

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-thrombotic) 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

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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
1997 CAST, Chen	+	+	+	+	+	+	+
2000 CSPS, Gotoh	+	+	+	+	+	+	+
2003 TOPALS, Ito	?	?	?	?	+	+	+
2005 Chairangsarit	?	?	●	+	+	+	+
2005 TOSS, Kwon	+	+	+	+	+	+	+
2008 CASISP, Huang	+	+	+	+	+	+	+
2008 Fukuuchi	+	+	+	+	+	+	+
2008 PRoFESS, Sacco	+	+	+	+	+	+	●
2008 S-ACCESS, Shinohara	+	+	+	+	+	+	+
2009 Guo	+	+	?	?	+	+	+
2009 Uchiyama	+	+	+	+	+	+	+
2010 CLAIR, Wong	+	+	●	+	+	+	+
2010 CSPS2, Shinohara	+	+	+	+	+	+	+
2011 CAIST, Lee	+	+	+	+	+	+	+
2011 JASAP, Uchiyama	+	+	+	+	+	+	+
2011 TOSS2, Kwon	+	+	+	+	+	+	+
2012 ECLIPse, Han	+	+	+	+	+	+	+
2012 Nakamura	?	?	?	?	+	+	+
2013 CHANCE, Wang	+	+	+	+	+	+	+
2014 Yi	+	+	?	?	+	+	+
2015 CATHARSIS, Uchiyama	+	+	?	?	+	+	+
2015 He	+	+	●	●	+	+	+
2015 Yi	+	+	?	?	+	+	+
2016 COMPRESS, Hong	+	+	+	+	+	+	+
2016 SOCRATES(A), Wang	●	+	+	+	+	+	+
2017 MAESTRO, Han	+	+	●	●	+	+	+
2017 Zuo	?	?	?	?	+	+	+
2018 PICASSO, Kim	+	+	+	+	+	+	+
2019 ADS, Aoki	+	+	●	●	+	+	+
2019 PRASTRO-I, Ogawa	+	+	+	+	+	+	+
2019 PRINCE, Wang	+	+	●	+	+	+	+
2020 THALES, Johnston	+	+	+	+	+	+	●

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

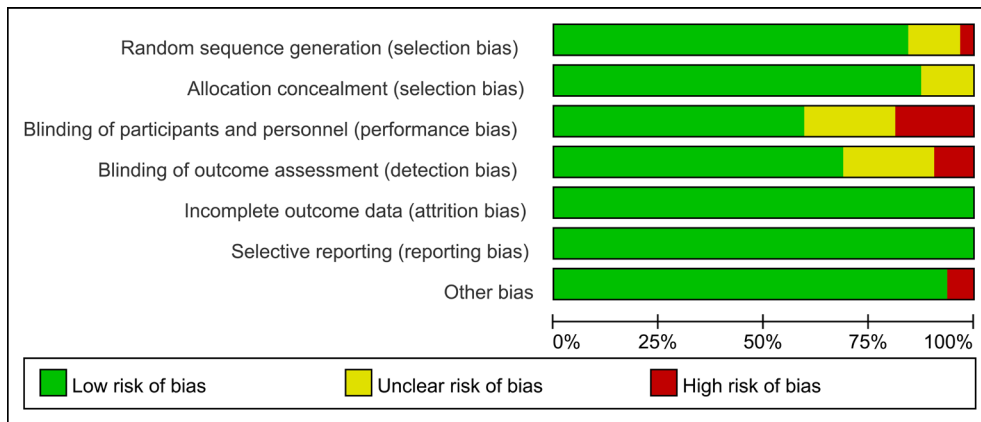


Figure S2 Total graph of the risk of bias of the entire network meta-analysis. Random sequence generation: TOPALS¹², Chairangsarit¹³, Nakamura²⁷, and Zuo³⁶ did not describe their detailed randomization methods; Wang³⁴ is the sub-analysis of the Asian population in the SOCRATES⁵² trial. Blinding of the participants, personnel, and outcome assessment: TOPALS¹², Guo¹⁹, Nakamura²⁷, Yi2014²⁹, CATHARSIS³⁰, Yi2015³², and Zuo³⁶ did not describe the methods they used to blind the participants and personnel, or to blind the outcome assessments; He³¹, MAESTRO³⁵, and ADS³⁸ were open-label trials. Other types of bias: PRoFESS¹⁷ and THALES⁴¹ were worldwide trials and did not contain only an Asian population.

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	-	-

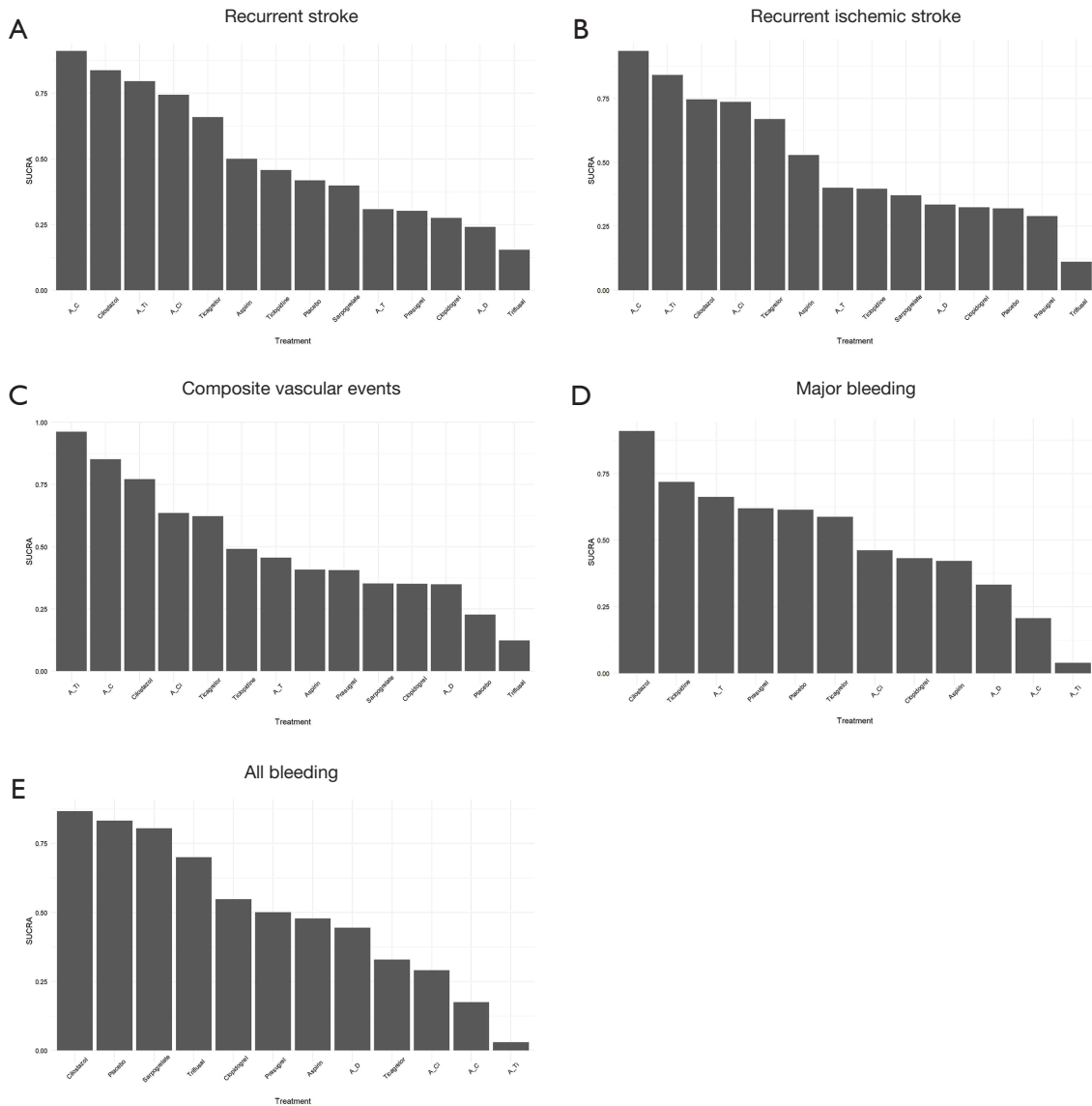


Figure S3 Surface under the cumulative ranking curve (SUCRA) rankograms of the antiplatelet regimens. (A) SUCRA rankogram of the antiplatelet regimens for the recurrent stroke. Aspirin plus clopidogrel ranked first, followed by cilostazol. (B) SUCRA rankogram of the antiplatelet regimens for the recurrent 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.

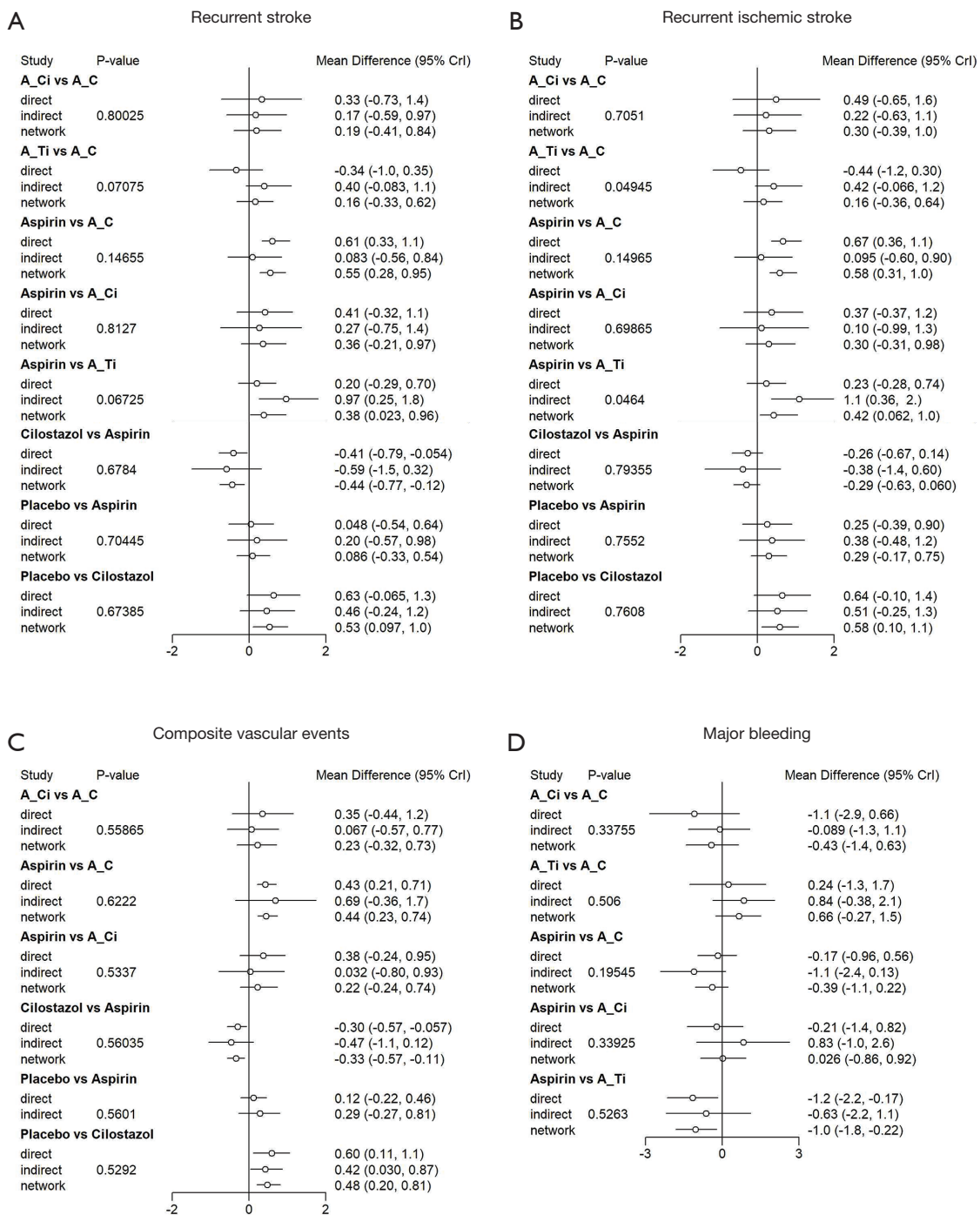


Figure S4 Inconsistency assessments using the node-splitting method. (A) Inconsistency assessments using the node-splitting method for the recurrent stroke. There was no evidence of inconsistencies between the effect estimates of direct and indirect evidence (all P-value of >0.05). (B) Inconsistency 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).

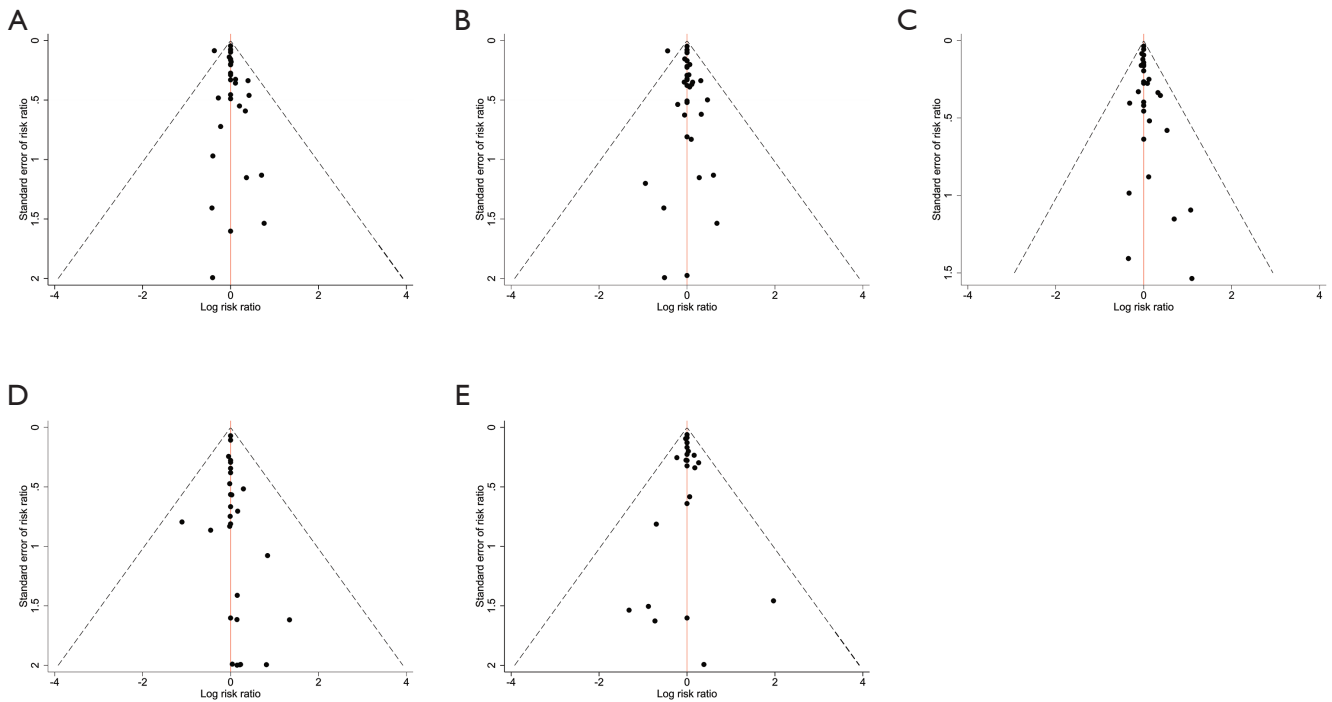


Figure S5 Funnel plots of the antiplatelet regimens of the enrolled trials. The symmetrical shape of the funnel plots demonstrates that there is no evidence of publication bias in this network meta-analysis. (A) Recurrent stroke, (B) Recurrent ischemic stroke, (C) Composite vascular events, (D) Major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

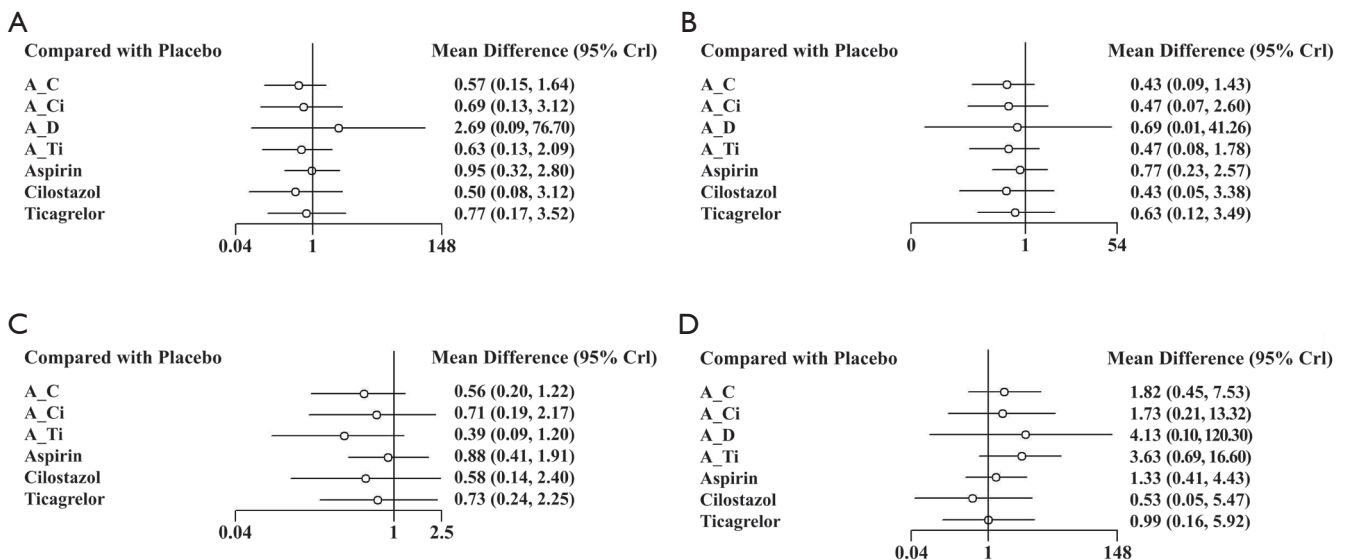


Figure S6 Forrest plots of the antiplatelet regimens compared with placebo for (A) recurrent stroke, (B) recurrent ischemic stroke, (C) composite vascular events, and (D) major bleeding, in the subgroup analysis (less than 72 hours).

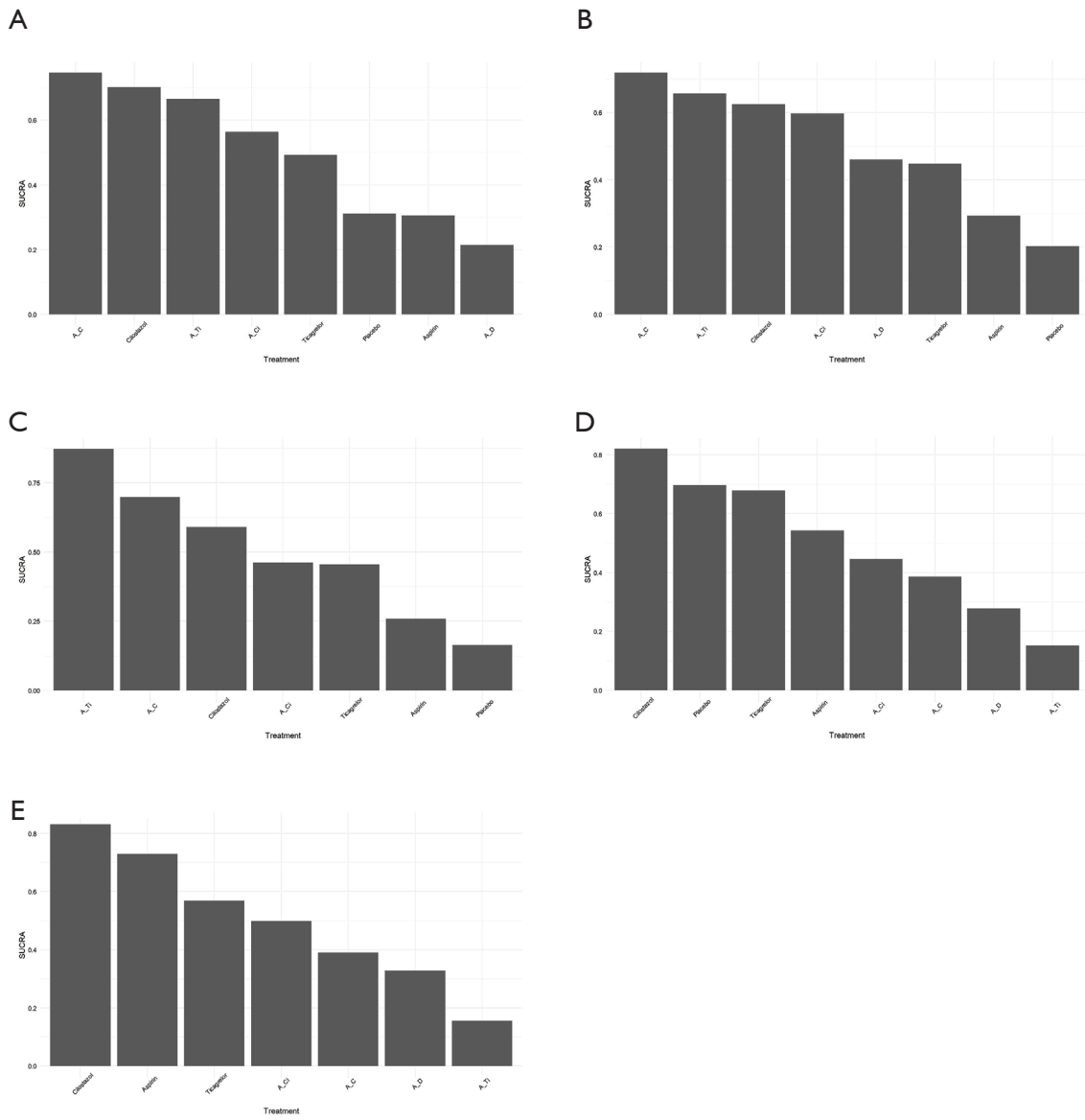


Figure S7 Surface under the cumulative ranking curve (SUCRA) rankograms of the antiplatelet regimens for (A) recurrent stroke, (B) recurrent ischemic stroke, (C) composite vascular events, and (D) major bleeding, in the subgroup analysis (less than 72 hours).

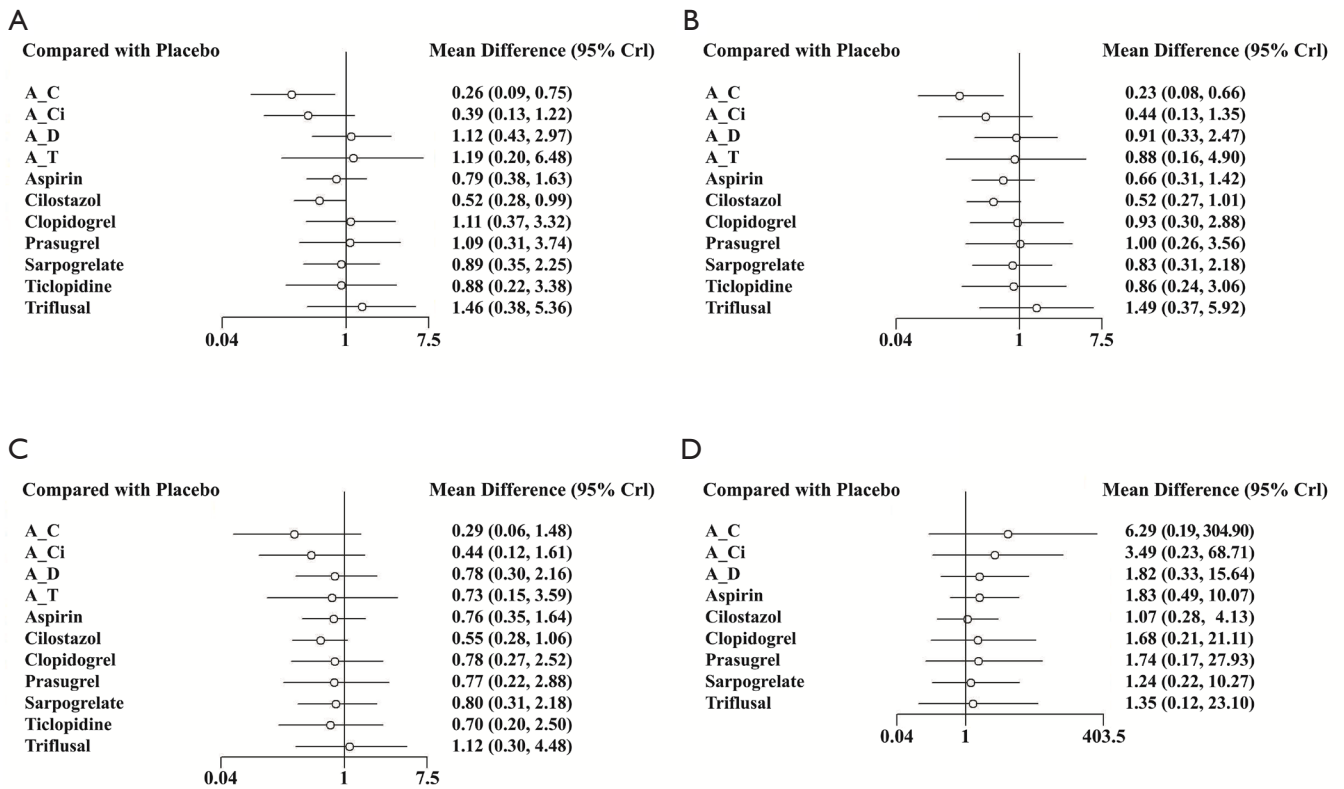


Figure S8 Forrest plots of the antiplatelet regimens compared with a placebo for (A) recurrent stroke, (B) recurrent ischemic stroke, (C) composite vascular events, and (D) all bleeding, in the subgroup analysis (not less than 72 hours).

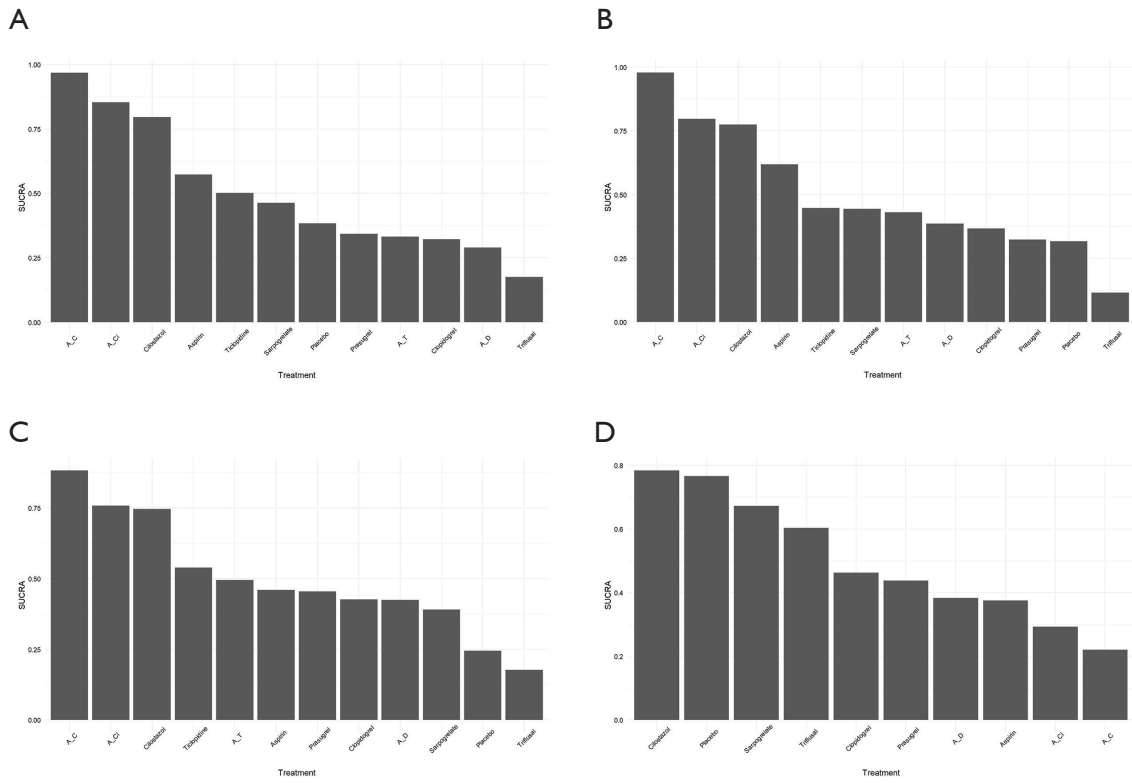


Figure S9 Surface under the cumulative ranking curve (SUCRA) rankograms of the antiplatelet regimens for (A) recurrent stroke, (B) recurrent ischemic stroke, (C) composite vascular events, and (D) all bleeding, in the subgroup analysis (not less than 72 hours).