Title page

Full title: Cilostazol for secondary prevention of stroke and cognitive decline: Systematic review and meta-analysis

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Abstract

Background and Purpose: Cilostazol, a phosphodiesterase 3' inhibitor, is used in Asia-Pacific countries for stroke prevention, but rarely used elsewhere. In addition to weak antiplatelet effects, it stabilises endothelium, aids myelin repair and astrocyte-neuron energy transfer in laboratory models, effects that may be beneficial in preventing small vessel disease (SVD) progression.

Methods: A systematic review and meta-analysis of unconfounded randomised controlled trials (RCTs) of cilostazol to prevent stroke, cognitive decline or radiological SVD lesion progression. Two reviewers searched for papers (01/01/19-16/07/19) and extracted data. We calculated Peto odds ratios (OR) and 95% confidence intervals (CI) for recurrent ischaemic, haemorrhagic stroke, death, adverse symptoms, with sensitivity analyses. The review is registered (CRD42018084742).

Results: We included 20 RCTs (n=10505), 18 in ischaemic stroke (total n=10449) and two in cognitive impairment (n= 56); most were performed in Asia-Pacific countries. Cilostazol decreased recurrent ischaemic stroke (17 trials, n=10225, OR=0.68, 95%CI=0.57 to 0.81, P<0.0001), haemorrhagic stroke (16 trials, n=9736, OR=0.43, 95%CI=0.29,0.64, P=0.0001), deaths (OR=0.64, 95%CI=0.49, 0.83, P<0.0009), systemic bleeding (n=8387, OR=0.73, 95%CI=0.54, 0.99, P=0.04), but increased headache and palpitations, compared with placebo, aspirin or clopidogrel. Cilostazol reduced recurrent ischaemic stroke more when given long (>6months) vs short-term without increasing haemorrhage, and in trials with larger proportions (>40%) of lacunar stroke. Data were insufficient to assess effects on cognition, imaging, functional outcomes or tolerance.

Conclusions: Cilostazol appears effective for long term secondary stroke prevention without increasing haemorrhage risk. However, most trials related to Asia-Pacific patients and more trials in Western countries should assess its effects on cognitive decline, functional outcome and tolerance, particularly in lacunar stroke and other presentations of SVD.

Introduction

Cerebral small vessel disease (SVD) causes 25% of ischaemic stroke, most intracerebral haemorrhages, most vascular cognitive impairment and up to 45% of dementias, and other important ageing related co-morbidities.{Hachinski, 2019 #11743} There is no specific treatment to prevent SVD progression. In a review of SVDs mechanisms and therapeutic agents with relevant modes of action,[1] we identified several licenced drugs including cilostazol, a phosphodiesterase 3′ inhibitor. In addition to mild antiplatelet effects,[2] cilostazol has several actions targeting processes involved in SVD pathophysiology: endothelial dysfunction, myelin repair, neuroprotection and inflammation.[1]

Cilostazol is used for stroke prevention in Asia-Pacific countries, but in Western countries it is used mostly for symptomatic peripheral vascular disease. Previous systematic reviews suggested that cilostazol prevented recurrent stroke.{Uchiyama, 2009 #8977}[3,4] However, further trials have been published since the last review, no review has assessed cilostazol's effects in relevant subgroups and few assessed adverse effects (bleeding, headaches, palpitations, etc) that could limit cilostazol tolerance.

We performed a systematic review and meta-analysis to determine the effect of cilostazol on stroke recurrence, cognitive decline, radiological progression of SVD, intracerebral haemorrhage, death and adverse symptoms in patients with stroke or cognitive presentations of SVD.

Methods

We published the systematic review protocol on PROSPERO (registration No. CRD42018084742) in March 2018 and performed the review according to PRISMA standards.[5]

We searched MEDLINE and EMBASE between 1990 and 16 July 2019 (see Supplement) for original articles reporting prospective randomised controlled trials of cilostazol in patients with stroke, small vessel disease, mild cognitive impairment or dementia. We also searched clinical trial registries (www.isrctn.com; eudract.ema.europa.eu; www.strokecenter.org/), conference proceedings, bibliographies of review papers, previous systematic reviews and trials papers for relevant trials not identified in the search, and finally for secondary publications of included trials that might provide additional outcomes.

We included randomised, controlled, unconfounded, trials in patients with stroke, mild cognitive impairment or dementia, or radiological features of SVD, who were randomised to

treatment with cilostazol. Control groups received placebo tablets, another antiplatelet or received no cilostazol (open label). We excluded trials only published as conference abstracts, where translation into English was not possible, or where the full text was not available.

We included trials that reported any of the following: recurrent stroke (all, ischaemic, haemorrhagic), incident dementia, incident mild cognitive impairment, change in cognitive test scores including domain specific scores, intracranial haemorrhage, other major/fatal bleeding, other systemic bleeding complications, death, myocardial infarction, dependency in activities of daily living, symptoms related to cilostazol use (such as nausea, headache, palpitations), change in white matter hyperintensities (WMH), progression/development of lacunes, microbleeds, perivascular spaces, brain atrophy (assessed by volume or validated score).

Two reviewers screened titles and abstracts of all identified articles (GB, CM), independently performed full text review of relevant papers, extracted data from included papers using standardised forms, and cross-checked their findings.

We extracted data on trial setting (hospital, community, etc), number of participants, sex, inclusion illness, diagnosis method including cognitive testing, proportion with lacunar stroke, randomisation methods, time from onset of inclusion illness to randomisation, blinding, treatment dose, duration, control allocation, concomitant antiplatelet or other agents, methods of outcome assessment, and proportion of patients with outcomes as listed above by intention to treat populations. We assessed study quality using the CONSORT criteria.[6]

Discrepancies between the two reviewers were resolved by discussion and a third reviewer (JMW) who cross-checked all data extraction.

Meta-analysis: We entered data into RevMan5 (version 5.3) software package. For most analyses, we grouped trials according to: a) their time to randomisation (randomising in acute/subacute versus later after stroke); and b) use of other prescribed antiplatelet drug (none, cilostazol plus aspirin or clopidogrel versus aspirin or clopidogrel, cilostazol versus aspirin or clopidogrel) and meta-analysed each outcome. We meta-analysed symptoms by type. For death from all causes, we assumed no deaths in studies that did not report deaths. We used Peto odds ratio (OR) and 95% confidence intervals (CI) for the meta-analyses, a preferred method where outcome events are infrequent.[7]

In exploratory sensitivity analyses, we ranked trials according to the proportion of patients with small vessel (lacunar) ischaemic stroke, dichotomised into <40% and ≥40% or unspecified. We also tested time from stroke to start of treatment, and other antiplatelet drugs used.

We performed a meta-regression to test whether time to start treatment, proportion of patients with lacunar stroke, study duration or comparison antiplatelet agent influenced the effect of cilostazol, using R version 3.6.2 (https://cran.r-project.org/) meta package.

We assessed risk of bias using funnel plots and heterogeneity using I^2 and Chi^2 tests.

Results

We identified 572 articles but excluded 505 after abstract screening, and a further 43 after full text review (Figure 1). We included 20 unconfounded, original RCT's, published in 24 papers, including 10505 participants (Table 1).

Characteristics of Included Trials

The 20 trials had a median sample size of 183, range 20-2672. Eighteen trials included patients with stroke (n=10449, Table 1) and two included patients with cognitive impairment or dementia of Alzheimer's type and radiological evidence of SVD (n=56).[8,9]

Of the 18 trials in patients with stroke, two only included patients with lacunar stroke (n= 515),[10, 11] three only included patients with intracranial artery stenosis (n=755),[12-14] six only included patients with non-cardioembolic ischaemic stroke (n=5264),[15-20] most trials excluded patients with cardioembolic stroke regardless of other inclusion criteria, and one trial included patients at high risk of intracerebral haemorrhage (n=1534).[21] In 9/18 trials, the stroke was lacunar in ≥40% of participants (n=6943); in the other nine trials, <40% of patients had a lacunar ischaemic stroke or the subtype proportion was not specified (n=3262).

The time to randomisation after diagnosis was <two weeks in eight (n=1940),[11,13,14,18-20,22,23] between two weeks and six months in five (n=2123),[12,17,24-26] and six months or later in six trials (n=6406; including the one trial in cognitive decline/dementia)[9,10,15,16,21,27] and was not stated in the other trial in cognitive decline.[8] The duration of trial treatment was four weeks in three (n=344),[18,19,27] 10 weeks in one (n=57),[10] four months in four (n=1236),[11,20,22,23] six-to-eight months in five (n=753; including both trials in cognitive decline/dementia)[8,9,13,14,17], 12

months in one (n=68)[26] and between 12 months and five years in six trials (n=8034).[12,15,16,21,24,25]

Eight trials used placebo tablets, the rest were open label (Table 1). One trial in stroke and one in Alzheimer's disease tested cilostazol versus control in the absence of any other antiplatelet drug; nine trials tested cilostazol plus aspirin or clopidogrel versus aspirin or clopidogrel; eight trials tested cilostazol versus aspirin or clopidogrel, and one trial tested cilostazol plus aspirin versus clopidogrel plus aspirin.

Of the 18 trials that included patients with stroke, one[27] did not record recurrent stroke outcomes, and one[9] that included patients with cognitive impairment reported recurrent stroke, therefore 18 trials provided data on recurrent stroke (all, ischaemic, Supplement Table I). Sixteen trials reported recurrent haemorrhagic stroke, 18 reported death, three trials reported cognitive outcomes (two trials in patients with cognitive impairment, one trial in stroke),[8-10] 10 trials reported major cardiac outcomes, seven assessed functional outcome (modified Rankin scale) but only five gave results (precluding meta-analysis of effects of cilostazol on dependency), and about half the trials reported adverse symptoms (headache, nausea, palpitations, systemic bleeding; Supplement Table II). Outcomes are summarised in Table 2.

Recurrent Ischaemic Stroke:

Eighteen trials (n=10225) reported recurrent ischaemic stroke (cilostazol 5127, control 5098). Cilostazol decreased recurrent ischaemic stroke (OR=0.68, 95%CI=0.57, 0.81, P<0.0001), Figure 2, without heterogeneity. Most benefit appeared in the nine trials testing cilostazol started more than two weeks after stroke (median 76 days; omitted in three trials) and given long term, where the ORs are all less than one regardless of comparator group or concomitant antiplatelet drug use (see sensitivity analyses below). In contrast, in the eight trials starting cilostazol within two weeks of stroke (median 9.6 days; omitted in four trials) and assessing outcome at one to four months, the ORs all overlapped one, although the acute/subacute trials were smaller than the later-implementation/longer duration trials. A similar effect was seen for any recurrent stroke (18 trials, n=10225, 5127 allocated cilostazol, 5098 allocated control) where cilostazol decreased the odds of any recurrent stroke (OR=0.61, 95%CI=0.523, 0.72, P<0.00001), without heterogeneity (Figure I).

Haemorrhagic stroke:

Sixteen trials (n=9736) reported recurrent haemorrhagic stroke (cilostazol 4885, control 4851). Overall, cilostazol reduced haemorrhagic stroke (OR=0.43, 95%CI=0.29, 0.64, P=0.0001),

Figure 3, without heterogeneity. The pattern of effect was similar to that seen in all stroke and ischaemic stroke although the reduced sample resulted in fewer individually significant results.

Major Adverse Cardiovascular Events:

Ten trials reported a composite outcome of MACE (cilostazol 4470, control 4478). Cilostazol decreased MACE (OR=0.66, 95%CI=0.57, 0.76, P<0.00001), without heterogeneity (Figure S2). Most benefit occurred in trials testing long-term cilostazol starting six months or more after stroke, where summary ORs are less than one regardless of whether cilostazol was compared with placebo or aspirin or of concomitant antiplatelet drug use.

Death:

Eighteen trials reported death from any cause (cilostazol 5123, control 5742). Overall, cilostazol decreased the odds of death (OR=0.64, 95%CI=0.49, 0.83, P=0.0009), Figure III, without heterogeneity. Most benefit occurred in trials randomising patients late after diagnosis whilst trials randomising soon after stroke were more equivocal.

Cognition:

Two trials provided meta-analysable results (cilostazol 29, control 27; Figure IV) but data were too sparse to draw conclusions. One trial (LACI-1) that could not be meta-analysed reported a mean difference (adjusted for baseline) in Trail Making Test A of -4.0 (-12.7 to 4.7, P=0.37).

Radiological markers of SVD:

Only three trials reported SVD imaging markers although each reported a different measure (silent infarcts, new ischaemic lesion, microbleeds). Overall 55/557 participants allocated cilostazol developed an imaging lesion compared to 48/581 allocated control (OR=1.22, 95% CI=0.81, 1.84, P=0.34).

Adverse symptoms:

The types of symptoms reported by each study varied (Supplement Table II). In general, patients allocated cilostazol had more headache, dizziness, palpitations, tachycardia and diarrhoea, but less constipation and non-stroke bleeding events (Table 2, Figure V). There was no heterogeneity for the above outcomes apart from systemic bleeding and palpitations (palpitations I^2=54%, Chi^2=19.43, P=0.02; systemic bleeding I^2=69%, Chi^2=25.6, P=0.001).

Sensitivity analyses

Lacunar vs non-lacunar stroke: In the eight trials with <40% or unstated proportion of patients with lacunar stroke (cilostazol 1639, control 1623), cilostazol did not reduce recurrent ischaemic stroke (OR=0.72, 95%CI=0.49, 1.07, P=0.10, without heterogeneity), Figure VIA. In the nine trials with 40% or more patients with lacunar stroke (cilostazol 3477, control 3466; of which, six trials, total n=4964, included 58% or more lacunar strokes), cilostazol reduced recurrent ischaemic stroke (OR=0.64, 95%CI=0.52, 0.79, P<0.0001, without heterogeneity). However, the effect of cilostazol on recurrent ischaemic stroke did not differ between the two subgroups (<40% or ≥40% with lacunar stroke), on formal testing (Chi^2 for difference=0.27, P=0.60, I^2=0%, P=0.60, without heterogeneity).

Time from stroke to treatment: Patients allocated treatment within two weeks of stroke, and where treatment was generally continued for no more than four months, those allocated cilostazol had similar rates of recurrent ischaemic stroke (21/972) than those allocated control (19/968), OR=1.10, 95%CI=0.58, 2.05, P=0.78 without heterogeneity, Figure VIB. In patients starting treatment beyond two weeks after stroke (median), and where treatment was generally continued for six months to five years, those allocated to cilostazol had fewer recurrent ischaemic strokes (189/4155) than those allocated control (286/4130), OR=0.65, 95%CI=0.54, 0.78. P<0.00001, without heterogeneity. However there was no evidence of a between group difference (acute versus late, Chi^2 2.47, P=0.12, with moderate heterogeneity, I^2=59.5%).

Concomitant antiplatelet drugs: Trials which randomised between cilostazol and no cilostazol in the absence or presence of concomitant aspirin or clopidogrel showed similar benefit for cilostazol (no aspirin, OR=0.51, 95%CI=0.33, 0.79, P=0.003; all patients received aspirin or clopidogrel, OR=0.51, 95%CI=0.35, 0.74, P=0.0004), Figure VIC. However in trials where cilostazol was compared to aspirin or clopidogrel, including one trial randomising to cilostazol + aspirin versus clopidogrel+aspirin,[14] there was no definite benefit of cilostazol (OR=0.81, 95%CI=0.65, 1.02, P=0.08). Across the three subgroups, there was evidence of between-subgroup differences (Chi^2 6.31, P=0.04), and moderate heterogeneity (I^2=68.3%). Restricting the analysis to trials comparing cilostazol with one antiplatelet drug in the absence of another antiplatelet drug by excluding the TOSS2 trial, showed benefit of cilostazol over the other antiplatelet drug (OR=0.78, 95%CI=0.62 to 0.99, P=0.04, without heterogeneity) and removed the evidence of between-subgroup difference (Chi^2 5,19, P=0.07), but retained heterogeneity, (I^2=61.4%).

Meta-regression: Meta-regression of time to treatment, duration of treatment, and proportion of lacunar strokes, adjusted for comparator antiplatelet agent, did not identify any significant subgroup effects on outcomes of recurrent ischaemic or haemorrhagic stroke.

Sources of bias:

The median trial quality was 23.5/37 (minimum 14, maximum 35), with methods sections attaining the lowest scores on average (Supplement Table III, Figure VII).

Funnel plots on all stroke, and ischaemic stroke showed some skew suggesting reporting bias but not for haemorrhagic stroke did not show any skew (Figure VIII).

Discussion

Cilostazol reduced recurrent stroke, recurrent ischaemic stroke, recurrent haemorrhagic stroke, death and MACE compared with control, in the presence or absence of aspirin, or when compared directly with aspirin (data were limited for comparison with clopidogrel). Most benefit occurred in trials that randomised patients at two or more weeks after stroke and administered cilostazol for at least six months or longer, without evidence of increased risk with long-term treatment. There were very few data on the effect of cilostazol on functional outcome, cognitive decline, or radiological markers of SVD. Adverse symptoms such as headache, palpitations, dizziness, and diarrhoea were clearly increased with cilostazol although, importantly, systemic bleeding events were reduced.

The review limitations are related to the available data and include variation between trials in antiplatelet drug use, times to randomisation after stroke, durations of treatment, not reporting dependency outcomes, and lack of information on stroke subtypes. Included studies varied greatly in sample size and some studies had no events in either group for certain outcomes. Antiplatelet therapy has changed since some studies were completed. Guidelines now advise dual antiplatelets short term after TIA or minor ischaemic stroke, followed by clopidogrel longer term. Only one study compared cilostazol to clopidogrel and both groups also received aspirin.[14] Only two trials recruited patients with cognitive presentations and only one trial in stroke assessed cognition. The median trial quality was moderate (23.5/37). Thus, despite the total available data from trials of cilostazol totalling over 10,000 patients, the conclusions have limitations. There were also strengths of the review, including prospective protocol registration, assessment of methodological quality, double assessment of papers and data extraction, and careful harmonisation of the trials for analysis.

Cilostazol may have more benefit on several outcomes where participants were randomised later after stroke. Although arbitrary, the trials naturally dichotomised into those randomising within two weeks of stroke and those randomising at more than two weeks after stroke, of which about a third randomised between two weeks and six months and two thirds randomised after six months. Trials randomising more than six months after stroke had long durations of treatment and follow-up. Thus, the apparent benefit of cilostazol in trials randomising late rather than early may reflect the paucity of acute trials, shorter duration of treatment, higher proportion of lacunar strokes, or that cilostazol is less effective in preventing early recurrent stroke. Similar results have been seen with another phosphodiesterase inhibitor dipyridamole (PDE5 inhibitor) with mild-antiplatelet and pro-endothelial effects[1] which reduced stroke recurrence whilst increasing headache, mostly in Western populations. The risk of stroke recurrence varies by stroke subtype, atherothromboembolic stroke recurrence risk being highest immediately after TIA/minor stroke, then declining, whereas lacunar stroke has lower risk of early recurrence but the rate remains elevated in the longer term.

Cilostazol's apparent greater benefit late after stroke could reflect several possible mechanisms. Weaker antiplatelet effects[2] and hence inferior stroke prevention compared to aspirin or clopidogrel early after TIA/stroke (when stronger antiplatelet activity may be more beneficial) is supported by the neutral effect of cilostazol on ischaemic stroke recurrence compared to aspirin or clopidogrel (Figure VIC). Increasing benefit of cilostazol late after stroke was also demonstrated in CASISP, which found no difference in recurrent stroke between cilostazol and aspirin within six months of stroke, but increasing benefit of cilostazol versus aspirin thereafter.[25] The increased benefit of cilostazol later after stroke may reflect that its mechanisms of action are more relevant to lacunar stroke where recurrence occurs late, supported by increased benefit in trials including more patients with lacunar stroke (Figure VIA). Potential benefits for lacunar stroke include endothelial stabilisation, improved myelin repair and better astrocyte-to-neuronal energy supply,[1,10] all of which may take some time to accrue. The lower cerebral and systemic haemorrhage risks would also confer benefit over other antiplatelet drugs which typically have higher bleeding risk the longer they are given, a reason for early stopping of the SPS3 Trial (dual versus single antiplatelet drugs) for lacunar stroke[28], and seen in the present meta-analysis even in the presence of other antiplatelet drugs. The PICASSO trial suggests that the benefits of cilostazol may extend to reducing recurrent stroke and systemic bleeding even in patients at high risk of intracerebral haemorrhage.[21]

More data are needed to overcome the limitations of the current data, to determine the effect of cilostazol on functional and cognitive outcomes after stroke, and on delaying cognitive

decline. If the effects of cilostazol seen in laboratory models translate to people (myelin repair, improved neuronal energy supply and endothelial stabilisation) and help to prevent progression of brain injury, then cilostazol might also prevent physical decline seen in SVD. Future studies should compare cilostazol to modern antiplatelet regimes, stratify patients by stroke or cognitive impairment, provide more data on cognitive, imaging and functional outcomes, and on tolerability and compliance. Several ongoing studies address these issues. LACI-2 (ISRCTN 14911850) is assessing cilostazol long-term after lacunar ischaemic stroke in the UK including one year cognitive and brain MRI follow up (target n=400). The COMCID trial (Asia-Pacific) is assessing cilostazol's effects on cognitive function, incident dementia and hippocampal volumes (NCT02491268). Other trials are assessing short-term effects of cilostazol on cerebrovascular reactivity (e.g. Oxford Haemodynamic Adaptation to Reduce Pulsatility Trial (OxHARP), NCT03855332, target n=76).

Cilostazol shows promise for ischaemic stroke prevention, with lower risk of haemorrhagic complications, particularly long term. Its place in stroke therapy may be in chronic secondary prevention rather than the acute phase. However most data are from Asia Pacific countries where stroke aetiologies and other factors may differ from other world regions, hence the need for more data. Despite its encouraging safety profile (lower bleeding risk and death), cilostazol causes several symptoms (headache, palpitations, diarrhoea, nausea) which may limit tolerance, requiring more data to guide future routine use. It is licenced in Europe and the Americas for treatment of symptomatic peripheral vascular disease and stroke prevention where other antiplatelet agents have failed or are not tolerated. However more evidence is needed before it is used more widely in stroke in routine practice.

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CM – Article search and data extraction, meta-analysis, drafting and review of manuscript

GWB – Protocol design, article search and data extraction, analysis, drafting and review of manuscript

JPA – review of protocol and manuscript

PMB - Protocol design, article search and data extraction, review of manuscript

JMW – Review conception, protocol design, supervision, analysis, drafting and review of manuscript.

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Conflict(s)-of-Interest/Disclosure(s)

JMW, PMB, GWB, JPA, FD, worked on the LACI-1 and LACI-2 trials testing cilostazol in lacunar stroke. PMB led systematic reviews of dipyridamole.

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Table 1: Characteristics of Included Studies

	Study details					Cilostazol group			Control group		
Study and country where done	**Total n**	**Time from diagnosis to random-isation**	**Treatment duration**	**Patient group**	**Stroke subtype**	**Cilos-tazol n**	**Cilostazol dose**	**Additional treatment**	**Control n**	**Control treatment**	**Control dose**
ARCC[27] Korea	244	At least 2 weeks to ≥365 days	4 weeks	Ischaemic stroke	NS	125	100mg bd	Aspirin 100mg daily	119	Placebo and Aspirin	Aspirin 100mg daily
CAIST[22] Korea	458	48 hours	90 days	Ischaemic stroke	58% SVD, 28% LA, 1% CE, 12% other	231	200mg daily	-	227	Aspirin	300mg daily
CASID[8] Korea	36	NS	24 weeks	Probable Alzheimer Disease with white matter lesions	Not applicable	18	100mg bd (2 weeks) then 200mg bd	-	18	Placebo	NS
CASISP[25] China	719	1-6 months	Up to 540 days	Ischaemic stroke	NS	360	NS	-	359	Aspirin	NS
CATHARSIS[12] Japan	163	2 weeks to 6 months	2 years	Ischaemic stroke, >50% stenosis ipsilat intracran ICA or MCA	All non-CE ischaemic stroke	83	200mg daily	Aspiring 100mg daily	80	Aspirin	100mg daily
CSPS[24] Japan	1067	1-6 months	Cil=632.2± 467.7 days Cont=695.1 ±456.3 days	Ischaemic stroke	75% lacunar, 14% athero-thrombotic 9% mixed, 2% UK	533	100mg twice daily	-	534	Placebo	100mg twice daily
CSPS2[15] Japan	2672	Up to 26 weeks	1-5years	non-CE Ischaemic stroke	65% lacunar, 32% athero-	1337	100mg twice daily	-	1335	Aspirin	81mg daily

					thrombotic, 3% UK						
CSPS.com[16] Japan	1879	8-180 days	6 months to 3.5 years	Non-CE Ischaemic stroke	49% lacunar, 42% athero-thrombotic, 9% other/UK	932	100mg twice daily*	Aspirin 81mg or 100mg daily or Clopidogrel 50mg or 75mg daily	947	Aspirin or Clopidogrel	Aspirim=81 mg or 100mg daily Clopidogrel =50mg or 75mg daily
ECLIPse[11] Korea	203	7 days	90 days	Lacunar ischaemic stroke	100% lacunar	100	100mg twice daily	Aspirin 100mg daily	103	Placebo and Aspirin	Placebo= 100mg twice daily Aspirin=10 0 mg daily
Guo[26] China	68	1-6 months	12 months	Ischaemic stroke	NS	34	100mg twice daily	-	34	Aspirin	100mg daily
Johkura[17] Japan	106	1-6 months	6 months	Non-CE ischaemic stroke	NS but all supra-tentorial, c/o dizziness	57	200mg daily	-	49	Aspirin	100mg daily
LACI-1[10] UK	57	Up to 4 years	Treatment (Cil: 9wks; Cil+ISMN immediate start: 7wks; Cil+ISMN delayed: 6wks) Control: 11wks	Lacunar stroke	100% lacunar	42	100mg twice daily**	Aspirin 75mg or Clopidogrel 75mg daily	15	Aspirin or Clopidogrel	75mg daily
Lee[23] Korea	80	Within 7 days	90 days	Ischaemic stroke or TIA	NS	40	100mg twice daily	Placebo Aspirin	40	Placebo and Aspirin	Placebo=b d Aspirin=10 0 mg daily
Nakamura[18] Japan	76	48 hours	6 months	Non-CE ischaemic stroke	47% SVD, 20% LA atheroma,	38	100mg twice daily	Aspirin 300mg daily (4	38	Aspirin	300mg daily (4 days) then

					33% other/UK			days) then 100mg daily			100mg daily
Ohnuki[19] Japan	24	Within 1 week	4 weeks	Non-CE ischaemic stroke	41% lacunar, 25% athero-thrombotic, 6% other	13	200mg daily	Aspirin 100mg daily	11	Aspirin	100mg daily
PICASSO[21] Korea	1534	180 days	Median = 1.9yrs IQR=1.0-3.0	Ischaemic stroke at high risk of ICH	Prior ICH or ≥2 micro-bleeds	766	100mg bd	Aspirin placebo daily	768	Aspirin and placebo	Aspirin=100mg daily Placebo=bd
Sakurai[9] Japan	20	More than 6 months	6 months	Possible Alzheimer Disease and SVD lesions	Not applicable	11	100mg daily		9	Aspirin or Clopidogrel	Aspirin=100mg daily Clopidogrel=50-75mg daily
Shimizu (Tohoku)[20] Japan	507	24 hours	3 months	Non-CE progressing ischaemic stroke	67% lacunar, 28% athero-thrombotic, 5% other	251	200mg daily	Aspirin 300mg daily	256	Aspirin	Aspirin 300mg daily
TOSS[13] Korea	135	2 weeks	6 months	Ischaemic stroke, intracranial ICA or MCA stenosis	NS	67	100mg bd	Aspirin 100mg daily	68	Placebo and Aspirin	Aspirin 100mg daily
TOSS-2[14] Korea	457	2 weeks	7 months	Ischaemic stroke, intracranial ICA or MCA stenosis	NS	232	100mg bd	Aspirin 75-150mg daily	225	Clopidogrel and Aspirin	Clopidogrel=75mg daily Aspirin=75-150mg daily

NS=not stated; UK=unknown; SVD=small vessel disease; ICH=intracerebral haemorrhage; LA=large artery; CE=cardioembolic; Cil=cilostazol; cont=control; ICA=internal carotid artery; MCA=middle cerebral artery; mg=milligrams; bd=twice daily; ipsilat=ipsilateral; intracran=intracranial; c/o=complaining of; IQR=interquartile range;

Table 2: Summary of main results

Outcome	Trials N	Participants total N	Cilostazol n/N	Control n/N	OR/SMD (95% CI)	P	Subgroup I^2 (%)	Chi^2 P
All stroke	18	10,225	242/5127	384/5098	0.61 (0.52, 0.72)	<0.00001	33.5	0.18
Ischaemic stroke	18	10,225	210/5127	305/5098	0.68 (0.57, 0.81)	<0.00001	44.5	0.11
Haemorrhagic stroke	16	9736	30/4885	72/4851	0.43 (0.29, 0.64)	<0.0001	0	0.55
MACE	10	8948	320/4470	470/4478	0.66 (0.57, 0.76)	<0.00001	2.5	0.39
Death, all cause	18	10,865	93/5123	144/5742	0.64 (0.49, 0.83)	0.0009	18.0	0.30
Cognition	2	56	80	72	0.03 (-0.29, 0.35)	0.84	0.0	0
Headache	14	9582	743/4804	413/4779	2.00 (1.76, 2.28)	<0.00001	69	0.0001
Dizziness	9	6837	349/3419	292/3418	1.22 (1.04, 1.44)	0.02	15	0.31
Palpitations	10	9,147	281/4566	124/4581	3.14 (2.57, 3.84)	<0.00001	54	0.02
Tachycardia	5	5,396	145/2698	33/2698	3.74 (2.77, 5.06)	<0.00001	43	0.15
Diarrhoea	5	4,064	303/2434	126/2403	2.21 (1.78, 2.74)	<0.00001	41	0.13
Constipation	3	4,664	189/2334	268/2330	0.68 (0.56, 0.82)	0.0001	0	0.72
Nausea	4	3,095	76/1548	53/1547	1.47 (1.02, 2.11)	0.04	0	0.88
Systemic bleeding	12	8,387	79/4211	102/4176	0.73 (0.54, 0.99)	0.04	69	0.001
Sensitivity analysis: effect on ischaemic stroke by sub-group								
Ischaemic stroke sub-type:[a] *<40% lacunar stroke*	8	3262	68/1639	101/1623	0.72 (0.49,1.07)	0.10	14	0.32
≥40% lacunar stroke	9	6943	142/3477	222/3466	0.64 (0.52, 0.79)	<0.0001	0	0.54
Test for subgroup difference Chi^2=0.27, P=0.60, I^2=0								
Time to treatment:[a] *<2 weeks of stroke (9.6 days)*[b]	8	1940	21/972	19/968	1.1 (0.58 2.05)	0.78	0	0.81
≥2 weeks of stroke (76 days)[b]	10	8285	189/4155	286/4130	0.65 (0.54, 0.78)	<0.0001	0	0.52
Test for subgroup difference Chi^2= 2.47, P=0.12, I^2=59.5								
Additional antiplatelet drugs: *Cil vs no Cil, no antiplatelet*	1	1067	30/533	57/534	0.51 (0.33, 0.79)	0.003	n/a	n/a
Cil+Asp or Clop vs Asp or Clop	8	3044	40/1526	78/1518	0.51 (0.35, 0.74)	0.0004	0	0.88
Cil vs Asp or Clop	9	6114	140/3068	170/3046	0.81 (0.65, 1.02)	0.08	0	0.68
Test for subgroup difference Chi^2=6.31, P=0.04, I^2=68.3								

n/N=number of events/total number allocated to that group; OR=odds ratio; SMD= standardised mean difference; [a] Comparison is any cilostazol versus no cilostazol; [b] median time to randomisation/treatment; n/a = not applicable; Cil=cilostazol. CI=confidence interval.

Figure legends

Figure 1. PRISMA flow chart of study identification

Figure 2. Effect of cilostazol on ischaemic stroke

Figure 3. Effect of cilostazol on haemorrhagic stroke