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Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack (Review)

Naqvi IA, Kamal AK, Rehman H

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[Intervention Review]

Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack

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ABSTRACT

Background

Stroke is a leading cause of morbidity and mortality worldwide. Antiplatelet agents are considered to be the cornerstone for secondary prevention of stroke, but the role of using multiple antiplatelet agents early after stroke or transient ischaemic attack (TIA) to improve outcomes has not been established.

Objectives

To determine the effectiveness and safety of initiating, within 72 hours after an ischaemic stroke or TIA, multiple antiplatelet agents versus fewer antiplatelet agents to prevent stroke recurrence. The analysis explores the evidence for different drug combinations.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched 6 July 2020), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 7 of 12, 2020) (last searched 6 July 2020), MEDLINE Ovid (from 1946 to 6 July 2020), Embase (1980 to 6 July 2020), ClinicalTrials.gov, and the WHO ICTRP. We also searched the reference lists of identified studies and reviews and used the Science Citation Index Cited Reference search for forward tracking of included studies.

Selection criteria

We selected all randomised controlled trials (RCTs) that compared the use of multiple versus fewer antiplatelet agents initiated within 72 hours after stroke or TIA.

Data collection and analysis

We extracted data from eligible studies for the primary outcomes of stroke recurrence and vascular death, and secondary outcomes of myocardial infarction; composite outcome of stroke, myocardial infarction, and vascular death; intracranial haemorrhage; extracranial haemorrhage; ischaemic stroke; death from all causes; and haemorrhagic stroke. 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 studies. We rated the certainty of the evidence using the GRADE approach.

Main results

We included 15 RCTs with a total of 17,091 participants. Compared with fewer antiplatelet agents, multiple antiplatelet agents were associated with a significantly lower risk of stroke recurrence (5.78% versus 7.84%, risk ratio (RR) 0.73, 95% confidence interval (CI) 0.66 to 0.82; P < 0.001; moderate-certainty evidence) with no significant difference in vascular death (0.60% versus 0.66%, RR 0.98, 95% CI 0.66 to 1.45; P = 0.94; moderate-certainty evidence). There was a higher risk of intracranial haemorrhage (0.42% versus 0.21%, RR 1.92, 95% CI 1.05 to 3.50; P = 0.03; low-certainty evidence) and extracranial haemorrhage (6.38% versus 2.81%, RR 2.25, 95% CI 1.88 to 2.70; P < 0.001; high-certainty evidence) with multiple antiplatelet agents. On secondary analysis of dual versus single antiplatelet agent therapy, benefit for stroke recurrence (5.73% versus 8.06%, RR 0.71, 95% CI 0.62 to 0.80; P < 0.001; moderate-certainty evidence) was maintained as well as risk of extracranial haemorrhage (1.24% versus 0.40%, RR 3.08, 95% CI 1.74 to 5.46; P < 0.001; high-certainty evidence). The composite outcome of stroke, myocardial infarction, and vascular death (6.37% versus 8.77%, RR 0.72, 95% CI 0.64 to 0.82; P < 0.001; moderate-certainty evidence) and ischaemic stroke (6.30% versus 8.94%, RR 0.70, 95% CI 0.61 to 0.81; P < 0.001; high-certainty evidence) were significantly in favour of dual antiplatelet therapy, whilst the risk of intracranial haemorrhage became less significant (0.34% versus 0.21%, RR 1.53, 95% CI 0.76 to 3.06; P = 0.23; low-certainty evidence).

Authors' conclusions

Multiple antiplatelet agents are more effective in reducing stroke recurrence but increase the risk of haemorrhage compared to one antiplatelet agent. The benefit in reduction of stroke recurrence seems to outweigh the harm for dual antiplatelet agents initiated in the acute setting and continued for one month. Further studies are required in different populations to establish comprehensive safety profiles and long-term outcomes to establish duration of therapy.

PLAIN LANGUAGE SUMMARY

Use of multiple versus fewer antiplatelet drugs for preventing early recurrence after stroke or transient ischaemic attack

Review question

Are multiple antiplatelet drugs better than fewer antiplatelet drugs for preventing early recurrence after stroke?

Background

Stroke is the second most common non-communicable disease in the world, and carries a high risk of recurrence. Most recurrences occur early after stroke, and effective treatments are needed to prevent recurrence. Current guidelines recommend the use of an antiplatelet drug like aspirin after a stroke or transient ischaemic attack (mini-stroke). However, the safety and benefit of using more than one antiplatelet drug early after stroke has not been clearly established.

Study characteristics

We compared the use of multiple versus fewer antiplatelet drugs early after stroke. The evidence is current to 6 July 2020. We included 15 clinical trials with a total of 17,091 participants from a range of Asian, European and North American populations. The most common antiplatelet combinations tested were aspirin and dipyridamole, and aspirin and clopidogrel.

Key results

We found that multiple antiplatelet drugs reduced the risk of stroke recurrence but increased the risk of bleeding compared with fewer antiplatelet drugs. Two antiplatelet drugs appear to be more effective in preventing early stroke recurrence than a single antiplatelet drug, but there is an increased risk of side effects, especially bleeding. The benefits of dual antiplatelet drugs started immediately after a stroke seems to outweigh the risks for the first month.

Certainty of the evidence

The certainty of evidence was generally moderate or high.

SUMMARY OF FINDINGS

Summary of findings 1. Multiple compared to fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack

Multiple compared to fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or TIA

Patient or population: preventing early recurrence after ischaemic stroke or TIA
Setting: inpatient and outpatient
Intervention: multiple antiplatelet agents
Comparison: fewer antiplatelet agents

Outcomes at ≥ 3 months	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or TIA	Risk difference with multiple agents			
Stroke	Study population		RR 0.73 (0.66 to 0.82)	16,707 (14 RCTs)	⊕⊕⊕⊖ Moderate[a,b,c,d,e]
	78 per 1000	21 fewer per 1000 (27 fewer to 14 fewer)			
Vascular death	Study population		RR 0.98 (0.67 to 1.45)	15,901 (11 RCTs)	⊕⊕⊕⊖ Moderate[a,b,c,d,e]
	7 per 1000	0 fewer per 1000 (2 fewer to 3 more)			
Myocardial infarction	Study population		RR 1.38 (0.63 to 2.99)	11,411 (3 RCTs)	⊕⊕⊕⊕ High
	2 per 1000	1 more per 1000 (1 fewer to 4 more)			
Stroke, myocardial infarction, or vascular death	Study population		RR 0.72 (0.64 to 0.82)	12,932 (7 RCTs)	⊕⊕⊕⊖ Moderate[a,b,c,d,e]
	88 per 1000	25 fewer per 1000 (32 fewer to 16 fewer)			
Intracranial haemorrhage	Study population		RR 1.92 (1.05 to 3.50)	14,287 (6 RCTs)	⊕⊕⊖⊖ Low[a,b,c,d,e]
	2 per 1000	2 more per 1000			

		(0 fewer to 5 more)			
Extracranial haemorrhage	Study population		RR 2.14 (1.79 to 2.57)	10,658 (7 RCTs)	⊕⊕⊕⊕ High
	29 per 1000	36 more per 1000 (25 more to 48 more)			
Ischaemic stroke	Study population		RR 0.73 (0.64 to 0.83)	13,121 (3 RCTs)	⊕⊕⊕⊕ High
	76 per 1000	21 fewer per 1000 (27 fewer to 13 fewer)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio; **TIA:** transient ischaemic attack

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We found overall risk to be high in De Martiis and Petrovska-Cvetkovska 2008, in which information regarding controlling for bias was mostly not available. The most common source of bias was performance bias, which was not controlled for in 6 of the 14 included studies (Chairangsarit 2005; EARLY-trial; ESPIRIT; De Martiis; Nakamura 2010; Petrovska-Cvetkovska 2008). This was due to unblinding of participants when they did not receive placebos for the additional antiplatelet agent that the intervention group received.
[b]Performance bias was the most frequently encountered bias due to unblinding of study participants. However, detection bias was often controlled for even when participants were not blinded.
[c]Only Chairangsarit 2005 was at high risk of attrition bias. This study reported 11 of 38 participants (28.9%) lost to follow-up. It was unclear in Petrovska-Cvetkovska 2008, which did not report participants lost to follow-up. Both of these were two of only five studies that reported intracranial haemorrhage.
[d]Only Petrovska-Cvetkovska 2008 was at unclear risk of reporting bias, as information regarding all expected outcomes was not available.
[e]We found two studies (De Martiis and Petrovska-Cvetkovska 2008) where no information was available regarding sequence generation as at unclear risk of selection bias.

Summary of findings 2. Dual compared to one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack

Dual compared to one antiplatelet agent for preventing early recurrence after ischaemic stroke or TIA

Patient or population: preventing early recurrence after ischaemic stroke or TIA
Setting: inpatient and outpatient
Intervention: dual antiplatelet agents
Comparison: one antiplatelet agent

Outcomes at ≥ 3 months	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with 1 antiplatelet agent for preventing early recurrence after ischaemic stroke or TIA	Risk difference with dual agents			
Stroke	Study population		RR 0.71 (0.62 to 0.80)	13,637 (13 RCTs)	⊕⊕⊕⊖ Moderate[a,b,c,d,e]
	81 per 1000	23 fewer per 1000 (31 fewer to 16 fewer)			
Vascular death	Study population		RR 0.84 (0.54 to 1.30)	12,831 (10 RCTs)	⊕⊕⊕⊖ Moderate[a,b,c,d,e]
	7 per 1000	1 fewer per 1000 (3 fewer to 2 more)			
Myocardial infarction	Study population		RR 1.38 (0.63 to 2.99)	11,411 (3 RCTs)	⊕⊕⊕⊕ High
	2 per 1000	1 more per 1000 (1 fewer to 4 more)			
Stroke, myocardial infarction, or vascular death	Study population		RR 0.72 (0.64 to 0.82)	12,932 (7 RCTs)	⊕⊕⊕⊖ Moderate[a,b,c,d,e]
	88 per 1000	25 fewer per 1000 (32 fewer to 16 fewer)			
Intracranial haemorrhage	Study population		RR 1.53 (0.76 to 3.06)	11,217 (5 RCTs)	⊕⊕⊖⊖ Low[a,b,c,d,e]
	1 per 1000	1 more per 1000 (0 fewer to 3 more)			
Extracranial haemorrhage	Study population		RR 3.08 (1.74 to 5.46)	7586 (6 RCTs)	⊕⊕⊕⊕ High
	456 per 1000	948 more per 1000 (337 more to 2032 more)			
Ischaemic stroke	Study population		RR 0.70 (0.61 to 0.81)	10,051 (2 RCTs)	⊕⊕⊕⊕ High
	89 per 1000	27 fewer per 1000 (35 fewer to 17 fewer)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio; **TIA:** transient ischaemic attack

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[e]We found two studies (De Martiis and Petrovska-Cvetkovska 2008) where no information was available regarding sequence generation as at unclear risk of selection bias.

BACKGROUND

Description of the condition

Over one million new strokes are reported each year in high-income countries (Bamford 1990), whilst the low-income countries sustain twice that incidence (Lopez 2006). About 30% of these strokes are recurrent events (Goldstein 2006). Transient ischaemic attacks (TIAs) and minor ischaemic strokes are often precursors to serious vascular events including recurrent strokes, the risk being at its maximum within the first 48 hours of the onset (Coull 2004).

Antiplatelet agents, especially aspirin as a single agent, have been shown to reduce the risk of early recurrent ischaemic stroke by 7 per 1000 people treated and improve the long-term functional outcome, with 13 more people alive and independent per 1000 people treated. However, this is accompanied by a minimal increase in the risk of haemorrhage (2 per 1000 people). The International Stroke Trial and the Chinese Acute Stroke Trial both document the effective role of aspirin in acute stroke treatment as early as within 48 hours of onset (Chen 2000).

Recent studies have used multiple antiplatelet agents in addition to aspirin in the acute phase of stroke, based on the assumption that the additional platelet blockade will translate into superior clinical outcomes compared with a single antiplatelet agent or less intensive antiplatelet therapy for a typical duration of at least three months, or occasionally less (CHANCE; COMPRESS; FASTER PILOT; POINT; TARDIS).

Use of multiple antiplatelet therapy may be effective in the setting of acute ischaemic stroke or TIA, by minimising clinical disability associated with tissue injury along with reducing the risk of recurrence of serious vascular events. In terms of the safety profile, long-term multiple therapy may be harmful compared with single antiplatelet therapy. A meta-analysis is needed to determine whether multiple antiplatelet agents are indeed more effective than fewer antiplatelet agents in preventing early recurrence of stroke or TIA and, if so, to determine its safety profile as well as duration of treatment.

Description of the intervention

The included antiplatelet agents are given alone or in combination with other antiplatelet agents, and work via different mechanisms to prevent platelet aggregation (Born 2006).

At antiplatelet doses of 75 to 325 mg/day, aspirin irreversibly inhibits the platelet cyclooxygenase (COX)-1 dependent thromboxane A_2 formation that is responsible for platelet aggregation (Patrono 1994).

Dipyrimadole inhibits the activity of adenosine deaminase and phosphodiesterase, which leads to an accumulation of adenosine, adenine nucleotide, and cyclic adenosine monophosphate (cAMP). These mediators inhibit platelet aggregation and may cause vasodilatation via release of prostacyclin or prostaglandin D_2 (PGD_2) (d'Esterre 2010).

A combination drug consisting of two antiplatelet agents (aspirin and extended-release dipyridamole) has been found to be more effective than aspirin alone. Like aspirin it increases plasma endothelial nitric acid oxidase (eNOS), thus preventing platelet aggregation, and also reduces oxidised low-density lipoproteins (oxLDLs), but for a longer duration than with aspirin alone (Serebruany 2010).

Clopidogrel, a new thienopyridine derivative similar to ticlopidine, requires in vivo biotransformation to an unidentified active metabolite. This active metabolite irreversibly blocks the $P2Y_{12}$ component of adenosine diphosphate (ADP) receptors, thus preventing activation of the glycoprotein (GP) IIb/IIIa receptor complex and reducing platelet aggregation. Platelets blocked by clopidogrel are affected for the remainder of their life span (D'Sa 1999).

Cilostazol increases the cAMP levels in platelets via inhibition of cyclic AMP phosphodiesterase 3 (PGE3) (Minami 1997). It also inhibits the uptake of adenosine. This leads to its dual action of reversible inhibition of platelet aggregation along with vasodilatation and inhibition of vascular smooth muscle cell proliferation.

How the intervention might work

Antiplatelet combination therapy may work better than using a single antiplatelet agent. Given together, different agents with different modes of action and variable onset of action may work synergistically, thus inhibiting platelets more effectively and with a faster onset of action. There has been growing evidence that combination antiplatelet therapy also reduces the micro-emboli in the brain in acute ischaemic stroke. The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial found a relative risk reduction of 39.8% (95% confidence interval (CI) 13.8 to 58.0, P = 0.0046) in micro-embolic signals on transcranial Doppler ultrasound (TCD) amongst participants on dual therapy compared with aspirin monotherapy (Markus 2005). Another study showed similar results, with a relative risk reduction of 42.4% (95% CI 4.6 to 65.2, P = 0.025), on combination therapy with aspirin and clopidogrel (Wong 2010).

Why it is important to do this review

The early management of people with an acute cerebral ischaemic event (stroke or TIA) may have a substantial impact on clinical outcomes. The non-randomised EXPRESS study compared multifaceted and very early intervention with standard care and suggested this was associated with an 80% reduction in the 90-day risk of stroke recurrence. However, it was not possible to adjust fully for confounding factors, and it was not clear which components of the intervention accounted for the effects observed.

OBJECTIVES

To determine the effectiveness and safety of initiating, within 72 hours after an ischaemic stroke or TIA, multiple antiplatelet agents versus fewer antiplatelet agents to prevent stroke recurrence. The analysis explores the evidence for different drug combinations.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) where participants took any combination of antiplatelet agents, starting within 72 hours of an acute ischaemic stroke or TIA, versus fewer agents, and

who were systematically followed up for development of stroke or TIA for a minimum of one month on the treatment.

Types of participants

We included participants with clinical manifestations of an acute ischaemic stroke or TIA who were given the intervention within 72 hours of onset and continued therapy for at least one month after diagnosis. We excluded any trials that included participants previously administered anticoagulants, including heparin, heparinoids, or direct thrombin inhibitors, for any duration.

Types of interventions

We included trials of combinations of orally administered antiplatelet agents, which may include but were not limited to aspirin, thienopyridine derivatives, dipyridamole, cilostazol, triflusal, buflomedil, and sarpogrelate. We excluded data from any treatment arm in which the intervention was aspirin at a dose of less than 30 mg daily.

We addressed multiple versus fewer agent combinations. The comparisons based on the intervention versus control arms in the included trials were as follows.

- A + B versus A or B (multiple versus single agent)
- A + B + C versus C or A + B (multiple versus fewer agents)

Types of outcome measures

Primary outcomes

The primary outcome measure was stroke (of any type including fatal stroke) or vascular death during follow-up of at least three months after initiation of therapy.

Secondary outcomes

We assessed the secondary outcomes at the final scheduled follow-up of at least 90 days after initiation of therapy. These included components of the composite outcome (stroke, myocardial infarction (MI), or vascular death) as well as the composite outcome of stroke, MI or vascular death.

- MI (non-fatal or fatal)
- Stroke, MI, or vascular death during the follow-up period
- Intracranial haemorrhage (fatal or non-fatal)
- Extracranial haemorrhage (fatal or non-fatal)
- Stroke (ischaemic or haemorrhagic, fatal or non-fatal)
- Death from any cause

For studies where there was more than one follow-up period, we included outcome data according to follow-up at one week, one month, three months, and six months, as available. Otherwise, we included the longest period recorded to extract outcome data (at least 90 days).

Search methods for identification of studies

See the 'Specialized register' information at the Cochrane Stroke Group's website. We searched for relevant trials in all languages and arranged translation of trial reports where necessary.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (last searched 6 July 2020), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 7 of 12, July 2020) (last searched 6 July 2020) (Appendix 1), MEDLINE Ovid (1946 to 6 July 2020) (Appendix 2), and Embase Ovid (1980 to 6 July 2020) (Appendix 3).

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Trials Information Specialist and adapted it for the other databases.

In an effort to identify further published, unpublished, and ongoing trials, we searched the ongoing trials registers.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 6 July 2020) (Appendix 4)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; searched 6 July 2020) (Appendix 5)

Searching other resources

We also searched the reference lists of identified studies and reviews, and used the Science Citation Index Cited Reference search for forward tracking of included studies.

Data collection and analysis

We reviewed all studies that met our inclusion criteria. These included:

- adult men and women, 18 years of age or older;
- acute stroke or TIA (onset defined by last seen normal);
- given antiplatelet therapy within 72 hours of onset, with control arm participants receiving one or more antiplatelet agents (aspirin at least 30 mg daily if used as the antiplatelet agent);
- on antiplatelet therapy for at least one month;
- clinical trials with random allocation of participants into two or more treatment groups, including a control group;
- information on vascular outcomes (fatal and non-fatal) during the follow-up period.

We extracted data from each study on participants enrolled, inclusive of criteria for enrolment; the process of treatment allocation, concealment, and blinding; total number of participants enrolled in the study and assigned to each treatment arm; number of participants lost to follow-up in each treatment arm; reasons for loss to follow-up in either treatment arm; method and duration of follow-up; outcome events measured during follow-up; and any adverse effects secondary to treatment that were encountered during follow-up.

We analysed all data using intention-to-treat analyses. We rated the certainty of evidence using the GRADE system.

Selection of studies

Three review authors (IAN, AKK, HR) independently screened the titles and abstracts of all reports identified by the searches of electronic bibliographic databases, excluding obviously irrelevant records. We obtained the full texts of the remaining studies and selected trials for inclusion in the review. The review authors were

not blinded to the names of authors, institutions, journals, and results when they made the eligibility decision. The senior review author (AKK) acted as arbiter if there was no consensus.

Data extraction and management

We designed a specific questionnaire for data extraction that included information to identify the source of data, eligibility, methods (including sequence generation and allocation), details of participants (e.g. number, age, gender), interventions (i.e. dose and type of antiplatelet agent used), outcomes, and results. Two review authors independently extracted data from each study, resolving any differences through discussion.

Assessment of risk of bias in included studies

We assessed the risk of bias of each included study using Cochrane's 'Risk of bias' tool as described in Chaper 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This tool addresses seven specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. We assigned each domain as at low, high, or an unclear risk of bias based on the information available.

Measures of treatment effect

We used risk ratio (RR) with 95% confidence interval (CI) to measure treatment effects for dichotomous data. We extracted data for randomised participants in each trial as well as outcome event data to calculate pooled RRs.

Unit of analysis issues

For studies where there was more than one follow-up period, we included outcome data according to follow-up at one week, one month, three months, and six months, as available, to measure any difference in outcome events over time. Otherwise, we included the longest period recorded to extract outcome data, at least three months. For non-fatal events, we only recorded the first event for each participant.

Dealing with missing data

We recorded the amount of missing data for outcome variables during data extraction. If this was substantial (i.e. 20% or more), we assumed the missing data showed no benefit from the antiplatelet agent given and performed sensitivity analyses to assess the effect of this assumption on the summary risk ratios.

Assessment of heterogeneity

We assessed the presence of heterogeneity using the I^2 statistic, with a value above 50% indicating heterogeneity.

Assessment of reporting biases

We used funnel plots to assess the presence of publication bias.

Data synthesis

We assessed the effect of treatment amongst trials comparing the same combination antiplatelet therapy with one or more antiplatelet agents.

In the absence of significant heterogeneity, we used a fixed-effect meta-analysis model for combining data. If we found heterogeneity, we explored it by sensitivity analysis followed by the use of a random-effects model, if required.

For dichotomous data, we presented results as a summary of RRs with 95% CIs.

Subgroup analysis and investigation of heterogeneity

We assessed the I^2 statistic for heterogeneity, which showed less than 50% heterogeneity. We did not perform subgroup analysis as many of our studies were subanalyses of secondary prevention studies, and data regarding subsets were not clearly reported. However, we identified one large trial of one-month duration. The inclusion of this trial into an exploratory analysis at one month was a change from the protocol of this review.

Sensitivity analysis

We performed sensitivity analyses for studies with substantial missing data of more than 20%. If we included studies with substantial missing data, we analysed data without these studies to assess the robustness of the pooled RRs.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias), as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), for the following main outcomes of analysis.

- Stroke
- Vascular death
- MI
- Stroke, MI, or vascular death
- Intracranial haemorrhage
- Extracranial haemorrhage
- Ischaemic stroke

We created a 'Summary of findings' table in which we presented the key findings of the review, including a summary of the quantity of data, the magnitude of effect size, and the overall certainty of evidence. We also created a second 'Summary of findings' table to compare dual versus single antiplatelet agents, as most of the available trials compared two versus one antiplatelet, and this is a clinically important comparison.

RESULTS

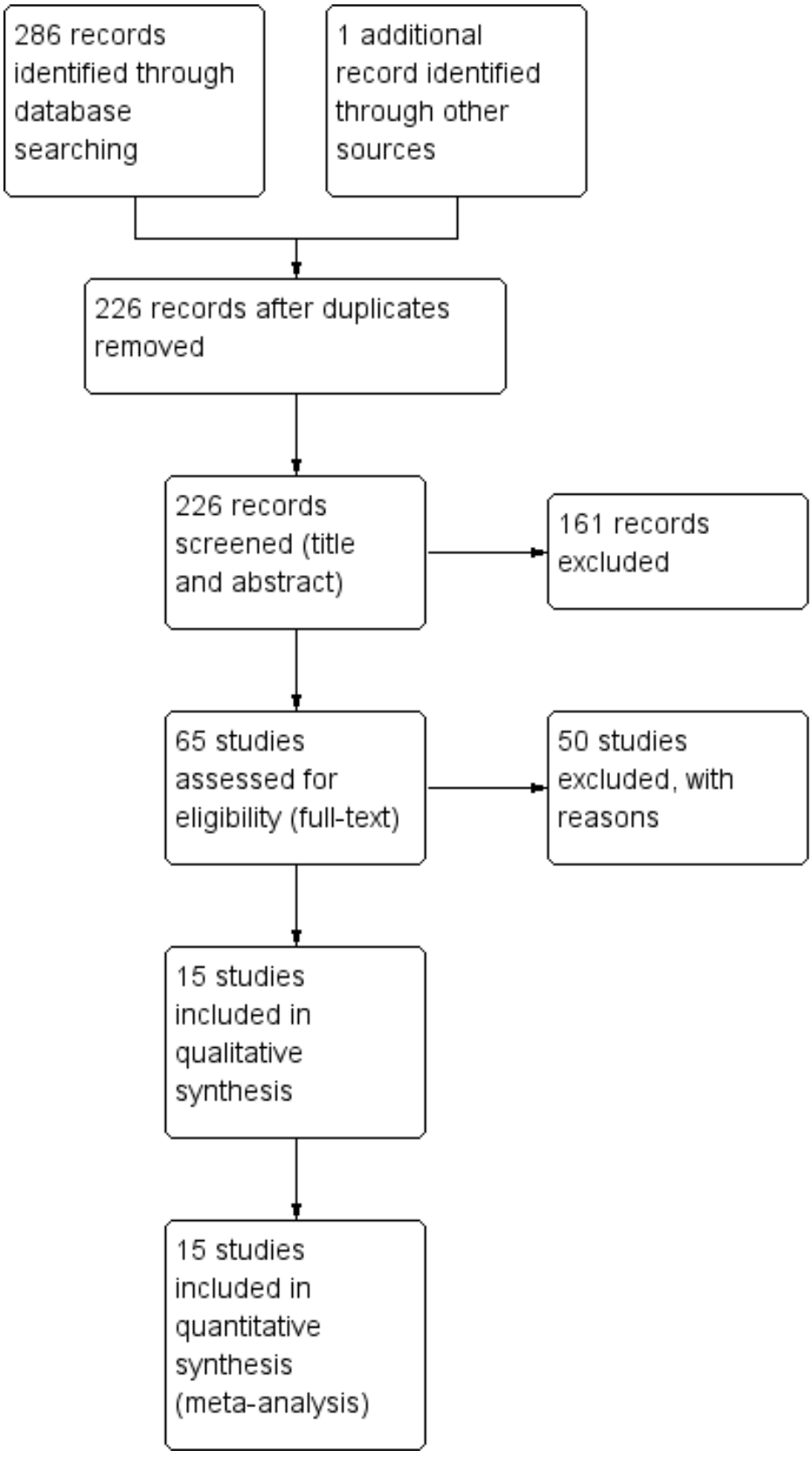
Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Our searches identified a total of 287 potentially relevant studies. After duplicates were removed, 226 records were screened using title and abstract after which 161 records were excluded. The remaining 65 records underwent full-text screening and 50 were excluded. Fifteen trials were included in the review (Figure 1).

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies.

Fifteen studies met our inclusion criteria and are included in the review (Chairangsarit 2005; CHANCE; CHARISMA; COMPRESS; De Martiis; EARLY-trial; ESPIRIT; ESPS 2; FASTER PILOT; MATCH 2001; Nakamura 2010; Petrovska-Cvetkovska 2008; POINT; PRoFESS; TARDIS). The trials enrolled a total of 17,091 participants. In all, 8493 participants were randomised to the intervention group receiving multiple antiplatelets and 8598 participants to the control group. Whilst nine of the 15 studies were conducted in Europe or North America (De Martiis; EARLY-trial; ESPIRIT; ESPS 2; MATCH 2001; Petrovska-Cvetkovska 2008; PRoFESS), CHANCE, which accounted for 46% of all participants, was conducted in China.

The most common antiplatelet combinations tested were aspirin and dipyridamole (6 studies: Chairangsarit 2005; De Martiis; EARLY-trial; ESPIRIT; ESPS 2; PRoFESS) and aspirin and clopidogrel (7 studies: CHANCE; CHARISMA; COMPRESS; FASTER PILOT; MATCH 2001; Petrovska-Cvetkovska 2008; POINT). One study including three antiplatelet combinations versus aspirin and dipyridamole or clopidogrel met our inclusion criteria (TARDIS). Only Nakamura 2010 tested a combination that included cilostazol (aspirin and cilostazol). Aspirin was usually employed as the control antiplatelet agent (11 studies: Chairangsarit 2005; CHANCE; CHARISMA; COMPRESS; EARLY-trial; ESPIRIT; ESPS 2; FASTER PILOT; Nakamura 2010; Petrovska-Cvetkovska 2008; POINT). Other controls included clopidogrel, MATCH 2001; PRoFESS; TARDIS, and dipyridamole, De Martiis; ESPS 2. As per study protocol, all these medications were given orally. Most studies did report a loading dose employed for aspirin, clopidogrel, and dipyridamole, and doses varied slightly in different studies but were within therapeutic range.

The range of follow-up varied from 30 days to 3.5 years.

All 15 trials reported stroke as an outcome, whilst 11 studies also reported vascular death (Chairangsarit 2005; CHANCE; COMPRESS; EARLY-trial; ESPIRIT; ESPS 2; FASTER PILOT; Nakamura 2010; Petrovska-Cvetkovska 2008; POINT; PRoFESS). Secondary outcomes reported included the composite outcome of stroke, MI, and death (8 studies: CHANCE; COMPRESS; EARLY-trial; ESPIRIT; FASTER PILOT; MATCH 2001; POINT; PRoFESS), intracranial haemorrhage (6 studies: Chairangsarit 2005; CHANCE; COMPRESS; Petrovska-Cvetkovska 2008; PRoFESS; TARDIS), and extracranial haemorrhage (8 studies: CHARISMA; COMPRESS; EARLY-trial; ESPIRIT; MATCH 2001; POINT; PRoFESS; TARDIS), being reported most frequently. One study, COMPRESS, followed participants for one month only and could not be included in the analysis of participants followed for at least three months.

Excluded studies

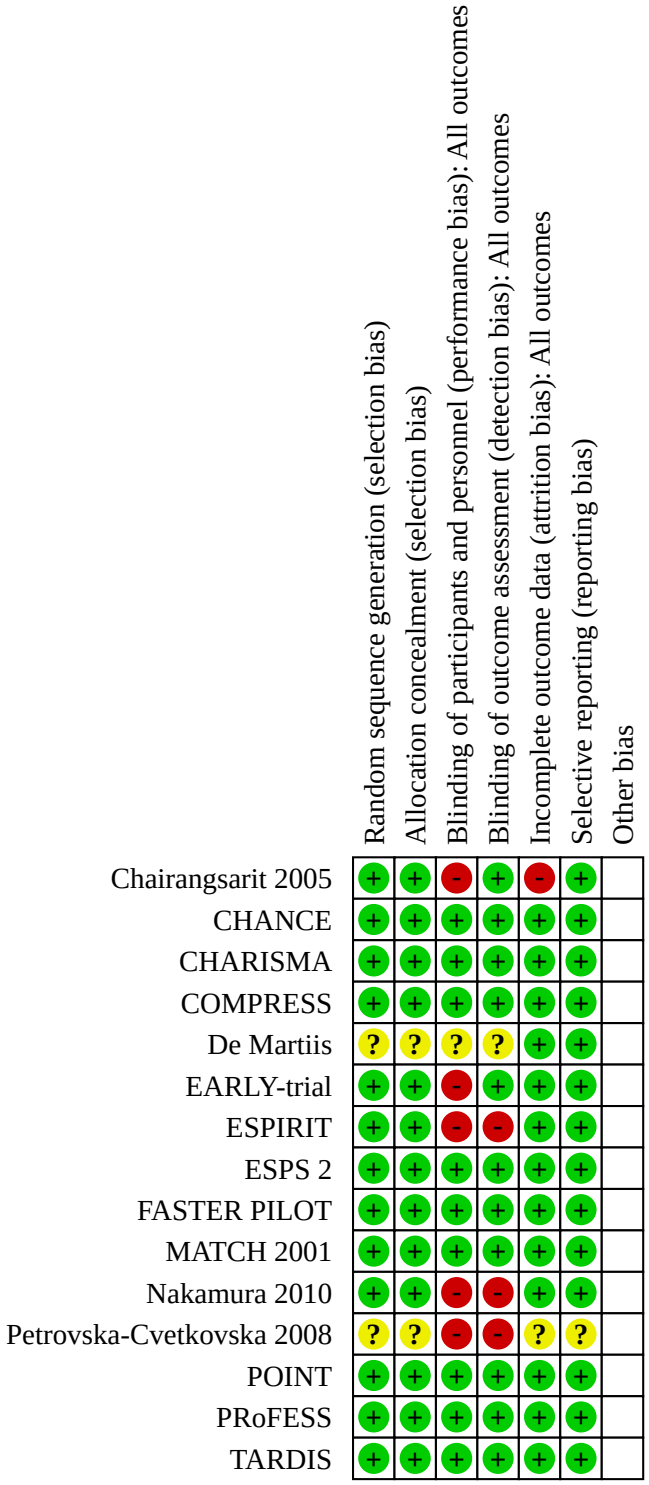
See Characteristics of excluded studies.

We excluded 50 trials after full-text screening that failed to meet the eligibility criteria. Common reasons for exclusion included comparison of single antiplatelet agents, use of anticoagulants, and failure to randomise within 72 hours of the ischaemic event.

Risk of bias in included studies

See Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Risk of bias was low in most studies. Risk was found to be high in De Martiis and Petrovska-Cvetkovska 2008, where information regarding controlling for bias was not available. At least nine studies were high-quality studies where the study design controlled for all possible biases (CHANCE; CHARISMA; COMPRESS; ESPS 2; FASTER PILOT; MATCH 2001; POINT; PRoFESS; TARDIS). The most common source of bias was performance bias, which was not controlled for in six of the 15 included studies (Chairangsarit 2005; De Martiis; EARLY-trial; ESPIRIT; Nakamura 2010; Petrovska-Cvetkovska 2008). This was due to unblinding of participants when they did not receive placebos for the additional antiplatelet agent that the intervention group received.

Allocation

Most studies were at low risk of selection bias. Two studies (De Martiis and Petrovska-Cvetkovska 2008) where no information was available regarding sequence generation were assessed as at unclear risk of bias.

Blinding

Performance bias was the most frequently encountered bias due to the unblinding of study participants. However, detection bias was often controlled even when participants were not blinded.

Incomplete outcome data

Only Chairangsarit 2005 was assessed as at high risk of attrition bias. This study reported 11 of 38 (28.9%) of participants lost to follow-up. We assessed Petrovska-Cvetkovska 2008 as at unclear risk of bias, as information regarding all participants was not available, and participants lost to follow-up were not reported.

Selective reporting

Reporting bias was not obvious, with outcomes reported as planned in the included studies.

Other potential sources of bias

None.

Effects of interventions

See: **Summary of findings 1** Multiple compared to fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack; **Summary of findings 2** Dual compared to one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack

The effects of interventions are categorised into primary and secondary outcomes. The results presented were composite numbers from all the included trials. These included a comparison of multiple versus fewer agents, with a secondary analysis of dual- versus single-agent therapy, and are divided into subcategories of actual drug comparisons. There were up to six subcategories based on the included trials, as described in the table below.

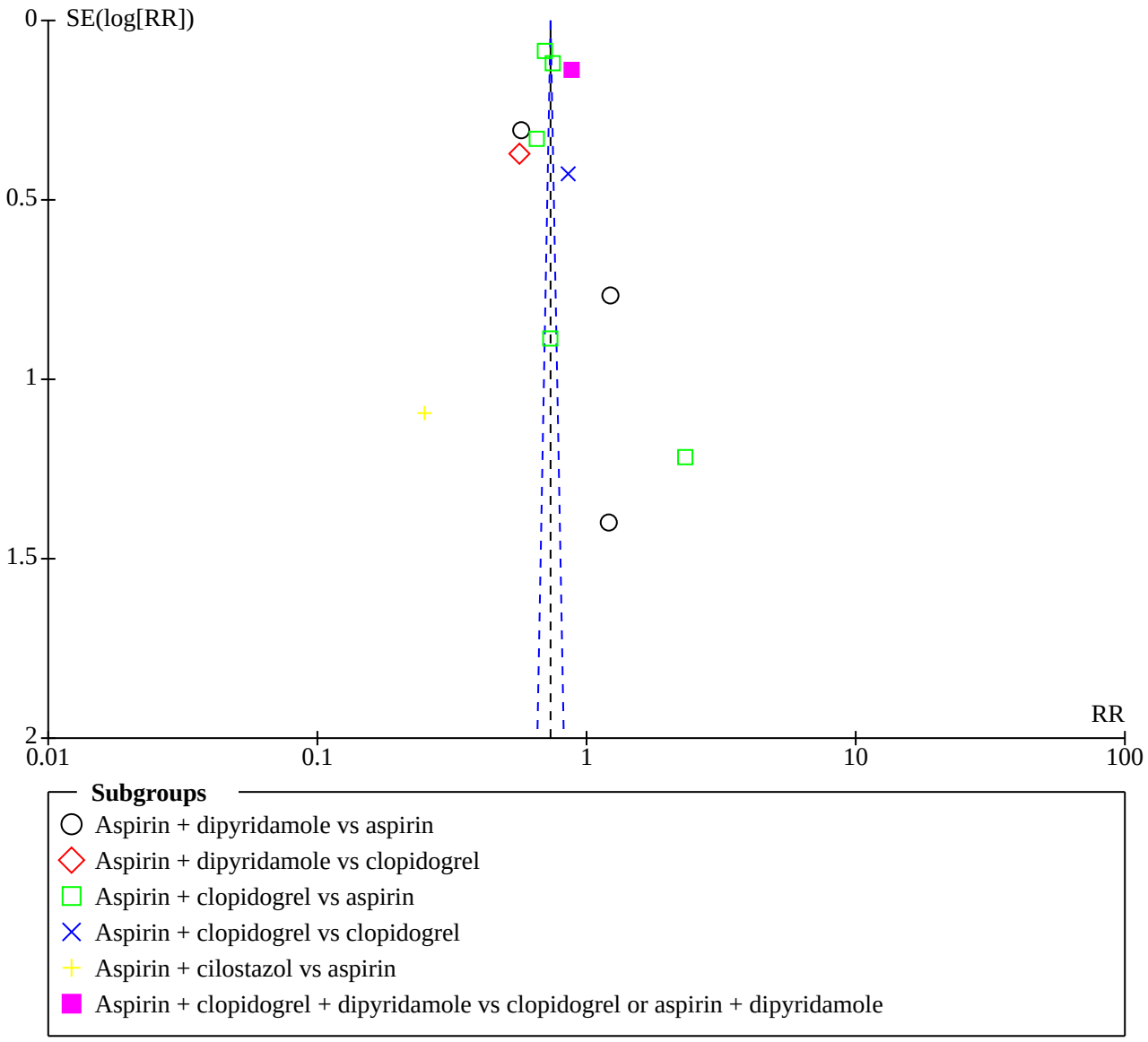
Intervention	**Comparison (fewer antiplatelet agents)**		
(multiple antiplatelet agents)	**Aspirin**	**Clopidogrel**	**Clopidogrel alone or aspirin + dipyridamole**
Aspirin + dipyridamole	**Subcategory: aspirin + dipyridamole vs aspirin** Chairangsarit 2005; De Martiis; EARLY-trial; ESPIRIT; ESPS 2	**Subcategory: aspirin + dipyridamole vs clopidogrel** PRoFESS	-
Aspirin + clopidogrel	**Subcategory: aspirin + clopidogrel vs aspirin** CHANCE; CHARISMA; COMPRESS; FASTER PILOT; Petrovska-Cvetkovska 2008; POINT	**Subcategory: aspirin + clopidogrel vs clopidogrel** MATCH 2001	-
Aspirin + cilostazol	**Subcategory: aspirin + cilostazol vs aspirin** Nakamura 2010	-	-
Aspirin + clopidogrel + dipyridamole	-	-	**Subcategory: aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole** TARDIS

Primary outcomes

Stroke

See Analysis 1.1; Figure 3.

Figure 3. Funnel plot of comparison: 1 Primary outcomes, outcome: 1.1 Stroke.



Stroke was found to be lower in the multiple antiplatelet group in 10 of 14 studies at three months (CHANCE; COMPRESS; EARLY-trial; FASTER PILOT; MATCH 2001; Nakamura 2010; Petrovska-Cvetkovska 2008; POINT; PRoFESS; TARDIS). Two studies did not report a single case of stroke recurrence (Chairangsarit 2005; De Martiis), whilst three studies had a higher number of strokes when participants received dual agents (CHARISMA; ESPIRIT; ESPS 2). The common factor in these three studies was the small number of events in each group, since they were all subanalyses of larger studies. CHANCE, which constituted 46% of participants, followed by POINT at 24%, and TARDIS 16%, showed a significant difference in favour of the intervention group in decrementing response. Overall, 480 of the 8299 (5.78%) participants receiving multiple antiplatelets had an episode of stroke, whilst 659 of the 8408 (7.84%) participants in the control group had an event. The risk ratio was found to be significant (RR 0.73, 95% confidence interval (CI) 0.66 to 0.82; P < 0.001; moderate-certainty evidence), with a number needed to treat for an additional beneficial outcome (NNTB) of 48 participants to prevent one episode using more than a single antiplatelet agent.

As most of the studies compared dual versus single antiplatelet therapy, we conducted a secondary analysis that compared the effectiveness of different dual combinations with single antiplatelet

therapy (A + B versus A or B or C). Most dual versus single antiplatelet therapy trials studied a combination of A + B versus A. We excluded two trials from this analysis: COMPRESS because it measured outcomes at one month alone and not at three months as in the other trials, and TARDIS because it tested multiple antiplatelet therapy against dual or single agents (A + B + C versus C or A + B) and was the only study with this comparison.

In terms of the primary outcome of stroke, 387 of the 6759 (5.73%) participants receiving dual antiplatelets had an episode of stroke, whilst 554 of the 6878 (8.06%) participants in the control group had an event. The risk ratio was found to be significant (RR 0.71, 95% CI 0.62 to 0.80; P < 0.001; moderate-certainty evidence), that is 23 fewer events per 1000 with an NNTB of 43 participants to prevent one stroke using dual antiplatelet agents instead of single antiplatelet therapy.

Moreover, the combination of aspirin-clopidogrel independently showed a significantly lower incidence of stroke in the intervention group compared to the control group (RR 0.72, 95% CI 0.63 to 0.82; P < 0.001) (Analysis 6.1) (6 studies: CHANCE; CHARISMA; FASTER PILOT; MATCH 2001; Petrovska-Cvetkovska 2008; POINT). Five of these studies used aspirin in the control group apart from MATCH 2001 that used clopidogrel. The aspirin-dipyridamole combination used in six studies showed a lower incidence of stroke in the dual combination group (RR 0.62, 95% CI 0.40 to 0.95; P = 0.03) (Analysis 7.1) (6 studies: Chairangsarit 2005; De Martiis; EARLY-trial; ESPIRIT; ESPS 2; PRoFESS). All of these used aspirin in the control group apart from PRoFESS that used clopidogrel.

Vascular death

See Analysis 1.2.

Eleven studies reported vascular death (Chairangsarit 2005; CHANCE; EARLY-trial; ESPIRIT; ESPS 2; FASTER PILOT; Nakamura 2010; Petrovska-Cvetkovska 2008; POINT; PRoFESS; TARDIS). Of these, vascular death occurred in 47 of 7882 (0.6%) participants in the intervention group and 53 of 8019 (0.66%) in the control group. The overall association was not significant (RR 0.98, 95% CI 0.67 to 1.45; P = 0.94; moderate-certainty evidence). This finding was related to the large sample size of CHANCE. The difference could not be estimated in five studies where the outcome was assessed but no cases were reported (Chairangsarit 2005; FASTER PILOT; Nakamura 2010; Petrovska-Cvetkovska 2008; PRoFESS).

When we removed TARDIS from the analysis to assess this primary outcome in terms of dual versus single antiplatelet therapy, the results were similar with vascular death in 34 out of 6342 participants in the intervention group and 46 out of 6489 in the control group (RR 0.84, 95% CI 0.54 to 1.30; P = 0.43; moderate-certainty evidence).

Secondary outcomes

2.1 Myocardial infarction

See Analysis 2.1.

Myocardial infarctions were reported in only three of the 15 included studies at three or more months (CHANCE; POINT; PRoFESS). All three of these studies examined dual versus single antiplatelet therapy, and the proportion was higher in the intervention group compared to the control group. There were 15 episodes in 5688 participants (0.26%) in the dual antiplatelet group and 11 episodes in 5723 participants (0.19%) in the control group. This association was not significant (RR 1.38, 95% CI 0.63 to 2.99; P = 0.42).

2.2 Stroke, myocardial infarction, or vascular death

See Analysis 2.2.

Composite results from stroke, MI, and vascular death were reported in seven included studies that compared dual to single antiplatelet agent therapy (CHANCE; EARLY-trial; ESPIRIT; FASTER PILOT; MATCH 2001; POINT; PRoFESS). A total of 412 cases from 6468 participants (6.37%) were reported in the intervention group compared to 567 cases from 6464 participants (8.77%) in the control group. The association was found to be significant (RR 0.72, 95% CI 0.64 to 0.82; P < 0.001; moderate-certainty evidence), with 25 fewer events per 1000 in the intervention group. This finding suggests that to prevent one death from either stroke, MI, and vascular death, 42 participants needed to be treated with dual antiplatelet agents.

Three studies, COMPRESS, POINT, and PRoFESS subgroup, reported follow-up outcome data at an earlier time point, that is one month from treatment (Analysis 5.1). A total of 114 cases from 3271 participants (3.49%) were reported in the intervention group compared to 158 cases from 3303 participants (4.78%) in the control group. The association was found to be significant (RR 0.73, 95% CI 0.57 to 0.92; P = 0.008).

2.3 Intracranial haemorrhage

See Analysis 2.3.

Six studies reported intracranial haemorrhage at three or more months (Chairangsarit 2005; CHANCE; Petrovska-Cvetkovska 2008; POINT; PRoFESS; TARDIS). The incidence was found to be higher in the multiple antiplatelet therapy group compared to the control group, with a total of 30 cases of 7156 participants (0.42%) in the intervention group and 15 cases of 7131 participants (0.21%) in the control group. The association was found to be significant (RR 1.92, 95% CI 1.05 to 3.50; P = 0.03; low-certainty evidence), with two more haemorrhages per 1000 in the intervention group.

On secondary analysis for dual versus single antiplatelet agent therapy, once TARDIS was excluded, a total of 19 cases of 5616 participants (0.34%) were reported in the intervention group compared to 12 cases of 5601 participants (0.21%) in the control group (Analysis 4.3). The association was not significant in this scenario (RR 1.53, 95% CI 0.76 to 3.06; P = 0.23), with one more haemorrhage per 1000 in the intervention group.

2.4 Extracranial haemorrhage

See Analysis 2.4.

Seven studies reported extracranial haemorrhage (CHARISMA; EARLY-trial; ESPIRIT; MATCH 2001; POINT; PRoFESS; TARDIS). The incidence was found to be higher in the intervention group compared to the control group: extracranial haemorrhage was reported in 340 of 5325 participants (6.38%) in the intervention group and 150 of 5333 participants (2.81%) in the control group. TARDIS contributed 88.6% of the data to this analysis with a large effect. The association was found to be significant (RR 2.25, 95% CI 1.88 to 2.70; P < 0.001).

This result was maintained on secondary analysis for dual versus single antiplatelet agent therapy (RR 3.08, 95% CI 1.74 to 5.46; P < 0.001) (Analysis 4.4).

2.5 Ischaemic stroke

See Analysis 2.5.

Ischaemic and haemorrhagic stroke were differentiated in CHANCE, POINT, and TARDIS. Ischaemic stroke occurred in 362 participants in the intervention group (5.52%) and 500 participants in the control group (7.62%). This association was found to be significant (RR 0.73, 95% CI 0.64 to 0.82, P < 0.001; high-certainty evidence). There were 21 fewer events per 1000 in the intervention group, with an NNTB of 48 to prevent one ischaemic stroke.

For studies that reported dual versus antiplatelet agent therapy, the association was again significant in favour of dual antiplatelet therapy, with 27 fewer ischaemic strokes per 1000 in the intervention group (RR 0.70, 95% CI 0.61 to 0.81; P < 0.001) (Analysis 4.5).

2.6 Haemorrhagic stroke

See Analysis 2.6.

Three studies reported ischaemic and haemorrhagic strokes separately (CHANCE; POINT; TARDIS). Of these, 27 of the 6556 participants (0.41%) receiving dual antiplatelet, CHANCE; POINT, and triple antiplatelet therapy, TARDIS, developed haemorrhagic stroke, whilst 16 of the 6565 participants (0.24%) receiving single agents (or dual agents as in TARDIS) developed haemorrhagic stroke. The association was not significant (RR 1.69, 95% CI 0.91 to 3.13; P = 0.10; high-certainty evidence).

This result was maintained on secondary analysis for dual versus single antiplatelet agent therapy once TARDIS was excluded (RR 1.19, 95% CI 0.53 to 2.64; P = 0.86) (Analysis 4.6).

2.7 Death from any cause

See Analysis 2.7.

Four studies reported death from any cause (CHANCE; POINT; PRoFESS; TARDIS). Overall, 59 participants in the intervention group (0.82%) and 56 participants in the control group (0.77%) died from all causes. There was no significant difference between groups (RR 1.05, 95% CI 0.73 to 1.51; P = 0.79).

This result was maintained on secondary analysis for dual versus single antiplatelet agent therapy (RR 1.19, 95% CI 0.72 to 1.96; P = 0.50) (Analysis 4.7).

DISCUSSION

Summary of main results

We undertook this review to compare the use of multiple versus fewer antiplatelet agents to prevent recurrence after stroke or transient ischaemic attack (TIA). We analysed data from 15 studies. All combination therapies utilised aspirin as one of the drugs; the other drugs were either clopidogrel (7 studies), dipyridamole (6 studies), or cilostazol (1 study). The control group was typically a single agent and most frequently aspirin, with clopidogrel and dipyridamole used as controls infrequently. One study tested all three agents against aspirin and dipyridamole or clopidogrel alone.

The CHANCE trial consisted of 46.3% of the total number of participants included in the review. This was a multicentre study based in China that compared the effects of dual antiplatelets against a single antiplatelet agent after acute stroke. It reported efficacy outcomes and safety profile in detail. This was in contrast to four other secondary prevention studies which had different primary objectives, but as their subsets met our study criteria they were included in the analysis. Studies that were conducted prior to the 1990s tended not to report the study design and the safety profiles in detail.

Analysis revealed that multiple antiplatelet agents were associated with significantly lower incidence of stroke compared to fewer antiplatelet agents in people with a history of stroke or TIA. There was a relative reduction of 27% (95% CI 18% to 34%) corresponding to 21 strokes, ranging between 14 and 27 strokes (95% CI), avoided for every 1000 people treated with multiple antiplatelets compared to treatment with fewer (typically single) agents. Thus to avoid one stroke after an episode of stroke or TIA, 48 people need to be treated with multiple antiplatelets for a period of at least 30 days to avoid an event (Summary of findings 1). On secondary analysis, dual versus single antiplatelet therapy held this benefit, with a relative reduction of 29% (95% CI 20% to 38%), that is 23 strokes avoided for every 1000 people treated with dual antiplatelet therapy (Summary of findings 2).

Vascular death was the other primary outcome analysed in our review. Unlike stroke, however, this was not reported in all the included studies. In the 11 studies that did report vascular death, there was a slightly lower incidence in the intervention group compared to the control group. Multiple antiplatelets reduced the risk of vascular death by 0.06% compared to fewer antiplatelet agents. The association was not significant (95% CI 0.67 to 1.45; P = 0.94). This was perhaps because five of the eleven studies that reported vascular death did not report a single event in either arm. This would in turn suggest that a follow-up period of three months is not sufficient to evaluate this outcome. Analysis of trials comparing only dual versus single antiplatelet therapy yielded similar results (RR 0.84, 95% CI 0.54 to 1.30; P = 0.43).

The composite outcome of stroke, myocardial infarction, or vascular death was associated with a reduction of 28%, which corresponds to 25 fewer strokes per 1000, with an NNTB of 42 people for participants who received dual antiplatelet therapy versus a single agent. On subgroup analysis of three studies that addressed follow-up at one month, this outcome was again associated with a relative reduction of 27%.

The most commonly reported adverse events were intracranial haemorrhage (6 studies) and extracranial haemorrhage (7 studies). As expected, the proportion of intracranial and extracranial haemorrhage reported in the intervention group of multiple antiplatelets was higher compared to the control group. Intracranial haemorrhage was significantly higher in this comparison (RR 1.92, 95% CI 1.05 to 3.50; P = 0.03), with two more events per 1000. The association was found to be significant for extracranial haemorrhage as well, with 36 more events per 1000. Of note, the data in this group were largely affected by TARDIS, which contributed 88.6% of the total data included, and compared multiple antiplatelet therapy versus single or dual antiplatelet therapy with a significantly higher proportion of events in the intervention arm, raising concern over the safety of triple antiplatelet therapy. However, when dual antiplatelet

therapy was compared to single antiplatelet therapy, the risk of intracranial haemorrhage was found to be statistically insignificant (RR 1.53, 95% CI 0.76 to 3.06; P = 0.23) with one more event per 1000. Nonetheless, the risk of extracranial haemorrhage remained significant (RR 3.08, 95% CI 1.74 to 5.46; P < 0.001).

When considering duration of treatment, subgroup analysis revealed benefit at one month of dual antiplatelet therapy initiated with 72 hours of symptom onset. The POINT study indicated the benefit from dual antiplatelet therapy to be more than the risk of major haemorrhage (including intracranial haemorrhage) at one-week (2.9% composite outcome of ischaemic stroke, myocardial infarction, or ischaemic vascular death versus 0.3% major haemorrhage risk, P = 0.04) and one-month follow-up (3.9% composite outcome and 0.5% major haemorrhage risk, P = 0.02). Furthermore, secondary analysis to assess the time course for benefit and risk revealed an optimal duration of 21 days for dual therapy. However, this significance was lost at three-month follow-up with an increased risk of bleeding. In CHANCE, where early dual antiplatelet therapy was found to be effective and safe, participants in the intervention arm were administered dual antiplatelet therapy for 21 days, followed by monotherapy alone. Although these two studies differed not only in ethnicity but also in stroke mechanisms involved, the results were consistent for the first month. These data suggest that dual antiplatelet therapy for the duration of one month, or arguably 21 days, confers benefit in terms of secondary prevention of stroke, without a significantly increased risk of bleeding.

Almost half of the participants contributing data were from one study alone (CHANCE), based in China, which would seem to significantly affect the results. However, even on exclusion of the CHANCE study, the primary results did not change. There was a statistically lower incidence of stroke, more specifically ischaemic stroke, in the group receiving multiple antiplatelets or dual agents versus those receiving a single agent. Similarly, adverse outcomes such as intracranial haemorrhage also remained unchanged.

Adverse outcomes other than haemorrhage that were included in the protocol, such as myocardial infarction, were only reported in a few studies. It was therefore difficult to reach a conclusion regarding these adverse events.

Overall completeness and applicability of evidence

Our review analysed 15 trials, mostly of which were of good quality. However, trials pre-1990 were not clearly reported in terms of design and safety profiles. One finding, although accounted for, is that almost half the data were contributed by CHANCE alone. However, it is important to note that the primary and secondary outcomes did not change drastically even after CHANCE was excluded from the analyses, and so the greater benefit to risk is maintained. It may be argued that this was observed most when dual antiplatelet therapy was continued for the first month of therapy.

This review applies to atherothrombotic strokes and not cardioembolic strokes, which puts into perspective the population to whom these findings can be applied. The participants included in the analysis received at least one month of therapy, and the range of follow-up, although for 3.5 years in some cases, was limited to three months in most cases.

Perhaps the biggest limitation of this analysis stems from the inclusion of studies whose subset analyses were used since they often failed to report safety profiles as measures of interest. We thus lacked information on outcomes such as myocardial infarction and overall mortality, and so no conclusions can be made regarding these outcomes. Estimations can be made, however, for safety in terms of haemorrhage, which was more frequently reported with the combination of multiple versus fewer antiplatelet agents than of dual versus single antiplatelet use.

The trials included in this review mostly used clopidogrel (usual dose 75 mg) or dipyridamole (usual dose 400 mg) in combination with aspirin (dose 75 mg to 81 mg), and loading doses were often used. CHANCE used a loading dose of 300 mg of clopidogrel, whilst POINT used 600 mg.

It appears that, at least in the short term after an atherothrombotic stroke, a dual antiplatelet agent approach with loading doses may prevent 23 strokes per 1000 people, as well as 25 strokes, myocardial infarctions, and vascular deaths per 1000 people against one intracranial haemorrhage per 1000 people administered therapy for one month.

Quality of the evidence

The evidence for this review came from well-designed trials; however, study designs were not well reported for studies that were conducted prior to 1990. Subset analyses often limit the outcomes of interest. The certainty of evidence was based on the GRADE approach, and the evidence for the primary outcomes was downgraded for risk of bias in the included trials. Another domain rated was the magnitude of effect, where a large effect was noted in the secondary outcomes of intracranial and extracranial haemorrhage.

We performed sensitivity analyses as Chairangsarit 2005 reported more than 20% missing data at 28.9%. We analysed data without this study and found the robustness of the pooled RRs adequate for the primary outcomes of stroke (RR 0.73 95% CI 0.66 to 0.82; P < 0.001) and vascular death (RR 0.98, 95% CI 0.67 to 1.45; P = 0.94).

Potential biases in the review process

We do not report any conflicts of interest. The protocol was designed and registered to study this topic prior to collection of data and analysis, and at a time when some of the included trials were still ongoing and unpublished. We excluded non-randomised studies due to their high susceptibility of error and bias. We reviewed data independently and then cross-checked them centrally to avoid biases in observations and conclusions. Variation in frequency and dose of drugs in the included trials were within limits of those used in clinical practice and would not have made a difference to the review outcome.

Agreements and disagreements with other studies or reviews

The conclusions presented in our study are in agreement with a previous systematic review by Geeganage 2012, which concurred that dual antiplatelets are effective and may be safe in preventing recurrence of stroke when compared to monotherapy.

AUTHORS' CONCLUSIONS

Implications for practice

The results of our review indicate that, in the high-risk phase after stroke, multiple antiplatelet agents are more effective than single agents at preventing stroke recurrence. The evidence is strongest for secondary stroke prevention in people with ischaemic stroke. Most of the evidence comes from trials comparing two antiplatelet agents versus a single agent and, in those trials, the risk of adverse events was less than the benefit in terms of preventing stroke. There was a lack of evidence regarding multiple versus multiple antiplatelet agents. Further refinement of the benefit and risk of two antiplatelet agents and the optimal duration of treatment will depend on future research.

Implications for research

Our analysis highlights the lack of data regarding the use of dual antiplatelets. As mentioned previously, one study from Asia contributed a large portion of the participants, and so future studies need to be undertaken in other populations to establish the effectiveness of dual antiplatelets. Studies should focus on the efficacy and safety profile of using dual antiplatelets, in shorter follow-up periods. Additional trials that address variation in underlying aetiologies as well as disease severity may provide more insight.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Chairangsarit 2005

Study characteristics	
Methods	Randomised, open-label, blind assessment
Participants	Participants with acute ischaemic stroke enrolled within 48 hours after clinical onset. Age should be more than 45 years. CT or MRI of the brain confirmed cerebral infarction and excluded haemorrhagic stroke or brain tumour. 38 participants were enrolled in the study (20 men, 18 women). Participants were followed up through clinic visits at 1 month, 3 months, and 6 months.
Interventions	Aspirin 300 mg once daily vs aspirin 300 mg once daily plus dipyridamole 75 mg 3 times a day
Outcomes	Primary outcome: recurrent ischaemic stroke and TIA

Chairangsarit 2005 *(Continued)*

	Secondary outcome: vascular death due to MI or any type of stroke
Notes	During the 9-month screening period, 39 of 60 eligible participants were recruited and followed up for 6 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blinded randomisation
Allocation concealment (selection bias)	Low risk	Methods described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participant is aware of treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	11 of 38 (28.9%) participants lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

CHANCE

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial
Participants	5170 participants (3350 men, 1750 women) of Chinese ethnicity took part in the study. Participants had a history of stroke or TIA. Age of participants was greater than 40 years. Participants with acute non-disabling ischaemic stroke (NIHSS ≤ 3 at the time of randomisation) that can be treated with study drug within 24 hours of symptoms onset; or TIA (neurological deficit attributed to focal brain ischaemia, with resolution of the deficit within 24 hours of symptom onset), that can be treated with study drug within 24 hours of symptoms onset and with moderate-to-high risk of stroke recurrence (ABCD2 score ≥ 4 at the time of randomisation)
Interventions	Clopidogrel 75 mg once daily (loading dose 300 mg first day) and aspirin 75 mg vs placebo and aspirin 75 mg. On the first day all participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg per day. 165 participants in the combination group and 146 participants in the aspirin-only group had stopped taking their medicine at the time of follow-up.
Outcomes	Primary outcome: any stroke (ischaemic or haemorrhage) at 90 days follow-up Secondary outcome: participants with the 3-month new clinical vascular events (ischaemic stroke/haemorrhagic stroke/TIA/MI/vascular death) as a cluster and evaluated individually. Modified Rankin Scale score changes (continuous) and dichotomised at percentage with score 0 to 2 vs 3 to 6 at 3-month

CHANCE *(Continued)*

	follow-up. Further efficacy exploratory analysis: impairment (changes in NIHSS scores at 3-month follow-up) and quality of life (EuroQol EQ-5D scale)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised, automated system random assignment
Allocation concealment (selection bias)	Low risk	Site randomisation different from primary team
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy, double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 of 2584 participants (0.8%) in the combination group (clopidogrel + aspirin) and 16 of 2586 participants (0.6%) in the aspirin-alone group were lost to follow-up.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported

CHARISMA

Study characteristics	
Methods	Randomised, multicentre, parallel-group, double-blind, placebo-controlled trial
Participants	Individuals with symptomatic cerebrovascular disease within the previous 5 years
Interventions	Aspirin 75 to 162 mg once daily plus clopidogrel 75 mg once daily vs aspirin 75 to 162 mg daily + placebo
Outcomes	Primary outcome: stroke Secondary outcome: MI, vascular death, or the composite of stroke, MI, vascular death
Notes	Subanalysis of a larger CHARISMA trial of participants with recent event

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Methods described

CHARISMA *(Continued)*

Allocation concealment (selection bias)	Low risk	Methods described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

COMPRESS

Study characteristics	
Methods	RCT
Participants	Participants with cerebral ischaemic stroke identified on DWI within 48 hours from symptom onset, relevant cerebral atherosclerosis on MRA, study drug administration within 48 hours from symptom onset, and mRS is 0 to 2 before the stroke
Interventions	Clopidogrel plus aspirin (75 mg/d without loading dose plus 300 mg loading dose followed by 100 mg/d) vs aspirin alone (300 mg loading dose followed by 100 mg/d) for 30 days + placebo
Outcomes	Primary outcome: number of participants with new lesions after the onset of acute atherothrombotic stroke (7 or 30 day, or both, on DWI) Secondary outcomes: distribution of mRS scores (time frame: 30 days after the onset of stroke throughout the study period), non-fatal stroke, MI and vascular death (composite, first-ever), all types of stroke, number of participants with bleeding episode (major and minor) during the follow-up period, number of participants with symptomatic ICH at 1 month
Notes	Conducted in 10 Korean centres; 2 participants crossed over from intervention to control arm
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	1:1 ratio stratified random assignment performed centrally by a computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Independent adjudication committee
Blinding of participants and personnel (performance bias)	Low risk	Placebo (matched to clopidogrel for taste, colour, and size)

COMPRESS *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

De Martiis

Study characteristics		
Methods	Prospective, controlled study	
Participants	Individuals under age 65 who had experienced at least 1 transient atherothrombotic cerebral event according to Joint Committee for Stroke facilities	
Interventions	Dipyridamole 400 mg per day vs aspirin 100 mg + dipyridamole 300 mg per day	
Outcomes	Ischaemic events (stroke, TIA), deaths (stroke, cardiovascular, all-cause mortality)	
Notes	Subanalysis of participants recruited early in a secondary prevention trial	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information regarding randomisation
Allocation concealment (selection bias)	Unclear risk	No method described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of placebo pills provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No method described
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 of 197 (5.6%) participants enrolled lost to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes reported

EARLY-trial

Study characteristics		
Methods	Prospective, randomised, open-label, blinded, endpoint trial in 46 stroke units in Germany	
Participants	Individuals aged > 18 years presenting with symptoms of an acute ischaemic stroke causing measurable neurological defect (NIHSS 5 to 20). Randomised and treated within 24 hours	
Interventions	Aspirin 25 mg and extended-release dipyridamole 200 mg twice daily vs 100 mg aspirin once daily	
Outcomes	mRS score and vascular adverse events (non-fatal stroke, TIA, non-fatal MI, and bleeding complications)	
Notes	Subset	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised using a pseudorandom number generator
Allocation concealment (selection bias)	Low risk	Through telephone interview
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	20% discontinued treatment due to various causes
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

ESPIRIT

Study characteristics	
Methods	RCT
Participants	Participants referred to the hospital within 6 months of reporting a TIA or minor ischaemic stroke (grade < 3 on mRS)
Interventions	Aspirin 325 mg vs aspirin 325 mg + dipyridamole 200 mg twice daily
Outcomes	Fatal and non-fatal ischaemic strokes and cardiac events (fatal and non-fatal MI, sudden death, and death from cardiovascular causes)

ESPIRIT *(Continued)*

Notes	Subanalysis of a larger study on anticoagulation, focus on antiplatelet intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used centralised randomisation via phone, fax, email
Allocation concealment (selection bias)	Low risk	Computer-generated allocation concealment by clinical epidemiologist not involved in clinical trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study design for pragmatic outcome assessment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded study design for pragmatic outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	106 (3.8%) lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes accounted for

ESPS 2

Study characteristics

Methods	Randomised, placebo-controlled, double-blinded study
Participants	Individuals older than 18 years with TIA or stroke within the preceding 3 months
Interventions	Aspirin 50 mg daily alone vs aspirin 50 mg once daily plus modified release dipyridamole 400 mg daily vs modified-release dipyridamole 400 mg alone vs placebo
Outcomes	Stroke, death, and stroke or death
Notes	Subset analysis of those treated early

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation done through minimisation technique
Allocation concealment (selection bias)	Low risk	Sequence generated centrally

ESPS 2 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Medicine cessation in 479 of 1650 participants (29%) in intervention group and 851 of 3303 participants (25.7%) in control group. Although the dropout rates are significant, the sample size is large enough to justify attrition.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

FASTER PILOT

Study characteristics	
Methods	Double-blinded RCT
Participants	185 women and 187 men recruited in the trial. Participants had a history of stroke or TIA. Age of participants had to be greater than 40 years and should not have been eligible for thrombolysis or acute intervention. Symptoms present for at least 5 minutes and included weakness or language disturbance. Enrolment must be done within 24 hours of symptom onset. Exclusion criteria included pure sensory symptoms, presumed cardiac source of emboli, and stroke/TIA mimics. 194 participants assigned to groups without clopidogrel (control) and 198 participants assigned to clopidogrel group. Participants were followed up in clinic at 10 days and 90 days. 1 participant was lost to follow-up in each group.
Interventions	Aspirin 81 mg (day 1: aspirin 162 mg) once daily plus clopidogrel 75 mg (300 mg loading dose) once daily vs aspirin only 81 mg (day 1: aspirin 162 mg) To ensure follow-ups, telephone calls were made at 2, 30, 60, and 90 days.
Outcomes	Primary outcome: any stroke at 90 days Secondary outcome: composite of any stroke, MI, and vascular death
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Pharmacist provided predetermined kits.

FASTER PILOT *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 (1.8%) participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Expected outcomes reported

MATCH 2001

Study characteristics		
Methods	Randomised, double-blind, placebo controlled	
Participants	Individuals > 40 years with TIA or ischaemic stroke in last 3 months and at least 1 risk factor	
Interventions	Aspirin 75 mg per day + clopidogrel 75 mg per day vs clopidogrel 75 mg per day	
Outcomes	First occurrence of an event	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Methods described
Allocation concealment (selection bias)	Low risk	Used interactive voice response system (telephone)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 of 7599 participants (0.1%) lost to follow-up
Selective reporting (reporting bias)	Low risk	Expected outcomes reported

Nakamura 2010

Study characteristics	
Methods	Randomised. Unclear allocation and blinding
Participants	76 participants (56 men and 20 women) of Japanese ethnicity with a history of non-cardioembolic stroke Mean age of participants was between 66 and 67 years. There were 38 participants in each group, with 4 participants lost to follow-up in each group. Participants in the combination treatment group (aspirin + cilostazol) complained of drug eruption (1 participant) and palpitations (3 participants). Participants in the aspirin-only group reported drug eruption (2 participants), gastrointestinal bleeding (1 participant), and acute coronary event (1 participant). Participants were followed at 14 days and then at 6 months.
Interventions	Cilostazol 100 mg twice daily plus aspirin 300 mg once daily for 4 days and a lower dose of aspirin from day 5 until 6 months The other group received only aspirin 300 mg once daily for 4 days and a lower dose of aspirin from day 5 until 6 months.
Outcomes	Primary outcome: neurological deterioration or stroke recurrence within 14 days Secondary outcome: neurological deterioration or stroke recurrence within 6 months
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random allocation
Allocation concealment (selection bias)	Low risk	Random allocation concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 of 76 participants (10.5%) lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Petrovska-Cvetkovska 2008

Study characteristics	
Methods	Randomised, open-label. Unclear outcome assessment blinding and allocation concealment
Participants	Participants had a history of TIA, were randomised within the first 24 hours. 40 participants received aspirin 75 mg + clopidogrel 75 mg and 44 received aspirin (100 mg to 325 mg) alone.
Interventions	1 group received oral aspirin 75 mg and oral clopidogrel 75 mg once daily while the other group received oral aspirin 100 mg to 325 mg alone. Participants were followed up for 1 year.
Outcomes	Primary outcome: recurrent TIA or stroke Secondary: intracranial or systemic adverse effects
Notes	2 other groups received statins

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly described
Selective reporting (reporting bias)	Unclear risk	Not clearly described

POINT

Study characteristics	
Methods	RCT
Participants	Individuals with high-risk TIA (defined as an ABCD2 score > 4) or minor ischaemic stroke (with NIHSS < 3) and study drug administered within 12 hours of time last known free of new ischaemic symptoms
Interventions	Clopidogrel plus aspirin versus aspirin alone
Outcomes	Primary outcome: new ischaemic vascular events (ischaemic stroke, MI, and ischaemic vascular death)

POINT *(Continued)*

	Secondary outcomes: risk of ischaemic stroke, intracranial haemorrhage, and major haemorrhage, and composite of the primary outcome and major haemorrhage
Notes	Subgroup analysis at 30 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random selection by computer software
Allocation concealment (selection bias)	Low risk	Allocation concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment by independent study group
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for as lost to follow-up or ceased treatment
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported

PRoFESS

Study characteristics

Methods	Randomised. Allocation concealment
Participants	1360 participants (884 men and 476 women) with a history of stroke. Age of participants was greater than 55 years. Participants had to be hospitalised with stable stroke. 5 of 672 participants in the combination group (aspirin + extended-release dipyridamole) and 7 of 688 participants in the clopidogrel-only group were lost to follow-up. 36 participants complained of headache in the combination group, whilst 3 participants in the clopidogrel-only group reported adverse effects.
Interventions	Aspirin 25 mg twice daily plus extended-release dipyridamole 200 mg twice daily vs clopidogrel 75 mg alone once daily followed for 90 days
Outcomes	Primary outcome: mRS at 30 days Secondary outcome: recurrent stroke, haemorrhagic transformation
Notes	Subset of participants enrolled early

Risk of bias

Bias	Authors' judgement	Support for judgement

PRoFESS *(Continued)*

Random sequence generation (selection bias)	Low risk	Methods described.
Allocation concealment (selection bias)	Low risk	Methods described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 of 1360 participants (0.8%) lost to follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported

TARDIS

Study characteristics	
Methods	RCT
Participants	Individuals with acute non-cardioembolic ischaemic stroke (less than 48 hours of onset) or acute TIA (less than 48 hours of onset) with 1 or more of: crescendo TIA (greater than 1 TIA within 1 week), and/or admitted on dual antiplatelet therapy (aspirin/dipyridamole, aspirin/clopidogrel, clopidogrel/dipyridamole), and/or with an ABCD2 score > 5
Interventions	Aspirin, clopidogrel, and dipyridamole vs aspirin and dipyridamole or clopidogrel
Outcomes	Primary outcome: ordinal stroke severity at 90 days Secondary outcomes: binary and ordinal outcomes of stroke, TIA, MI, acute coronary syndrome, composite vascular outcome, death. Also safety (ordinal bleeding events), tolerability, and feasibility. Additional measures included transcranial Doppler for embolic events, laboratory measures (FBC and P-Selectin), clinical efficacy (NIHSS), function (mRS, BI), cognition (TICS), quality of life (EuroQoL, EQ-5D), mood (Zung), disposition, days at home, and economic activity
Notes	Estimated study completion date: March 2017 (5 years duration from start-up phase) 3096 participants recruited from the UK and internationally, to assess the efficacy, safety, and health economics of triple therapy, with endpoints measured at 7, 35, and 90 days.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based 1:1 ratio simple randomisation, with stratification and minimisation

TARDIS *(Continued)*

Allocation concealment (selection bias)	Low risk	Methods described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome blinded assessment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes validated and categorised by expert adjudicators masked to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for as lost to follow-up or refused.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported

BI: Barthel Index
CT: computed tomography
DWI: diffusion weighted imaging
FBC: full blood count
ICH: intracerebral haemorrhage
MI: myocardial infarction
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
RCT: randomised controlled trial
TIA: transient ischaemic attack
TICS: Telephone Interview for Cognitive Status

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

Study	Reason for exclusion
AICLA	Participants were not randomised in the first 72 hours.
AMBDAP	Primary endpoint was embolic signals.
APACHE-AF 2014	Anticoagulants are compared in the study; our review is restricted to antiplatelet agents alone.
APLAUD 2000	Participants were not randomised in the first 72 hours.
Apollonio 1989	Measure of outcome was change in stenosis.
ATARI	Unclear time to randomisation
AVERROES	Compared single antiplatelet vs anticoagulant: aspirin vs apixaban
Bath 2002	Multiple antiplatelet agents were administered for long-term secondary prevention, not for prevention of early recurrence of ischaemic stroke or TIA.
CADISS	Anticoagulants are compared in the study; our review is restricted to antiplatelet agents alone.

Study	Reason for exclusion
Caneschi 1985	Participants were not randomised in the first 72 hours.
CARESS	Treatment given for only 7 days.
CATHARSIS	Participants were not randomised in the first 72 hours.
CCS 1978	Participants were not randomised in the first 72 hours.
CLAIR	Follow-up period short. Did not measure clinical outcome
CLOSURE	Anticoagulants compared in the study; our review is restricted to antiplatelet agents alone.
CSPS.com	Aspirin and cilostazol vs aspirin; however, participants were not randomised in the first 72 hours
Fan 2004	Unclear treatment duration
Fujimoto 2010	Treatment for less than 1 month
Fujimoto 2011	Treatment for less than 1 month
Hashemilar 2011	Microembolic signals used to measure outcome.
Herskovits 1981	Participants were not randomised within the first 72 hours.
Herskovits 1985a	Participants were not randomised within the first 72 hours.
Herskovits 1985b	Participants were not randomised within the first 72 hours.
Herskovits 1989	Participants were not randomised within the first 72 hours.
JASAP	Participants were not randomised in the first 72 hours.
Khazaei 2018	Unclear time of enrolment from stroke onset, and primary outcome was secondary TIA
PATICI 1985	Participants were not enrolled within 72 hours.
PERFORM	Compared single antiplatelet agents
PLATO 2009	Compared single antiplatelet agents
PRCASA	Primary outcome measure was restenosis measured through cerebral angiography.
RE-SPECT-ESUS 2014	Anticoagulants compared in the study; our review is restricted to antiplatelet agents alone.
Rizky 2015	Unclear time of enrolment from stroke onset
Sancho Rieger 1984	Compared single antiplatelet agents, ticlopidine vs dipyridamole
Satoh 1994	Compared same antiplatelet doses (pyrazolopyridine)
SOCRATES 2014	Compared single antiplatelet agents
SPS3	Unclear time to randomisation
Stakhovskaya 2001	Participants were not randomised within 72 hours.

Study	Reason for exclusion
TACS 2000	Participants were not randomised in the first 72 hours.
Terayama 2008	Stroke recurrence not reported, and only progression of event followed.
TOPALS	Participants were not randomised in the first 72 hours.
TOSS	Participants were not randomised in the first 72 hours.
Uchiyama 1989	Unclear time to randomisation
Uchiyama 1991	Unclear time to randomisation
Uchiyama 1992	Unclear time to randomisation
UMPIRE	Compared different risk factor control medications. Combination pill vs single
Vaya 1988	Studied effect on platelet reactivity
WASID 1998	Anticoagulants were compared in the study; our review is restricted to antiplatelet agents alone.
WOEST 2013	Anticoagulants were used at baseline.
Zuo 2017	Participants were randomised in the first 7 days instead of first 72 hours.

TIA: transient ischaemic attack

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

THALES 2018

Study name	THALES
Methods	RCT
Participants	Participants are ≥ 40 years of age with non-cardioembolic ischaemic stroke of NIHSS of ≤ 5 or high-risk TIA (defined as ABCD^2 score of ≥ 6 or with ipsilateral large vessel stenosis of ≥ 50%). Participants are randomised within 24 hours of the time last known free of new ischaemic symptoms, and study drug is administered immediately afterwards.
Interventions	Ticagrelor and aspirin compared with aspirin
Outcomes	The primary efficacy outcome is time from randomisation to first subsequent stroke or death through 30 days of treatment. The primary safety outcome is time to first severe bleeding event based on the GUSTO definition.
Starting date	22 January 2018
Contact information	
Notes	Met primary endpoint as presented at International Stroke Conference, final results pending.

GUSTO: Global Use of Strategies To Open up coronary arteries
NIHSS: National Institutes of Health Stroke Scale
RCT: randomised controlled trial

TIA: transient ischaemic attack

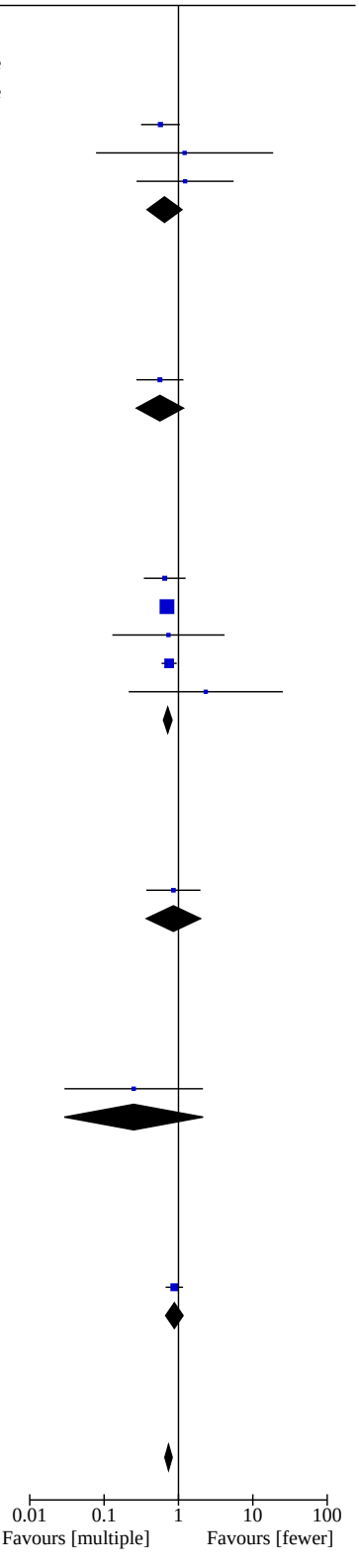
DATA AND ANALYSES

Comparison 1. Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Stroke	14	16707	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.66, 0.82]
1.1.1 Aspirin + dipyridamole vs aspirin	5	977	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.11]
1.1.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.17]
1.1.3 Aspirin + clopidogrel vs aspirin	5	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.63, 0.82]
1.1.4 Aspirin + clopidogrel vs clopidogrel	1	485	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.37, 1.97]
1.1.5 Aspirin + cilostazol vs aspirin	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.13]
1.1.6 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole	1	3070	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.15]
1.2 Vascular death	11	15901	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.67, 1.45]
1.2.1 Aspirin + dipyridamole vs aspirin	4	868	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.11]
1.2.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2.3 Aspirin + clopidogrel vs aspirin	4	10527	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.63, 2.98]
1.2.4 Aspirin + cilostazol vs aspirin	1	76	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2.5 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole	1	3070	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.74, 4.61]

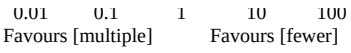
Analysis 1.1. Comparison 1: Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 1: Stroke

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Aspirin + dipyridamole vs aspirin						
De Martiis	0	69	0	40		Not estimable
Chairangsarit 2005	0	20	0	18		Not estimable
EARLY-trial	16	283	26	263	4.1%	0.57 [0.31 , 1.04]
ESPIRIT	1	43	1	52	0.1%	1.21 [0.08 , 18.77]
ESPS 2	2	32	8	157	0.4%	1.23 [0.27 , 5.51]
Subtotal (95% CI)		**447**		**530**	**4.7%**	**0.65 [0.38 , 1.11]**
Total events:	19		35			
Heterogeneity: Chi² = 1.06, df = 2 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.57 (P = 0.12)						
1.1.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	11	672	20	688	3.0%	0.56 [0.27 , 1.17]
Subtotal (95% CI)		**672**		**688**	**3.0%**	**0.56 [0.27 , 1.17]**
Total events:	11		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
1.1.3 Aspirin + clopidogrel vs aspirin						
FASTER PILOT	14	198	21	194	3.2%	0.65 [0.34 , 1.25]
CHANCE	212	2584	303	2586	46.3%	0.70 [0.59 , 0.83]
Petrovska-Cvetkovska 2008	2	40	3	44	0.4%	0.73 [0.13 , 4.17]
POINT	116	2432	156	2449	23.8%	0.75 [0.59 , 0.95]
CHARISMA	2	98	1	114	0.1%	2.33 [0.21 , 25.27]
Subtotal (95% CI)		**5352**		**5387**	**73.9%**	**0.72 [0.63 , 0.82]**
Total events:	346		484			
Heterogeneity: Chi² = 1.23, df = 4 (P = 0.87); I² = 0%						
Test for overall effect: Z = 4.93 (P < 0.00001)						
1.1.4 Aspirin + clopidogrel vs clopidogrel						
MATCH 2001	10	250	11	235	1.7%	0.85 [0.37 , 1.97]
Subtotal (95% CI)		**250**		**235**	**1.7%**	**0.85 [0.37 , 1.97]**
Total events:	10		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
1.1.5 Aspirin + cilostazol vs aspirin						
Nakamura 2010	1	38	4	38	0.6%	0.25 [0.03 , 2.13]
Subtotal (95% CI)		**38**		**38**	**0.6%**	**0.25 [0.03 , 2.13]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.21)						
1.1.6 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole						
TARDIS	93	1540	105	1530	16.1%	0.88 [0.67 , 1.15]
Subtotal (95% CI)		**1540**		**1530**	**16.1%**	**0.88 [0.67 , 1.15]**
Total events:	93		105			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
Total (95% CI)		**8299**		**8408**	**100.0%**	**0.73 [0.66 , 0.82]**
Total events:	480		659			
Heterogeneity: Chi² = 5.94, df = 11 (P = 0.88); I² = 0%						
Test for overall effect: Z = 5.33 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.66, df = 5 (P = 0.60), I² = 0%						



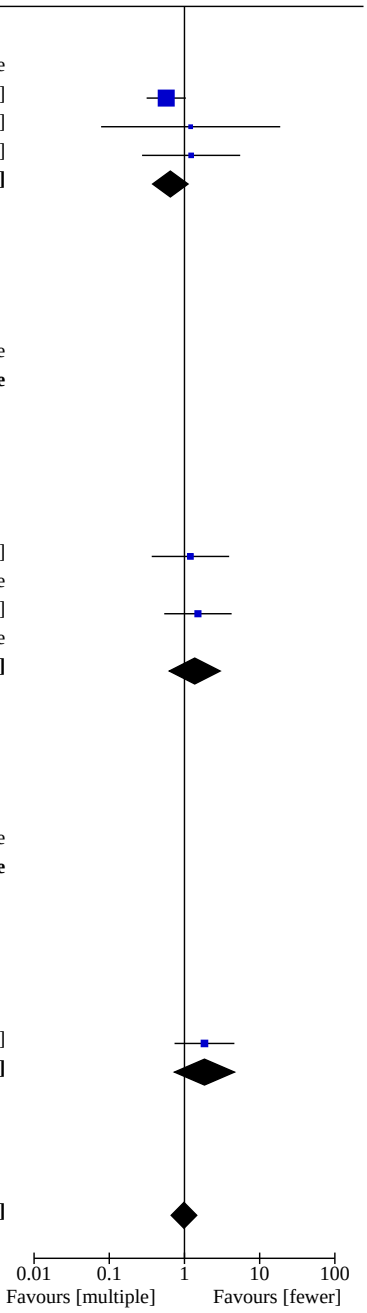
Analysis 1.1. (Continued)

Heterogeneity: Chi² = 5.54, df = 11 (P = 0.88); I² = 0%
Test for overall effect: Z = 5.33 (P < 0.00001)
Test for subgroup differences: Chi² = 3.66, df = 5 (P = 0.60), I² = 0%



Analysis 1.2. Comparison 1: Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 2: Vascular death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Aspirin + dipyridamole vs aspirin						
Chairangsarit 2005	0	20	0	18		Not estimable
EARLY-trial	16	283	26	263	55.5%	0.57 [0.31 , 1.04]
ESPIRIT	1	43	1	52	1.9%	1.21 [0.08 , 18.77]
ESPS 2	2	32	8	157	5.6%	1.23 [0.27 , 5.51]
Subtotal (95% CI)		**378**		**490**	**62.9%**	**0.65 [0.38 , 1.11]**
Total events:	19		35			
Heterogeneity: Chi² = 1.06, df = 2 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.57 (P = 0.12)						
1.2.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	0	672	0	688		Not estimable
Subtotal (95% CI)		**672**		**688**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.3 Aspirin + clopidogrel vs aspirin						
CHANCE	6	2584	5	2586	10.3%	1.20 [0.37 , 3.93]
FASTER PILOT	0	198	0	194		Not estimable
POINT	9	2432	6	2449	12.3%	1.51 [0.54 , 4.24]
Petrovska-Cvetkovska 2008	0	40	0	44		Not estimable
Subtotal (95% CI)		**5254**		**5273**	**22.6%**	**1.37 [0.63 , 2.98]**
Total events:	15		11			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
1.2.4 Aspirin + cilostazol vs aspirin						
Nakamura 2010	0	38	0	38		Not estimable
Subtotal (95% CI)		**38**		**38**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.5 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole						
TARDIS	13	1540	7	1530	14.5%	1.85 [0.74 , 4.61]
Subtotal (95% CI)		**1540**		**1530**	**14.5%**	**1.85 [0.74 , 4.61]**
Total events:	13		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)		**7882**		**8019**	**100.0%**	**0.98 [0.67 , 1.45]**
Total events:	47		53			
Heterogeneity: Chi² = 5.83, df = 5 (P = 0.32); I² = 14%						
Test for overall effect: Z = 0.08 (P = 0.94)						
Test for subgroup differences: Chi² = 4.77, df = 2 (P = 0.09), I² = 58.1%						



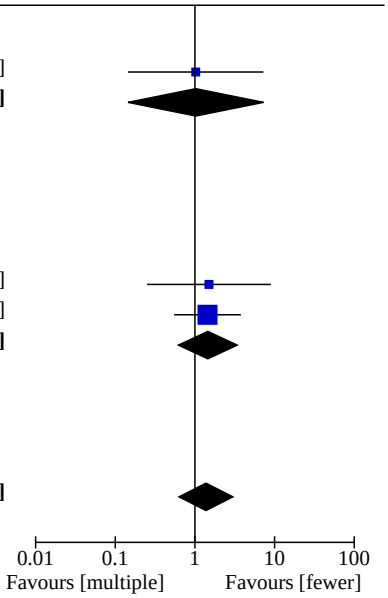
Comparison 2. Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Myocardial infarction	3	11411	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.63, 2.99]
2.1.1 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.14, 7.25]
2.1.2 Aspirin + clopidogrel vs aspirin	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.62, 3.39]
2.2 Stroke, myocardial infarction, or vascular death	7	12932	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.64, 0.82]
2.2.1 Aspirin + dipyridamole vs aspirin	2	638	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.42, 1.07]
2.2.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.38, 1.34]
2.2.3 Aspirin + clopidogrel vs aspirin	3	10443	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.64, 0.82]
2.2.4 Aspirin + clopidogrel vs clopidogrel	1	491	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.41, 1.59]
2.3 Intracranial haemorrhage	6	14287	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.05, 3.50]
2.3.1 Aspirin + dipyridamole vs aspirin	1	38	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.12, 62.70]
2.3.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3.3 Aspirin + clopidogrel vs aspirin	3	9819	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.57, 2.86]
2.3.4 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole	1	3070	Risk Ratio (M-H, Fixed, 95% CI)	3.18 [1.17, 8.66]
2.4 Extracranial haemorrhage	7	10658	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [1.88, 2.70]
2.4.1 Aspirin + dipyridamole vs aspirin	2	638	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.06, 14.61]
2.4.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.40, 3.54]
2.4.3 Aspirin + clopidogrel vs aspirin	2	5097	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [2.19, 10.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4.4 Aspirin + clopidogrel vs clopidogrel	1	491	Risk Ratio (M-H, Fixed, 95% CI)	3.67 [0.41, 32.62]
2.4.5 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole	1	3072	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [1.78, 2.61]
2.5 Ischaemic stroke	3	13121	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.64, 0.83]
2.5.1 Aspirin + clopidogrel vs aspirin	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.81]
2.5.2 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole	1	3070	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.36]
2.6 Haemorrhagic stroke	3	13121	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.91, 3.13]
2.6.1 Aspirin + clopidogrel vs aspirin	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.53, 2.64]
2.6.2 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole	1	3070	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [1.00, 7.70]
2.7 Death from any cause	4	14502	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.73, 1.51]
2.7.1 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.26, 2.78]
2.7.2 Aspirin + clopidogrel vs aspirin	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.73, 2.23]
2.7.3 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole	1	3091	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.54, 1.55]

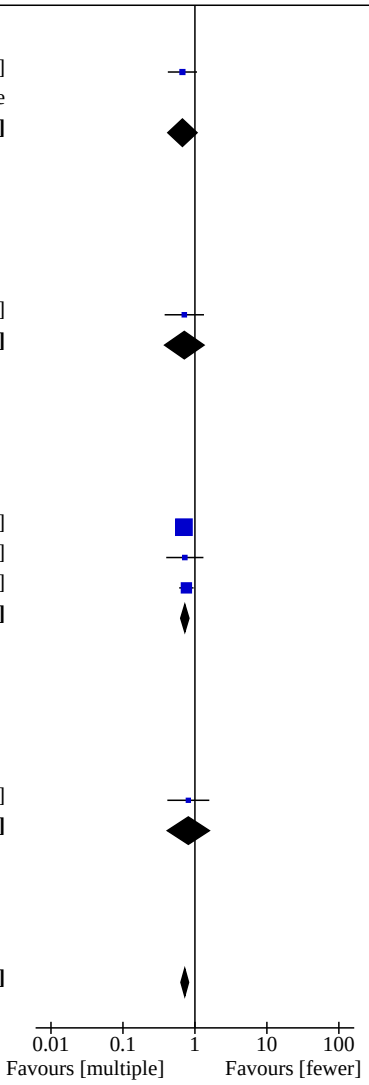
Analysis 2.1. Comparison 2: Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 1: Myocardial infarction

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	2	672	2	688	18.0%	1.02 [0.14 , 7.25]
Subtotal (95% CI)		**672**		**688**	**18.0%**	**1.02 [0.14 , 7.25]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
2.1.2 Aspirin + clopidogrel vs aspirin						
CHANCE	3	2584	2	2586	18.3%	1.50 [0.25 , 8.98]
POINT	10	2432	7	2449	63.7%	1.44 [0.55 , 3.77]
Subtotal (95% CI)		**5016**		**5035**	**82.0%**	**1.45 [0.62 , 3.39]**
Total events:	13		9			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Total (95% CI)		**5688**		**5723**	**100.0%**	**1.38 [0.63 , 2.99]**
Total events:	15		11			
Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						



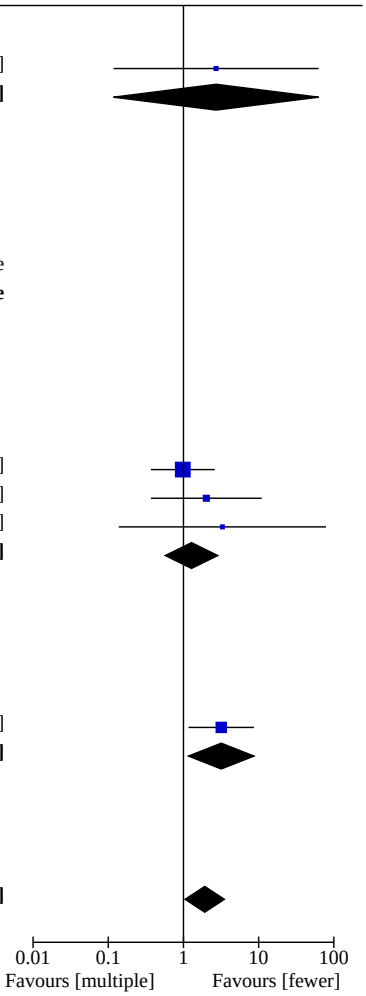
Analysis 2.2. Comparison 2: Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 2: Stroke, myocardial infarction, or vascular death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Aspirin + dipyridamole vs aspirin						
EARLY-trial	27	283	37	260	6.8%	0.67 [0.42 , 1.07]
ESPIRIT	0	43	0	52		Not estimable
Subtotal (95% CI)		**326**		**312**	**6.8%**	**0.67 [0.42 , 1.07]**
Total events:	27		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
2.2.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	16	672	23	688	4.0%	0.71 [0.38 , 1.34]
Subtotal (95% CI)		**672**		**688**	**4.0%**	**0.71 [0.38 , 1.34]**
Total events:	16		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
2.2.3 Aspirin + clopidogrel vs aspirin						
CHANCE	216	2584	307	2586	54.0%	0.70 [0.60 , 0.83]
FASTER PILOT	17	198	23	194	4.1%	0.72 [0.40 , 1.31]
POINT	121	2432	160	2449	28.0%	0.76 [0.61 , 0.96]
Subtotal (95% CI)		**5214**		**5229**	**86.1%**	**0.72 [0.64 , 0.82]**
Total events:	354		490			
Heterogeneity: $Chi^2 = 0.30$, df = 2 (P = 0.86); $I^2 = 0\%$						
Test for overall effect: Z = 4.84 (P < 0.00001)						
2.2.4 Aspirin + clopidogrel vs clopidogrel						
MATCH 2001	15	256	17	235	3.1%	0.81 [0.41 , 1.59]
Subtotal (95% CI)		**256**		**235**	**3.1%**	**0.81 [0.41 , 1.59]**
Total events:	15		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
Total (95% CI)		**6468**		**6464**	**100.0%**	**0.72 [0.64 , 0.82]**
Total events:	412		567			
Heterogeneity: $Chi^2 = 0.51$, df = 5 (P = 0.99); $I^2 = 0\%$						
Test for overall effect: Z = 5.25 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.21$, df = 3 (P = 0.98), $I^2 = 0\%$						



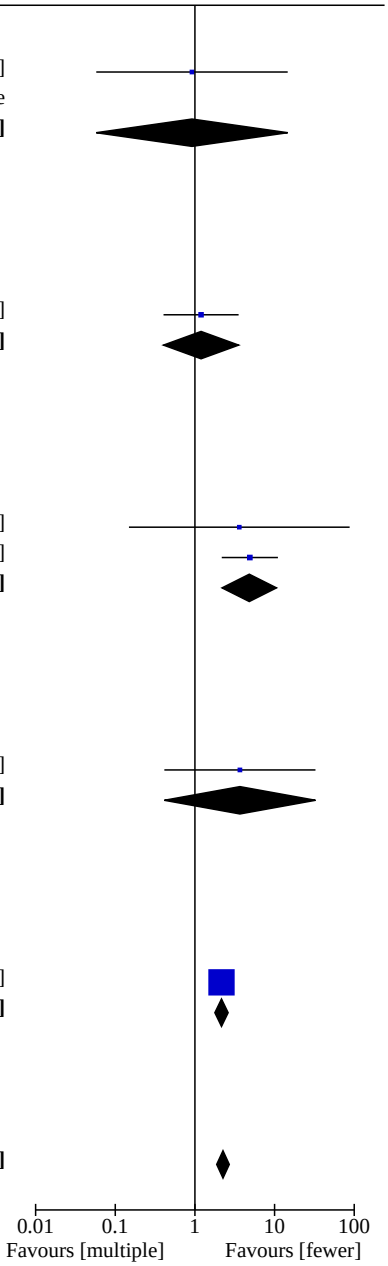
Analysis 2.3. Comparison 2: Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 3: Intracranial haemorrhage

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Aspirin + dipyridamole vs aspirin						
Chairangsarit 2005	1	20	0	18	3.3%	2.71 [0.12 , 62.70]
Subtotal (95% CI)		**20**		**18**	**3.3%**	**2.71 [0.12 , 62.70]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
2.3.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	0	672	0	688		Not estimable
Subtotal (95% CI)		**672**		**688**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.3 Aspirin + clopidogrel vs aspirin						
CHANCE	8	2452	8	2402	50.2%	0.98 [0.37 , 2.61]
POINT	4	2432	2	2449	12.4%	2.01 [0.37 , 10.99]
Petrovska-Cvetkovska 2008	1	40	0	44	3.0%	3.29 [0.14 , 78.59]
Subtotal (95% CI)		**4924**		**4895**	**65.6%**	**1.28 [0.57 , 2.86]**
Total events:	13		10			
Heterogeneity: Chi² = 0.90, df = 2 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
2.3.4 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole						
TARDIS	16	1540	5	1530	31.2%	3.18 [1.17 , 8.66]
Subtotal (95% CI)		**1540**		**1530**	**31.2%**	**3.18 [1.17 , 8.66]**
Total events:	16		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.26 (P = 0.02)						
Total (95% CI)		**7156**		**7131**	**100.0%**	**1.92 [1.05 , 3.50]**
Total events:	30		15			
Heterogeneity: Chi² = 2.95, df = 4 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.12 (P = 0.03)						
Test for subgroup differences: Chi² = 1.99, df = 2 (P = 0.37), I² = 0%						



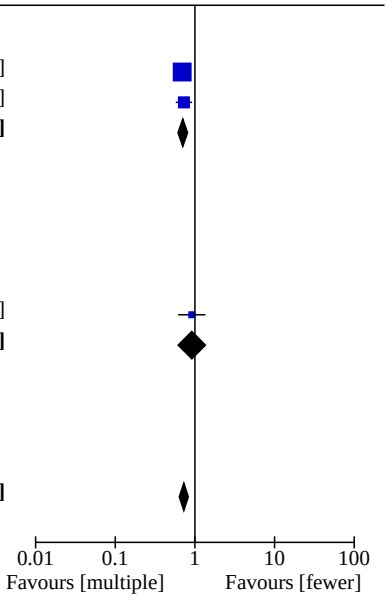
Analysis 2.4. Comparison 2: Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 4: Extracranial haemorrhage

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Aspirin + dipyridamole vs aspirin						
EARLY-trial	1	283	1	260	0.7%	0.92 [0.06 , 14.61]
ESPIRIT	0	43	0	52		Not estimable
Subtotal (95% CI)		**326**		**312**	**0.7%**	**0.92 [0.06 , 14.61]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
2.4.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	7	672	6	688	3.9%	1.19 [0.40 , 3.54]
Subtotal (95% CI)		**672**		**688**	**3.9%**	**1.19 [0.40 , 3.54]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
2.4.3 Aspirin + clopidogrel vs aspirin						
CHARISMA	1	98	0	118	0.3%	3.61 [0.15 , 87.54]
POINT	34	2432	7	2449	4.6%	4.89 [2.17 , 11.01]
Subtotal (95% CI)		**2530**		**2567**	**4.9%**	**4.81 [2.19 , 10.57]**
Total events:	35		7			
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.86); I^2 = 0%						
Test for overall effect: Z = 3.92 (P < 0.0001)						
2.4.4 Aspirin + clopidogrel vs clopidogrel						
MATCH 2001	4	256	1	235	0.7%	3.67 [0.41 , 32.62]
Subtotal (95% CI)		**256**		**235**	**0.7%**	**3.67 [0.41 , 32.62]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
2.4.5 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole						
TARDIS	293	1541	135	1531	89.8%	2.16 [1.78 , 2.61]
Subtotal (95% CI)		**1541**		**1531**	**89.8%**	**2.16 [1.78 , 2.61]**
Total events:	293		135			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.88 (P < 0.00001)						
Total (95% CI)		**5325**		**5333**	**100.0%**	**2.25 [1.88 , 2.70]**
Total events:	340		150			
Heterogeneity: Chi^2 = 5.70, df = 5 (P = 0.34); I^2 = 12%						
Test for overall effect: Z = 8.77 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 5.65, df = 4 (P = 0.23), I^2 = 29.3%						



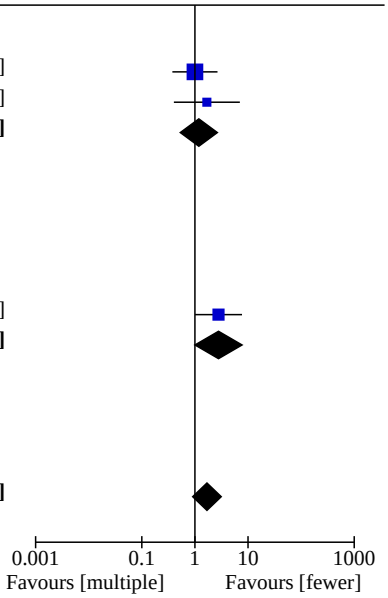
Analysis 2.5. Comparison 2: Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 5: Ischaemic stroke

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Aspirin + clopidogrel vs aspirin						
CHANCE	204	2584	295	2586	59.0%	0.69 [0.58 , 0.82]
POINT	112	2432	155	2449	30.9%	0.73 [0.57 , 0.92]
Subtotal (95% CI)		**5016**		**5035**	**90.0%**	**0.70 [0.61 , 0.81]**
Total events:	316		450			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 4.98 (P < 0.00001)						
2.5.2 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole						
TARDIS	46	1540	50	1530	10.0%	0.91 [0.62 , 1.36]
Subtotal (95% CI)		**1540**		**1530**	**10.0%**	**0.91 [0.62 , 1.36]**
Total events:	46		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)		**6556**		**6565**	**100.0%**	**0.73 [0.64 , 0.83]**
Total events:	362		500			
Heterogeneity: Chi² = 1.62, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 4.84 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.50, df = 1 (P = 0.22), I² = 33.2%						

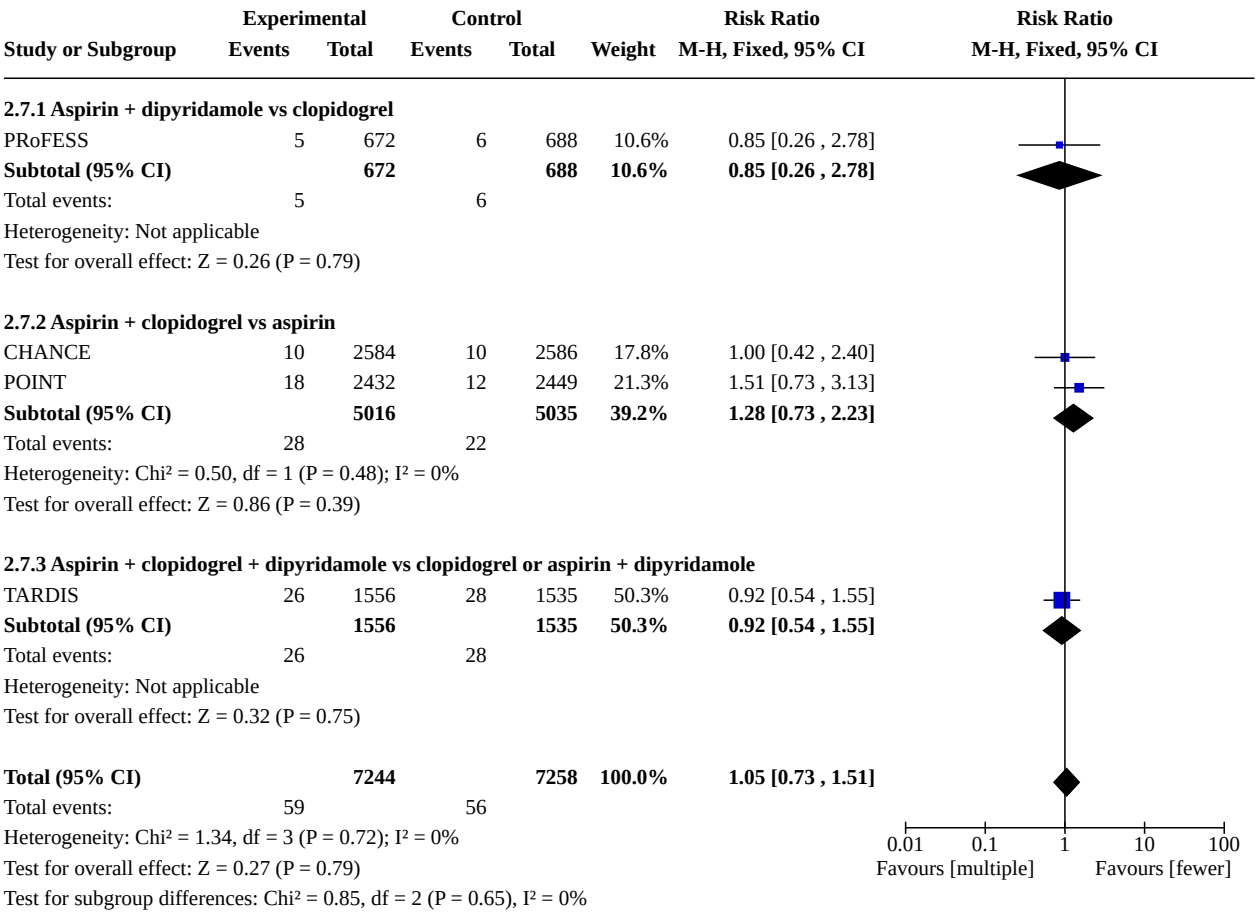


Analysis 2.6. Comparison 2: Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 6: Haemorrhagic stroke

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 Aspirin + clopidogrel vs aspirin						
CHANCE	8	2584	8	2586	50.0%	1.00 [0.38 , 2.66]
POINT	5	2432	3	2449	18.7%	1.68 [0.40 , 7.01]
Subtotal (95% CI)		**5016**		**5035**	**68.7%**	**1.19 [0.53 , 2.64]**
Total events:	13		11			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.68)						
2.6.2 Aspirin + clopidogrel + dipyridamole vs clopidogrel or aspirin + dipyridamole						
TARDIS	14	1540	5	1530	31.3%	2.78 [1.00 , 7.70]
Subtotal (95% CI)		**1540**		**1530**	**31.3%**	**2.78 [1.00 , 7.70]**
Total events:	14		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
Total (95% CI)		**6556**		**6565**	**100.0%**	**1.69 [0.91 , 3.13]**
Total events:	27		16			
Heterogeneity: Chi² = 2.02, df = 2 (P = 0.36); I² = 1%						
Test for overall effect: Z = 1.66 (P = 0.10)						
Test for subgroup differences: Chi² = 1.66, df = 1 (P = 0.20), I² = 39.9%						



Analysis 2.7. Comparison 2: Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 7: Death from any cause

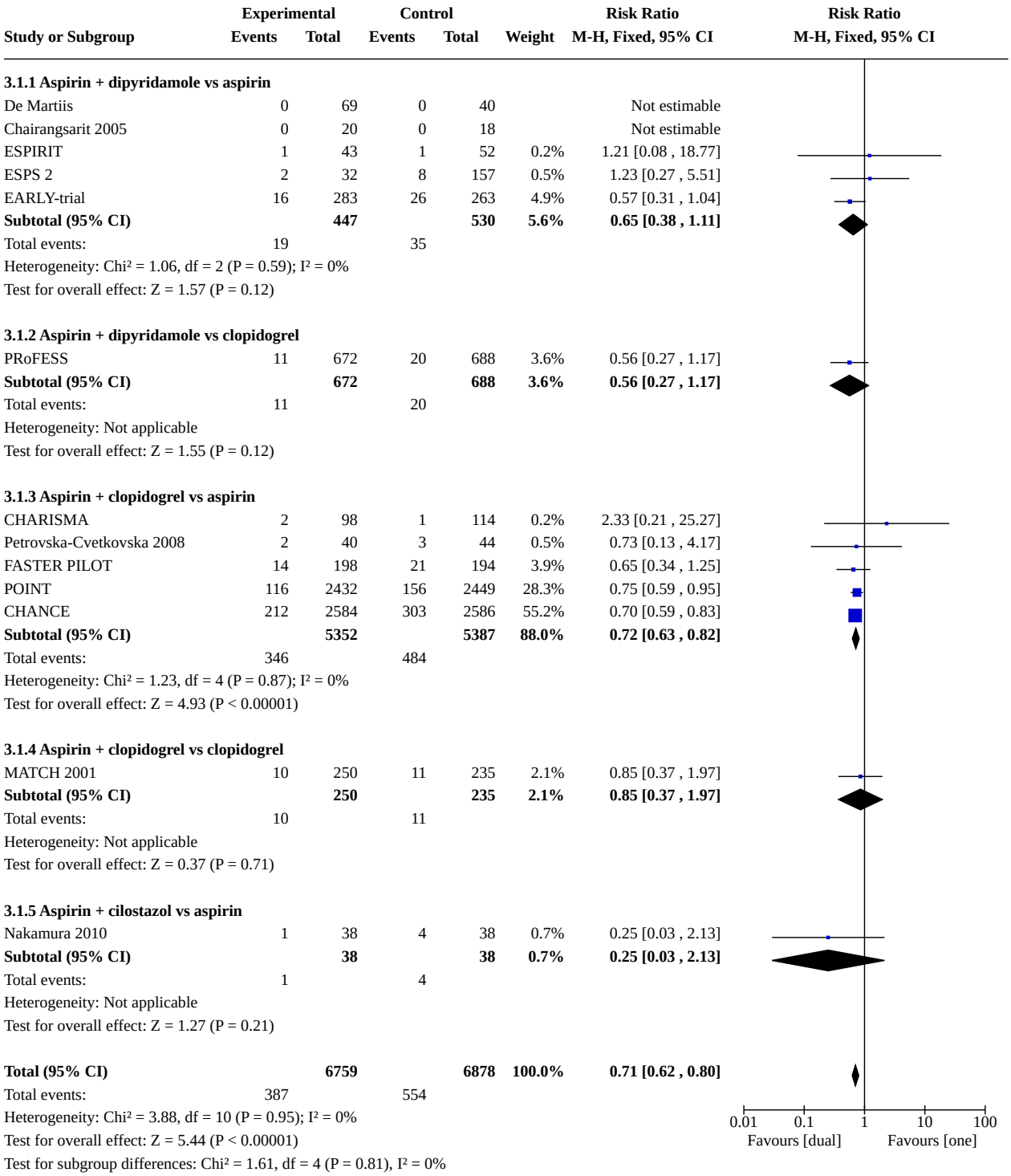


Comparison 3. Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack

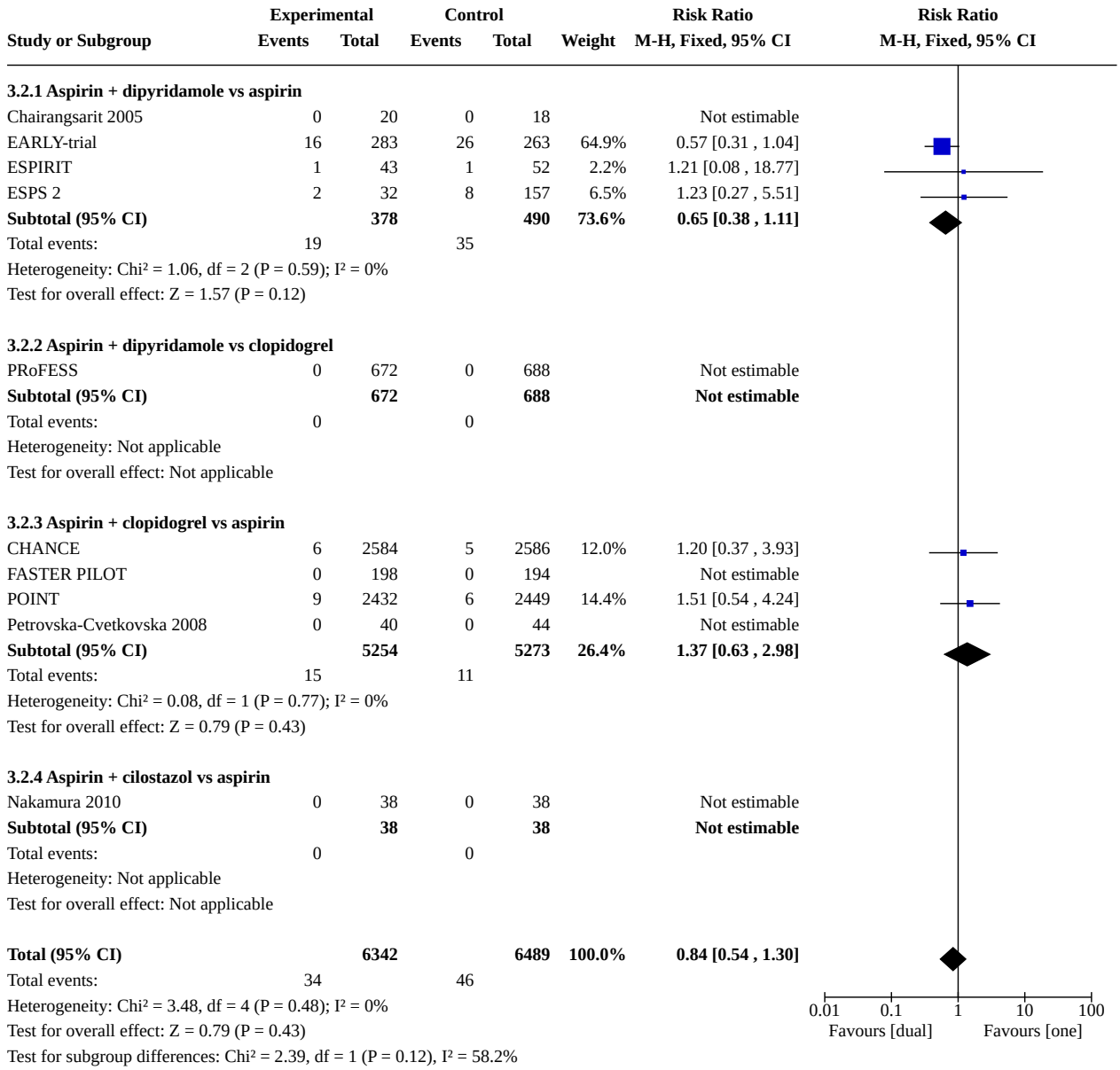
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Stroke	13	13637	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.62, 0.80]
3.1.1 Aspirin + dipyridamole vs aspirin	5	977	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.11]
3.1.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.17]
3.1.3 Aspirin + clopidogrel vs aspirin	5	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.63, 0.82]
3.1.4 Aspirin + clopidogrel vs clopidogrel	1	485	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.37, 1.97]
3.1.5 Aspirin + cilostazol vs aspirin	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.13]
3.2 Vascular death	10	12831	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2.1 Aspirin + dipyridamole vs aspirin	4	868	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.11]
3.2.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2.3 Aspirin + clopidogrel vs aspirin	4	10527	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.63, 2.98]
3.2.4 Aspirin + cilostazol vs aspirin	1	76	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 3.1. Comparison 3: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 1: Stroke



Analysis 3.2. Comparison 3: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 2: Vascular death



Comparison 4. Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack

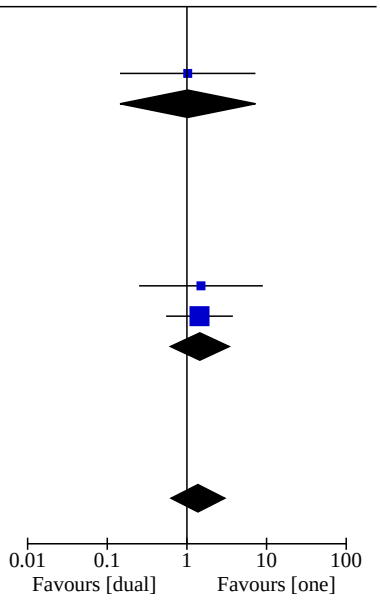
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Myocardial infarction	3	11411	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.63, 2.99]
4.1.1 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.14, 7.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.2 Aspirin + clopidogrel vs aspirin	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.62, 3.39]
4.2 Stroke, myocardial infarction, or vascular death	7	12932	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.64, 0.82]
4.2.1 Aspirin + dipyridamole vs aspirin	2	638	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.42, 1.07]
4.2.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.38, 1.34]
4.2.3 Aspirin + clopidogrel vs aspirin	3	10443	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.64, 0.82]
4.2.4 Aspirin + clopidogrel vs clopidogrel	1	491	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.41, 1.59]
4.3 Intracranial haemorrhage	5	11217	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.76, 3.06]
4.3.1 Aspirin + dipyridamole vs aspirin	1	38	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.12, 62.70]
4.3.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3.3 Aspirin + clopidogrel vs aspirin	3	9819	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.72, 3.02]
4.4 Extracranial haemorrhage	6	7586	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [1.74, 5.46]
4.4.1 Aspirin + dipyridamole vs aspirin	2	638	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.06, 14.61]
4.4.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.40, 3.54]
4.4.3 Aspirin + clopidogrel vs aspirin	2	5097	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [2.19, 10.57]
4.4.4 Aspirin + clopidogrel vs clopidogrel	1	491	Risk Ratio (M-H, Fixed, 95% CI)	3.67 [0.41, 32.62]
4.5 Ischaemic stroke	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.81]
4.5.1 Aspirin + clopidogrel vs aspirin	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.81]
4.6 Haemorrhagic stroke	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.53, 2.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.6.1 Aspirin + dipyridamole vs aspirin	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.53, 2.64]
4.7 Death from any cause	3	11411	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.72, 1.96]
4.7.1 Aspirin + clopidogrel vs aspirin	2	10051	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.73, 2.23]
4.7.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.26, 2.78]

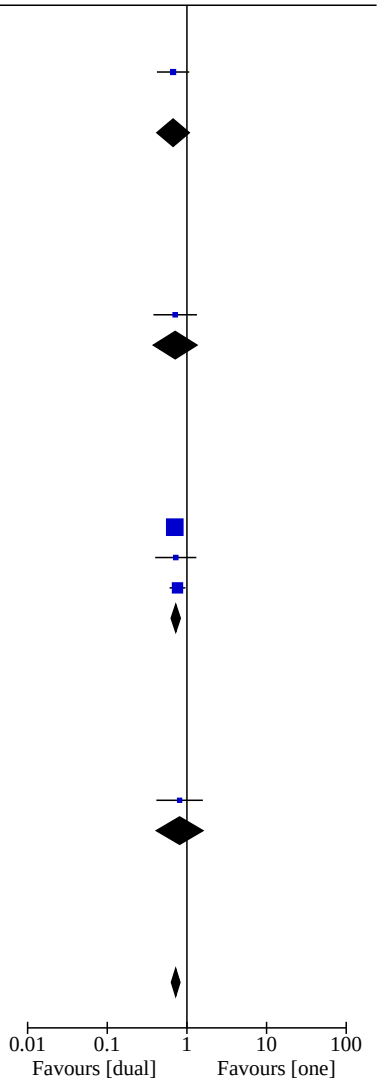
Analysis 4.1. Comparison 4: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 1: Myocardial infarction

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	2	672	2	688	18.0%	1.02 [0.14 , 7.25]
Subtotal (95% CI)		**672**		**688**	**18.0%**	**1.02 [0.14 , 7.25]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
4.1.2 Aspirin + clopidogrel vs aspirin						
CHANCE	3	2584	2	2586	18.3%	1.50 [0.25 , 8.98]
POINT	10	2432	7	2449	63.7%	1.44 [0.55 , 3.77]
Subtotal (95% CI)		**5016**		**5035**	**82.0%**	**1.45 [0.62 , 3.39]**
Total events:	13		9			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Total (95% CI)		**5688**		**5723**	**100.0%**	**1.38 [0.63 , 2.99]**
Total events:	15		11			
Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						



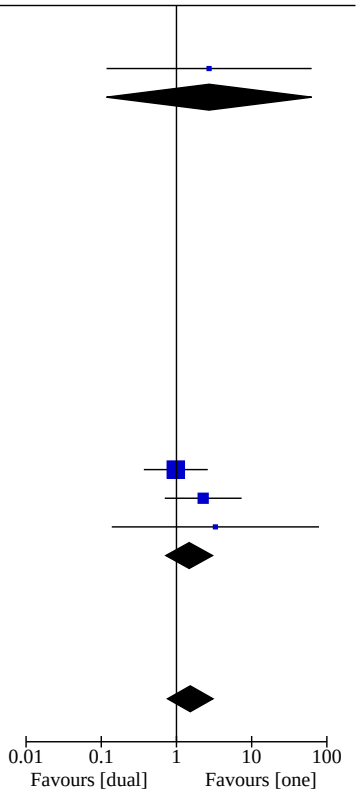
Analysis 4.2. Comparison 4: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 2: Stroke, myocardial infarction, or vascular death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Aspirin + dipyridamole vs aspirin						
EARLY-trial	27	283	37	260	6.8%	0.67 [0.42 , 1.07]
ESPIRIT	0	43	0	52		Not estimable
Subtotal (95% CI)		**326**		**312**	**6.8%**	**0.67 [0.42 , 1.07]**
Total events:	27		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
4.2.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	16	672	23	688	4.0%	0.71 [0.38 , 1.34]
Subtotal (95% CI)		**672**		**688**	**4.0%**	**0.71 [0.38 , 1.34]**
Total events:	16		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
4.2.3 Aspirin + clopidogrel vs aspirin						
CHANCE	216	2584	307	2586	54.0%	0.70 [0.60 , 0.83]
FASTER PILOT	17	198	23	194	4.1%	0.72 [0.40 , 1.31]
POINT	121	2432	160	2449	28.0%	0.76 [0.61 , 0.96]
Subtotal (95% CI)		**5214**		**5229**	**86.1%**	**0.72 [0.64 , 0.82]**
Total events:	354		490			
Heterogeneity: Chi^2 = 0.30, df = 2 (P = 0.86); I^2 = 0%						
Test for overall effect: Z = 4.84 (P < 0.00001)						
4.2.4 Aspirin + clopidogrel vs clopidogrel						
MATCH 2001	15	256	17	235	3.1%	0.81 [0.41 , 1.59]
Subtotal (95% CI)		**256**		**235**	**3.1%**	**0.81 [0.41 , 1.59]**
Total events:	15		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
Total (95% CI)		**6468**		**6464**	**100.0%**	**0.72 [0.64 , 0.82]**
Total events:	412		567			
Heterogeneity: Chi^2 = 0.51, df = 5 (P = 0.99); I^2 = 0%						
Test for overall effect: Z = 5.25 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 0.21, df = 3 (P = 0.98), I^2 = 0%						

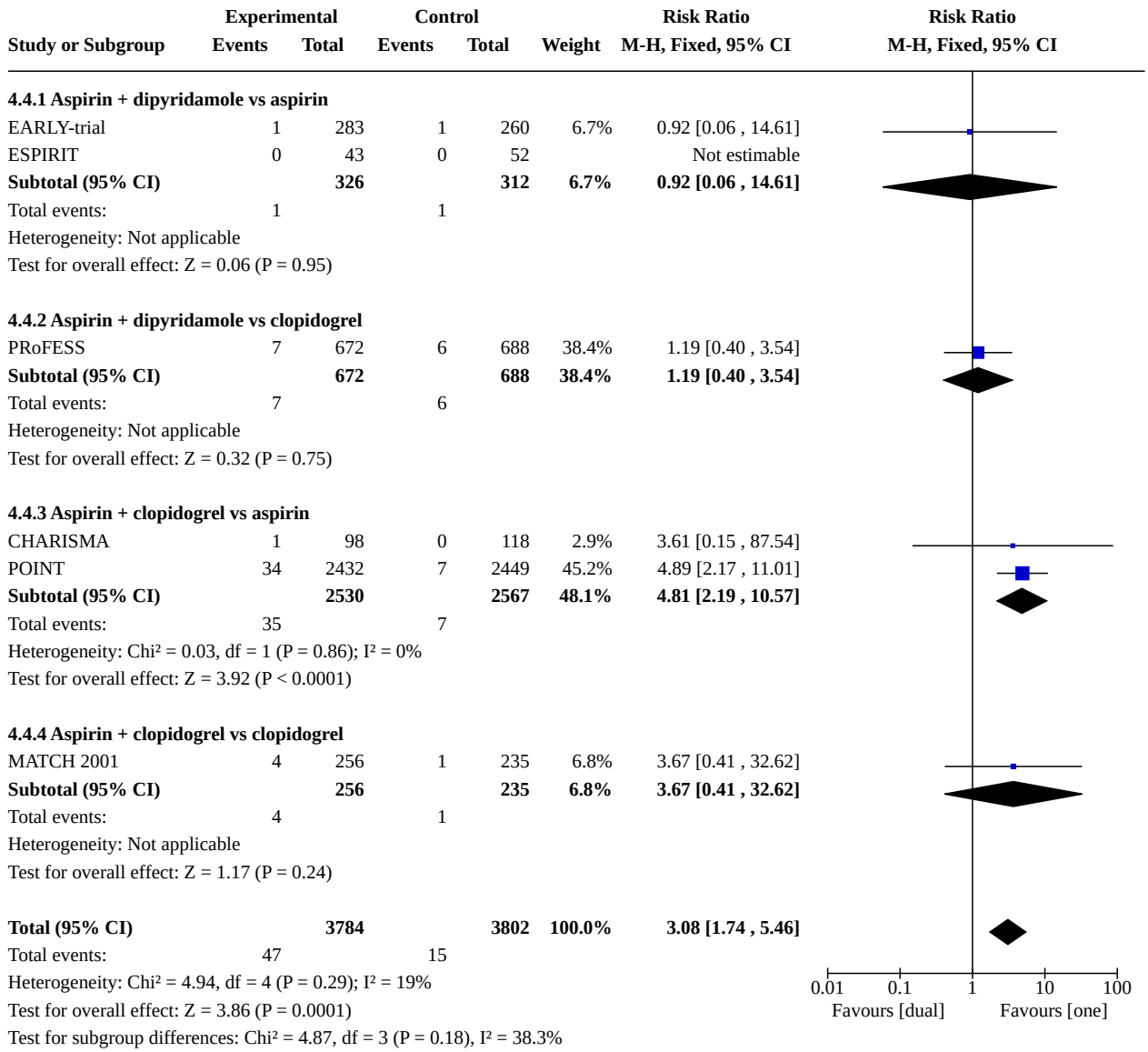


Analysis 4.3. Comparison 4: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 3: Intracranial haemorrhage

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Aspirin + dipyridamole vs aspirin						
Chairangsarit 2005	1	20	0	18	4.0%	2.71 [0.12 , 62.70]
Subtotal (95% CI)		**20**		**18**	**4.0%**	**2.71 [0.12 , 62.70]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
4.3.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	0	672	0	688		Not estimable
Subtotal (95% CI)		**672**		**688**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.3.3 Aspirin + clopidogrel vs aspirin						
CHANCE	8	2452	8	2402	61.8%	0.98 [0.37 , 2.61]
POINT	9	2432	4	2449	30.5%	2.27 [0.70 , 7.35]
Petrovska-Cvetkovska 2008	1	40	0	44	3.6%	3.29 [0.14 , 78.59]
Subtotal (95% CI)		**4924**		**4895**	**96.0%**	**1.48 [0.72 , 3.02]**
Total events:	18		12			
Heterogeneity: Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.29)						
Total (95% CI)		**5616**		**5601**	**100.0%**	**1.53 [0.76 , 3.06]**
Total events:	19		12			
Heterogeneity: Chi² = 1.58, df = 3 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.23)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%						

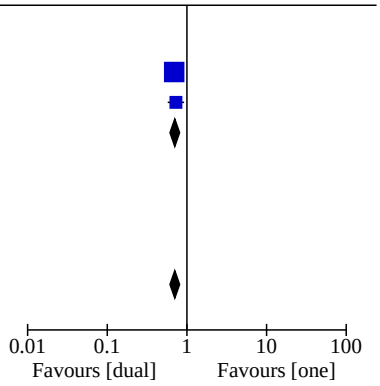


Analysis 4.4. Comparison 4: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 4: Extracranial haemorrhage



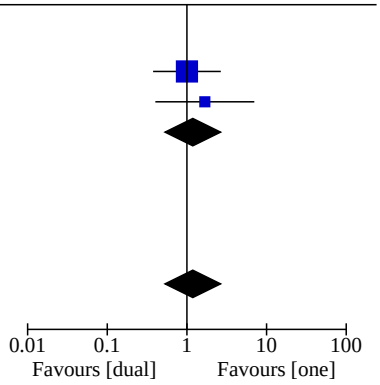
Analysis 4.5. Comparison 4: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 5: Ischaemic stroke

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.1 Aspirin + clopidogrel vs aspirin						
CHANCE	204	2584	295	2586	65.6%	0.69 [0.58 , 0.82]
POINT	112	2432	155	2449	34.4%	0.73 [0.57 , 0.92]
Subtotal (95% CI)		**5016**		**5035**	**100.0%**	**0.70 [0.61 , 0.81]**
Total events:	316		450			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 4.98 (P < 0.00001)						
Total (95% CI)		**5016**		**5035**	**100.0%**	**0.70 [0.61 , 0.81]**
Total events:	316		450			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 4.98 (P < 0.00001)						
Test for subgroup differences: Not applicable						



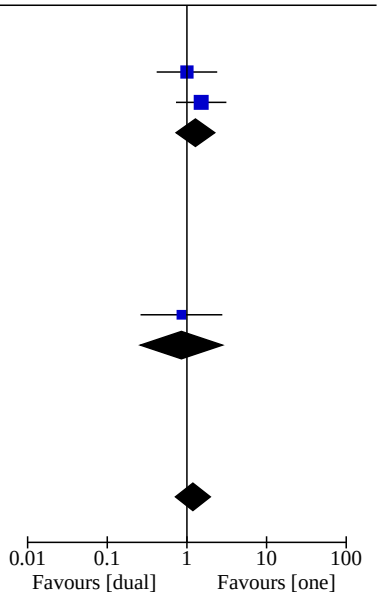
Analysis 4.6. Comparison 4: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 6: Haemorrhagic stroke

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.6.1 Aspirin + dipyridamole vs aspirin						
CHANCE	8	2584	8	2586	72.8%	1.00 [0.38 , 2.66]
POINT	5	2432	3	2449	27.2%	1.68 [0.40 , 7.01]
Subtotal (95% CI)		**5016**		**5035**	**100.0%**	**1.19 [0.53 , 2.64]**
Total events:	13		11			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.68)						
Total (95% CI)		**5016**		**5035**	**100.0%**	**1.19 [0.53 , 2.64]**
Total events:	13		11			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.68)						
Test for subgroup differences: Not applicable						



Analysis 4.7. Comparison 4: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 7: Death from any cause

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 Aspirin + clopidogrel vs aspirin						
CHANCE	10	2584	10	2586	35.8%	1.00 [0.42 , 2.40]
POINT	18	2432	12	2449	42.9%	1.51 [0.73 , 3.13]
Subtotal (95% CI)		**5016**		**5035**	**78.7%**	**1.28 [0.73 , 2.23]**
Total events:	28		22			
Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
4.7.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	5	672	6	688	21.3%	0.85 [0.26 , 2.78]
Subtotal (95% CI)		**672**		**688**	**21.3%**	**0.85 [0.26 , 2.78]**
Total events:	5		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.79)						
Total (95% CI)		**5688**		**5723**	**100.0%**	**1.19 [0.72 , 1.96]**
Total events:	33		28			
Heterogeneity: Chi² = 0.87, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%						

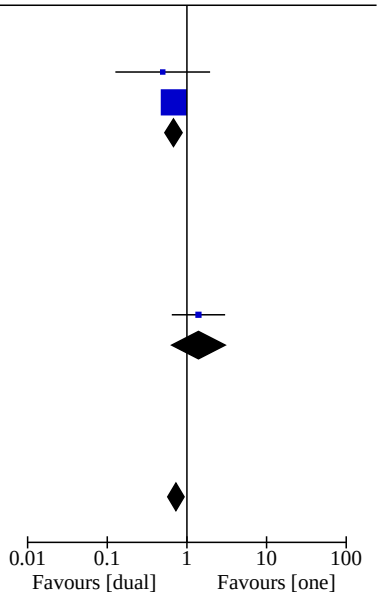


Comparison 5. Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack at one month

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Stroke, myocardial infarction, or vascular death	3	6574	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.92]
5.1.1 Aspirin + clopidogrel vs aspirin	2	5214	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.53, 0.87]
5.1.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.65, 3.02]

Analysis 5.1. Comparison 5: Dual versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack at one month, Outcome 1: Stroke, myocardial infarction, or vascular death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Aspirin + clopidogrel vs aspirin						
COMPRESS	3	167	6	166	3.8%	0.50 [0.13 , 1.95]
POINT	96	2432	141	2449	89.3%	0.69 [0.53 , 0.88]
Subtotal (95% CI)		**2599**		**2615**	**93.1%**	**0.68 [0.53 , 0.87]**
Total events:	99		147			
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 3.06 (P = 0.002)						
5.1.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	15	672	11	688	6.9%	1.40 [0.65 , 3.02]
Subtotal (95% CI)		**672**		**688**	**6.9%**	**1.40 [0.65 , 3.02]**
Total events:	15		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
Total (95% CI)		**3271**		**3303**	**100.0%**	**0.73 [0.57 , 0.92]**
Total events:	114		158			
Heterogeneity: Chi² = 3.26, df = 2 (P = 0.20); I² = 39%						
Test for overall effect: Z = 2.65 (P = 0.008)						
Test for subgroup differences: Chi² = 3.06, df = 1 (P = 0.08), I² = 67.3%						

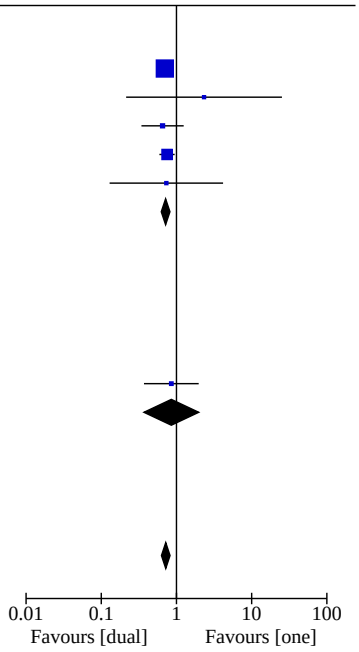


Comparison 6. Aspirin and clopidogrel versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Stroke	6	11224	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.63, 0.82]
6.1.1 Aspirin + clopidogrel vs aspirin	5	10739	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.63, 0.82]
6.1.2 Aspirin + clopidogrel vs clopidogrel	1	485	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.37, 1.97]

Analysis 6.1. Comparison 6: Aspirin and clopidogrel versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 1: Stroke

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 Aspirin + clopidogrel vs aspirin						
CHANCE	212	2584	303	2586	61.2%	0.70 [0.59 , 0.83]
CHARISMA	2	98	1	114	0.2%	2.33 [0.21 , 25.27]
FASTER PILOT	14	198	21	194	4.3%	0.65 [0.34 , 1.25]
POINT	116	2432	156	2449	31.4%	0.75 [0.59 , 0.95]
Petrovska-Cvetkovska 2008	2	40	3	44	0.6%	0.73 [0.13 , 4.17]
Subtotal (95% CI)		**5352**		**5387**	**97.7%**	**0.72 [0.63 , 0.82]**
Total events:	346		484			
Heterogeneity: Chi² = 1.23, df = 4 (P = 0.87); I² = 0%						
Test for overall effect: Z = 4.93 (P < 0.00001)						
6.1.2 Aspirin + clopidogrel vs clopidogrel						
MATCH 2001	10	250	11	235	2.3%	0.85 [0.37 , 1.97]
Subtotal (95% CI)		**250**		**235**	**2.3%**	**0.85 [0.37 , 1.97]**
Total events:	10		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
Total (95% CI)		**5602**		**5622**	**100.0%**	**0.72 [0.63 , 0.82]**
Total events:	356		495			
Heterogeneity: Chi² = 1.39, df = 5 (P = 0.93); I² = 0%						
Test for overall effect: Z = 4.93 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%						

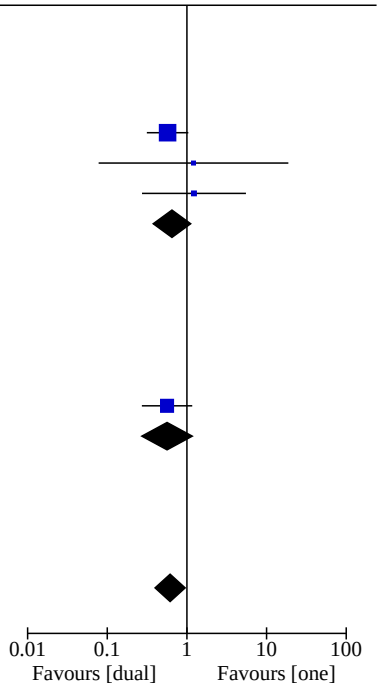


Comparison 7. Aspirin and dipyridamole versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Stroke	6	2337	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.40, 0.95]
7.1.1 Aspirin + dipyridamole vs aspirin	5	977	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.11]
7.1.2 Aspirin + dipyridamole vs clopidogrel	1	1360	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.17]

Analysis 7.1. Comparison 7: Aspirin and dipyridamole versus one antiplatelet agent for preventing early recurrence after ischaemic stroke or transient ischaemic attack, Outcome 1: Stroke

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 Aspirin + dipyridamole vs aspirin						
Chairangsarit 2005	0	20	0	18		Not estimable
De Martiis	0	69	0	40		Not estimable
EARLY-trial	16	283	26	263	53.5%	0.57 [0.31 , 1.04]
ESPIRIT	1	43	1	52	1.8%	1.21 [0.08 , 18.77]
ESPS 2	2	32	8	157	5.4%	1.23 [0.27 , 5.51]
Subtotal (95% CI)		**447**		**530**	**60.7%**	**0.65 [0.38 , 1.11]**
Total events:	19		35			
Heterogeneity: Chi² = 1.06, df = 2 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.57 (P = 0.12)						
7.1.2 Aspirin + dipyridamole vs clopidogrel						
PRoFESS	11	672	20	688	39.3%	0.56 [0.27 , 1.17]
Subtotal (95% CI)		**672**		**688**	**39.3%**	**0.56 [0.27 , 1.17]**
Total events:	11		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Total (95% CI)		**1119**		**1218**	**100.0%**	**0.62 [0.40 , 0.95]**
Total events:	30		55			
Heterogeneity: Chi² = 1.16, df = 3 (P = 0.76); I² = 0%						
Test for overall effect: Z = 2.19 (P = 0.03)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%						



APPENDICES

Appendix 1. CENTRAL search strategy

#1MeSH descriptor: [Cerebrovascular Disorders] this term only1425
#2MeSH descriptor: [Basal Ganglia Cerebrovascular Disease] this term only10
#3MeSH descriptor: [Brain Ischemia] explode all trees3534
#4MeSH descriptor: [Carotid Artery Diseases] this term only471
#5MeSH descriptor: [Carotid Artery Thrombosis] this term only18
#6MeSH descriptor: [Intracranial Arterial Diseases] this term only10
#7MeSH descriptor: [Cerebral Arterial Diseases] this term only26
#8MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees308
#9MeSH descriptor: [Stroke] explode all trees9502
#10(isch?emi* near/6 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva or attack*)):ti,ab,kw15375
#11((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) near/5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab,kw16412
#12tia*10578
#13{or #1-#12}39827
#14MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees3834
#15(antiplatelet& or anti-platelet* or antiaggreg* or anti-aggreg* or (platelet* near/5 inhibit*) or (thrombocyt* near/5 inhibit*)):ti,ab,kw10918
#16(alprostadil* or aspirin* or dipyridamol* or disintegrin* or epoprostenol* or iloprost* or ketanserin* or ketorolac tromethamine* or milrinone* or mopidamol* or pentoxifyllin* or ticlopidine* or thiophen* or trapidil* or prasugrel or terutroban):ti,ab,kw22091
#17(acetyl salicylic acid* or acetyl?salicylic acid or clopidogrel* or picotamide* or ligustrazine* or levamisol$ or suloctidil* or ozagrel* or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or triflusal):ti,ab,kw10586
#18(Dispril or Albyl* or Ticlid* or Persantin* or Plavix or Aggrenox or Pletal):ti,ab,kw393

#19MeSH descriptor: [Platelet Glycoprotein GPIIb-IIIa Complex] explode all trees and with qualifier(s): [antagonists & inhibitors - AI, drug effects - DE]492
#20(((glycoprotein iib* or gp iib*) near/5 (antagonist* or inhibitor*)) or GR144053 or GR-144053 or abciximab* or tirofiban* or eftifibatid*):ti,ab,kw2378
#21ReoPro or Integrilin* or Aggrastat271
#22MeSH descriptor: [Platelet Activation] explode all trees and with qualifier(s): [drug effects - DE]1833
#23MeSH descriptor: [Blood Platelets] explode all trees and with qualifier(s): [drug effects - DE]1101
#24(sulphinpyrazone or sulfinpyrazone or indobufen):ti,ab,kw236
#25{or #14-#24}32587
#26#13 and #254527

Appendix 2. MEDLINE search strategy

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$1.tw.
5. or/1-4
6. exp platelet aggregation inhibitors/
7. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj5 inhibit$) or (thrombocyt$ adj5 inhibit$)).tw.
8. (alprostadil$ or aspirin$ or dipyridamol$ or disintegrin$ or epoprostenol$ or iloprost$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or pentoxifyllin$ or ticlopidine$ or thiophen$ or trapidil$ or prasugrel or terutroban).tw.
9. (acetyl salicylic acid$ or acetyl?salicylic acid or clopidogrel$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or triflusal).tw.
10. (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix or Aggrenox or Pletal).tw.
11. Platelet Glycoprotein GPIIb-IIIa Complex/ai, de [Antagonists & Inhibitors, Drug Effects]
12. (((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-44053 or abciximab$ or tirofiban$ or eftifibatid$).tw.
13. (ReoPro or Integrilin$ or Aggrastat).tw.
14. exp Platelet Activation/de [Drug Effects]
15. exp Blood Platelets/de [Drug Effects]
16. (sulphinpyrazone or sulfinpyrazone or indobufen).tw.
17. or/6-16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. clinical trials as topic.sh.
23. random$.ab.
24. trial.ti.
25. or/18-24
26. exp animals/ not humans.sh.
27. 25 not 26
28. 5 and 17 and 27

Appendix 3. Embase search strategy

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. (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$1.tw.
5. or/1-4
6. exp antithrombocytic agent/
7. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj5 inhibit$) or (thrombocyt$ adj5 inhibit$)).tw.
8. (alprostadil$ or aspirin$ or dipyridamol$ or disintegrin$ or epoprostenol$ or iloprost$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or pentoxifyllin$ or ticlopidine$ or thiophen$ or trapidil$ or prasugrel or terutroban).tw,tn.
9. (acetyl salicylic acid$ or acetyl?salicylic acid or clopidogrel$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or triflusal).tw,tn.

10. (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix or Aggrenox or Pletal).tw,tn.
11. exp fibrinogen receptor/
12. (((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or abciximab$ or tirofiban$ or eftifibatid$).tw.
13. (ReoPro or Integrilin$ or Aggrastat).tw,tn.
14. exp thrombocyte activation/
15. exp thrombocyte/
16. (sulphinpyrazone or sulfinpyrazone or indobufen).tw.
17. or/6-16
18. 5 and 17
19. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/
20. Randomization/
21. Controlled clinical trial/ or "controlled clinical trial (topic)"/
22. control group/ or controlled study/
23. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
24. Crossover Procedure/
25. Double Blind Procedure/
26. Single Blind Procedure/ or triple blind procedure/
27. placebo/ or placebo effect/
28. (random$ or RCT or RCTs).tw.
29. (controlled adj5 (trial$ or stud$)).tw.
30. (clinical$ adj5 trial$).tw.
31. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
32. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
33. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
34. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
35. (cross-over or cross over or crossover).tw.
36. (placebo$ or sham).tw.
37. trial.ti.
38. (assign$ or allocat$).tw.
39. controls.tw.
40. or/19-39
41. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
42. 18 and 40
43. 42 not 41

Appendix 4. ClinicalTrials.gov search strategy

(antiplatelet agents OR platelet aggregation inhibitors) AND (ischaemic stroke OR brain ischaemia OR cerebral infarction OR ischaemic attack) [DISEASE]

Appendix 5. WHO ICTRP search strategy

Condition: stroke OR ischaemic attack
Intervention: antiplatelet OR alprostadil OR aspirin OR dipyridamol OR disintegrin OR epoprostenol OR iloprost OR ketanserin OR ketorolac OR tromethamine OR milrinone OR mopidamol OR pentoxifylline OR ticlopidine OR thiophene OR trapidil OR prasugrel OR terutroban
Recruitment status is: ALL
Phases are: ALL
Display synonyms:
- ischemic attack - ACCIDENT CEREBROVASCULAR, ACCIDENT; CEREBRAL, ACCIDENT; CEREBROVASCULAR, APOPLEXY, APOPLEXY, CEREBROVASCULAR, APOPLEXY; CEREBRAL, BRAIN ATTACK, BRAIN VASCULAR ACCIDENT, BRAIN VASCULAR ACCIDENTS, CEREBRAL VASCULAR ACCIDENT, CEREBRAL VASCULAR EVENTS, CEREBRAL; ACCIDENT, CEREBRAL; APOPLEXY, CEREBROVASCULAR ACCIDENT, CEREBROVASCULAR ACCIDENT (DISORDER), CEREBROVASCULAR ACCIDENT NOS, CEREBROVASCULAR ACCIDENT, NOS, CEREBROVASCULAR ACCIDENTS, CEREBROVASCULAR APOPLEXY, CEREBROVASCULAR; ACCIDENT, CVA, CVA (CEREBRAL VASCULAR ACCIDENT), CVA (CEREBROVASCULAR ACCIDENT), CVA NOS, CVAS (CEREBROVASCULAR ACCIDENT), NEURO: CEREBROVASCULAR ACCIDENT, VASCULAR ACCIDENT, BRAIN, VASCULAR ACCIDENTS, BRAIN, stroke - OXPENTIFYLLINE, PENTOXYFYLLINE, PENTOXYPHYLLINE, PTX, pentoxifylline - ABBOTT BRAND OF TROMETAMOL, THAM, TRI(HYDROXYMETHYL)AMINOMETHANE, TRIS BUFFER, TRIS(HYDROXYMETHYL)AMINOMETHANE, TRIS-(HYDROXYMETHYL) AMINOMETHANE, TRISAMINE, TROMETAMOL, TROMETAMOL ABBOTT BRAND, tromethamine - EPOPROSTANOL, PGI2, PGX, PROSTACYCLIN, PROSTAGLANDIN I 02, PROSTAGLANDIN I(2), PROSTAGLANDIN I2, PROSTAGLANDIN PGI2, PROSTAGLANDIN PGI>2<, PROSTAGLANDIN PGI2, PROSTAGLANDIN X, epoprostenol - antiplatelet - ticlopidine - disintegrin - DIPYRAMIDOLE, dipyridamol - (11ALPHA,13E,15S)-11,15-DIHYDROXY-9-OXOPROST-13-EN-1-OIC ACID, LIPO PGE1, LIPO-PGE1, PGE 01, PGE1, PGE1ALPHA, PROSTAGLANDIN E 01, PROSTAGLANDIN E1, PROSTAGLANDIN E1, PROSTAGLANDIN E1ALPHA, PROSTAGLANDIN PGE1, PROSTAGLANDIN PGE>1<, PROSTAGLANDIN PGE1, PROSTAGLANDIN PGE1 (SUBSTANCE), alprostadil - 3-((6-AMINO-(4-CHLOROBENZENESULFONYL)-2-METHYL-5,6,7,8-TETRAHYDRONAPHT)-1-YL)PROPIONIC ACID, terutroban - 3-(2-(4-(4-

FLUOROBENZOYL)PIPERIDINOL)ETHYL)-2,4(1H,3H)-QUINAZOLINEDIONE, ketanserin - THIOFURAN, THIOLE, thiophene - prasugrel - mopidamol - milrinone - ketorolac - TRAPYMIN, trapidil - iloprost - 2-(ACETYLOXY)BENZOIC ACID, ACETYLSALICYCLIC ACID, ACETYLSALICYLIC ACID, ACID, ACETYLSALICYLIC, AMPICILLIN, ASA, aspirin

WHAT'S NEW

Date	Event	Description
24 September 2020	Amended	An amendment has been made to the 'Authors conclusions' section of the Abstract

HISTORY

Protocol first published: Issue 3, 2012
Review first published: Issue 8, 2020

CONTRIBUTIONS OF AUTHORS

IAN drafted the protocol, developed tools for data abstraction, reviewed studies, performed data analysis, and drafted the manuscript. AKK conceived the idea, assisted in reviewing studies, manuscript editing and provided oversight. HR reviewed papers, added studies for analysis, and assisted in manuscript writing.

DECLARATIONS OF INTEREST

Imama A Naqvi: none known
Ayeesha K Kamal: none known
Hasan Rehman: none known

SOURCES OF SUPPORT

Internal sources

- The Aga Khan University Hospital, Pakistan

  Library access, electronic support, and professional development

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We conducted a secondary analysis of dual versus single antiplatelets, as most of the included studies compared dual antiplatelets to a single agent.

Although we did not initially intend to do so, we explored a trial of one-month duration as a change in the protocol (COMPRESS), and included this in analysis with trials that clearly reported relevant outcome data at one month.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Cause of Death; Confidence Intervals; Drug Therapy, Combination [adverse effects] [methods]; Hemorrhage [chemically induced] [epidemiology]; Intention to Treat Analysis; Intracranial Hemorrhages [chemically induced] [epidemiology]; Ischemic Attack, Transient [*prevention & control]; Myocardial Infarction [epidemiology]; Odds Ratio; Platelet Aggregation Inhibitors [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Secondary Prevention [*methods]; Stroke [epidemiology] [*prevention & control]; Time Factors

MeSH check words

Humans