Supplementary Data

Table of contents

Search strategy

MEDLINE

1. (stroke or cerebrovascular accident* or cerebrovascular event*).mp.
2. (cerebral infarct* or brain infarct* or intracranial infarct* or lacunar infarct*).mp.
3. (cerebral isch?emi* or brain isch?emi* or intracranial isch?emi* or transient isch?emic attack* or TIA or TIAS).mp.
4. exp stroke/ or Ischemic Attack, Transient/ or exp brain ischemia/ or exp Cerebrovascular disorders/
5. 1 or 2 or 3 or 4
6. (cilostazol or pletal or PDE?3 inhibitor or phosphodiesterase?3 inhibitor).mp.
7. exp cilostazol/
8. 6 or 7
9. 5 and 8

EMBASE

1. (stroke or cerebrovascular accident* or cerebrovascular event*).mp.
2. (cerebral infarct* or brain infarct* or intracranial infarct* or lacunar infarct*).mp.
3. (cerebral isch?emi* or brain isch?emi* or intracranial isch?emi* or transient isch?emic attack* or TIA or TIAS).mp.
4. exp cerebrovascular accident/ or transient ischemic attack/ or brain ischemia/ or brain infarction/ or brain stem infarction/ or cerebellum infarction/
5. 1 or 2 or 3 or 4
6. (cilostazol or pletal or PDE?3 inhibitor or phosphodiesterase?3 inhibitor).mp.
7. exp cilostazol/
8. 6 or 7
9. 5 and 8

Cochrane Library

1. stroke or cerebrovascular accident* or cerebrovascular event*
2. cerebral infarct* or brain infarct* or intracranial infarct* or lacunar infarct*
3. cerebral isch?emi* or brain isch?emi* or intracranial isch?emi* or transient isch?emic attack* or TIA or TIAS
4. MeSH descriptor: [Stroke] explode all trees
5. MeSH descriptor: [Ischemic Attack, Transient] explode all trees
6. MeSH descriptor: [Brain Ischemia] explode all trees
7. MeSH descriptor: [Cerebrovascular Disorders] explode all trees
8. {OR #1-#7}
9. cilostazol or pletal or PDE?3 inhibitor or phosphodiesterase?3 inhibitor
10. MeSH descriptor: [Cilostazol] explode all trees
11. {OR #9-#10}
12. #8 AND #11

Web of Science

(stroke or cerebrovascular accident or cerebrovascular event or cerebral infarct or brain infarct or intracranial infarct or lacunar infarct or cerebral ischemia or brain ischemia or intracranial ischemia or transient ischemic attack or TIA or TIAS) AND (cilostazol or pletal or PDE 3 inhibitor or phosphodiesterase 3 inhibitor)

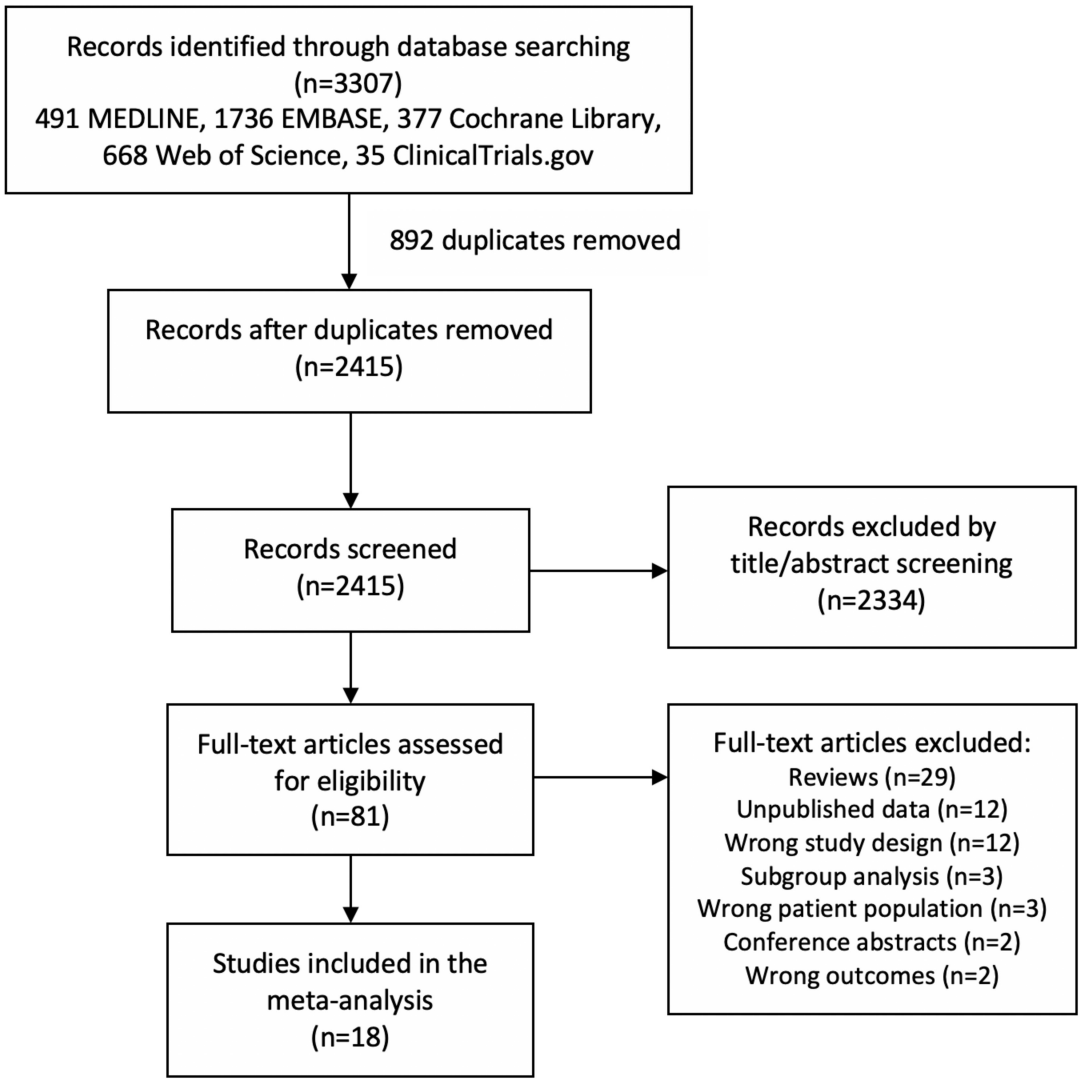
ClinicalTrials.gov

Condition: stroke OR cerebrovascular accident OR cerebrovascular disorders OR cerebral infarct OR brain infarct OR intracranial infarct OR lacunar infarct OR cerebral ischemia OR brain ischemia OR intracranial ischemia OR transient ischemic attack OR TIA

Intervention: cilostazol OR pletal OR “PDE 3 inhibitor” OR “phosphodiesterase 3 inhibitor”

PRISMA flow diagram

Figure 1: PRISMA flow diagram depicting the selection of relevant studies



Version 2 of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2)

Figure 1: Quality of included randomized trials assessed via Risk of Bias 2 (RoB 2) tool

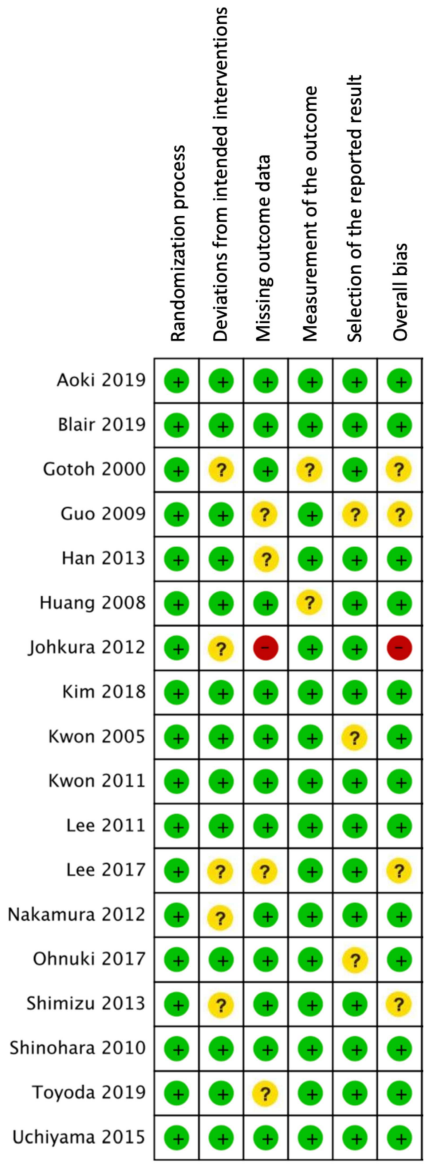


Table 1: RoB 2 signalling questions used to assess the quality of included studies

Domain	Signalling questions	Aoki 2019	Blair 2019	Gotoh 2000	Guo 2009	Han 2013	Huang 2008
Bias arising from the randomisation process	**1.1** Was the allocation sequence random?	Y	Y	Y	Y	Y	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Y	Y	PY	Y	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	N	N	N
	Risk-of-bias judgement	Low	Low	Low	Low	Low	Low
	Optional: What is the predicted direction of bias arising from the randomization process?						
Bias due to deviations from the intended interventions (effect of assignment to intervention)	**2.1** Were participants aware of their assigned intervention during the trial?	Y	PY	N	NI	N	N
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	PY	N	NI	N	N
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	PN	PN		PN		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?						
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?						
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y	PN	Y	Y	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			PN			
	Risk-of-bias judgement	Low	Low	SC	Low	Low	Low
	Optional: What is the predicted direction of bias due to deviations from intended interventions?						
Bias due to missing outcome data	**3.1** Were data for this outcome available for all, or nearly all, participants randomized?	PY	PY	PY	NI	PN	PY
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?				NA	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?				NI	NI	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?				PN	PN	
	Risk-of-bias judgement	Low	Low	Low	SC	SC	Low
	Optional: What is the predicted direction of bias due to missing outcome data?						
Bias in measurement of the outcome	**4.1** Was the method of measuring the outcome inappropriate?	N	PN	PN	PN	PN	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	PN	NI	PN	PN	NI
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	PY	PN	N	NI	N	N
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN			PN		
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?						
	Risk-of-bias judgement	Low	Low	SC	Low	Low	SC
	Optional: What is the predicted direction of bias in measurement of the outcome?						
Bias in selection of the reported result	**5.1** Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Y	Y	NI	Y	Y
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...						
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	N	PN	PN	PN
	5.3 ... multiple eligible analyses of the data?	N	PN	PN	PN	PN	N
	Risk-of-bias judgement	Low	Low	Low	SC	Low	Low
	Optional: What is the predicted direction of bias due to selection of the reported result?						
Overall bias	**Risk-of-bias judgement**	Low	Low	SC	SC	Low	Low
	Optional: What is the overall predicted direction of bias for this outcome?						

Domain	Signalling questions	Johkura 2012	Kim 2018	Kwon 2005	Kwon 2011	Lee 2011	Lee 2017
Bias arising from the randomisation process	**1.1** Was the allocation sequence random?	Y	Y	Y	Y	Y	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Y	PY	Y	Y	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	N	N	N
	Risk-of-bias judgement	Low	Low	Low	Low	Low	Low
	Optional: What is the predicted direction of bias arising from the randomization process?						
Bias due to deviations from the intended interventions (effect of assignment to intervention)	**2.1** Were participants aware of their assigned intervention during the trial?	PY	N	N	N	N	N
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	N	PN	N	N	N
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	PN					
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?						
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?						
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI	Y	PY	Y	Y	PN
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	PN					PN
	Risk-of-bias judgement	SC	Low	Low	Low	Low	SC
	Optional: What is the predicted direction of bias due to deviations from intended interventions?						
Bias due to missing outcome data	**3.1** Were data for this outcome available for all, or nearly all, participants randomized?	PN	Y	PN	PY	PN	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	PN		Y		PY	NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI					NI
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PY					PN
	Risk-of-bias judgement	High	Low	Low	Low	Low	SC
	Optional: What is the predicted direction of bias due to missing outcome data?						
Bias in measurement of the outcome	**4.1** Was the method of measuring the outcome inappropriate?	N	N	PN	N	PN	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	PN	PN	PN	PN	PN
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	PN	N	PN	N	N	N
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?						
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?						
	Risk-of-bias judgement	Low	Low	Low	Low	Low	Low
	Optional: What is the predicted direction of bias in measurement of the outcome?						
Bias in selection of the reported result	**5.1** Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	Y	NI	Y	Y	PY
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...						
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	PN	N	N	PN
	5.3 ... multiple eligible analyses of the data?	N	PN	PN	PN	PN	PN
	Risk-of-bias judgement	Low	Low	SC	Low	Low	Low
	Optional: What is the predicted direction of bias due to selection of the reported result?						
Overall bias	**Risk-of-bias judgement**	High	Low	Low	Low	Low	SC
	Optional: What is the overall predicted direction of bias for this outcome?						

Domain	Signalling questions	Nakamura 2012	Ohnuki 2017	Shimizu 2013	Shinohara 2010	Toyoda 2019	Uchiyama 2015
Bias arising from the randomisation process	**1.1** Was the allocation sequence random?	Y	Y	Y	Y	Y	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	PY	Y	Y	Y	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	N	N	N
	Risk-of-bias judgement	Low	Low	Low	Low	Low	Low
	Optional: What is the predicted direction of bias arising from the randomization process?						
Bias due to deviations from the intended interventions (effect of assignment to intervention)	**2.1** Were participants aware of their assigned intervention during the trial?	NI	PY	Y	N	Y	Y
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	PY	Y	N	N	Y
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	PN	PN	Y		PN	PN
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			PY			
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			PY			
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PN	PY	PY	Y	Y	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	PN					
	Risk-of-bias judgement	SC	Low	SC	Low	Low	Low
	Optional: What is the predicted direction of bias due to deviations from intended interventions?						
Bias due to missing outcome data	**3.1** Were data for this outcome available for all, or nearly all, participants randomized?	PN	PY	PY	PY	PN	PY
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	PY				PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?					PY	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?					PN	
	Risk-of-bias judgement	Low	Low	Low	Low	SC	Low
	Optional: What is the predicted direction of bias due to missing outcome data?						
Bias in measurement of the outcome	**4.1** Was the method of measuring the outcome inappropriate?	PN	PN	N	PN	PN	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	PN	PN	PN	PN	PN
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	NI	NI	NI	N	N	Y
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	PN	N			PN
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?						
	Risk-of-bias judgement	Low	Low	Low	Low	Low	Low
	Optional: What is the predicted direction of bias in measurement of the outcome?						
Bias in selection of the reported result	**5.1** Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	NI	Y	Y	Y	Y
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...						
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	PN	N	N	N	N
	5.3 ... multiple eligible analyses of the data?	PN	PN	PN	PN	PN	PN
	Risk-of-bias judgement	Low	SC	Low	Low	Low	Low
	Optional: What is the predicted direction of bias due to selection of the reported result?						
Overall bias	**Risk-of-bias judgement**	Low	Low	SC	Low	Low	Low
	Optional: What is the overall predicted direction of bias for this outcome?						

Forest plots

Figure 1: Forest plot depicting risk of major adverse cardiovascular events (MACE)

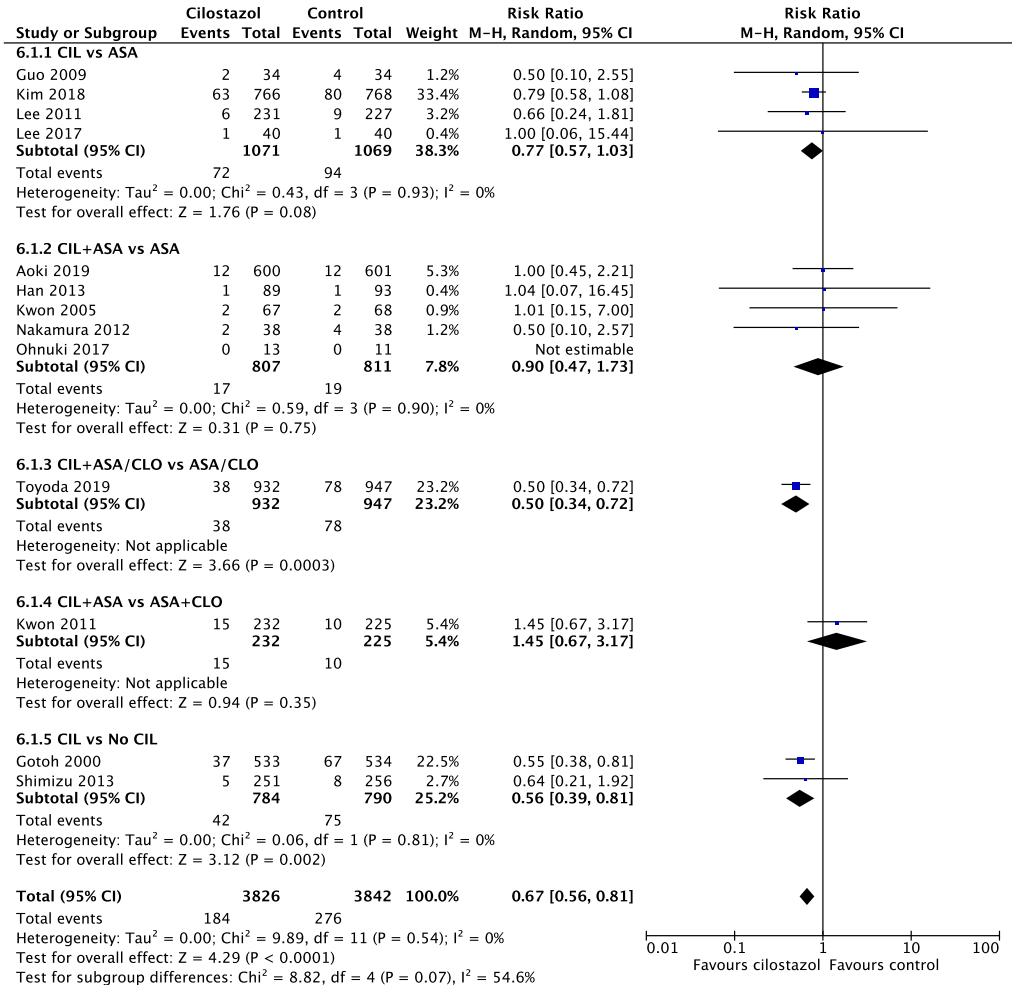


Figure 2: Forest plot depicting good functional outcome (mRS 0-1)

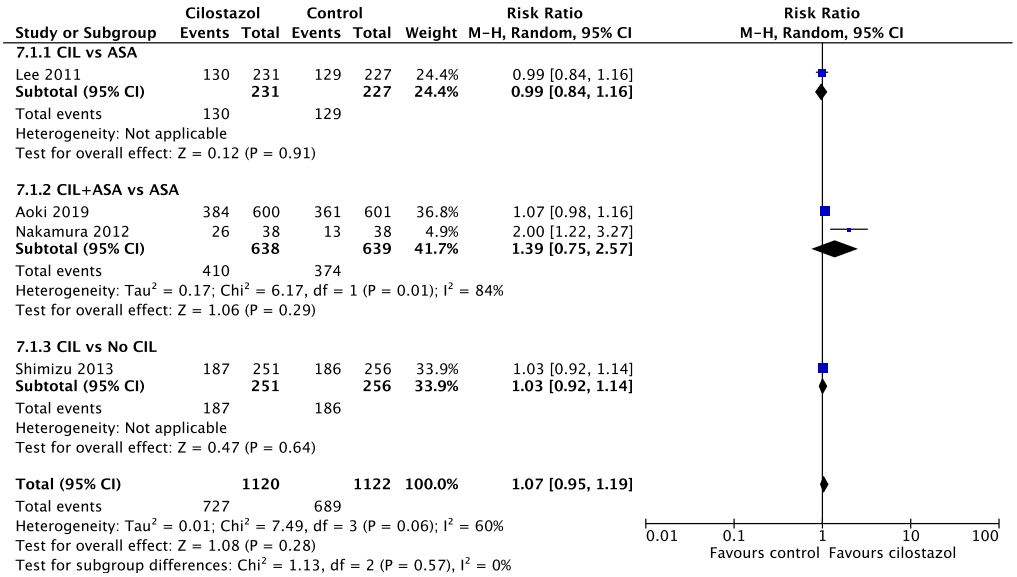


Figure 3: Forest plot depicting risk of adverse drug events leading to treatment discontinuation

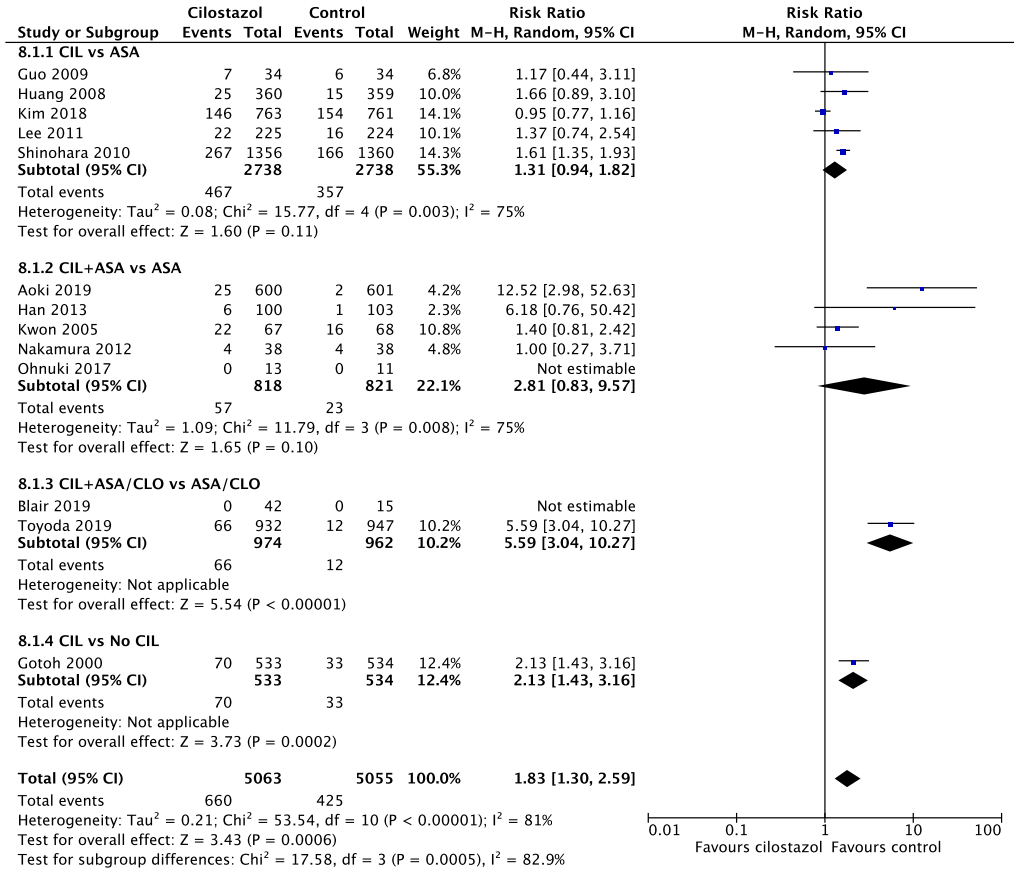
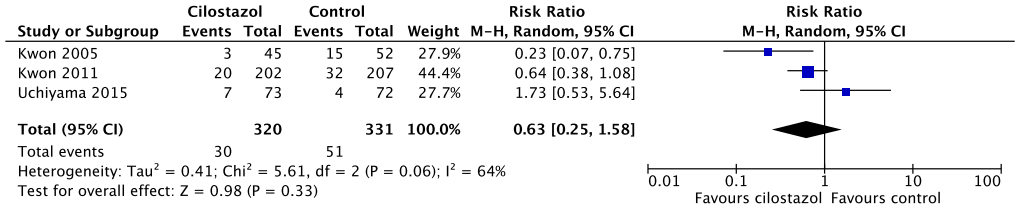


Figure 4: Forest plot depicting risk of ICAS progression or worsening



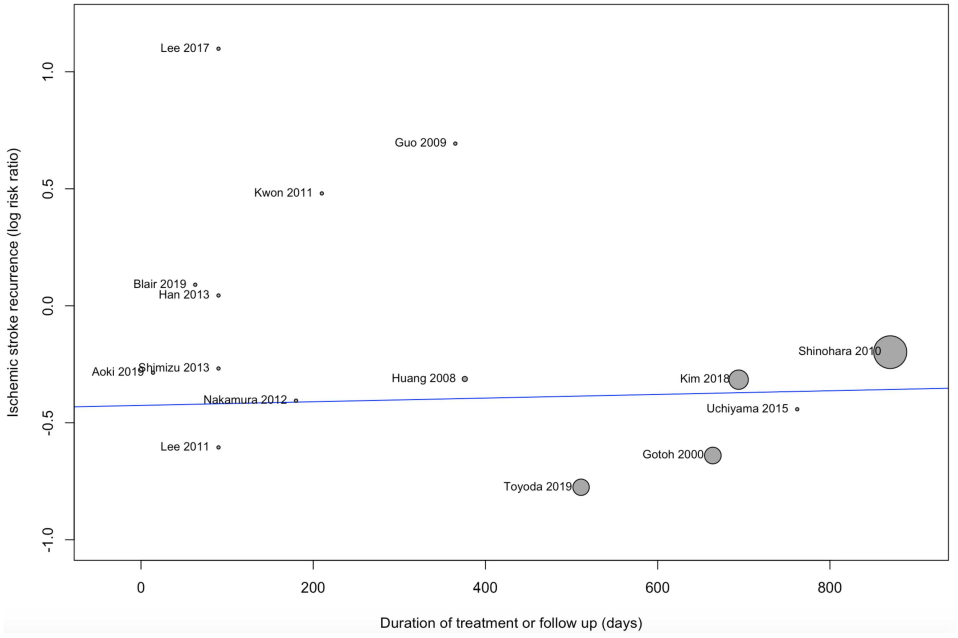
Meta regression analysis

Table 1: Characteristics of included studies

Study ID	Duration of treatment or follow-up (days)	Time from stroke onset to randomization or treatment (days)	Proportion of total participants with lacunar infarction (%)
Aoki 2019 (ADS)	14	-	44
Blair 2019 (LACI-1)	63	203	100
Gotoh 2000 (CSPS)	664	83	74.4
Guo 2009	365	-	-
Han 2013 (ECLIPse)	90	5	100
Huang 2008 (CASISP)	376	78.5	-
Johkura 2012	180	-	-
Kim 2018 (PICASSO)	694	17	-
Kwon 2005 (TOSS)	180	-	-
Kwon 2011 (TOSS-2)	210	7.93	-
Lee 2011 (CAIST)	90	1.42	58
Lee 2017	90	-	84.8
Nakamura 2012	180	1	47
Ohnuki 2017	28	-	54
Shimizu 2013	90	0.417	67.5
Shinohara 2010 (CSPS 2)	870	-	65
Toyoda 2019 (CSPS.com)	511	26	49
Uchiyama 2015 (CATHARSIS)	762	-	-

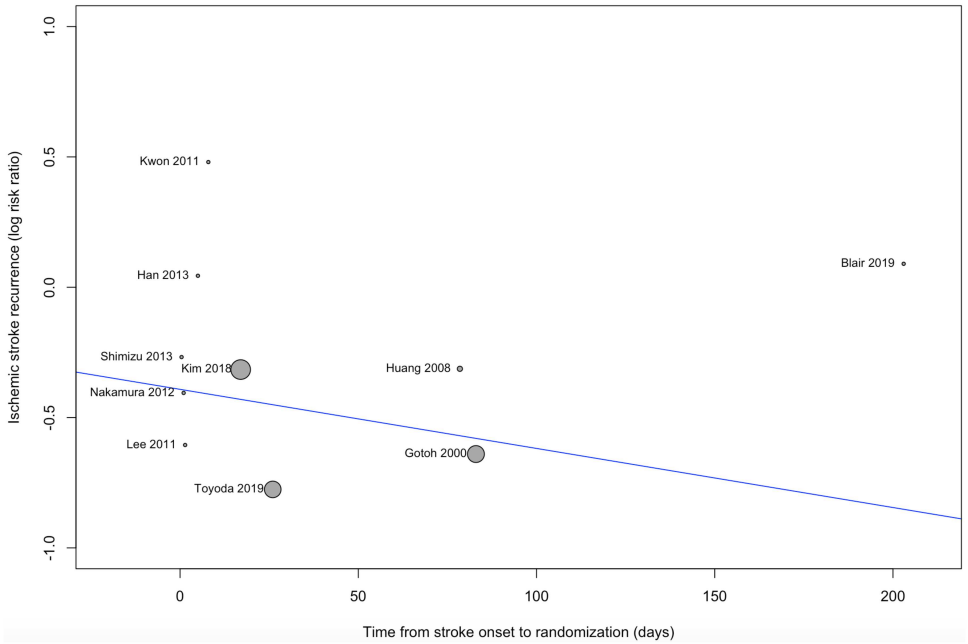
*All studies with insufficient data were excluded from the meta-regression. Where possible, the mean value was used. If the mean was unavailable, the median value was used.

Figure 1: Meta-regression of duration of treatment on ischemic stroke recurrence (15 studies)



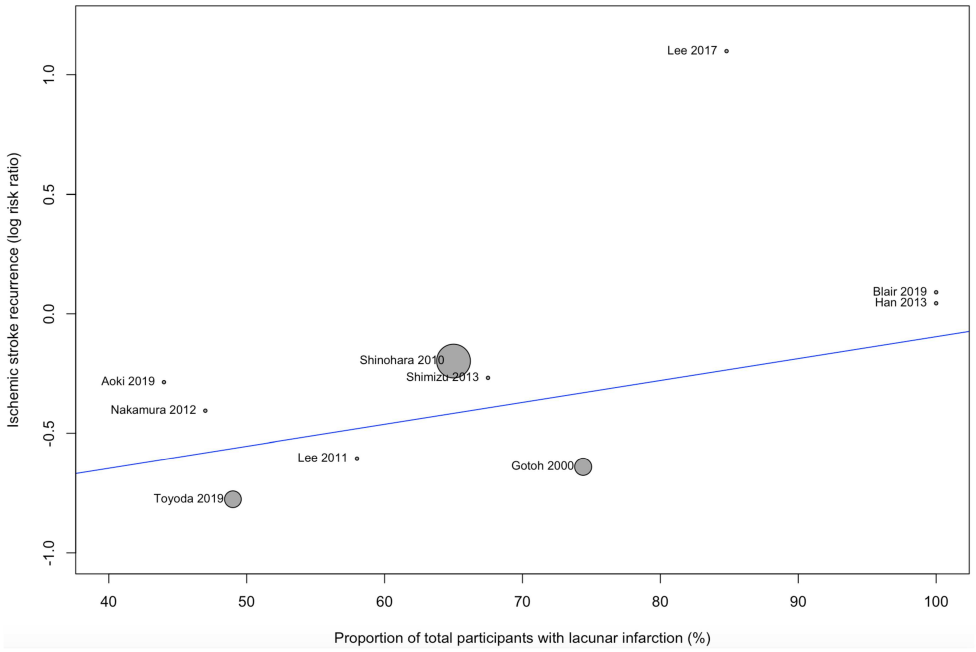
	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.4258	0.2478	-1.7183	0.0857	-0.9115	0.0599
duration	0.0001	0.0004	0.2150	0.8298	-0.0006	0.0008

Figure 2: Meta-regression of time from stroke onset to randomization on ischemic stroke recurrence (10 studies)



	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-0.3916	0.1712	-2.2870	0.0222	-0.7272	-0.0560	*
tonset	-0.0023	0.0033	-0.6825	0.4949	-0.0088	0.0042	

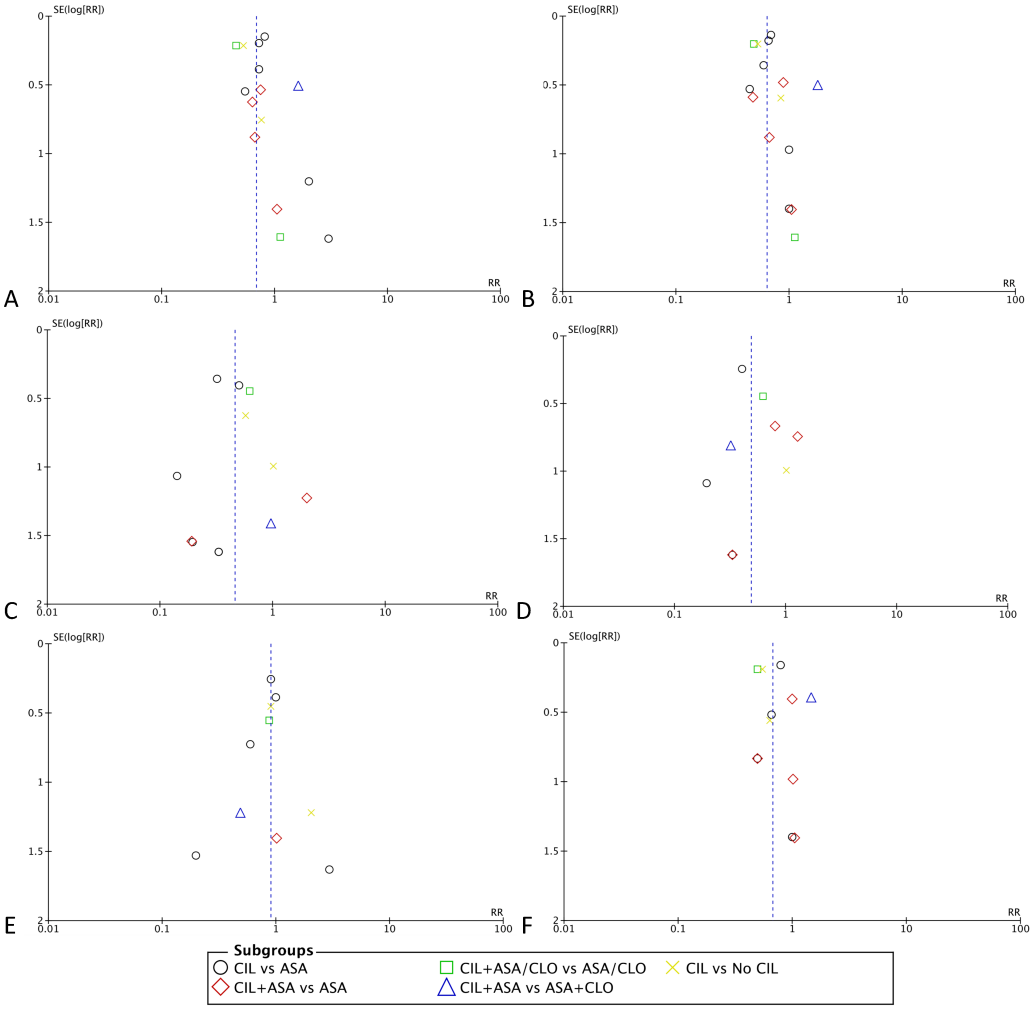
Figure 3: Meta-regression of proportion of patients with lacunar infarction on ischemic stroke recurrence (10 studies)



	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-1.0124	0.6329	-1.5997	0.1097	-2.2529	0.2280
laci	0.0092	0.0099	0.9219	0.3566	-0.0103	0.0287

Funnel plots to evaluate publication bias

Table 1: Funnel plots



A: ischemic stroke recurrence
B: any stroke recurrence
C: intracranial hemorrhage
D: major hemorrhagic events
E: mortality
F: major adverse cardiovascular events (MACE)

Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Table 1: GRADE summary of findings table

Cilostazol for secondary stroke prevention					
Patient or population: Acute or chronic ischemic stroke patients **Intervention:** Cilostazol mono or combination therapy **Comparison:** Single or dual antiplatelet therapy; best medical therapy; placebo					
Outcome	**Absolute effect**		**Relative risk (95% CI)**	**No. of patients (studies)**	**Quality of evidence**
	Control	**Cilostazol**			
Ischemic stroke recurrence	56/1000	38/1000	0.69 (0.58-0.81)	11,429 (18)	High
	Difference: 18 fewer per 1000 (95% CI 11 fewer to 23 fewer)				
Any stroke recurrence	69/1000	44/1000	0.64 (0.54-0.74)	11,429 (18)	High
	Difference: 25 fewer per 1000 (95% CI 18 fewer to 32 fewer)				
Intracranial hemorrhage	15/1000	6/1000	0.46 (0.31-0.68)	11,429 (18)	High*
	Difference: 9 fewer per 1000 (95% CI 5 fewer to 10 fewer)				
Major hemorrhagic events	23/1000	11/1000	0.49 (0.34-0.70)	8041 (14)	High*
	Difference: 12 fewer per 1000 (95% CI 7 fewer to 15 fewer)				
Mortality	14/1000	13/1000	0.90 (0.64-1.25)	10,046 (15)	Moderate due to imprecision
	Difference: 1 fewer per 1000 (95% CI 5 fewer to 4 more)				
MACE	72/1000	48/1000	0.67 (0.56-0.81)	7668 (13)	High
	Difference: 24 fewer per 1000 (95% CI 32 fewer to 14 fewer)				
mRS 0-1	61/100	65/100	1.07 (0.95-1.19)	2242 (4)	Low due to imprecision & inconsistency
	Difference: 4 more per 100 (95% CI 3 fewer to 12 more)				
ADE leading to drug discontinuation	84/1000	130/1000	1.83 (1.30-2.59)	10,118 (13)	Moderate due to inconsistency
	Difference: 46 more per 1000 (95% CI 25 more to 134 more)				

*Intracranial hemorrhage and major hemorrhagic events: Downgraded due to imprecision, upgraded due to large effect size (relative risk reduction ≥0.50)

Table 2: GRADE components

Outcome	**Risk of bias**	**Imprecision***	**Inconsistency**	**Indirectness**	**Publication bias**
Ischemic stroke	N	N	N	N	N
Any stroke	N	N	N	N	N
Intracranial hemorrhage	N	Y	N	N	N
Major hemorrhagic events	N	Y	N	N	N
Mortality	N	Y	N	N	N
MACE	N	N	N	N	N
mRS 0-1	N	Y	Y (I^2=60%)	N	**NA**
ADE leading to drug discontinuation	N	N	Y (I^2=81%)	N	N

*Imprecision defined as optimal information size not met or 95% CI does not exclude no effect

Table 3: Optimal information size for each outcome (α=0.05, β=0.2, relative risk reduction = 25%)

Outcome	Cilostazol event rate	Control event rate	Optimal information size (per arm)	Achieved?
Ischemic stroke	0.0379	0.0556	3759	Y
Any stroke	0.0437	0.0691	2985	Y
Intracranial hemorrhage	0.00646	0.0151	14,320	N
Major hemorrhagic events	0.0109	0.0232	9279	N
Mortality	0.0127	0.0144	15,068	N
MACE	0.0481	0.0718	2867	Y
mRS 0-1	0.649	0.614	164	Y
ADE leading to drug discontinuation	0.130	0.0841	2421	Y

MACE: major adverse cardiovascular events
ADE: adverse drug events

Reference: Kane SP. Sample Size Calculator. ClinCalc: https://clincalc.com/Stats/SampleSize.aspx. Updated July 24, 2019. Accessed August 29, 2020.

Definitions of outcomes utilized by trials

Table 1: Definition of any stroke recurrence

Study ID	Definition / Justification
Aoki 2019	Ischemic stroke + ICH
Blair 2019	Ischemic stroke + ICH
Gotoh 2000	Cerebral infarction + ICH
Guo 2009	Ischemic stroke + ICH
Han 2013	Recurrent stroke
Huang 2008	Ischemic stroke + symptomatic hemorrhagic stroke
Johkura 2012	Recurrent stroke
Kim 2018	"Focal neurological deficit (>24 hours) from cerebrovascular causes or transient focal neurological deficit (≤24 hours) with a new evidence of stroke in brain imagings, including ischemic stroke, hemorrhagic stroke, and unclassified stroke."
Kwon 2005	"During the follow-up period, strokes or transient ischemic attacks did not occur…"
Kwon 2011	Ischemic stroke + hemorrhagic stroke
Lee 2011	Recurrent strokes (assumed to refer to ischemic stroke) + ICH
Lee 2017	Ischemic stroke + intracerebral hemorrhage
Nakamura 2012	Ischemic stroke (confirmed by worsened or additional neurological deficits and corresponding DWI positive lesions) + ICH
Ohnuki 2017	"No adverse effects, including recurrent ischemic or hemorrhagic stroke… occurred in either group…"
Shimizu 2013	Cerebral infarction + ICH
Shinohara 2010	Cerebral infarction + ICH
Toyoda 2019	Ischemic stroke + ICH
Uchiyama 2015	Ischemic stroke + ICH

Table 2: Definition of intracranial hemorrhage

Study ID	Definition / Justification
Aoki 2019	Intracerebral hemorrhage + SAH
Blair 2019	Intracranial bleeding. "There were no deaths or major hemorrhages…"
Gotoh 2000	Cerebral hemorrhage + SAH
Guo 2009	Intracerebral hemorrhage + SAH
Han 2013	"there were no major adverse events in either group"
Huang 2008	Severe cerebral bleeds
Johkura 2012	"No bleeding event... was reported"
Kim 2018	Cerebral hemorrhage, including intracerebral hemorrhage + SAH
Kwon 2005	"No serious adverse event was reported in relation to study medication."
Kwon 2011	Hemorrhagic stroke + hemorrhagic conversion
Lee 2011	ICH
Lee 2017	Intracerebral hemorrhage
Nakamura 2012	"No symptomatic intracranial hemorrhages occurred in either group during the entire follow-up period."
Ohnuki 2017	Intracranial bleeding. "No adverse effects, including recurrent ischemic or hemorrhagic stroke… occurred in either group…"
Shimizu 2013	Intracerebral hemorrhage + SAH
Shinohara 2010	Cerebral hemorrhage + SAH
Toyoda 2019	Hemorrhagic stroke + subdural or epidural hemorrhage
Uchiyama 2015	ICH, including cerebral hemorrhage + SAH

Table 3: Definition of major hemorrhagic events

Study ID	Definition / Justification
Aoki 2019	ICH + serious ECH
Blair 2019	"There were no deaths or major hemorrhages."
Han 2013	"there were no major adverse events in either group"
Johkura 2012	"no bleeding event… was reported"
Kwon 2005	"only 2 minor bleeding complications were observed in the placebo group"
Kwon 2011	Major hemorrhagic complications (life-threatening or major bleeding)
Lee 2011	Life-threatening or major bleeding Note: 1 life-threatening bleed from cilostazol group occurred before study drug administration, and was excluded.
Lee 2017	ICH + serious ECH. No ECH was stated under "serious adverse events".
Nakamura 2012	Major bleeding complications
Ohnuki 2017	"No adverse effects, including recurrent ischemic or hemorrhagic stroke… occurred in either group…"
Shimizu 2013	ICH + major systemic bleeding. "No major systemic bleeding occurred during the study period."
Shinohara 2010	Cerebral hemorrhage + SAH + hemorrhage requiring hospital admission
Toyoda 2019	"severe or life-threatening bleeding as defined in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries classification, which includes symptomatic intracranial hemorrhage (hemorrhagic stroke and subdural or epidural hemorrhage) and bleeding resulting in substantial hemodynamic compromise requiring treatment…"
Uchiyama 2015	Major hemorrhage

Table 4: Definition of major adverse cardiovascular events (MACE)

Study ID	Definition / Justification
Aoki 2019	Stroke, myocardial infarction, vascular death, life-threatening bleeding
Gotoh 2000	Cerebral infarction, ICH, myocardial infarction, vascular death
Guo 2009	Ischemic stroke, ICH, acute coronary events, vascular death
Han 2013	Assuming 0 ICH, 0 MI, 0 vascular deaths. "During the trial, there were no major adverse events in either group."
Kim 2018	Composite of major vascular events, e.g. stroke, MI, vascular death
Kwon 2005	Stroke, acute coronary events, vascular death
Kwon 2011	Stroke, myocardial infarction, vascular death
Lee 2011	Stroke, myocardial infarction, vascular death, cardiovascular events requiring hospitalization
Lee 2017	No mention of MACE, other than ischemic stroke recurrence and intracerebral hemorrhage, under the list of adverse events
Nakamura 2012	Stroke, acute coronary events, vascular death
Ohnuki 2017	"No adverse effects, including recurrent ischemic or hemorrhagic stroke… occurred in either group…"
Shimizu 2013	Cerebral infarction, ICH/SAH, congestive heart failure. *Unclear if vascular deaths were included.*
Toyoda 2019	Stroke, myocardial infarction, vascular death

Table 5: Definition of adverse drug events which led to treatment discontinuation

Study ID	Definition / Justification
Aoki 2019	Adverse drug events
Blair 2019	"Dual drugs were tolerated similarly to either individual drug… In the dual drug groups, there was no evidence that… those who ceased to take tablets did so because of more symptoms."
Gotoh 2000	Adverse events, excluding vascular events or deaths
Guo 2009	Death, vascular events, other adverse events, poor compliance
Han 2013	Adverse events, e.g. headaches, dizziness, malaise
Huang 2008	Adverse events
Kim 2018	Adverse events
Kwon 2005	Serious adverse events, excluding vascular events or deaths
Lee 2011	Adverse events, including vascular events and bleeding
Nakamura 2012	Adverse events, including vascular events
Ohnuki 2017	"No adverse effects, including recurrent ischemic or hemorrhagic stroke… occurred in either group…"
Shinohara 2010	Adverse drug reactions
Toyoda 2019	Adverse events

ECH, extracranial hemorrhage; ICH, intracranial hemorrhage; SAH, subarachnoid hemorrhage.