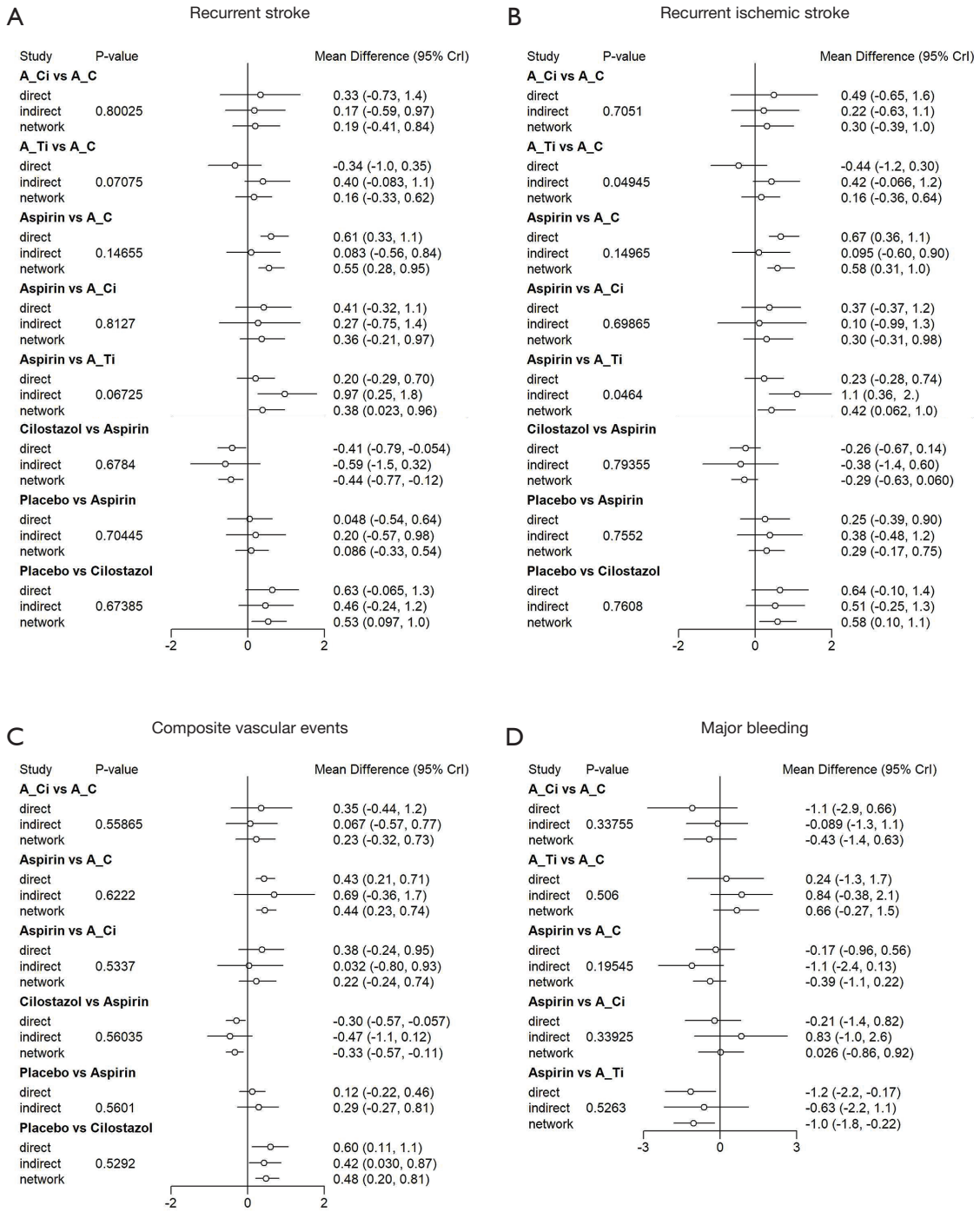

Figure S4 Inconsistency assessments using the node-splitting method. (A) Inconsistency assessments using the node-splitting method for the recurrent stroke. There was no evidence of inconsistencies between the effect estimates of direct and indirect evidence (all P-value of >0.05). (B) Inconsistency assessments using the node-splitting method for the recurrent ischemic stroke. There was no evidence of inconsistencies between the effect estimates of direct and indirect evidence except in the aspirin *vs.* aspirin plus ticagrelor (P-value=0.046). (C) Inconsistency assessments using the node-splitting method for the composite vascular events. There was no evidence of inconsistencies between the effect estimates of direct and indirect evidence (all P-value of >0.05). (D) Inconsistency assessments using the node-splitting method for the major bleeding. There was no evidence of inconsistencies between the effect estimates of direct and indirect evidence (all P-value of >0.05).

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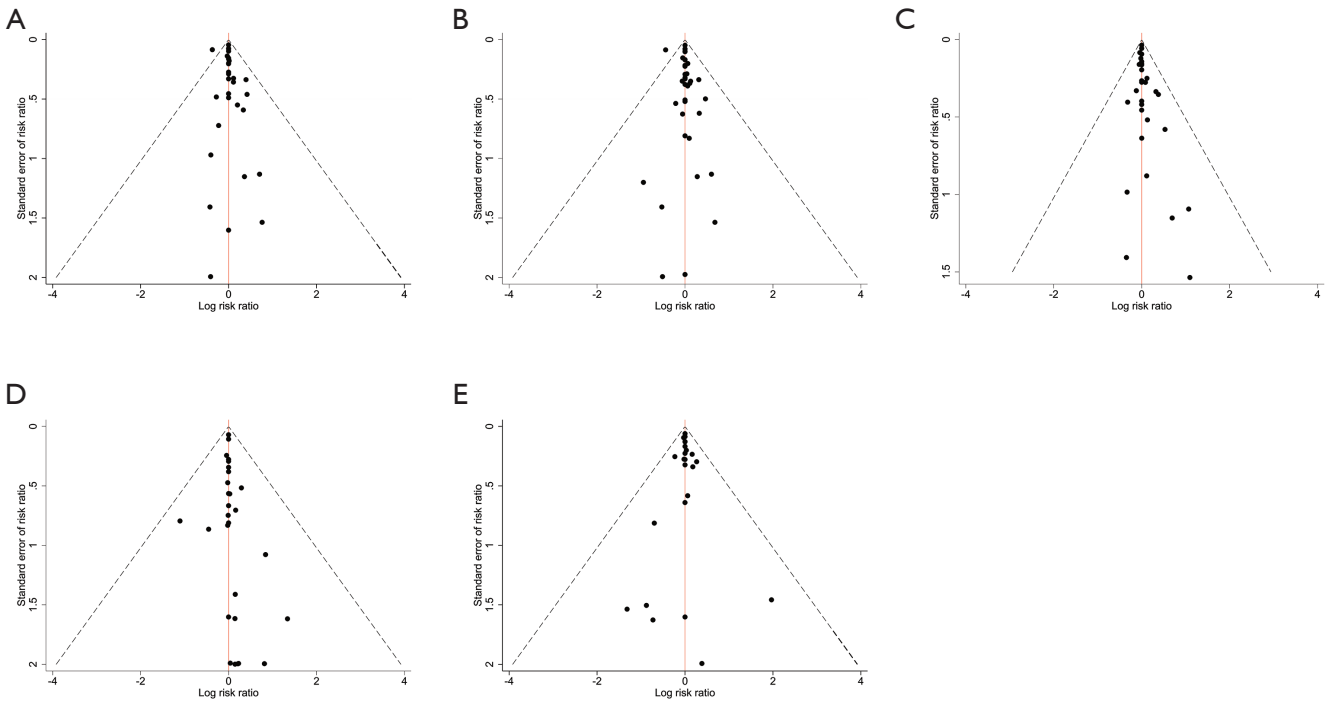

Figure S5 Funnel plots of the antiplatelet regimens of the enrolled trials. The symmetrical shape of the funnel plots demonstrates that there is no evidence of publication bias in this network meta-analysis. (A) Recurrent stroke, (B) Recurrent ischemic stroke, (C) Composite vascular events, (D) Major bleeding, and (E) All bleeding.

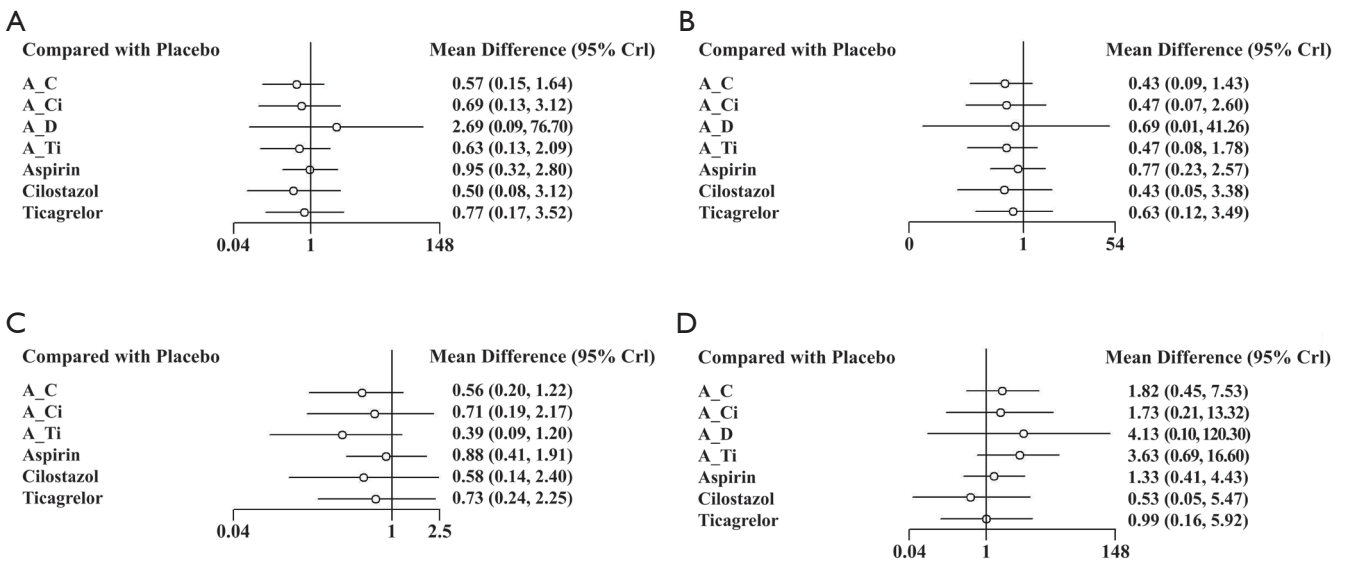

Figure S6 Forrest plots of the antiplatelet regimens compared with placebo for (A) recurrent stroke, (B) recurrent ischemic stroke, (C) composite vascular events, and (D) major bleeding, in the subgroup analysis (less than 72 hours).

http://dx.doi.org/10.21037/atm-20-7951

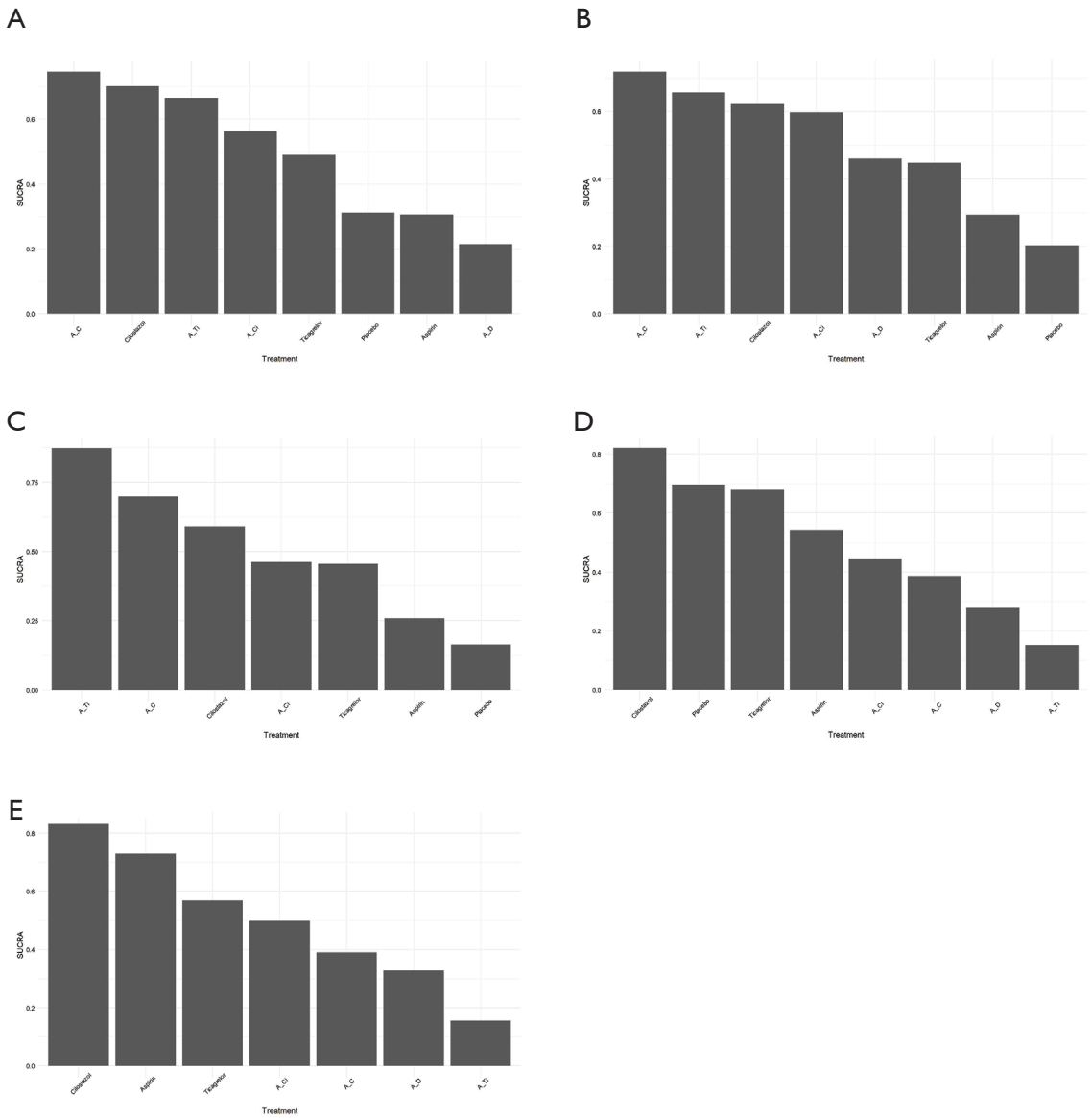

Figure S7 Surface under the cumulative ranking curve (SUCRA) rankograms of the antiplatelet regimens for (A) recurrent stroke, (B) recurrent ischemic stroke, (C) composite vascular events, and (D) major bleeding, in the subgroup analysis (less than 72 hours).

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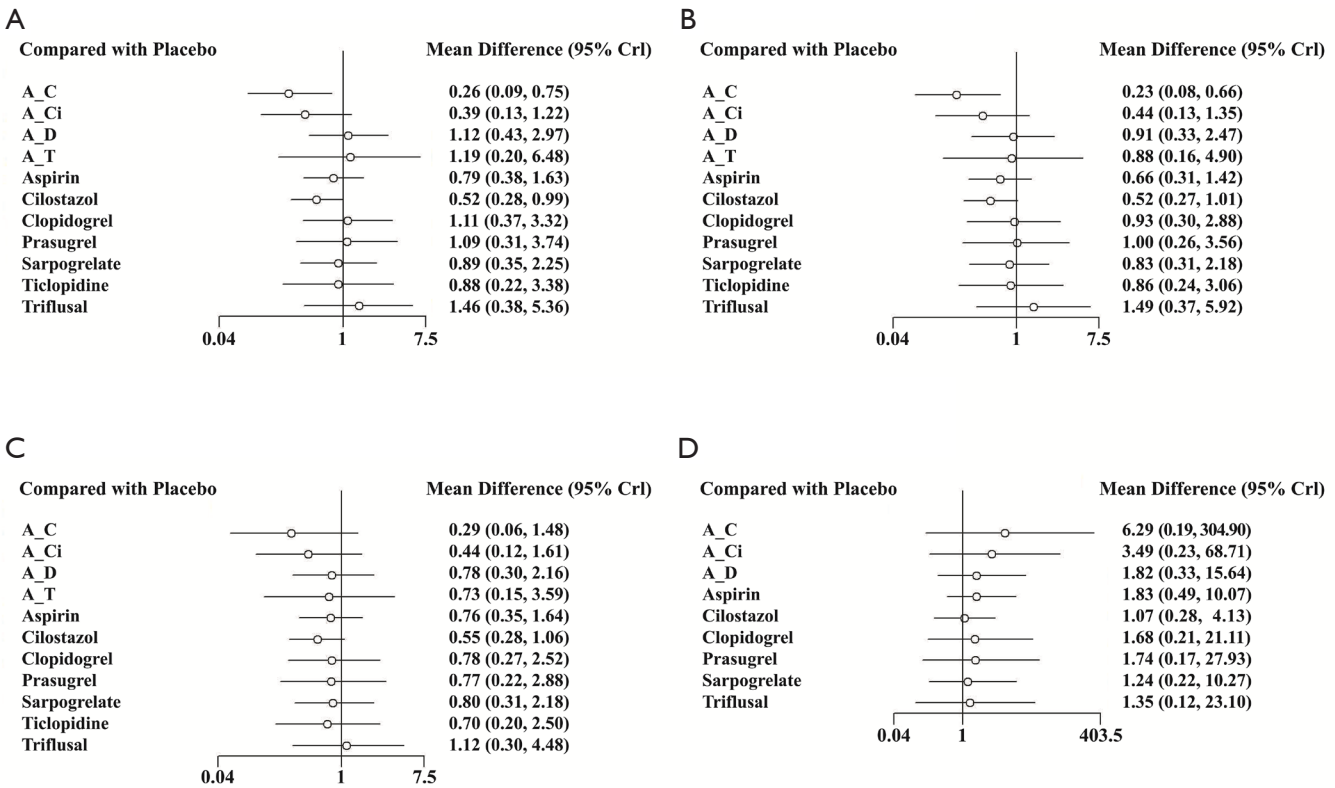

Figure S8 Forrest plots of the antiplatelet regimens compared with a placebo for (A) recurrent stroke, (B) recurrent ischemic stroke, (C) composite vascular events, and (D) all bleeding, in the subgroup analysis (not less than 72 hours).

http://dx.doi.org/10.21037/atm-20-7951

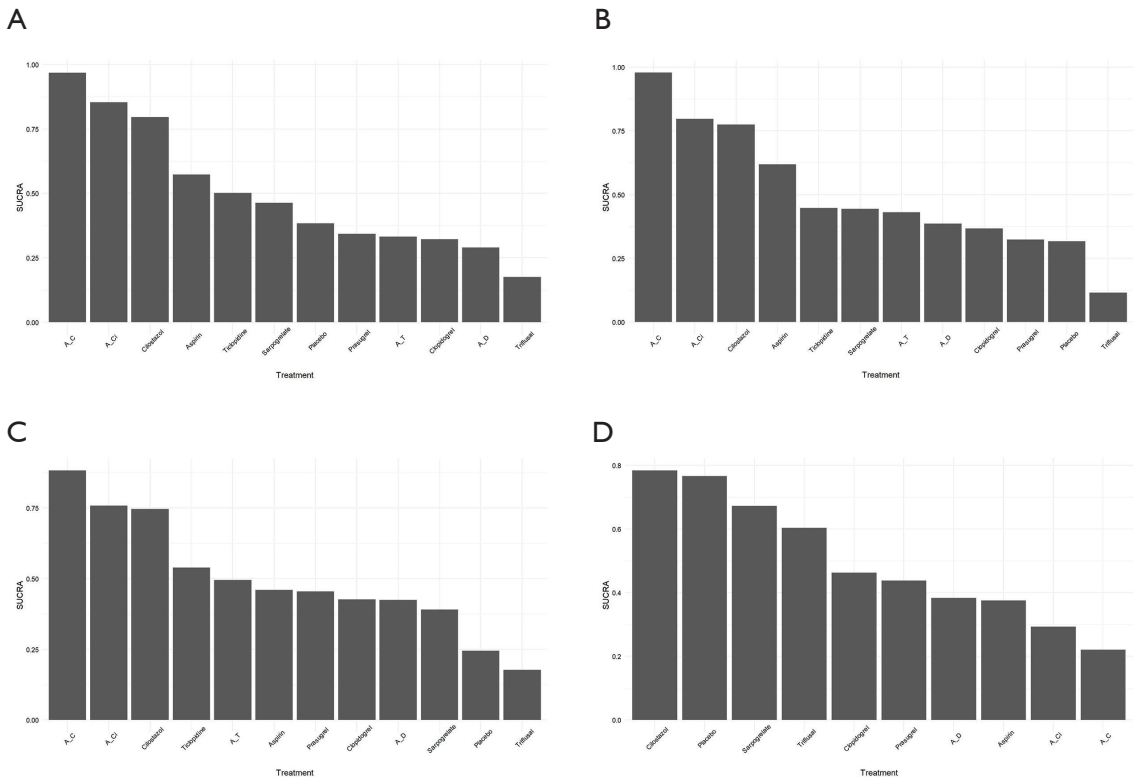

Figure S9 Surface under the cumulative ranking curve (SUCRA) rankograms of the antiplatelet regimens for (A) recurrent stroke, (B) recurrent ischemic stroke, (C) composite vascular events, and (D) all bleeding, in the subgroup analysis (not less than 72 hours).

http://dx.doi.org/10.21037/atm-20-7951