Supplementary Data

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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





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

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Aoki 2019	+	Ŧ	Ŧ	÷	÷	+
Blair 2019	+	Ŧ	Ŧ	•	Ŧ	+
Gotoh 2000	•	?	•	?	Ŧ	?
Guo 2009	Ŧ	Ŧ	?	Ŧ	?	?
Han 2013	+	Ŧ	?	+	÷	+
Huang 2008	Ŧ	Ŧ	Ŧ	?	Ŧ	•
Johkura 2012	Ŧ	?	•	Ŧ	Ŧ	
Kim 2018	+	Ŧ	+	•	÷	+
Kwon 2005	÷	÷	Ŧ	÷	?	Ŧ
Kwon 2011	÷	Ŧ	÷	÷	÷	÷
Lee 2011	Ŧ	Ŧ	Ŧ	Ŧ	÷	+
Lee 2017	÷	?	?	+	Ŧ	?
Nakamura 2012	÷	?	Ŧ	÷	÷	+
Ohnuki 2017	+	Ŧ	÷	÷	?	÷
Shimizu 2013	Ŧ	?	Ŧ	Ŧ	Ŧ	?
Shinohara 2010	÷	Ŧ	Ŧ	Ŧ	Ŧ	÷
Toyoda 2019	Ŧ	Ŧ	?	Ŧ	Ŧ	÷
Uchiyama 2015	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ

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
	1.1 Was the allocation sequence random?	Y	Y	Y	Y	Y	Y
	1.2 Was the allocation sequence concealed until participants	Y	Y	Y	РҮ	Y	РҮ
Bias arising	were enrolled and assigned to interventions?						
from the	1.3 Did baseline differences between intervention groups	Ν	N	N	Ν	N	N
nrocess	Risk-of-bias judgement	Low	Low	Low	Low	Low	Low
process	Optional: What is the predicted direction of bias arising from	2010	LOW	LOW	LOW	LOW	LOW
	the randomization process?						
	2.1 Were participants aware of their assigned intervention	~	DV/		NU		
	during the trial?	T	PY	N	NI	N	N
	2.2 Were carers and people delivering the interventions aware	Y	PY	N	NI	N	N
	2.3 If V/PV/NI to 2.1 or 2.2: Were there deviations from the						
Bias due to	intended intervention that arose because of the trial context?	PN	PN		PN		
deviations	2.4 If Y/PY to 2.3: Were these deviations likely to have affected						
from the	the outcome?						
intended	2.5 If Y/PY/NI to 2.4: Were these deviations from intended						
interventions	intervention balanced between groups?						
(effect of	2.6 Was an appropriate analysis used to estimate the effect of	Y	Y	PN	Y	Y	Y
assignment to	assignment to intervention?						
intervention)	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			DN			
	the group to which they were randomized?			r in			
	Risk-of-bias judgement	Low	Low	SC	Low	Low	Low
	Optional: What is the predicted direction of bias due to						
	deviations from intended interventions?						
	3.1 Were data for this outcome available for all, or nearly all,	PY	PY	РҮ	NI	PN	PY
	participants randomized?						
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?				NA	NA	
Bias due to	3.3 If N/PN to 3.2. Could missingness in the outcome depend						
missing	on its true value?				NI	NI	
outcome data	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome				DN	DN	
	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?	N	DN	DN	DN	DN	DN
	4.1 Was the method of measuring the outcome happropriate?	N	PN	PN	PN	PN	PN
	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						
Bias in	of the intervention received by study participants?	PY	PN	N	NI	N	N
measurement	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have	PN			PN		
of the	been influenced by knowledge of intervention received?						
outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome						
	Pisk-of-bias judgement	Low	Low	50	Low	Low	50
	Optional: What is the predicted direction of bias in	LOW	LOW	30	LOW	LOW	50
	measurement of the outcome?						
	5.1 Were the data that produced this result analysed in						
	accordance with a pre-specified analysis plan that was finalized	Y	Y	Y	NI	Y	Y
	before unblinded outcome data were available for analysis?						
Bias in	Is the numerical result being assessed likely to have been						
selection of	selected, on the basis of the results, from						
the reported	definitions time points) within the outcome domain?	Ν	N	N	PN	PN	PN
result	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?						
	Risk-of-bias judgement	Low	Low	SC	SC	Low	Low
Overall bias	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
	1.1 Was the allocation sequence random?	Y	Y	Y	Y	Y	Y
	1.2 Was the allocation sequence concealed until participants	v	v	DV	v	v	DV
Bias arising	were enrolled and assigned to interventions?						
from the	1.3 Did baseline differences between intervention groups	N	N	N	N	N	N
randomisation	suggest a problem with the randomization process?						-
process	Risk-ot-bias judgement	Low	Low	Low	Low	Low	Low
	Optional: What is the predicted direction of bias arising from						
	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						
Bias due to	intended intervention that arose because of the trial context?	PN					
deviations	2.4 If Y/PY to 2.3: Were these deviations likely to have affected						
from the	the outcome?						
intended	2.5 If Y/PY/NI to 2.4: Were these deviations from intended						
interventions	intervention balanced between groups?						
(effect of	2.6 Was an appropriate analysis used to estimate the effect of	NI	Y	РҮ	Y	Y	PN
assignment to	assignment to intervention?						
intervention)	2.7 It N/PN/NI to 2.6: Was there potential for a substantial	DN					DAL
	impact (on the result) of the failure to analyse participants in the group to which they were randomized?	PN					PN
	Pick-of-bias judgement	50	Low	Low	Low	Low	50
	Optional: What is the predicted direction of hias due to	30	LUW	LUW	LOW	LUW	30
	deviations from intended interventions?						
	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
Bias due to	3.3 If N/PN to 3.2: Could missingness in the outcome depend	NI					NI
missing	on its true value?						141
outcome data	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome	PY					PN
	depended on its true value?						
	Risk-ot-bias judgement	High	Low	Low	Low	Low	SC
	Optional: What is the predicted direction of bias due to missing						
	A 1 Was the method of measuring the outcome inappropriate?	N	N	DN	N	DN	DN
	4.1 Was the method of measuring the outcome mappropriate:	IN I		r IN	i N	FIN	FIN
	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						
Bias in	of the intervention received by study participants?	PN	N	PN	N	N	N
measurement	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have						
of the	been influenced by knowledge of intervention received?						
outcome	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?						
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized	DV	v	NI	v	v	DV
	before unblinded outcome data were available for analysis?						
	Is the numerical result being assessed likely to have been						
Bias in	selected, on the basis of the results, from						
selection of	5.2 multiple eligible outcome measurements (e.g. scales,	N	м	DN	N	м	DN
result	definitions, time points) within the outcome domain?	IN	IN	PN	IN	IN	PN
result	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?						
	KISK-OF-DIAS JUDGEMENT	High	LOW	LOW	LOW	LOW	SC
Overall blas	optional: what is the overall predicted direction of blas for this outcome?						
L	outcome:			1			1

Domain	Signalling questions	Nakamura 2012	Ohnuki 2017	Shimizu 2013	Shinohara 2010	Toyoda 2019	Uchiyama 2015
	1.1 Was the allocation sequence random?	Y	Y	Y	Y	Y	Y
Bias arising	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	РҮ	ΡΥ	Y	Y	Y	РҮ
from the randomisation	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Ν	Ν	N	Ν	Ν
process	Risk-of-bias judgement	Low	Low	Low	Low	Low	Low
	Optional: What is the predicted direction of bias arising						
	from the randomization process?						
	2.1 Were participants aware of their assigned intervention during the trial?	NI	РҮ	Y	N	Y	Y
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	РҮ	Y	N	Ν	Y
Bias due to deviations	2.3 If <u>Y/PY/NI to 2.1 or 2.2</u> : Were there deviations from the intended intervention that arose because of the trial context?	PN	PN	Y		PN	PN
from the intended	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			РҮ			
interventions (effect of	2.5 <u>If Y/PY/NI to 2.4</u> : Were these deviations from intended intervention balanced between groups?			РҮ			
assignment to	2.6 Was an appropriate analysis used to estimate the	PN	РҮ	РҮ	Y	Y	Y
interventiony	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 accurate which the number of a participants of the failure to analyse participants and the substantial for a subst	PN					
	In the group to which they were randomized?	sc	Low	50	Low	Low	Low
	Optional: What is the predicted direction of bias due to	30	LOW	30	LUW	LOW	LOW
	deviations from intended interventions?						
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN	РҮ	ΡΥ	РҮ	PN	РҮ
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	РҮ				PN	
Bias due to missing	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?					PY	
outcome data	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?			-			
	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 base differed between interpretion 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 proceived by study participants?	NI	NI	NI	N	N	Y
Bias in	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome						
measurement of the	have been influenced by knowledge of intervention received?	PN	PN	Ν			PN
outcome	4.5 If <u>Y/PY/NI to 4.4</u> : 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?						
	accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	NI	Y	Y	Y	Y
Bias in	Is the numerical result being assessed likely to have been						
selection of	5.2 multiple eligible outcome measurements (e.g.						
the reported result	scales, definitions, time points) within the outcome domain?	Ν	PN	Ν	Ν	Ν	Ν
	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 Optional: What is the overall predicted direction of bias	Low	Low	SC	Low	Low	Low
	for this outcome?						

Forest plots

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

	Cilosta	ızol	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
6.1.1 CIL vs ASA							
Guo 2009	2	34	4	34	1.2%	0.50 [0.10, 2.55]	
Kim 2018	63	766	80	768	33.4%	0.79 [0.58, 1.08]	
Lee 2011	6	231	9	227	3.2%	0.66 [0.24, 1.81]	
Lee 2017	1	40	1	40	0.4%	1.00 [0.06, 15.44]	
Subtotal (95% CI)		1071		1069	38.3%	0.77 [0.57, 1.03]	•
Total events	72		94				
Heterogeneity: Tau ² =	= 0.00; Cl	$ni^2 = 0.$	43, df =	3 (P =	0.93); l ² =	= 0%	
Test for overall effect:	Z = 1.76	5 (P = 0)).08)				
	•						
A - H: 2010	A 10	600	10	601	F 20/	1 00 [0 45 0 01]	
AOKI 2019	12	600	12	001	5.5%	1.00 [0.45, 2.21]	
Han 2015 Kutan 2005	1	69	1	95	0.4%	1.04 [0.07, 16.45]	
Nakamura 2012	2	20	2	20	1.20/		
Nakamura 2012 Obruki 2017	2	20 12	4	20	1.270	0.30 [0.10, 2.37]	
Subtotal (95% CI)	0	807	0	811	7 8%	0 90 [0 47 1 73]	
Total events	17	007	10	011	110/0	0.50 [0.17, 175]	
Heterogeneity: Tau ² -	- 0 00. CI	$ni^2 = 0$	50 df -	3 (P -	0 00)· 1 ² -	- 0%	
Test for overall effect:	-7 - 0.3	1 (P = () 75)	5(1 =	0.90), 1 -	- 0/0	
rest for overall effect.	. 2 = 0.5	L (I – C	,,,,,,				
6.1.3 CIL+ASA/CLO	vs ASA/C	LO					
Toyoda 2019	38	932	78	947	23.2%	0.50 [0.34, 0.72]	
Subtotal (95% CI)		932		947	23.2%	0.50 [0.34, 0.72]	◆
Total events	38		78				
Heterogeneity: Not ap	plicable						
Test for overall effect	: Z = 3.66	5 (P = 0)).0003)				
$6.1.4$ CII + Δ SA vs Δ S	∆+CIO						
Vuon 2011	15	222	10	225	E 40/	1 45 [0 67 2 17]	
Subtotal (95% CI)	13	232	10	225	5.4%	1.45 [0.67, 3.17]	
Total events	15	232	10	225	511/0	1115 [0107] 5117]	
Heterogeneity: Not an	nlicable		10				
Test for overall effect	7 = 0.94	1(P = 0)	35)				
rest for overall effect.	2 - 0.5-	+ (i – (
6.1.5 CIL vs No CIL							
Gotoh 2000	37	533	67	534	22.5%	0.55 [0.38, 0.81]	
Shimizu 2013	5	251	8	256	2.7%	0.64 [0.21, 1.92]	
Subtotal (95% CI)		784		790	25.2%	0.56 [0.39, 0.81]	◆
Total events	42		75				
Heterogeneity: Tau ² =	= 0.00; Cł	$1i^2 = 0.$	06, df =	1 (P =	0.81); I ² =	= 0%	
Test for overall effect	Z = 3.12	2 (P = 0)	0.002)				
Total (95% CI)		3826		3847	100.0%	0.67 [0.56, 0.81]	
Total events	184	3020	276	5042	100.0/0	0.07 [0.50, 0.01]	•
Heterogeneity: Tau ² -	- 0 00. 04	$ni^2 = 0$	89 df -	11 (P -	- 0 54)· 12	- 0%	
Test for overall effect	7 = 4.20		0.0001		- 0.9-7), 1	- 0/0	0.01 0.1 1 10 100
rescion overan effect.	2:	~ ~ ~ (2	Favours cilostazol Favours control

Test for subgroup differences: $Chi^2 = 8.82$, df = 4 (P = 0.07), $I^2 = 54.6\%$

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

	Cilosta	ızol	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
8.1.1 CIL vs ASA							
Guo 2009	7	34	6	34	6.8%	1.17 [0.44, 3.11]	
Huang 2008	25	360	15	359	10.0%	1.66 [0.89, 3.10]	+
Kim 2018	146	763	154	761	14.1%	0.95 [0.77, 1.16]	*
Lee 2011	22	225	16	224	10.1%	1.37 [0.74, 2.54]	
Shinohara 2010 Subtotal (95% CI)	267	1356 2738	166	1360 2738	14.3% 55.3%	1.61 [1.35, 1.93] 1.31 [0.94, 1.82]	▲
Total events	467		357				
Heterogeneity: Tau ² =	= 0.08; Cł	$ni^2 = 1!$	5.77, df =	= 4 (P =	= 0.003);	$l^2 = 75\%$	
Test for overall effect	Z = 1.60	O(P = 0)).11)				
8.1.2 CIL+ASA vs AS	A						
Aoki 2019	25	600	2	601	4.2%	12.52 [2.98, 52.63]	
Han 2013	6	100	1	103	2.3%	6.18 [0.76, 50.42]	+
Kwon 2005	22	67	16	68	10.8%	1.40 [0.81, 2.42]	+
Nakamura 2012	4	38	4	38	4.8%	1.00 [0.27, 3.71]	
Ohnuki 2017	0	13	0	11		Not estimable	
Subtotal (95% CI)		818		821	22.1%	2.81 [0.83, 9.57]	
Total events	57	2	23			2	
Heterogeneity: Tau ² =	= 1.09; Cł	$1i^2 = 1$	1.79, df =	= 3 (P =	= 0.008);	$l^2 = 75\%$	
lest for overall effect	Z = 1.65	S(P = 0)).10)				
8.1.3 CIL+ASA/CLO	vs ASA/C	LO					
Blair 2019	0	42	0	15		Not estimable	
Toyoda 2019	66	932	12	947	10.2%	5.59 [3.04, 10.27]	
Subtotal (95% CI)		974		962	10.2%	5.59 [3.04, 10.27]	\bullet
Total events	66		12				
Heterogeneity: Not ap	plicable						
lest for overall effect	Z = 5.54	4 (P < ().00001)				
8.1.4 CIL vs No CIL							
Gotoh 2000	70	533	33	534	12.4%	2.13 [1.43, 3.16]	
Subtotal (95% CI)		533		534	12.4%	2.13 [1.43, 3.16]	•
Total events	70		33				
Heterogeneity: Not ap	plicable						
lest for overall effect	: Z = 3.73	3 (P = 0	0.0002)				
Total (95% CI)		5063		5055	100.0%	1.83 [1.30, 2.59]	•
Total events	660		425				
Heterogeneity: Tau ² =	= 0.21; Cł	$1i^2 = 53$	3.54, df =	= 10 (P	< 0.0000	(1); $I^2 = 81\%$	
Test for overall effect	: Z = 3.43	3 (P = 0	0.0006)				Favours cilostazol Favours control
Test for subgroup dif	ferences:	$Chi^2 =$	17.58, d	lf = 3 (P = 0.000	$(5), 1^2 = 82.9\%$	

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

	Cilosta	ızol	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Kwon 2005	3	45	15	52	27.9%	0.23 [0.07, 0.75]	_
Kwon 2011	20	202	32	207	44.4%	0.64 [0.38, 1.08]	
Uchiyama 2015	7	73	4	72	27.7%	1.73 [0.53, 5.64]	
Total (95% CI)		320		331	100.0%	0.63 [0.25, 1.58]	-
Total events	30		51				
Heterogeneity: Tau ² =	= 0.41; Cl	$1i^2 = 5.$	61, df =	2 (P =	0.06); l ²	= 64%	0.01 0.1 1 10 100
Test for overall effect	: Z = 0.98	8 (P = 0).33)				Favours cilostazol Favours control

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)

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







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: Cilo	stazol mono or cor	nbination therapy	,						
Comparison: Sing	Comparison: Single or dual antiplatelet therapy; best medical therapy; placebo								
Outcome	Absolute effect		Relative risk	No. of patients	Quality of				
	Control	Cilostazol	(95% CI)	(studies)	evidence				
Ischemic stroke	56/1000	38/1000	0.69 (0.58-0.81)	11,429 (18)	High				
recurrence	Difference: 18 fev	wer per 1000							
	(95% Cl 11 fewer	to 23 fewer)							
Any stroke	69/1000	44/1000	0.64 (0.54-0.74)	11,429 (18)	High				
recurrence	Difference: 25 fev	wer per 1000							
	(95% CI 18 fewer	to 32 fewer)							
Intracranial	15/1000	6/1000	0.46 (0.31-0.68)	11,429 (18)	High*				
hemorrhage	Difference: 9 few	er per 1000							
	(95% CI 5 fewer t	o 10 fewer)							
Major	23/1000	11/1000	0.49 (0.34-0.70)	8041 (14)	High*				
hemorrhagic	Difference: 12 fev	wer per 1000							
events	(95% CI 7 fewer t	o 15 fewer)							
Mortality	14/1000	13/1000	0.90 (0.64-1.25)	10,046 (15)	Moderate				
	Difference: 1 few	er per 1000			due to				
	(95% CI 5 fewer t	o 4 more)			imprecision				
MACE	72/1000	48/1000	0.67 (0.56-0.81)	7668 (13)	High				
	Difference: 24 fev	wer 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				
	Difference: 4 mor	e per 100			imprecision &				
	(95% CI 3 fewer t	o 12 more)			inconsistency				
ADE leading to	84/1000	130/1000	1.83 (1.30-2.59)	10,118 (13)	Moderate				
drug	Difference: 46 m	ore per 1000			due to				
discontinuation	(95% CI 25 more	to 134 more)			inconsistency				

*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	Ν	Y	Ν	Ν	Ν
MACE	N	N	N	N	N
mRS 0-1	N	Y	Y (I ² =60%)	N	NA
ADE leading to drug discontinuation	Ν	N	Y (I ² =81%)	N	N

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

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	Υ
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	Υ
mRS 0-1	0.649	0.614	164	Υ
ADE leading to drug	0.130	0.0841	2421	Y

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

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

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

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

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