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Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin (Review)

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Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

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A B S T R A C T

Background

Aspirin is widely used for secondary prevention after stroke. Cilostazol has shown promise as an alternative to aspirin in Asian people with stroke.

Objectives

To determine the relative effectiveness and safety of cilostazol compared directly with aspirin in the prevention of stroke and other serious vascular events in patients at high vascular risk for subsequent stroke, those with previous transient ischaemic attack (TIA) or ischaemic stroke of arterial origin.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched September 2010), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 4), MEDLINE (1950 to May 2010) and EMBASE (1980 to May 2010). In an effort to identify further published, ongoing and unpublished studies we searched journals, conference proceedings and ongoing trial registers, scanned reference lists from relevant studies and contacted trialists and Otsuka Pharmaceutical Co Ltd.

Selection criteria

We selected all randomised controlled trials (RCTs) comparing cilostazol with aspirin where participants were treated for at least one month and followed systematically for development of vascular events.

Data collection and analysis

Data extracted from eligible studies included: (1) a composite outcome of vascular events (stroke, myocardial infarction or vascular death) during follow up (primary outcome); (2) separate outcomes of stroke (ischaemic or haemorrhagic, fatal or non-fatal), myocardial infarction (MI) (fatal or non-fatal), vascular death and death from all causes; and (3) main outcomes of safety including any intracranial, extracranial or gastrointestinal (GI) haemorrhage and other outcomes during treatment follow up (secondary outcomes). We computed an estimate of treatment effect and performed a test for heterogeneity between trials. We analysed data on an intention-to-treat basis and assessed bias for all included studies.

Main results

We included two RCTs with 3477 Asian participants. Compared with aspirin, cilostazol was associated with a significantly lower risk of composite outcome of vascular events (6.77% versus 9.39%, risk ratio (RR) 0.72, 95% confidence interval (CI) 0.57 to 0.91), and lower risk of haemorrhagic stroke (0.53% versus 2.01%, RR 0.26, 95% CI 0.13 to 0.55). In terms of outcome of safety compared with aspirin, cilostazol was significantly associated with minor adverse effects (8.22% versus 4.95%, RR 1.66, 95% CI 1.51 to 1.83).

Authors' conclusions

Cilostazol is more effective than aspirin in the prevention of vascular events secondary to stroke. Cilostazol has more minor adverse effects, although there is evidence of fewer bleeds.

P L A I N   L A N G U A G E   S U M M A R Y

Cilostazol versus aspirin for secondary prevention of vascular events after a stroke of arterial origin

Stroke is a public health problem. As lower and middle income countries make rapid economic progress they face the additional health burden of diseases of affluence like stroke and heart attacks. Unlike heart attack, stroke is a disease caused by more than one mechanism. In Asians, a larger proportion of ischaemic stroke is due to narrowing of the arteries at the base of the brain. Compared to Caucasians, Asians are more likely to have bleeds into their brain matter causing stroke, because of uncontrolled high blood pressure. The medication cilostazol thins the blood by blocking platelet accumulation and appears, from early reports, to be more effective than aspirin in the prevention of stroke, heart attacks and death from vascular causes in patients with stroke. This may be due to its inherent effectiveness, as well as chances of fewer brain bleeds. In this review of two randomised trials involving 3477 participants, we found that cilostazol was more effective for the prevention of stroke, heart attack and death from vascular causes in Asian patients with stroke. In terms of safety, it causes more side effects than aspirin but less serious bleeding in the brain and the body.

B A C K G R O U N D

Description of the condition

Stroke is the leading cause of sustained disability in the world today. Two-thirds of all strokes now occur in the developing world (Lopez 2006). It is important to study interventions that are relevant to the Asian population as it bears the brunt of the burden of global stroke mortality (Feldmann 1990). Moreover the distribution of types of strokes is different in this region, with a significantly higher proportion of intracranial haemorrhages (ICH) than in the developed world (Liu 2007). Individuals suffering from stroke are already at a very high risk of developing subsequent stroke (Wong 2002). In addition, they are at higher risk of morbidity from other clinical manifestations of atherosclerotic disease such as myocardial infarction (MI), angina or peripheral arterial disease (PAD) (Burke 1995). Although aspirin is beneficial for the secondary prevention of a wide spectrum of cardiovascular incidents, including stroke, it is also known to be associated with a risk of ICH. Cilostazol, a phosphodiesterase type 3 (PDE3) inhibitor,

has been tested in this population for secondary stroke prevention and appears to contribute to fewer intracranial haemorrhages than with aspirin while maintaining a significant reduction in the risk of recurrent strokes. In the Cilostazol Stroke Prevention Study, a phase III clinical trial involving more than 1000 Japanese patients, cilostazol was found to reduce the risk of secondary stroke by 41.7% compared with placebo (Matsumoto 2005). In a phase II clinical trial comparing the efficacy of cilostazol versus aspirin among 720 Chinese patients, stroke recurrence was reported in 12 patients in the cilostazol group and in 20 patients in the aspirin group. The estimated hazard ratio was 0.62 (95% confidence interval (CI) 0.30 to 1.26; P = 0.185). Also, cerebral haemorrhagic events were significantly more common in the aspirin group than in the cilostazol group (7 versus 1; P = 0.034) (Huang 2008).

Description of the intervention

Cilostazol is a selective and potent phosphodiesterase type 3 (PDE3) inhibitor (Minami 1997) that is both an antiplatelet and a vasodilating agent. PDE 3 increases the breakdown of cyclic

adenosine monophosphate (cAMP) (Ikeda 1999). Inhibition of PDE3 increases the levels of cAMP. Since both platelets and vascular smooth muscle cells contain PDE 3A, inhibition leads to decreased platelet aggregation. Cilostazol inhibits the uptake of adenosine (Liu 2000). This leads to an enhanced adenosine action via A1 and A2 receptors. In platelets and vascular smooth muscle cells A2 mediated increases in cAMP enhance the consequences of PDE inhibition, that is result in additional increases in cAMP. Aspirin is a non-selective irreversible inhibitor of cyclooxygenase (COX) and has anti-inflammatory and antiplatelet effects. It decreases the formation of prostaglandins (PGs) and thromboxanes, which leads to decreased platelet aggregation and stabilization (Abramson 1989).

How the intervention might work

In addition to platelet inhibition, cilostazol has other effects on the circulatory system that may be relevant to stroke prevention. Both PDE inhibition and possibly inhibition of adenosine uptake act in concert to relax vascular smooth muscle cells and lead to vasodilatation. Monocyte chemoattractant protein 1 (MCP-1) plays a significant role in mediating monocyte recruitment in atherosclerotic lesions. Interestingly, cilostazol also inhibits the cytokine induced expression of MCP-1 probably due to cAMP elevation, which might contribute to an anti-inflammatory action (Nishio 1997).

Cilostazol acts as an antimitogenic agent by several mechanisms. It blocks the surface expression of the platelet fibrinogen receptor (G2b/3a) as well as alpha-granule secretion of P-selectin (Inoue 1999). P-selectin is assumed to be involved in platelet dependent mitogenesis. This effect might contribute to inhibition of re-stenosis. Heparin binding epidermal growth factor (HBEGF), which is also inhibited by cilostazol, is one the most potent mitogens for vascular smooth muscle cells and is found in macrophages and vascular smooth muscle cells (Kayanoki 1997). Cilostazol used for a period of 12 weeks has been shown to increase high density lipoproteins (HDL) by 10% and decrease triglycerides by 15% (Elam 1998). These multiple potential mechanisms of action may explain the efficacy of cilostazol.

Why it is important to do this review

Cilostazol has shown promise as an alternative to aspirin for Asian populations with ischaemic stroke (Shinohara 2008). The risk of primary intracranial haemorrhage (ICH) in people from these regions is 30% compared to 10% in the developed world (Liu 2007). Cilostazol appears to prevent more ischaemic strokes and cause less ICH than aspirin when used for secondary prevention of ischaemic stroke (Huang 2008).

Aspirin is the most widely prescribed agent for the prevention of stroke in the world today (Rother 2008). Aspirin overall reduces the risk of major vascular events by 13% (95% CI 6% to 19%) (Algra 1996). A study of 720 Chinese patients that compared treatment with a standard dose of aspirin at 100 mg per day to cilostazol 100 mg twice a day was associated with a reduction of recurrent stroke by 30% (95% CI -26% to 70%) (Huang 2008). A systematic review is necessary to evaluate the strength of these claims.

OBJECTIVES

The objective of this review was to determine the relative effectiveness and safety of the phosphodiesterase inhibitor (PDE 3A) cilostazol, compared directly with aspirin (frequently used as monotherapy for secondary prevention), in the prevention of stroke and other serious vascular events in patients at high vascular risk for subsequent stroke. That is, those people with previous transient ischaemic attack (TIA) and ischaemic stroke of arterial origin.

METHODS

Criteria for considering studies for this review

Types of studies

We included all truly randomised trials in which cilostazol was compared directly with aspirin and in which patients were followed up prospectively and systematically for at least one month for the occurrence of serious vascular events.

Types of participants

Eligible patients were those at high risk of stroke and other serious vascular events due to previous clinical manifestations of TIA or ischaemic stroke of arterial origin.

Types of interventions

Orally administered cilostazol at a minimum dose of 50 mg twice a day compared with aspirin at a minimum dose of 81 mg once a day.

Types of outcome measures

Primary outcomes

The main outcome measure of effectiveness was the composite outcome of stroke, myocardial infarction (MI), and vascular death.

Secondary outcomes

The secondary outcomes of effectiveness were the separate outcomes of stroke (ischaemic or haemorrhagic, non-fatal or fatal), MI (non-fatal or fatal), vascular death, and death from all causes. We classified deaths as due to ischaemic stroke, intracranial haemorrhage (ICH), MI, other vascular causes (for example sudden cardiac death, cardiac failure, pulmonary embolism, extracranial haemorrhage), non-vascular causes, and unknown causes (deaths that could not be assigned to any of the foregoing categories). The main outcomes of safety were any ICH, extracranial haemorrhage, and gastrointestinal haemorrhage. Other outcomes measuring safety were headache, gastrointestinal intolerance, palpitation, dizziness, tachycardia, precipitation of angina, and cardiac failure.

Search methods for identification of studies

See the 'Specialized Register' section in the Cochrane Stroke Group module.

Electronic searches

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor in September 2010, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 4), MEDLINE (1950 to May 2010) (Appendix 1), and EMBASE (1980 to May 2010) (Appendix 2).

Searching other resources

In an effort to identify further published, unpublished, and ongoing trials we undertook the following.

1. Handsearched journals and conference proceedings:
   i) Proceedings of the International Stroke Conference 2010, 24 to 26 February 2010, USA, San Antonio Texas (July 2010);
   ii) Proceedings of the 18th European Stroke Conference 2009, 26 to 29 May 2009, Sweden, Stockholm (May 2010);
   iii) Proceedings of the International Stroke Conference 2009, 18 to 20 February 2009, USA, San Diego, California (May 2010);
   iv) Proceedings of the 2nd International Conference on Hypertension, Lipids, Diabetes and Stroke Prevention 2008, 6 to 8 March 2008, Czech Republic, Prague (May 2010).
2. Searched the following international trials registers:
   i) ClinicalTrials.gov (http://www.clinicaltrials.gov/) (May 2010);
   ii) Current Controlled Trials (www.controlled-trials.com) (May 2010);
   iii) Stroke Trials Registry (www.strokecenter.org/trials/) (May 2010).
3. Contacted authors of identified trials and other researchers in the field (April 2010).

4. Contacted Otsuka Pharmaceutical Co Ltd, the manufacturer of cilostazol (May 2010).
5. Screened reference lists from relevant articles.

We searched for trials in all languages and arranged translation of potentially relevant trial reports that were published in languages other than English.

Data collection and analysis

We reviewed all potentially eligible studies. We extracted data on types of patients enrolled; entry and exclusion criteria; method of randomisation; process of treatment allocation concealment; the original numbers of patients assigned to the treatment and aspirin groups; number of patients lost to follow up in each treatment group; degree of adherence to treatment; method and duration of follow up; whether patients and trial staff were blinded to treatment allocation and, if so, what methods of blinding to treatment of patients, treating clinicians, and outcome assessors allocation were employed; definitions of outcome events; and treatment-specific side effects. We analysed data on the basis of an intention-to-treat analysis.

Selection of studies

We considered that all RCTs comparing cilostazol with aspirin in patients with a qualifying stroke or TIA were eligible for inclusion in this review. These patients should have been on treatment for at least one month and followed systematically for the development of vascular events.

Data extraction and management

We extracted data from published reports or from the original researchers by using a pre-designed data collection form. One review author (IN) independently extracted data and reviewed studies. Another review author (AKK) reviewed the studies, verified data entry and numbers to double check for errors. We resolved all disagreements by discussion and with a third review author as needed (BAK).

Assessment of risk of bias in included studies

We used the 'Risk of bias' table, part of the 'Characteristics of included studies' table, to delineate assessment of risk of bias in the included studies. This helped to address issues of bias including selection, allocation concealment, blinding, performance, attrition, detection, incomplete outcome data processing, and selective reporting. The content expert (AKK) reviewed the table. We scored each entry as 'low risk', 'high risk' or 'unclear risk' of bias. For each entry, we provided text detailing the description of design, conduct, or observation leading to the judgement. We incorporated bias assessment in the analyses by reporting an estimated

intervention effect based on all available studies, with a narrative discussion on the risk of bias in individual domains.

Measures of treatment effect

We determined treatment effect primarily by calculating effect estimators for signal trials, which were then combined by means of the Mantel-Haenszel (MH) method. The treatment effect was measured in terms of risk ratio (RR). The absolute risk reduction (ARR) and number needed to treat (NNT) were also calculated. For this purpose we used the calculator available on the Cochrane Stroke Group website (http://www.dcn.ed.ac.uk/csrg/NNT2.asp).

Unit of analysis issues

We did not include studies with crossover design or cluster randomisation in this analysis.

Dealing with missing data

We performed an intention-to-treat analysis; we included all those participants that were 'lost' in the appropriate assigned arm.

Assessment of heterogeneity

We used the I^2 statistic to test for heterogeneity between trials.

Assessment of reporting biases

We constructed a funnel plot and looked for asymmetry to assess reporting bias.

Data synthesis

We used a fixed-effect model to perform meta-analysis. Since there was no extreme heterogeneity within trials, we were able to perform meta-analysis.

Subgroup analysis and investigation of heterogeneity

Pre-specified subgroups included investigating any differences in the primary outcome in Caucasians versus Asians. For analysis of the differences of effect between subgroups, we planned to compare confidence intervals between subgroups and look for overlap. Since there were no studies from Caucasian populations, this could not be carried out.
We determined statistical significance with the Chi^2 test for heterogeneity.

Sensitivity analysis

We performed sensitivity analysis by removing studies that appeared to dominate the data set in terms of the primary outcome and analysed the results without them.

R E S U L T S

Description of studies

Results of the search

We retrieved a total of 15 hits by the search strategies employed. After screening we considered two trials relevant for inclusion, and we excluded the remaining 13 that did not meet the inclusion criteria.

Included studies

See: Characteristics of included studies
We identified two completed trials that fulfilled our eligibility criteria and these have been included in this review (CASISP 2008; CSPS II 2010). The trials included a total of 3477 participants, of which 2757 participated in CSPS II 2010.
Both studies were RCTs conducted in Asia: CASISP 2008 in China and CSPS II 2010 in Japan. The patients on average were 62 years of age and approximately two-thirds were men.
Cilostazol was compared with aspirin in 3477 patients with a history of ischaemic stroke of arterial origin within the previous one to 6.5 months, of which 1697 patients belonged to the cilostazol arm and 1694 patients belonged to the aspirin arm in the intention-to-treat analysis. All medication was given orally, though dosage differed for each trial. Cilostazol was given at 100 mg twice a day and aspirin at 81 mg once a day in the CSPS II 2010 trial, and at 100 mg twice a day and 100 mg once a day respectively in the CASISP 2008 trial.
The duration of follow up varied from one year (CASISP 2008) to five years (CSPS II 2010).
Both trials recorded stroke (of all types) as a primary outcome, while CASISP 2008 also included MI and vascular death as major outcome events.
A summary of the details of each trial is described in the Characteristics of included studies table.

Excluded studies

See: Characteristics of excluded studies
We excluded 13 studies as they did not meet the eligibility criteria for this review. Of these, four studies compared cilostazol

with placebo (Ahn 2001; CSPS 2000; Mitsuhashi 2004; TOSS 2005) and six other studies used a confounded comparison of interest (CATHARSIS 2009; ECLIPse 2009; Kohriyama 1994; Kikuchi 1985; Terayama 2008; TOSS II 2009). Moreover, eight of the excluded studies did not examine a clinical vascular event as the primary outcome (Ahn 2001; DAPC 2006; ECLIPse 2009; Kikuchi 1985; Kohriyama 1994; TOSS 2005; TOSS II 2009; Yasunaga 1985). In one excluded study the patient population did not present with ischaemic stroke or TIA (Suzuki 2010).

Risk of bias in included studies

See: Characteristics of included studies
Methodological quality of the two included studies (CASISP 2008; CSPS II 2010) was generally high in terms of treatment allocation and blinding. In these trials both the cilostazol and aspirin arms were well balanced for major prognostic factors at baseline (such as age, history of stroke, and use of diagnostic tools).

Allocation

Treatment allocation was randomised in both studies, and the methods of randomisation and allocation concealment were stated. In both trials (CASISP 2008; CSPS II 2010) double-dummy concealment was performed and all pills, placebo and other made to look alike.

Blinding

Blinding was adequately addressed in each trial, with reference to participant, caregiver, investigator, and outcome assessor. The CASISP study (CASISP 2008) stated that radiologists assigned to report diagnoses for the enrolled patients were blinded to clinical data. The CSPS II trial (CSPS II 2010) ensured blinding by sealing assignment lists immediately after assignment until the designated time of unmasking.

Incomplete outcome data

Both trials addressed incomplete outcome data, reporting on participants that were lost to follow up for different reasons.

Selective reporting

All patients that were selected were accounted for and all the data recorded were presented in both studies.

Other potential sources of bias

No other potential sources of bias were noted.
In the CSPS II 2010 trial the sponsor, Otsuka Pharmaceutical Ltd, had a role in the study design, data collection, and data analysis but was not involved in the data interpretation or writing of the report.

Effects of interventions

Of the 3477 randomised participants with a history of previous stroke in the past one to 6.5 months, intention-to-treat analysis included 1697 patients in the cilostazol group and 1694 patients in the aspirin group.
The results given below are a culmination of those presented in the two trials (CASISP 2008; CSPS II 2010). They address the composite outcome of vascular events (stroke, MI, or vascular death) and each of these separately as specific outcome events.

Stroke, myocardial infarction (MI), or vascular death during follow up

Data indicated that cilostazol was associated with a significantly lower risk of composite outcome of vascular events (stroke, MI, or vascular death): cilostazol 115/1697 (6.77%) versus aspirin 159/1694 (9.39%), RR 0.72 (95% CI 0.57 to 0.91). This corresponds to the avoidance of about 26 vascular events (95% CI 9 to 40) per 1000 patients treated for an average of three years when compared to aspirin. It meant that for each vascular event prevented by cilostazol 39 patients (95% CI 26 to 117) needed to be treated for an average of three years (Analysis 1.1).

Stroke (all types) during follow up

The two trials collectively showed that cilostazol significantly decreased stroke of all types compared to aspirin, and therefore it is an even more effective intervention for the secondary prevention of stroke: cilostazol 94/1697 (5.54%) versus aspirin 141/1694 (8.32%), RR 0.67 (95% CI 0.52 to 0.86). This corresponds to the avoidance of about 27 strokes (95% CI 12 to 41) per 1000 patients treated for an average of three years. For each stroke to be prevented 37 patients (95% CI 25 to 87) needed to be treated with cilostazol for an average of thee years (Analysis 1.2).

Ischaemic stroke during follow up

Both trials provided data on stroke subtypes. With respect to reduction of ischaemic stroke (fatal and non-fatal) there was a non-significant trend in favour of cilostazol: cilostazol 83/1697 (4.89%) versus aspirin 103/1694 (6.08%), RR 0.80 (95% CI 0.61 to 1.07) (Analysis 1.3).

Haemorrhagic stroke (ICH) during follow up

Data pooled from both trials identified a significant trend towards a reduction of haemorrhagic stroke among patients treated with

cilostazol: 9/1697 (0.53%) versus aspirin 34/1694 (2.01%), RR 0.26 (95% CI 0.13 to 0.55) (Analysis 1.4).

Myocardial infarction (MI) during follow up

Available data from both studies provided inconclusive evidence of a reduction in MI among patients treated with cilostazol: 15/1697 (0.88%) versus aspirin 13/1694 (0.77%), RR 1.15 (95% CI 0.55 to 2.41) (Analysis 1.5).

Vascular death during follow up

Data from the CCSPS II 2010 study did not indicate a significant reduction in vascular death during follow up: cilostazol 6/1697 (0.35%) versus aspirin 5/1694 (0.30%), RR 1.20 (95% CI 0.37 to 3.92). There were no data reported on this outcome event in the CASISP study (Analysis 1.6).

Death from any cause during follow up

Both trials reported death during the follow-up periods. However, these results did not point towards a difference in mortality: cilostazol 16/1697 (0.94%) versus aspirin 18/1694 (1.06%), RR 0.89 (95% CI 0.45 to 1.74) (Analysis 1.7).

Extracranial haemorrhage during follow up

In both trials, patients that were given cilostazol had significantly fewer extracranial haemorrhagic events than those on aspirin: cilostazol 155/1697 (9.10%) versus aspirin 209/1694 (12.3%), RR 0.74 (95% CI 0.61 to 0.90) (Analysis 1.8).

Gastrointestinal (GI) haemorrhage during follow up

Patients in both arms of treatment reported GI haemorrhage events: cilostazol 17/1697 (1.00%) versus aspirin 30/1694 (1.77%), RR 0.57 (95% CI 0.31 to 1.02) (Analysis 1.9). The results were statistically inconclusive. In the CASISP 2008 study more people reported GI bleeding versus fecal occult blood on treatment with cilostazol than for those on aspirin, where only one event of upper GI bleeding was reported.

Other outcome measures of safety during follow up

Adverse effects of the interventional treatments were addressed in both studies. There was statistically significant evidence to indicate that more adverse effects were experienced by participants enrolled in the cilostazol arm: cilostazol 977/11,879 (8.22%) versus aspirin 587/11,858 (4.95%), RR 1.66 (95% CI 1.51 to 1.83) (Analysis 1.10).

Cilostazol was significantly more likely to cause each of the following adverse effects.

1.10.1. Headaches: cilostazol events 362/1697 (21.3%) versus aspirin 236/1694 (13.9%), RR 1.53 (95% CI 1.32 to 1.78).

1.10.2. Gastrointestinal intolerance: cilostazol 164/1697 (9.66%) versus aspirin 85/1694 (5.02%), RR 1.93 (95% CI 1.50 to 2.48).

1.10.3. Palpitations: cilostazol 161/1697 (9.49%) versus aspirin 106/1694 (6.26%), RR 1.52 (95% CI 1.20 to 1.92).

1.10.4. Dizziness: cilostazol 161/1697 (9.49%) versus aspirin 114/1694 (6.73%), RR 1.41 (95% CI 1.12 to 1.77).

1.10.5. Tachycardia: cilostazol 111/1697 (6.54%) versus aspirin 28/1694 (1.65%), RR 3.96 (95% CI 2.63 to 5.96).

With respect to cardiac adverse effects, results were inconclusive. Angina was reported in both arms: cilostazol 10/1697 (0.59%) versus aspirin 11/1694 (0.65%), RR 0.91 (95% CI 0.39 to 2.13); along with cardiac failure: cilostazol 8/1697 (0.47%) versus aspirin 7/1694 (0.41%), RR 1.14 (95% CI 0.41 to 3.14).

Sensitivity analysis

We performed sensitivity analysis by excluding the trial that appeared to dominate the data set (CSPS II 2010). This did not definitively change treatment effect but did render it imprecise. Outcome events were reduced in patients given cilostazol compared with aspirin but results were no longer statistically significant: cilostazol 13/360 (3.61%) versus aspirin 24/359 (6.69%), RR 0.54 (95% CI 0.28 to 1.04) (Analysis 2.1).

We did not note any statistically significant heterogeneity between the two included trials except in terms of palpitations as an outcome measure of safety, where the larger study (CSPS II 2010) dominated and changed the outcome of safety in favour of the aspirin arm.

We detected no evidence of reporting bias after analysing a funnel plot constructed for this purpose (Figure 1).

Figure 1.   Funnel plot of comparison: 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA, outcome: 1.1 Stroke, MI or vascular death during follow-up.
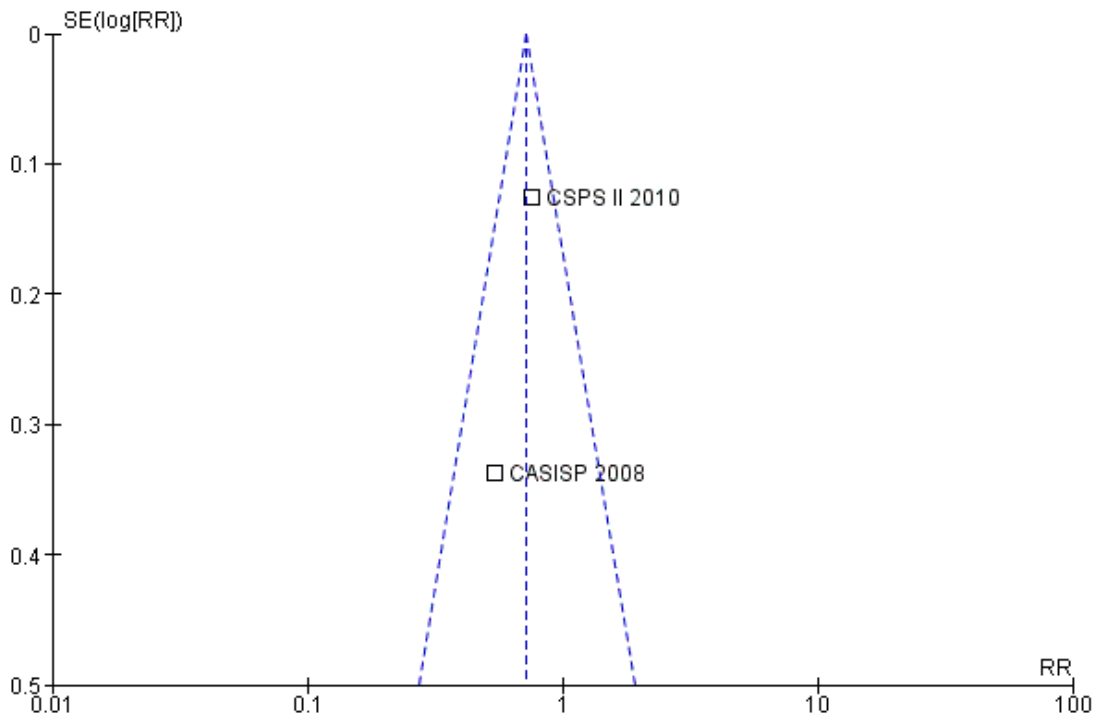
DISCUSSION

Summary of main results

We undertook this review to determine if, compared to aspirin, cilostazol is a better alternative for secondary prevention of vascular events in patients with a previous ischaemic stroke or TIA. We analysed the available data from two randomised trials directly comparing cilostazol to aspirin. The larger trial (CSPS II 2010) contributed about 80% of the patients randomised. It studied patients at high vascular risk (those with previous TIA or ischaemic stroke of arterial origin) and primarily evaluated the outcome of stroke of all types, with ischaemic stroke, death from all causes and a composite outcome as secondary endpoints. It also examined safety endpoints in terms of all significant haemorrhagic events. The smaller study, contributing about 20% of patients (CASISP 2008), assessed the composite outcome of vascular events (stroke, MI, and vascular death) and provided adequate data on each subtype of vascular events, along with outcomes of safety.

Combining the main outcome of serious vascular events into a composite outcome of stroke, MI and vascular death not only increases the statistical power and reliability of the analysis, but also provides a more cohesive measure of effectiveness. Analysis revealed that, compared to aspirin, cilostazol is significantly more effective in preventing vascular events (stroke, MI and vascular death) and stroke of all types, in patients with a history of stroke or TIA. Cilostazol showed an overall reduction in the composite outcome of 28%, ranging between 9% to 43% (95% CI), which corresponds to comparative avoidance of 26 events (ranging between nine to as high as 40 events) per 1000 patients treated for an average of three years. Thus for each vascular event to be prevented, 39 patients needed to be treated with cilostazol for an average of three years compared with aspirin, with a wider range of between 26 and 117 patients per event (95% CI).

In patients with a previous history of stroke or TIA, the proportional benefit of cilostazol over aspirin on the outcome of strokes of all type was very similar to that of the composite outcome of vascular events. Cilostazol demonstrated a reduction of about 33% (14% to 48%) compared with aspirin, corresponding to comparative avoidance of 27 events (95% CI 12 to 41) per 1000 patients treated for an average of three years. Thus for each stroke event to

be prevented, the number needed to treat (NNT) for an average of three years with cilostazol was 37 patients (95% CI 25 to 87) when compared to aspirin. Since it is known that in patients with previous history of stroke or TIA (that is patients at highest risk for subsequent vascular events) the greatest risk is of stroke, the composite outcome is bound to heavily reflect that outcome in terms of stroke of all types.

On subgroup analysis, cilostazol showed a 20% reduction in recurrence of ischaemic stroke subtypes compared with aspirin. Although this result was not statistically significant, it did indicate non-inferiority of cilostazol compared with aspirin in terms of secondary prevention of ischaemic stroke. In relation to haemorrhagic stroke during follow up, cilostazol showed an outstanding risk reduction of 74% (95% CI 45% to 87%) compared to aspirin, thereby demonstrating its safety and tolerability in a population that is inherently at higher risk of intracerebral haemorrhage.

In terms of adverse effects, the results of the review showed that cilostazol had a significantly higher adverse effect profile than aspirin, in terms of all other outcomes of safety including headache, gastrointestinal intolerance, palpitations, dizziness and tachycardia. In both trials (CASISP 2008; CSPS II 2010) it was noted that more recruited patients discontinued cilostazol compared with aspirin as a consequence of adverse drug reactions. Results from the CSPS II trial (CSPS II 2010) were inconclusive in terms of cardiac adverse effects, namely angina and cardiac failure, while CASISP (CASISP 2008) did not note any such events.

In safety analyses, aspirin caused more intracranial haemorrhage, extracranial haemorrhage and GI haemorrhage but, evaluated as separate outcomes, only extracranial haemorrhage was significantly higher in patients on aspirin compared with cilostazol. All of these outcome events were addressed specifically in both included trials. The CASISP 2008 trial reported symptomatic intracerebral haemorrhage along with two events of asymptomatic intracerebral haemorrhage with aspirin that were included in our analysis. Observational studies conclude that cilostazol shows no evidence of an increase in any bleeding abnormality (CSPS 2000). Therefore, it can be stated with a certain degree of reliability that cilostazol is associated with a lesser risk of bleeding events than aspirin.

Overall completeness and applicability of evidence

The two studies included in the review were double-blind randomised controlled trials that reported relevant outcome data. In CSPS II 2010 outcomes were assessed via clinical record review carried out by an independent data monitoring committee. These patients were regularly reviewed at six-month intervals for safety, adherence, and drug tolerability. The participants were all Asians and the maximum age at enrolment was 79 years. Importantly, the included strokes were all atherothrombotic (large vessel atherosclerosis and lacunes) in origin, and there were no patients with cardioembolic strokes recruited in these trials. A relevant patient ex-

clusion criterion was the absence of associated cardiovascular disease.

These studies show us that in the above populations and settings, cilostazol is relatively superior to aspirin in terms of a composite outcome of stroke, MI, and vascular death in Asian patients with stroke of arterial origin. Since Asians are at higher risk of intracerebral haemorrhage, and cilostazol-treated Asians had significantly fewer intracerebral haemorrhages than their aspirin-treated counterparts, cilostazol is a safer option in this setting.

With regard to patients with concomitant cardiovascular disease, the outcome of safety in terms of cardiac adverse effects of cilostazol compared with aspirin cannot be assessed in this review since patients with cardiovascular disease were excluded in both trials. Hence, it is clinically important to exclude cardiovascular disease in stroke patients prior to initiating cilostazol.

No comparator groups were available to compare for subgroup analysis. Stroke studies from other ethnic populations, including Caucasians, are needed to provide general applicability.

The dose used in the CASISP 2008 trial was at 100 mg twice daily and the same dose of 100 mg twice daily was used in CSPS II 2010. Studies show that lower doses of cilostazol are associated with fewer headaches requiring discontinuation, where 3.7% of patients on 100 mg twice daily required hospitalisation compared to1.3% on 50 mg twice daily (Robless 2008). Thus, to reduce the side-effect profile of cilostazol, it could be recommended to administer cilostazol in incremental doses starting from a minimum of 50 mg twice daily.

Cilostazol is more expensive than aspirin. Each cilostazol tablet costs 10 times more than that of aspirin, and bearing in mind that cilostazol requires double dosing, this makes each dose of cilostazol 20 times more costly compared with aspirin. To prevent one extra vascular event, 39 patients (95% CI 26 to 117 patients) need to be treated with cilostazol for a period of three years compared to aspirin. Whether this justifies prolonged treatment in resource-strapped settings needs further cost-benefit analysis.

Quality of the evidence

Overall the included evidence is based on well-designed trials.

Potential biases in the review process

The potential bias is that the data are restricted to Asians.

Agreements and disagreements with other studies or reviews

This review is in line with the general studies and reviews on this topic.

A U T H O R S ' C O N C L U S I O N S

Implications for practice

Aspirin is a well established monotherapy for the secondary prevention of stroke. For cilostazol to be on a par with aspirin in terms of clinical practice, it needs to not only be considerably more effective than aspirin in the prevention of serious vascular events after stroke but also to confer a tangible benefit in terms of safety and cost.

Current data indicate that cilostazol-treated patients experience a greater proportional reduction in risk of composite vascular events after stroke, including recurrent stroke, compared with aspirin. In terms of safety, cilostazol is clearly associated with fewer major bleeding events than aspirin. For long-term use, physicians must be aware that in the Asian stroke population cardiovascular disease must be excluded. In addition, physicians must be familiar with the minor adverse-effect profile of cilostazol. Moreover, the present cost of cilostazol is too high compared with aspirin for it to be considered for prolonged use in secondary prevention following stroke in many resource-poor Asian settings.

Implications for research

Further randomised trials with intention-to-treat design are required in diverse populations with ischaemic stroke to determine whether the benefit observed in reduction of vascular events after stroke is global or region specific.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CASISP 2008

Methods	R: computer-based stratified block randomisation on basis of pre-established scheme, stratified according to each site, aspirin-controlled trial C: double dummy: aspirin and cilostazol pills made to look the same B: double-blind: patients and clinicians, radiologists blinded to clinical data
Participants	Multicentre, China 720 patients randomised (2004 to 2005) Mean age: 60.2 years (18 to 75 years) Sex: 495 male, 225 female Inclusion criteria: cerebral infarction 1 to 6 months before entry, confirmed with neuroimaging, modified Rankin scale score of less than 4 at enrolment Exclusion criteria: history of intracranial haemorrhage, stroke secondary to cardiogenic embolism, serious damage of motorial function, dementia, serious complications or co-morbidity (uncontrolled accelerated type of hypertension, BP > 180/120 mmHg, diabetic acidosis, heart failure, renal failure, hepatocirrhosis, malignant tumour), contraindication of cilostazol and aspirin, need for co-medication of other antiplatelet agents, anticoagulants or fibrinolytic drugs, active peptic ulcer, pregnancy or breast feeding Patients with hypertension or high lipid concentrations were given antihypertensive drugs or statins, respectively, and were seen by doctors every month during the follow-up period. Liver and kidney function, electrocardiogram, and lipid profiles were monitored in all patients every 3 months
Interventions	Rx: cilostazol 100 mg twice daily oral versus aspirin 100 mg once daily oral Duration of treatment: 12 months
Outcomes	Primary outcomes: stroke recurrence (ischaemic, intracerebral haemorrhage, subarachnoid haemorrhage) Secondary outcomes: > 1 stroke, new myocardial infarction, transient ischaemic attack, vascular event (pulmonary embolism, deep vein thrombosis, peripheral arterial occlusive disease), death from vascular causes, death from all causes
Notes	360 participants in aspirin arm intention-to-treat analysis and 359 participants in cilostazol arm Compliance on aspirin: 47 discontinued, 3 died; reasons for withdrawal: 25 with adverse effects, 8 did not follow protocol, 6 lost to follow up, 8 withdrew due to other reasons, 3 died (1 myocardial infarction, 1 unknown, 1 drowned). Cilostazol: 35 discontinued, 5 died; reasons for withdrawal: 15 with adverse effects, 3 lack of effect, 7 did not follow protocol, 3 lost to follow up, 7 due to other causes, 5 died (2 myocardial infarction, 1 liver cancer, 1 pancreatitis, 1 suicide)

Risk of bias

Bias	Authors' judgement	Support for judgement

Allocation concealment (selection bias)	Low risk	Double-dummy, all pills made to look the same
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind (patients, clinicians) and radiologists reviewing reports
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients lost to follow up accounted for
Selective reporting (reporting bias)	Low risk	All selected patients accounted for
Other bias	Low risk	Free of detection bias, appropriate analysis

CSPS II 2010

Methods	R: computer-generated randomisation sequence by means of a dynamic balancing method with stratification by age, sex, and study institution using patient information obtained at registration. Randomization number was assigned to every drug pack. Patients were given treatment number identical to the numbered drug pack C: double dummy method. Parallel assignment, with placebo tablets identical to drug that patient was not assigned. The person responsible for drug allocation sealed assignment list immediately after assignment, and kept it sealed until designated point of unmasking B: all participants, study personnel, investigators, and sponsors were masked to treatment allocation
Participants	279 centres in Japan (2003 to 2006) 2757 patients Mean age: 63.5 years (20 to 80 years) Sex: 71.7% men Inclusion criteria: cerebral infarction within 26 weeks prior to enrolment and whose symptoms had remained stable, confirmed by neuroimaging, patients with no cardiac diseases that may be associated with cardiogenic cerebral embolism (mitral stenosis, prosthetic heart valve, endocarditis, myocardial infarction within 6 weeks after occurrence, ventricular aneurysm, endocardial thrombosis, mitral valve prolapse, atrial fibrillation, sick sinus syndrome, idiopathic cardiomyopathy, and patent foramen ovale), patients without asymptomatic cerebral infarction, those who had not undergone or scheduled for percutaneous transluminal angioplasty or revascularization for the treatment of cerebral infarction), without severe disturbances/impairment following cerebral infarction Exclusion criteria: patients with haemorrhage or bleeding tendency (haemophilia, capillary fragility, intracranial haemorrhage, haemorrhage in the digestive tract, haemorrhage in the urinary tract, haemoptysis, and haemorrhage in the vitreous body, pregnant, possibly pregnant, or nursing women, ischaemic heart failure, peptic ulcer, severe blood disorders, severe hepatic or renal disease, malignant neoplasm or patients who have received any therapy for malignant neoplasm within 5 years prior, history of hypersensitivity to salicylic acid formulations or ingredients of cilostazol tablets, aspirin asthma (asthma attacks induced by non-steroidal anti-inflammatory analgesic agents) or a history of as-

	pirin asthma, treatment with ticlopidine hydrochloride
Interventions	Cilostazol oral tablet, 100 mg twice a day and placebo of aspirin once daily versus aspirin oral tablet, 81 mg once a day and placebo of cilostazol twice a day Duration of treatment: 1 to 5 years
Outcomes	Primary outcome: occurrence of stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage) Secondary outcomes: first recurrence of cerebral infarction; ischaemic cerebrovascular events including cerebral infarction or transient ischaemic attack; death from any cause; and composite of completed stroke (cerebral infarction, cerebral haemorrhage, or sub-arachnoid haemorrhage), transient ischaemic attack, angina pectoris, myocardial in-farction, heart failure, or haemorrhage requiring hospital admission (excluding cerebral haemorrhage and subarachnoid haemorrhage)
Notes	Of the 2757 participants enrolled and randomly allocated, 23 in the cilostazol arm and 18 in the aspirin arm did not receive treatment due to withdrawal, recurrence of cerebral infarction, or met exclusion criteria Overall, 2716 participants received study drug treatment, of which 19 were ineligible for analysis in the cilostazol arm and 25 were ineligible in the aspirin arm Of these, a further 457 participants discontinued drug in the cilostazol arm, of which 267 were due to adverse drug reactions In the aspirin arm 336 participants discontinued treatment, of which 166 were due to adverse drug reactions Eventually 2672 were included in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Double-dummy method and parallel as-signment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinding (participant, caregiver, in-vestigator, sponsor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients lost to follow up accounted for
Selective reporting (reporting bias)	Low risk	All selected patients accounted for
Other bias	Low risk	All outcomes addressed

B: blinding
C: control
R: randomisation

Rx: treatment

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahn 2001	Cilostazol compared with placebo, not aspirin. Patient population not selected on basis of history of ischaemic stroke or TIA (diabetes type II). Outcome measure (intima-media thickness (IMT)) was not a vascular event, it is an intermediate biologic phenotype
CATHARSIS 2009	Confounded comparison of interest (aspirin versus aspirin + cilostazol). Secondary outcome measure (stenosis progression) was not a clinical vascular event, it is an intermediate biologic phenotype
CSPS 2000	Cilostazol compared with placebo, not aspirin
DAPC 2006	Outcome measure was not a vascular event (IMT changes), patient population not selected on basis of history of stroke or TIA (diabetes type II and atherosclerosis)
ECLIPse 2009	Confounded comparison of interest (aspirin + placebo versus aspirin + cilostazol), primary outcome not a clinical vascular event (pulsatility indices of transcranial doppler)
Kikuchi 1985	Compares ticlopidine versus aspirin versus cilostazol. Outcome measure was not a clinical vascular event (platelet aggregation)
Kohriyama 1994	Compares ticlopidine versus ticlopidine + aspirin versus cilostazol. Primary outcome measure not a clinical vascular event (platelet aggregation, coagulation and fibrinolysis)
Mitsuhashi 2004	Patient population not selected for stroke (diabetes type II). Cilostazol compared with placebo, not aspirin
Suzuki 2010	Patient population not selected for ischaemic stroke or TIA (subarachnoid haemorrhage)
Terayama 2008	Confounded for comparison of interest (aspirin versus aspirin + cilostazol)
TOSS 2005	Cilostazol compared with placebo, not aspirin. Primary outcome measure not a clinical vascular event (progression of symptomatic intracranial atherosclerosis)
TOSS II 2009	Confounded comparison of interest (cilostazol+aspirin versus clopidogrel+aspirin). Primary outcome measure was not a clinical vascular event (progression of symptomatic intracranial atherosclerosis)
Yasunaga 1985	Not a randomised, double-blind trial. Outcome measure not a clinical vascular event (platelet aggregation)

IMT: intima media thickness
TIA: transient ischaemic attack

DATA AND ANALYSES

Comparison 1.   Cilostazol versus aspirin in patients with ischaemic stroke or TIA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stroke, MI or vascular death during follow-up	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.57, 0.91]
2 Stroke (of all types) during follow-up	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.52, 0.86]
3 Ischaemic stroke during follow-up	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.61, 1.07]
4 Haemorrhagic stroke during follow-up	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.13, 0.55]
5 MI during follow-up	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.55, 2.41]
6 Vascular death during follow-up	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.37, 3.92]
7 Death from any cause during follow-up	2	3391	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.45, 1.74]
8 Extracranial haemorrhage during follow-up	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.61, 0.90]
9 Gastrointestinal haemorrhage during follow-up	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.02]
10 Other outcomes of safety during follow-up	2	23737	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.51, 1.83]
10.1 Headache	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.32, 1.78]
10.2 Gastrointestinal intolerance	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.50, 2.48]
10.3 Palpitations	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.20, 1.92]
10.4 Dizziness	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.12, 1.77]
10.5 Tachycardia	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	3.96 [2.63, 5.96]
10.6 Angina	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.39, 2.13]
10.7 Cardiac Failure	2	3391	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.41, 3.14]

Comparison 2.   Cilostazol versus aspirin in patients with ischaemic stroke or TIA - sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Composite vascular events (stroke, MI or vascular death during follow-up)	1	719	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.28, 1.04]

Analysis 1.1.   Comparison I Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome I Stroke, MI or vascular death during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: I Cilostazol versus aspirin in patients with ischaemic stroke or TIA

Outcome: I Stroke, MI or vascular death during follow-up

Study or subgroup	Cilostazol n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CASISP 2008	13/360	24/359		15.1 %	0.54 [0.28, 1.04]
CSPS II 2010	102/1337	135/1335		84.9 %	0.75 [0.59, 0.96]
Total (95% CI)	**1697**	**1694**		**100.0 %**	**0.72 [0.57, 0.91]**

Total events: 115 (Cilostazol), 159 (Aspirin)
Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² =0.0%
Test for overall effect: Z = 2.78 (P = 0.0055)
Test for subgroup differences: Not applicable

```
            0.01   0.1    I    10   100
        Favours experimental   Favours control
```
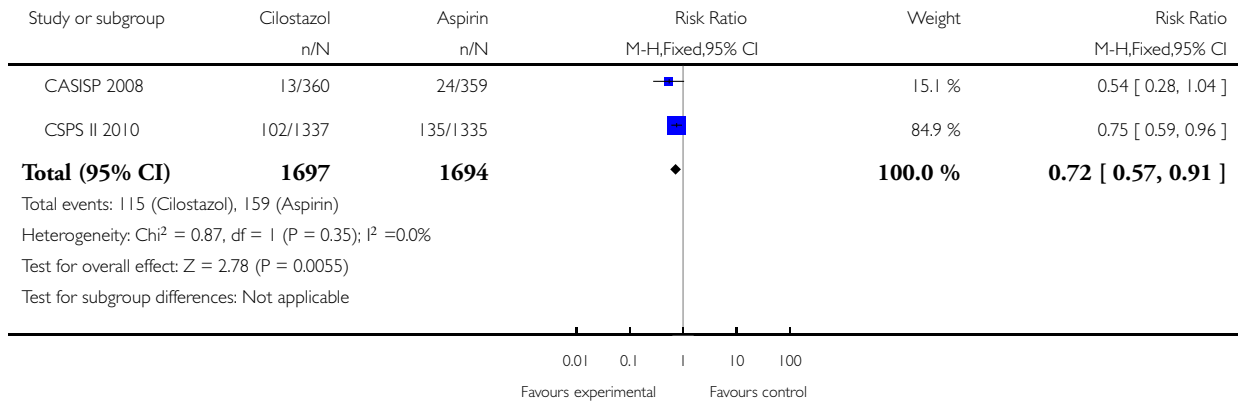
Analysis 1.2.   Comparison I Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome 2 Stroke (of all types) during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: I Cilostazol versus aspirin in patients with ischaemic stroke or TIA

Outcome: 2 Stroke (of all types) during follow-up

Study or subgroup	Cilostazol n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CASISP 2008	12/360	22/359		15.6 %	0.54 [0.27, 1.08]
CSPS II 2010	82/1337	119/1335		84.4 %	0.69 [0.52, 0.90]
Total (95% CI)	**1697**	**1694**		**100.0 %**	**0.67 [0.52, 0.86]**

Total events: 94 (Cilostazol), 141 (Aspirin)
Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² =0.0%
Test for overall effect: Z = 3.17 (P = 0.0015)
Test for subgroup differences: Not applicable

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            0.01   0.1    I    10   100
        Favours experimental   Favours control
```

Analysis 1.3. Comparison 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome 3 Ischaemic stroke during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA

Outcome: 3 Ischaemic stroke during follow-up

Study or subgroup	Cilostazol	Aspirin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
CASISP 2008	11/360	15/359		14.6 %	0.73 [0.34, 1.57]
CSPS II 2010	72/1337	88/1335		85.4 %	0.82 [0.60, 1.11]
Total (95% CI)	**1697**	**1694**		**100.0 %**	**0.80 [0.61, 1.07]**
Total events: 83 (Cilostazol), 103 (Aspirin)					
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 1.52 (P = 0.13)					
Test for subgroup differences: Not applicable					

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        0.01   0.1    1    10   100
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Favours experimental   Favours control

Analysis 1.4. Comparison 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome 4 Haemorrhagic stroke during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA

Outcome: 4 Haemorrhagic stroke during follow-up

Study or subgroup	Cilostazol n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CASISP 2008	1/360	7/359		20.6 %	0.14 [0.02, 1.15]
CSPS II 2010	8/1337	27/1335		79.4 %	0.30 [0.13, 0.65]
Total (95% CI)	**1697**	**1694**		**100.0 %**	**0.26 [0.13, 0.55]**

Total events: 9 (Cilostazol), 34 (Aspirin)

Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² =0.0%

Test for overall effect: Z = 3.57 (P = 0.00036)

Test for subgroup differences: Not applicable

```
        0.01    0.1     1     10    100
     Favours experimental   Favours control
```

Analysis 1.5. Comparison 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome 5 MI during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA

Outcome: 5 MI during follow-up

Study or subgroup	Cilostazol n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CASISP 2008	1/360	2/359		15.4 %	0.50 [0.05, 5.47]
CSPS II 2010	14/1337	11/1335		84.6 %	1.27 [0.58, 2.79]
Total (95% CI)	**1697**	**1694**		**100.0 %**	**1.15 [0.55, 2.41]**

Total events: 15 (Cilostazol), 13 (Aspirin)

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² =0.0%

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable

```
        0.01    0.1     1     10    100
     Favours experimental   Favours control
```

Analysis 1.6.   Comparison 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome 6 Vascular death during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA

Outcome: 6 Vascular death during follow-up

Study or subgroup	Cilostazol	Aspirin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
CASISP 2008	0/360	0/359			Not estimable
CSPS II 2010	6/1337	5/1335		100.0 %	1.20 [0.37, 3.92]
Total (95% CI)	**1697**	**1694**		**100.0 %**	**1.20 [0.37, 3.92]**
Total events: 6 (Cilostazol), 5 (Aspirin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
Test for subgroup differences: Not applicable					

0.01   0.1   1   10   100

Favours experimental   Favours control

Analysis 1.7.   Comparison 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome 7 Death from any cause during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA

Outcome: 7 Death from any cause during follow-up

Study or subgroup	Cilostazol n/N	Aspirin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
CASISP 2008	3/360	5/359		27.8 %	0.59 [0.14, 2.51]
CSPS II 2010	13/1337	13/1335		72.2 %	1.00 [0.46, 2.16]
Total (95% CI)	**1697**	**1694**		**100.0 %**	**0.89 [0.45, 1.74]**

Total events: 16 (Cilostazol), 18 (Aspirin)

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² =0.0%

Test for overall effect: Z = 0.35 (P = 0.73)

Test for subgroup differences: Not applicable

$$0.01 \quad 0.1 \quad 1 \quad 10 \quad 100$$

Favours experimental   Favours control

Analysis 1.8.   Comparison 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome 8 Extracranial haemorrhage during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA

Outcome: 8 Extracranial haemorrhage during follow-up
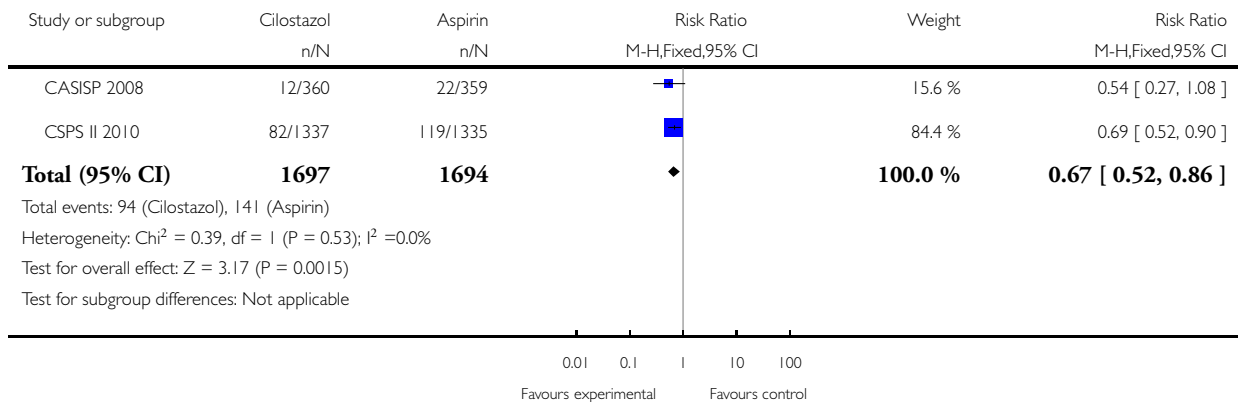
Study or subgroup	Cilostazol n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CASISP 2008	10/360	17/359		8.1 %	0.59 [0.27, 1.26]
CSPS II 2010	145/1337	192/1335		91.9 %	0.75 [0.62, 0.92]
Total (95% CI)	**1697**	**1694**		**100.0 %**	**0.74 [0.61, 0.90]**

Total events: 155 (Cilostazol), 209 (Aspirin)

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² =0.0%

Test for overall effect: Z = 3.02 (P = 0.0026)

Test for subgroup differences: Not applicable

$$0.01 \quad 0.1 \quad 1 \quad 10 \quad 100$$

Favours experimental   Favours control

Analysis 1.9. Comparison 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome 9 Gastrointestinal haemorrhage during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA

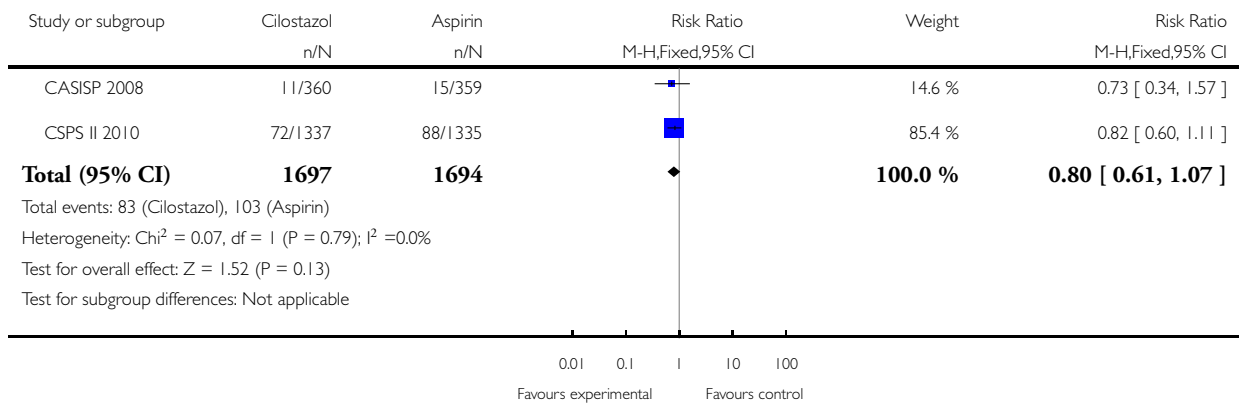Outcome: 9 Gastrointestinal haemorrhage during follow-up

Study or subgroup	Cilostazol	Aspirin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
CASISP 2008	9/360	9/359		30.0 %	1.00 [0.40, 2.48]
CSPS II 2010	8/1337	21/1335		70.0 %	0.38 [0.17, 0.86]
Total (95% CI)	**1697**	**1694**		**100.0 %**	**0.57 [0.31, 1.02]**

Total events: 17 (Cilostazol), 30 (Aspirin)
Heterogeneity: Chi^2 = 2.40, df = 1 (P = 0.12); I^2 =58%
Test for overall effect: Z = 1.89 (P = 0.059)
Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours experimental   Favours control
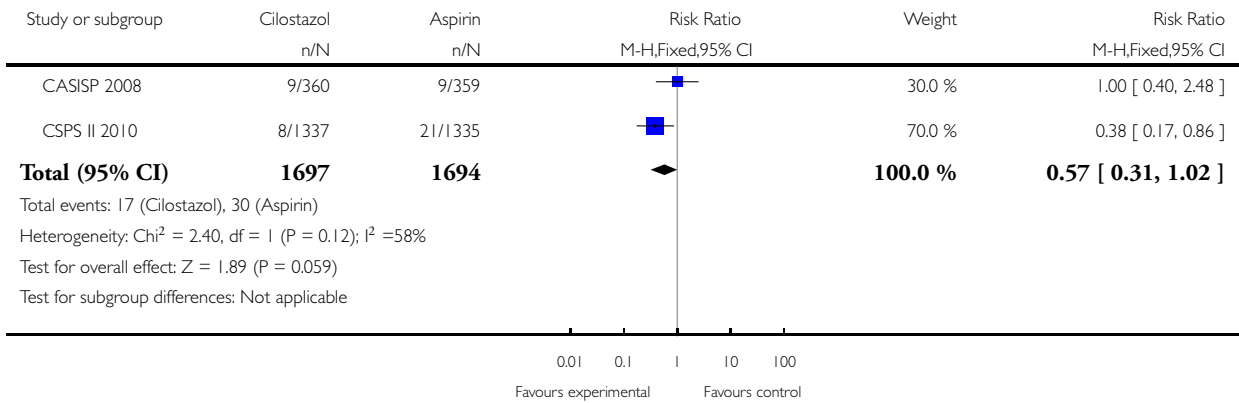
Analysis 1.10. Comparison 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA, Outcome 10 Other outcomes of safety during follow-up.

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

Comparison: 1 Cilostazol versus aspirin in patients with ischaemic stroke or TIA
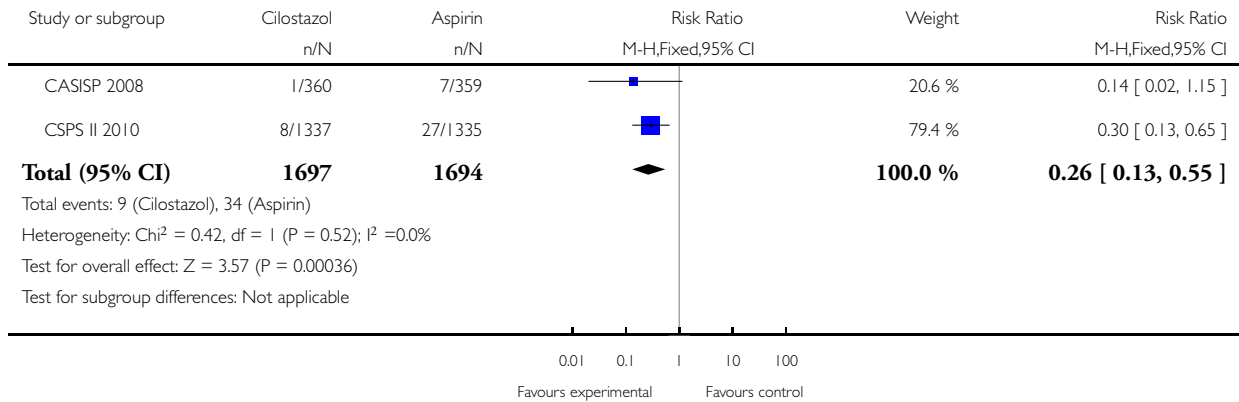
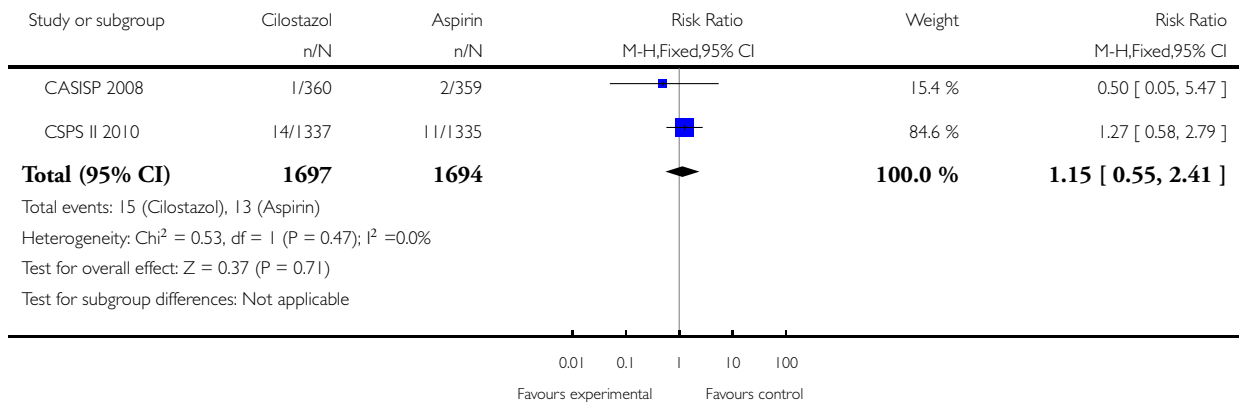Outcome: 10 Other outcomes of safety during follow-up
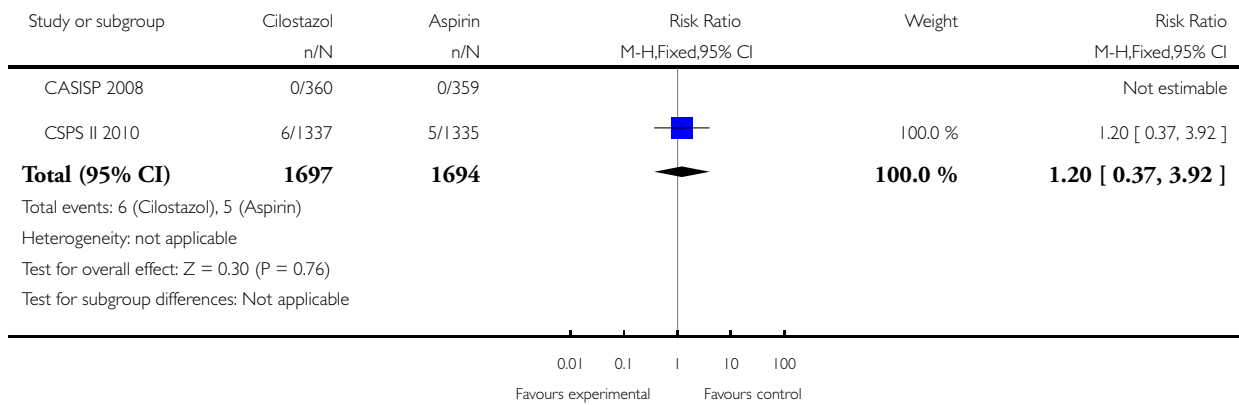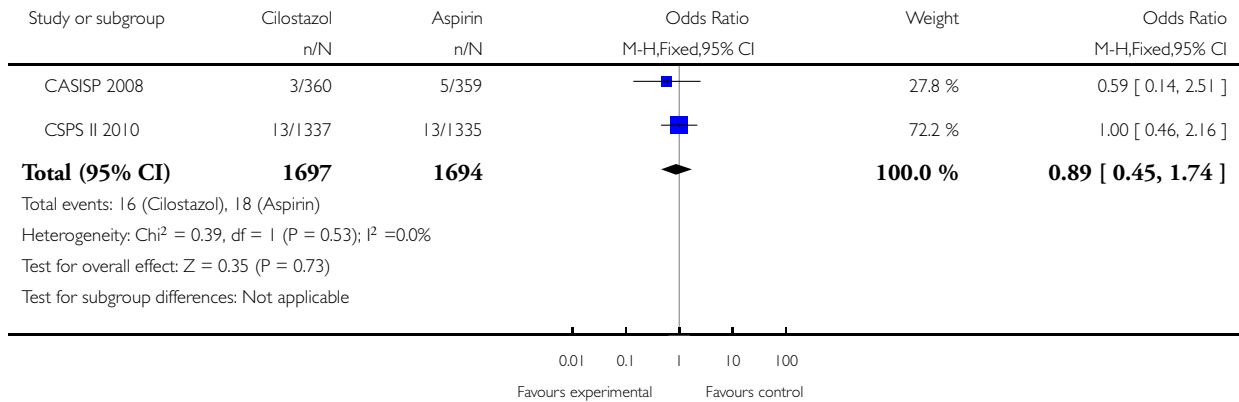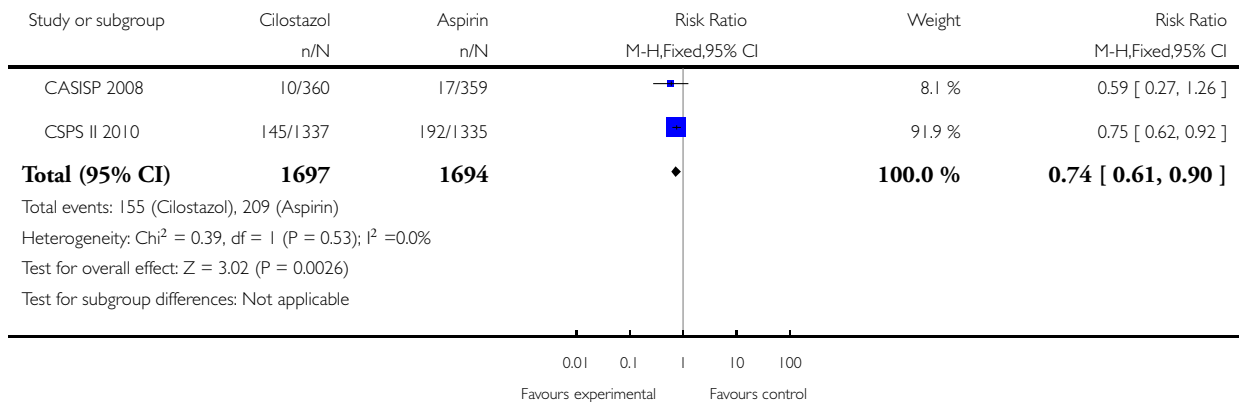
Study or subgroup	Cilostazol n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Headache					
CASISP 2008	49/360	19/359		3.2 %	2.57 [1.55, 4.28]
CSPS II 2010	313/1337	217/1335		37.0 %	1.44 [1.23, 1.68]
Subtotal (95% CI)	**1697**	**1694**		**40.2 %**	**1.53 [1.32, 1.78]**
Total events: 362 (Cilostazol), 236 (Aspirin)					
Heterogeneity: Chi² = 4.58, df = 1 (P = 0.03); I² =78%					
Test for overall effect: Z = 5.62 (P < 0.00001)					
2 Gastrointestinal intolerance					
CASISP 2008	0/360	0/359			Not estimable
CSPS II 2010	164/1337	85/1335		14.5 %	1.93 [1.50, 2.48]
Subtotal (95% CI)	**1697**	**1694**		**14.5 %**	**1.93 [1.50, 2.48]**
Total events: 164 (Cilostazol), 85 (Aspirin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.13 (P < 0.00001)					
3 Palpitations					
CASISP 2008	5/360	35/359		6.0 %	0.14 [0.06, 0.36]
CSPS II 2010	156/1337	71/1335		12.1 %	2.19 [1.67, 2.87]
Subtotal (95% CI)	**1697**	**1694**		**18.1 %**	**1.52 [1.20, 1.92]**
Total events: 161 (Cilostazol), 106 (Aspirin)					
Heterogeneity: Chi² = 32.26, df = 1 (P<0.00001); I² =97%					
Test for overall effect: Z = 3.44 (P = 0.00057)					
4 Dizziness					
CASISP 2008	32/360	17/359		2.9 %	1.88 [1.06, 3.32]
CSPS II 2010	129/1337	97/1335		16.5 %	1.33 [1.03, 1.71]
Subtotal (95% CI)	**1697**	**1694**		**19.4 %**	**1.41 [1.12, 1.77]**
Total events: 161 (Cilostazol), 114 (Aspirin)					
Heterogeneity: Chi² = 1.19, df = 1 (P = 0.28); I² =16%					
Test for overall effect: Z = 2.92 (P = 0.0035)					
5 Tachycardia					
CASISP 2008	22/360	7/359		1.2 %	3.13 [1.36, 7.24]
CSPS II 2010	89/1337	21/1335		3.6 %	4.23 [2.65, 6.77]

0.01   0.1   1   10   100

Favours experimental   Favours control

(*Continued* . . .)

Study or subgroup	Cilostazol	Aspirin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Subtotal (95% CI)	**1697**	**1694**	◆	**4.8 %**	**3.96 [2.63, 5.96]**

Total events: 111 (Cilostazol), 28 (Aspirin)

Heterogeneity: Chi^2 = 0.38, df = 1 (P = 0.54); I^2 =0.0%

Test for overall effect: Z = 6.59 (P < 0.00001)

6 Angina

CASISP 2008	0/360	0/359			Not estimable
CSPS II 2010	10/1337	11/1335		1.9 %	0.91 [0.39, 2.13]
Subtotal (95% CI)	**1697**	**1694**	◆	**1.9 %**	**0.91 [0.39, 2.13]**

Total events: 10 (Cilostazol), 11 (Aspirin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.22 (P = 0.82)

7 Cardiac Failure

CASISP 2008	0/360	0/359			Not estimable
CSPS II 2010	8/1337	7/1335		1.2 %	1.14 [0.41, 3.14]
Subtotal (95% CI)	**1697**	**1694**	◆	**1.2 %**	**1.14 [0.41, 3.14]**

Total events: 8 (Cilostazol), 7 (Aspirin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.26 (P = 0.80)

Total (95% CI)	**11879**	**11858**	◆	**100.0 %**	**1.66 [1.51, 1.83]**

Total events: 977 (Cilostazol), 587 (Aspirin)

Heterogeneity: Chi^2 = 61.64, df = 10 (P<0.00001); I^2 =84%

Test for overall effect: Z = 10.30 (P < 0.0001)

Test for subgroup differences: Chi^2 = 24.62, df = 6 (P = 0.00), I^2 =76%

```
        0.01    0.1     1     10    100
```

Favours experimental   Favours control

Analysis 2.1.   Comparison 2 Cilostazol versus aspirin in patients with ischaemic stroke or TIA - sensitivity analysis, Outcome 1 Composite vascular events (stroke, MI or vascular death during follow-up).

Review: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin

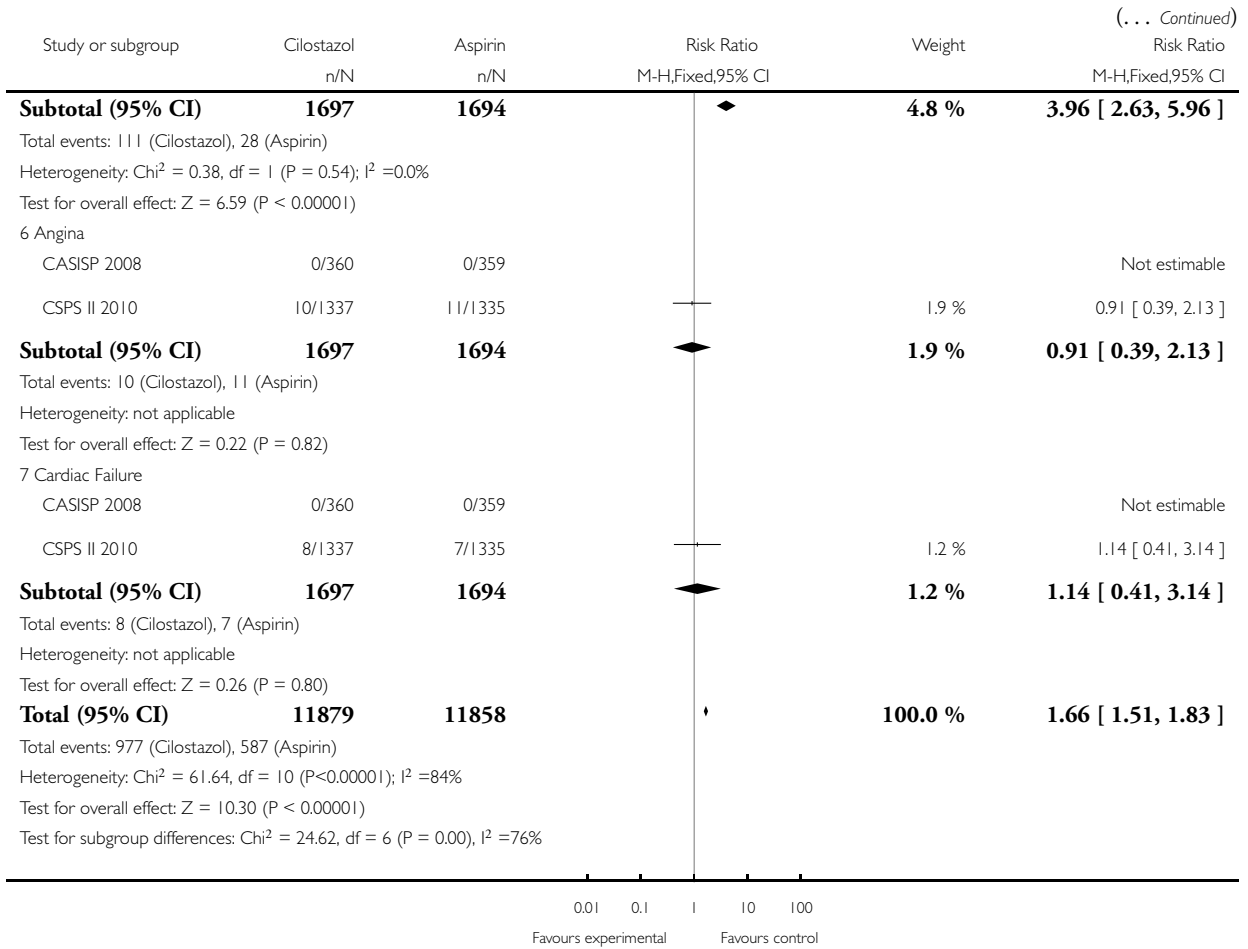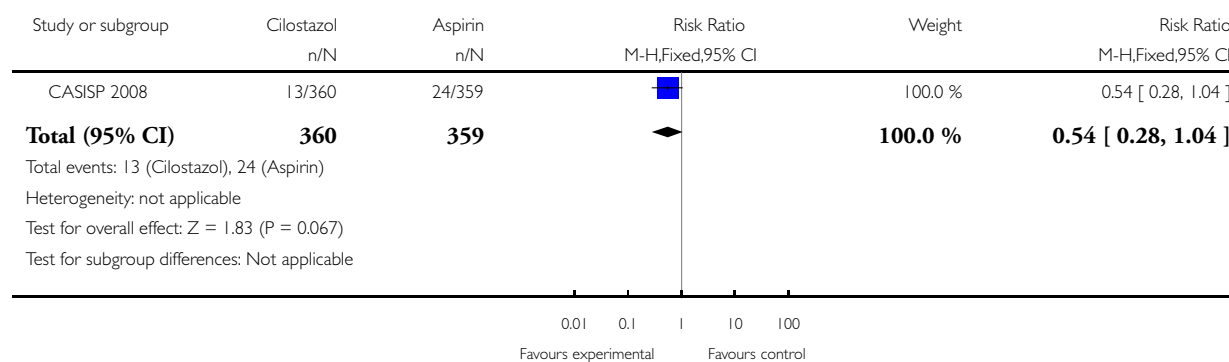Comparison: 2 Cilostazol versus aspirin in patients with ischaemic stroke or TIA - sensitivity analysis

Outcome: 1 Composite vascular events (stroke, MI or vascular death during follow-up)

Study or subgroup	Cilostazol n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CASISP 2008	13/360	24/359		100.0 %	0.54 [0.28, 1.04]
Total (95% CI)	**360**	**359**		**100.0 %**	**0.54 [0.28, 1.04]**

Total events: 13 (Cilostazol), 24 (Aspirin)

Heterogeneity: not applicable

Test for overall effect: Z = 1.83 (P = 0.067)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours experimental   Favours control

A P P E N D I C E S

Appendix 1. MEDLINE search strategy

We used the following search strategy for MEDLINE and adapted it for CENTRAL.

MEDLINE (Ovid)

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. tia$1.tw.
5. 1 or 2 or 3 or 4
6. (cilostazol or pletal or pletaal or OPC-13013 or OPC 13013 or OPC-21 or OPC 21).tw.
7. Aspirin/
8. (aspirin or acetylsalicylic acid or acetyl salicylic acid or acetosalicylic acid).tw.
9. 7 or 8
10. 5 and 6 and 9
11. limit 10 to humans

Appendix 2. EMBASE search strategy

We used the following search strategy for EMBASE.

EMBASE (Ovid)

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/
2. stroke patient/ or stroke unit/
3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
4. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
5. tia$1.tw.
6. 1 or 2 or 3 or 4 or 5
7. cilostazol/
8. (cilostazol or pletal or pletaal or OPC-13013 or OPC 13013 or OPC-21 or OPC 21).tw.
9. 7 or 8
10. acetylsalicylic acid/
11. (aspirin or acetylsalicylic acid or acetyl salicylic acid or acetosalicylic acid).tw.
12. 10 or 11
13. 6 and 9 and 12
14. limit 13 to human

WHAT'S NEW

Date	Event	Description
30 August 2011	Amended	The dose of cilostazol given in the CASISP trial has been corrected in the Results section of the text

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 1, 2011

Date	Event	Description
15 July 2011	Amended	The conclusions are unchanged. The erratum for CASISP has been incorporated and addressed

CONTRIBUTIONS OF AUTHORS

AKK conceived and designed the review, reviewed the studies, assisted in review writing and wrote the protocol. IN performed review of studies, data analysis and review writing, and assisted in protocol writing. MRH assisted in the protocol development stage. BAK assisted in review of relevant studies.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- The Aga Khan University Hospital, Pakistan.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Asian Continental Ancestry Group; Aspirin [adverse effects; *therapeutic use]; Brain Ischemia [complications]; Cause of Death; Cilostazol; Gastrointestinal Hemorrhage [chemically induced]; Myocardial Infarction [*prevention & control]; Platelet Aggregation Inhibitors [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Secondary Prevention [*methods]; Stroke [*complications; ethnology; prevention & control]; Tetrazoles [adverse effects; *therapeutic use]

MeSH check words

Humans