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Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients (Review)

Sudlow CLM, Mason G, Maurice JB, Wedderburn CJ, Hankey GJ

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Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD001246.

DOI: [10.1002/14651858.CD001246.pub2](https://doi.org/10.1002/14651858.CD001246.pub2).

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[Intervention Review]

Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients

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Editorial group: Cochrane Stroke Group

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2010.

Citation: Sudlow CLM, Mason G, Maurice JB, Wedderburn CJ, Hankey GJ. Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD001246. DOI: [10.1002/14651858.CD001246.pub2](https://doi.org/10.1002/14651858.CD001246.pub2).

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ABSTRACT

Background

Aspirin is the most widely studied and prescribed antiplatelet agent for preventing serious vascular events, reducing the odds of such events among high vascular risk patients by about a quarter. Thienopyridine derivatives inhibit platelet activation by a different mechanism and so may be more effective.

Objectives

To determine the effectiveness and safety of thienopyridine derivatives (ticlopidine and clopidogrel) versus aspirin for preventing serious vascular events (stroke, myocardial infarction (MI) or vascular death) in patients at high risk, and specifically in patients with a previous TIA or ischaemic stroke.

Search methods

We searched the trials registers of the Stroke, Heart and Peripheral Vascular Diseases Cochrane Review Groups (last searched July 2008), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2008), MEDLINE (1966 to August 2008) and EMBASE (1980 to August 2008). We also searched reference lists of relevant papers, and contacted other researchers and the pharmaceutical company Sanofi-BMS (December 2008).

Selection criteria

All unconfounded, double blind, randomised trials directly comparing a thienopyridine derivative with aspirin in high vascular risk patients.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality. We sought additional data from the principal investigators of the largest trials.

Main results

We included 10 trials involving 26,865 high vascular risk patients. The trials were generally of high quality. Aspirin was compared with ticlopidine in nine trials (7633 patients) and with clopidogrel in one trial (19,185 patients). Compared with aspirin, allocation to a thienopyridine produced a modest, just statistically significant, reduction in the odds of a serious vascular event (11.6% versus 12.5%; odds ratio (OR) 0.92, 95% confidence interval (CI) 0.85 to 0.99), corresponding to the avoidance of 10 (95% CI 0 to 20) serious vascular

events per 1000 patients treated for about two years. However, the wide confidence interval includes the possibility of negligible additional benefit. Compared with aspirin, thienopyridines significantly reduced gastrointestinal adverse effects. However, thienopyridines increased the odds of skin rash and diarrhoea, ticlopidine more than clopidogrel. Allocation to ticlopidine, but not clopidogrel, significantly increased the odds of neutropenia. In patients with TIA/ischaemic stroke, the results were similar to those for all patients combined.

Authors' conclusions

The thienopyridine derivatives are at least as effective as aspirin in preventing serious vascular events in patients at high risk, and possibly somewhat more so. However, the size of any additional benefit is uncertain and could be negligible. Clopidogrel has a more favourable adverse effects profile than ticlopidine and so is the thienopyridine of choice. It should be used as an alternative to aspirin in patients genuinely intolerant of or allergic to aspirin.

PLAIN LANGUAGE SUMMARY

Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients

Most strokes and heart attacks are caused by a blood clot blocking the blood supply to part of the brain (to cause stroke) or to the heart (to cause a heart attack). Aspirin prevents blood clots forming, and it can reduce the risk of a further heart attack or stroke in people who have had a stroke or heart attack or other symptoms of vascular disease. Clopidogrel and ticlopidine are two similar drugs called thienopyridines which prevent clots in a different way to aspirin. This review of 10 trials comparing either clopidogrel or ticlopidine with aspirin in about 27,000 people found that clopidogrel and ticlopidine were at least as effective as aspirin for the prevention of stroke and heart attacks, and might be slightly more effective. In terms of adverse effects, compared with aspirin, clopidogrel and ticlopidine caused less stomach upset and less bleeding from the gut, but more diarrhoea and skin rash. Ticlopidine produced more of these last two adverse effects than clopidogrel when compared with aspirin. Ticlopidine can also cause suppression of the bone marrow production of blood cells, which can be a serious complication. Clopidogrel is therefore the thienopyridine of choice since it is safer and better tolerated. However, since it is substantially more expensive than aspirin and not clearly more effective, it should generally only be used instead of aspirin in patients who are unable to take aspirin.

BACKGROUND

The burden of cardiovascular disease (mainly due to stroke and myocardial infarction (MI)) on patients, carers and communities is enormous. One strategy of reducing this burden is the effective prevention of serious vascular events (i.e. stroke, MI, or vascular death) among individuals who are at high risk as a result of previous clinical manifestations of atherosclerotic arterial disease (i.e. patients with a history of transient ischaemic attack (TIA) of the brain or eye, ischaemic stroke, MI or angina, or peripheral arterial disease (PAD)).

The most recently published systematic overview of the Antithrombotic Trialists' Collaboration (ATT) includes data from 287 randomised trials comparing antiplatelet therapy with control or one antiplatelet with another, in more than 200,000 individuals (ATT 2002). Many additional trials of aspirin at various doses and other antiplatelet drugs and also trials comparing the effects of adding aspirin to another antiplatelet drug with a different mechanism of action have been included since the previous published overview of the Antiplatelet Trialists' Collaboration (APT). The additional data strengthens the findings from the APT that antiplatelet therapy for individuals with clinical manifestations of atherosclerotic arterial disease reduced the odds of a subsequent serious vascular event by about a quarter (APT 1994).

The proportional odds reductions were similar for patients with arterial disease of the brain, heart or peripheral circulation, but the absolute risk reductions varied according to the baseline risk of a subsequent vascular event. For example, among patients with prior TIA or ischaemic stroke, antiplatelet therapy reduced the three-year risk of a subsequent serious vascular event from 21% to 18% (a 22% relative odds reduction and 3% absolute risk reduction), indicating that treating 1000 such patients for about three years prevented or delayed about 30 major vascular events (ATT 2002).

In the most recent ATT overview, two-thirds of the data comparing an antiplatelet regimen with control came from trials comparing aspirin alone with no antiplatelet therapy. Overall, aspirin reduced the relative odds of a serious vascular event by about a quarter. Neither indirect nor direct comparisons of different aspirin regimens showed any evidence of differences in effectiveness throughout a range of doses from 75 mg to 1500 mg per day (ATT 2002). The number of participants in trials assessing doses of less than 75 mg were relatively small and hence the results for benefits versus risks at this dose were not entirely conclusive (ATT 2002). Doses of 75 to 150 mg daily have been much more widely assessed and since higher doses are significantly more gastrotoxic (Patrono 1989) the current evidence supports the use of aspirin 75 to 150 mg daily for the prevention of vascular events in high risk individuals.

Indirect comparisons with aspirin of various different antiplatelet drugs in the most recent ATT overview showed no clear evidence of differences in the occurrence of vascular events, but the most promising drug in such comparisons was ticlopidine, which produced a 32% (95% confidence interval (CI) 21% to 42%) odds of a serious vascular event compared to a 23% (95% CI 19% to 27%) odds reduction with aspirin alone. However, indirect comparisons are unreliable and direct comparisons between ticlopidine and aspirin among a total of 3791 high vascular risk patients in four trials showed no definite difference, although there was a non-significant trend toward a lower rate of serious vascular events in those treated

with ticlopidine (odds reduction 12%, 95% CI -3% to 25%) (ATT 2002).

Whilst these results may reflect a truly greater benefit of ticlopidine compared with aspirin, they may merely reflect the play of chance. Nevertheless, it is biologically plausible that ticlopidine is a more effective antiplatelet agent than aspirin because it inhibits a completely different pathway of platelet activation. Aspirin inhibits platelet activation by inhibiting platelet cyclooxygenase, and thromboxane production (Patrono 1994). By contrast, ticlopidine inhibits the binding of adenosine diphosphate (ADP) to its receptor on platelets, thereby inhibiting ADP-dependent activation of the glycoprotein IIb-IIIa complex, the major receptor for fibrinogen on the platelet surface and the final common pathway of platelet activation (McTavish 1990).

The ATT overview also included a large randomised trial directly comparing another thienopyridine antiplatelet drug, clopidogrel, versus aspirin (CAPRIE). Clopidogrel is chemically related to ticlopidine and also inhibits platelet activation by selectively and irreversibly blocking the binding of ADP to its receptor on platelets. In platelet aggregation studies, clopidogrel 75 mg once daily produced inhibition of ADP-induced platelet aggregation equivalent to that of ticlopidine, 250 mg twice daily (Hebert 1993). It was licensed in the USA and Europe following the results of the large randomised, blinded trial of clopidogrel (75 mg once daily) versus aspirin (325 mg once daily) in 19,185 patients at risk of ischaemic events (CAPRIE). After a mean follow up of 1.91 years, an intention-to-treat analysis showed that patients randomised to take clopidogrel had an annual risk of ischaemic stroke, MI, or non-haemorrhagic vascular death (the primary outcome event) of 5.3%, compared with 5.8% for patients taking aspirin (relative risk reduction: 8.7%, 95% CI 0.3 to 16.5%; $P = 0.04$; absolute risk reduction: 0.5% per year). There were no major differences in terms of safety. In particular, there was no excess neutropenia or thrombocytopenia among patients treated with clopidogrel. This is in contrast to ticlopidine, which is associated with an excess of neutropenia and thrombocytopenia (Moloney 1993), and is no longer widely used in Europe, USA, or Australasia.

Since thienopyridine drugs are chemically related, and have very similar modes of action on platelets, we have considered all the available randomised trials comparing any thienopyridine derivative with aspirin together in order to (1) minimise bias that may arise from considering the results of one trial rather than all relevant trials addressing a similar question, and (2) reduce the effects of random error in the assessment of the benefits and risks of treatment. In general, because the relative difference between the clinically relevant benefits of two active treatments is likely to be small (say about 10%), large numbers of outcome events, and thus very large numbers of randomised patients (several tens of thousands), are required to assess any such difference reliably. In this updated version of our review we have been able to include several relevant randomised trials that have become available since the ATT overview was published.

OBJECTIVES

Our objective was to determine the relative effectiveness and safety of thienopyridine derivatives (ticlopidine and clopidogrel), compared directly with aspirin (the current most commonly used first line antiplatelet drug), for the prevention of stroke and other serious vascular events in patients at high vascular risk (i.e. those

with previous TIA, ischaemic stroke, MI, angina, or PAD), and specifically in patients with previous TIA and ischaemic stroke, amongst whom the risk of a subsequent stroke is particularly high.

METHODS

Criteria for considering studies for this review

Types of studies

We included all truly randomised trials in which a thienopyridine derivative (ticlopidine, clopidogrel or any other more recently developed thienopyridine) was compared directly with aspirin, and in which patients were followed up prospectively and systematically for the occurrence of serious vascular events for at least one month.

Types of participants

Eligible patients were those at high risk of occlusive arterial disease due to previous clinical manifestations of atherosclerotic arterial disease of the cerebral, coronary or peripheral circulations.

Types of interventions

Orally administered thienopyridine antiplatelet drug compared with aspirin.

Types of outcome measures

The main outcome measure of effectiveness was the composite outcome of stroke, MI, or death from a vascular cause.

Secondary outcomes of effectiveness were the separate outcomes of stroke (ischaemic or haemorrhagic, non-fatal or fatal), MI (non-fatal or fatal), vascular death, and death from all causes.

Deaths were classified as due to ischaemic stroke, intracranial haemorrhage, MI, other vascular causes (e.g. sudden cardiac death, cardiac failure, ruptured aortic aneurysm, pulmonary embolism, extracranial haemorrhage), non-vascular causes, or of unknown cause (deaths that could not be assigned to any of the foregoing categories).

The main outcomes of safety were any intracranial haemorrhage, extracranial haemorrhage, gastrointestinal haemorrhage, neutropenia and thrombocytopenia.

Other outcomes of safety were skin rash, diarrhoea, and the composite outcome of indigestion, nausea and vomiting.

We used each trial's own definitions of the outcome events. If we extracted data on 'any' or 'severe' occurrences of safety outcomes, we used each trial's own definition of 'severe'.

Search methods for identification of studies

See the 'Specialised register' section in the [Cochrane Stroke Group](#) module.

We searched the trials registers of the following Cochrane Review Groups: Stroke Group, Heart Group and Peripheral Vascular Diseases Group (last searched July 2008), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2008), MEDLINE (1966 to August 2008) ([Appendix 1](#)) and EMBASE (1980 to August 2008) ([Appendix 2](#)). We sought additional unpublished information and data from the principal

investigators of the CAPRIE trial ([CAPRIE](#)), from the manufacturer of ticlopidine and clopidogrel, Sanofi-BMS (last contact December 2008), and from the principal investigator of AAASPS ([AAASPS](#)). For the previous version of this review in 1999, we searched the Antithrombotic Trialists' database which is now no longer available.

We obtained translations of reports in languages other than English from native speakers of the relevant language or from contact with the original authors, or both.

Data collection and analysis

Two authors (CLMS and GH or GM) independently reviewed potentially eligible studies, and extracted available details on the types of patients enrolled, the entry and exclusion criteria, the randomisation method (i.e. generation and concealment of the randomisation sequence), the number of patients originally allocated to the treatment group (thienopyridine) and the control group (aspirin), the method and duration of follow up, the number of patients in each group lost to follow up, information on compliance with the treatment allocated, the definitions of outcome events, the number of outcome events in each treatment group, and any method used for blinding patients, treating clinicians and outcome assessors to treatment allocation.

We resolved any disagreements among the authors by discussion and mutual consensus.

We analysed data on the basis of intention to treat, including every patient who was assigned to each treatment group, regardless of whether they actually complied with the allocated treatment, were subsequently deemed ineligible or otherwise excluded, or subsequently lost to follow up. In the main analyses we assumed that patients who were randomised and then either excluded or lost to follow up had no outcome event.

We calculated a weighted estimate of the odds ratio (OR) for each outcome using the Peto fixed-effect method.

We calculated absolute risk reductions (ARR) using the risk difference and expressed these as events prevented per 1000 patients treated.

We used the χ^2 and I^2 statistics to assess heterogeneity between trials.

For the primary outcome we carried out subgroup analyses in which we assessed the effects of each thienopyridine drug versus aspirin separately. We performed similar subgroup analyses for the safety outcomes of neutropenia, thrombocytopenia, skin rash and diarrhoea, since we had identified differences between clopidogrel and ticlopidine with respect to these outcomes in the previous version of this review.

To assess for consistency of the main effects in participants presenting with a stroke or TIA, we repeated analyses for the primary outcome and for stroke outcomes for these participants only.

We performed a sensitivity analysis to test the robustness to losses to follow up of the result for the primary outcome of serious vascular events in all high risk patients. For each trial we assumed that amongst patients lost to follow up from the thienopyridine

group, the proportion of vascular events experienced was the same as in the aspirin group, and that amongst patients lost to follow up from the aspirin group, the proportion of vascular events experienced was the same as in the thienopyridine group.

RESULTS

Description of studies

We identified a total of 10 completed randomised trials that met our inclusion criteria (AAASPS; CAPRIE; De Lucia 2000; Japanese-B; Li 2000; Sadowski 1995; Schoop 1983; STAMI; TASS; Zhu 2001). All trials were conducted in the past 20 years, and included a total of 26,865 patients, most of whom participated in CAPRIE (19,185), TASS (3069), AAASPS (1809) and STAMI (1470).

The patients were on average about 62 years of age, and 70% were men.

Aspirin was compared with clopidogrel in one trial of 19,185 patients with a qualifying diagnosis of recent (within one week to six months) ischaemic stroke (6431 patients), recent (within 35 days) MI (6302 patients) or PAD (6452 patients) (CAPRIE). Aspirin was compared with ticlopidine in the remaining nine studies in a total of 7,633 patients. These patients had recently diagnosed TIA or mild ischaemic stroke (5828 patients) (AAASPS; De Lucia 2000; Japanese-B; Li 2000; TASS; Zhu 2001), MI or angina (1790 patients) (Sadowski 1995; STAMI) or PAD (62 patients) (Schoop 1983). In one trial, three different doses of aspirin were each compared to ticlopidine (Zhu 2001). The most common dose of aspirin used in the 10 trials was 325 mg.

In CAPRIE, some of the patients who presented with a recent MI had also experienced a previous stroke, and likewise, some patients with a recent ischaemic stroke had also had a previous MI.

The duration of follow up varied between three and 40 months, with an average of about two years.

All trials recorded death, stroke, MI, and vascular death as major outcome events with the exception of two (Li 2000; Zhu 2001). Seven trials (26,255 patients) contributed to the main primary outcome as no numerical data were available for one other trial (De Lucia 2000).

A summary of the details of each of the trials included is in the [Characteristics of included studies](#) table.

Risk of bias in included studies

The methodological quality of the CAPRIE, TASS and AAASPS studies was high. Treatment allocation was randomised in all studies but the methods of randomisation and allocation concealment were not stated in seven (De Lucia 2000; Japanese-B; Li 2000; Sadowski 1995; Schoop 1983; STAMI; Zhu 2001). In three of these neither patients nor investigators were blinded (Li 2000; Schoop 1983; Zhu 2001). There were no important imbalances in known prognostic factors at baseline that might invalidate the results.

Seven trials reported losses to follow up (AAASPS; CAPRIE; Japanese-B; Li 2000; STAMI; TASS; Zhu 2001). The proportion of patients lost to follow up was low, averaging 2% of the total number of patients. However, in AAASPS the proportion lost to follow up

may have been as high as 14% as it was unclear how many patients in each arm were actually lost to follow up and how many withdrew but were still followed up to the end of the trial. In order to account for these losses we performed a sensitivity analysis. We were unable to include one trial that contributed to the primary outcome in the sensitivity analysis as it did not include any information on losses to follow up (Sadowski 1995).

In three trials (Li 2000; Japanese-B; Zhu 2001) including a total of 850 patients, losses to follow up were not included in the analyses presented in the trial reports making true intention-to-treat analysis impossible. However, we included all patients lost to follow up in the analyses in the denominator for all but one trial for which the number in each treatment arm was unavailable (Zhu 2001).

Effects of interventions

Of the 26,865 patients randomised in the 10 trials, the qualifying event was a recent TIA or ischaemic stroke in 12,259 patients, recent MI in 8092 patients, and PAD in 6514 patients.

The results presented below are derived from data extracted from publications (AAASPS; CAPRIE; Japanese-B; Li 2000; Sadowski 1995; Schoop 1983; STAMI; TASS; Zhu 2001), supplemented by additional unpublished data provided by the principal investigators of the CAPRIE trial, and one internal report (Schoop 1983). No numerical data was available for one trial (De Lucia 2000). The results are illustrated in the figures.

The TASS study presented its results for outcomes of effectiveness in terms of first outcome events. For composite outcome events (e.g. stroke, MI or vascular death) this strategy ensures that no patient is counted more than once. However, for specific single outcome events (e.g. stroke) this strategy can lead to undercounting (e.g. a patient with a non-fatal MI followed by a non-fatal stroke during the follow-up period will only be counted as having a non-fatal MI). Therefore, in TASS, the absolute number of strokes and MIs may have been undercounted. This strategy should not affect the estimates of the proportional effects of treatment because it applies to patients in both treatment groups, and without bias.

All high vascular risk patients

Serious vascular events (stroke, MI, or vascular death)

Data from seven trials including 26,255 patients (98% of the total) showed that allocation to a thienopyridine was associated with a modest, just significantly lower risk of the composite outcome stroke, MI or vascular death (thienopyridine 1519/13119 (11.6%) versus aspirin 1641/13136 (12.5%), OR 0.92, 95% CI 0.85 to 0.99), corresponding to the avoidance of about 10 (95% CI 0 to 20) serious vascular events per 1000 patients treated with a thienopyridine rather than aspirin for an average of about two years (Analysis 1.1). There was moderate but not statistically significant heterogeneity between results for the seven trials ($I^2 = 38\%$; Chi^2 (6 df) = 9.7; $P = 0.1$). Results for the ticlopidine versus aspirin and clopidogrel versus aspirin trial subgroups were similar (Analysis 1.2).

Stroke of all types

Data were available from seven trials including 98% of the total number of patients in the 10 included trials. Allocation to a thienopyridine was associated with a modest but non-

significant reduction in the combination of fatal and non-fatal stroke (758/13114 (5.8%) versus 827/13130 (6.3%)) (OR 0.91, 95% CI 0.82 to 1.01), corresponding to the avoidance of about 5 (95% CI 0 to 10) strokes per 1000 patients treated for about two years ([Analysis 1.3](#)).

Ischaemic stroke or stroke of unknown pathological type

Data were available from five trials including 22,778 patients (85% of the total) ([CAPRIE](#); [Li 2000](#); [Schoop 1983](#); [TASS](#); [Zhu 2001](#)). There was a significant reduction in the combination of fatal and non-fatal ischaemic or unknown stroke among patients allocated a thienopyridine (622/11355 (5.5%)) compared with those allocated aspirin (704/11423 (6.2%)) (OR 0.89, 95% CI 0.79 to 0.99) ([Analysis 1.4](#)).

Haemorrhagic stroke (intracranial haemorrhage)

Data were available from four trials including 84% of the total number of patients in the 10 included trials. There was a non-significant trend toward a lower rate of haemorrhagic stroke among patients allocated a thienopyridine than among those allocated aspirin in the doses used (43/11324 (0.38%) versus 48/11321 (0.42%); OR 0.89, 95% CI 0.59 to 1.35) ([Analysis 1.5](#)).

Myocardial infarction

Data were available from seven trials including 98% of the total number of patients. Allocation to a thienopyridine was associated with a non-significant reduction in MI (421/13114 (3.2%) versus 472/13130 (3.6%); OR 0.89, 95% CI 0.78 to 1.02) ([Analysis 1.6](#)).

Vascular or unknown cause of death during follow up

Data were available from seven trials (98% of the total number of patients). Overall, there were slightly fewer vascular deaths (539/13119 (4.1%)) in the thienopyridine group than in the aspirin group (569/13136 (4.3%)) but the reduction was not statistically significant (OR 0.95, 95% CI 0.84 to 1.07) ([Analysis 1.7](#)).

Death from any cause

Seven trials including 26,255 patients (98% of the total) reported death during follow up. The mortality among patients allocated a thienopyridine (793/13119 (6.04%)) was not significantly different from that among patients allocated aspirin (824/13136 (6.27%)) (OR: 0.96, 95%CI 0.87 to 1.06) ([Analysis 1.8](#)).

Extracranial haemorrhage (including gastrointestinal haemorrhage)

Data were available on any extracranial haemorrhage from three trials including 22,316 patients (83% of the total), and on severe extracranial haemorrhage from two trials including 19,505 patients (73% of the total). There was no significant difference in either severe extracranial haemorrhage (100/9753 (1.03%) versus 102/9752 (1.05%); OR: 0.98, 95% CI 0.74 to 1.29) or any extracranial haemorrhage (986/11159 (8.84%) versus 988/11157 (8.86%); OR: 1.0, 95% CI 0.91 to 1.09) ([Analysis 1.9](#)).

Gastrointestinal (GI) haemorrhage

Two trials ([CAPRIE](#); [TASS](#)) in 22,254 patients (83% of the total) reported results for any GI haemorrhage and both revealed a statistically significant reduction among patients allocated a thienopyridine (198/11128 (1.8%)) compared with those allocated aspirin (276/11126 (2.5%)) (OR 0.71, 95% CI 0.59 to 0.86). Many

fewer patients experienced severe GI haemorrhage (reported in three trials: [AAASPS](#), [CAPRIE](#) and [Schoop 1983](#), in a total of 21,056 patients, 78% of the total), but the odds reduction was similar ([Analysis 1.10](#)). These odds reductions correspond to around seven (two severe) fewer gastrointestinal haemorrhages per 1000 patients treated for about two years with a thienopyridine instead of aspirin.

Indigestion/nausea/vomiting

Thienopyridines were also associated with a lower rate of indigestion, nausea and vomiting (1666/11893 (14%)) than aspirin (1925/11893 (16%)) (OR 0.84, 95% CI 0.78 to 0.90; 20 fewer patients with upper gastrointestinal symptoms per 1000 treated for about two years with a thienopyridine instead of aspirin). Many fewer patients experienced severe indigestion, nausea or vomiting, but the odds reduction was similar ([Analysis 1.11](#)).

Neutropenia

Two trials (22,254 patients, 83% of the total) reported results for any neutropenia ($< 1.2 \times 10^9/L$) and three trials (24,063 patients, 90% of the total) reported results for severe neutropenia ($< 1 \times 10^9/L$). Pooled results suggested an excess of neutropenia in patients allocated a thienopyridine (OR 1.61, 95% CI 1.01 to 2.55 for any neutropenia; OR 2.02, 95% CI 1.27 to 3.21 for severe neutropenia) ([Analysis 1.12](#)). However, since there was substantial and significant heterogeneity between the results of the trials included ($I^2 = 89\%$; Chi^2 (1 df) = 8.9; $P = 0.003$ for any neutropenia; $I^2 = 71\%$; Chi^2 (2 df) = 6.9; $P = 0.03$ for severe neutropenia), the pooled results are difficult to interpret. The heterogeneity may arise in part from different effects on neutropenia of clopidogrel and ticlopidine; considering these two thienopyridines separately, the results do not suggest an excess risk of any neutropenia for clopidogrel versus aspirin (10/9599 (0.1%) versus 16/9586 (0.17%)), OR 0.63, 95% CI 0.29 to 1.36), but show an excess risk of any neutropenia for ticlopidine versus aspirin (35/1529 (2.3%) versus 12/1540 (0.8%)), OR 2.72, 95% CI 1.53 to 4.84, excess of about 15 per 1000 treated for about two years with ticlopidine versus aspirin) ([Analysis 1.13](#)).

Thrombocytopenia

Three trials (22,464 patients, 84% of the total) reported results for severe thrombocytopenia and two (20,655 patients, 77% of the total) for any thrombocytopenia. The data for any thrombocytopenia ($< 100 \times 10^9/L$) showed no significant excess among patients treated with a thienopyridine. There was a non-significant trend towards an excess of severe thrombocytopenia ($< 80 \times 10^9/L$) among patients treated with a thienopyridine (22/11235 (0.2%) versus 13/11229 (0.12%)), OR: 1.67, 95% CI 0.86 to 3.25). There was no detectable heterogeneity between the trials included or between subgroups of trials grouped according to the thienopyridine compared with aspirin (ticlopidine or clopidogrel) ([Analysis 1.14](#); [Analysis 1.15](#)).

Skin rash

Five trials (25,595 patients, 95% of the total) reported results for skin rash. Compared with aspirin, allocation to a thienopyridine was associated with an excess of any skin rash, but there was substantial heterogeneity between the results for the different trials ($I^2 = 80\%$; Chi^2 (4 df) = 19.6; $P = 0.0006$) ([Analysis 1.16](#)). Much of this heterogeneity appeared to arise from differences between ticlopidine and clopidogrel in their effects on skin rash.

Subgroup analyses found that, compared with aspirin, ticlopidine produced about a twofold excess in skin rash (213/3196 (6.7%) versus 106/3214 (3.3%)), OR 2.08, 95% CI 1.66 to 2.61, excess of about 30 patients per 1000 treated for about two years with ticlopidine versus aspirin) while clopidogrel produced about a one-third excess (578/9599 (6.0%) versus 442/9586 (4.6%)), OR 1.32, 95% CI 1.17 to 1.50, excess of about 15 patients treated for about two years with clopidogrel versus aspirin ([Analysis 1.17](#)). Only one trial reported results for occurrence of severe skin rash ([CAPRIE](#)), revealing a higher rate with clopidogrel than aspirin, but this outcome occurred much less frequently ([Analysis 1.16](#)).

Diarrhoea

Five trials (25,595 patients, 95% of the total) reported results for diarrhoea. Allocation to a thienopyridine was associated with an excess of diarrhoea, but there was substantial heterogeneity between the results for the different trials ([Analysis 1.18](#)). This heterogeneity appeared to be accounted for by differences between ticlopidine and clopidogrel in their effects on diarrhoea. Subgroup analyses found that, compared with aspirin, ticlopidine produced about a twofold excess of diarrhoea (332/3196 (10.4%) versus 160/3214 (5%)), OR 2.3, 95% CI 1.89 to 2.77, excess of about 50 patients per 1000 treated for about two years with ticlopidine versus aspirin), while clopidogrel produced about a one-third excess (428/9599 (4.5%) versus 322/9586 (3.4%)), OR 1.34, 95% CI 1.16 to 1.55, excess of about 10 patients per 1000 treated for about two years with clopidogrel versus aspirin ([Analysis 1.19](#)). Data from the [CAPRIE](#) trial also revealed a trend towards a higher rate of severe diarrhoea with clopidogrel, compared with aspirin, but this outcome occurred much less frequently ([Analysis 1.18](#)).

TIA or ischaemic stroke patients

Serious vascular events (stroke, MI, or vascular death)

Data for the composite outcome event of stroke, MI or vascular death during follow up for TIA/ischaemic stroke patients were available from four trials ([AAASPS](#); [CAPRIE](#); [Japanese-B](#); [TASS](#)). There was a modest but non-significant reduction in the odds of stroke, MI or vascular death among patients allocated a thienopyridine (959/5834 (16.4%)) compared with those allocated aspirin (1009/5815 (17.4%)) (OR: 0.94, 95% CI 0.85 to 1.03), corresponding to the avoidance of 10 (95% CI 0 to 20) serious vascular events per 1000 patients treated for about two years ([Analysis 2.1](#)). This was similar to the overall result for this outcome for all high vascular risk patients ([Analysis 1.1](#)).

Stroke of all types

Data on stroke of all types during follow up for TIA/ischaemic stroke patients were available from five trials ([AAASPS](#); [CAPRIE](#); [Japanese-B](#); [Li 2000](#); [TASS](#)). There was a borderline statistically significant reduction in the odds of any stroke in the group of patients allocated a thienopyridine compared with those allocated aspirin: 632/5999 (10.5%) patients in the thienopyridine group had a stroke compared with 696/5979 (11.6%) in the aspirin group (OR: 0.89, 95% CI 0.8 to 1); 10 (95% CI 0 to 20) strokes avoided per 1000 patients treated for two years ([Analysis 2.3](#)). The odds reduction is very similar to the result for this outcome for all high vascular risk patients ([Analysis 1.3](#)) but the higher overall risk of stroke in this subgroup of patients means that the absolute reduction in stroke is about twice as large, albeit estimated with substantial uncertainty with a wide confidence interval.

Different pathological types of stroke

There was a significant reduction in odds of ischaemic or unknown stroke among patients allocated a thienopyridine (490/4927 (9.9%)) compared with those allocated aspirin (564/4902 (11.5%)) (OR 0.85, 95% CI 0.75 to 0.97) ([Analysis 2.2](#)), but no clear difference between the rate of haemorrhagic stroke among patients allocated a thienopyridine (34/7927 (0.7%)) and those allocated aspirin (35/4902 (0.7%)) (OR 0.96, 95% CI 0.6 to 1.55) ([Analysis 2.4](#)).

Sensitivity analysis

This analysis to assess robustness of overall results for the primary outcome to the potential bias caused by losses to follow up produced no material difference in the result (thienopyridine 1557/13119 (11.9%) versus aspirin 1673/13136 (12.7%); OR: 0.92, 95% CI 0.86 to 0.99) ([Analysis 3.1](#)).

DISCUSSION

This review summarises the available data from the 10 published randomised trials of a thienopyridine versus aspirin in patients at high risk of vascular events. Although data were incomplete for some of the outcome events, they were available for all outcomes of interest from the largest trial, contributing 71% of the patients randomised ([CAPRIE](#)), and for almost all of these outcomes for the second largest trial, contributing 11% of the patients randomised ([TASS](#)). Data were available for most outcomes of interest from the third and fourth largest trials contributing 12% of the patients randomised ([AAASPS](#); [STAMI](#)). However, information on the type of stroke was unavailable for both these trials and since the [STAMI](#) trial was undertaken in participants with previous MI it did not contribute to analyses in the subset of patients with recent TIA or ischaemic stroke. The remaining trials were small and contributed in total only 6% of the patients randomised so most of the data reflect the results of the four largest studies ([AAASPS](#); [CAPRIE](#); [STAMI](#); [TASS](#)).

Pooling the data from trials of clopidogrel and ticlopidine (the thienopyridines) versus aspirin increases the sample size and therefore the accuracy of the estimates. Similarly, combining the vascular outcome events into a composite outcome of stroke, MI or vascular death also increases the statistical power and it is this analysis which provides the most reliable (i.e. statistically robust) estimate of the effect of thienopyridines in high risk patients. This analysis reveals that the thienopyridines are just statistically significantly more effective than aspirin in preventing serious vascular events among high vascular risk patients, but the magnitude of the additional benefit is uncertain and could be negligible. The proportional odds (and risk) reduction was about 8%, but may be as low as 1% or as high as 15% (the 95% confidence limits). If the average absolute annual risk of a serious vascular event with aspirin therapy is about 6% per year ([CAPRIE](#)), our best estimate would be that substituting aspirin with a thienopyridine may reduce this rate to about 5.5% (92% of 6%), but could reduce it to anywhere between 5.1% (85% of 6%) and 5.9% (99% of 6%). This corresponds to an absolute risk reduction (ARR) of about 0.5%, ranging between 0.1% and 0.9%, and means that treating 1000 patients with thienopyridines may prevent between one and nine extra events each year compared with aspirin. The number of high vascular risk patients who would need to be treated with a thienopyridine to prevent one event per year, compared with aspirin, may therefore vary from 100 to 900.

In high vascular risk patients, the proportional effect of the thienopyridines, compared with aspirin, on each of the separate outcomes of stroke, MI and vascular death was similar to the effect on the primary outcome of serious vascular events (i.e. about 10% odds reduction). The reduction in stroke seems to be mainly due to a reduction in ischaemic stroke, since the thienopyridines were associated with a 11% reduction in the odds of ischaemic stroke and had no clear effect on haemorrhagic stroke compared with aspirin.

Caution should be exercised in the interpretation of subgroup analyses (e.g. in TIA/ischaemic stroke patients), particularly when the overall magnitude of the treatment effect (in all high vascular risk patients) is substantially uncertain. However, among patients with previous TIA/ischaemic stroke, the proportional reduction in the odds of the primary outcome of serious vascular events (and of each of the separate outcomes of stroke, MI and vascular death) associated with the thienopyridines was similar to that in all high risk patients.

Most of the trials included in this review included mainly white patients, although not all gave specific details of the ethnicity or ethnicities of the participants. One trial specifically included Black African-Americans only (AAASPS). Interestingly, in this trial there was a non-significant trend towards aspirin being more effective than ticlopidine for the primary outcome of vascular events as well as for its separate components. However, while it is possible that black and white patients respond differently to different antiplatelet drugs, perhaps because of their different distributions of ischaemic stroke subtypes, it is important to note that there was no statistically significant heterogeneity between the seven trials contributing data to the primary outcome, so that any apparent differences between trials (and between ethnic groups) may well have arisen due to chance alone.

In terms of adverse effects, the results of this review show that aspirin is associated with a greater risk of gastrointestinal haemorrhage and upper gastrointestinal adverse effects. It is worth bearing in mind that the most common dose of aspirin used in the trials included in this review was 325 mg daily. The lower doses of 75 to 150 mg daily that are generally in widespread use for prevention of vascular events in high risk patients nowadays may compare more favourably with clopidogrel with respect to gastrointestinal adverse effects. On the other hand, the thienopyridines are associated with a greater risk of skin rash and diarrhoea (ticlopidine more so than clopidogrel) and ticlopidine is associated with an excess of neutropenia while clopidogrel appears not to be. Observational studies have found ticlopidine to be associated with a significant excess both of thrombocytopenia and thrombotic thrombocytopenic purpura (Bennett 1999; Moloney 1993; Steinhubl 1999; Torok 1995), and have shown clopidogrel to be associated with a very small (but not negligible) risk of thrombotic thrombocytopenic purpura (Zakarija 2004). The data from these observational studies, as well as from our review, and from short-term direct randomised comparisons between clopidogrel and ticlopidine, both in the presence of aspirin, among patients undergoing coronary stenting procedures (Bertrand 2000; Müller 2000), show that clopidogrel and ticlopidine have similar efficacy but clopidogrel has a more favourable safety and tolerability profile,

For every 1000 patients treated for about two years with either clopidogrel or aspirin, aspirin causes around seven more patients

to have a gastrointestinal haemorrhage (two severe) and around 20 more to have upper gastrointestinal symptoms, while clopidogrel causes around 15 more patients to have a skin rash and around 10 more to have diarrhoea. It is difficult to compare these different outcomes directly, but these data would suggest that the two drugs have approximately similar safety and tolerability.

Clopidogrel is substantially more expensive than aspirin (£460 versus £2 per patient per year) (BNF 2008). Since it is not clearly more effective than aspirin, it should generally only be used as monotherapy in patients who are genuinely intolerant of or allergic to aspirin. Furthermore, in patients developing upper gastrointestinal adverse effects with aspirin, the addition of a proton pump inhibitor to aspirin is both safer and cheaper than switching to clopidogrel (Chan 2005). Proton pump inhibitors reduce the risk of upper gastrointestinal peptic ulcer bleeding for patients taking either aspirin or clopidogrel (Lanas 2007), but there are concerns about the effectiveness of clopidogrel given together with a proton pump inhibitor because these drugs are thought to inhibit the antiplatelet effects of clopidogrel, and a large observational study has suggested that this may adversely affect clinical outcomes (Ho 2009).

The combination of clopidogrel with aspirin has now been demonstrated in randomised trials to be of net benefit compared with aspirin alone in the early months after an acute coronary syndrome or percutaneous coronary intervention (Sabatine 2005). But, in patients with a prior ischaemic stroke or TIA the combination increased the risk of haemorrhage without increasing net benefit compared with clopidogrel alone (MATCH 2004), and in high vascular risk patients with a prior ischaemic stroke or TIA, peripheral arterial disease, stable coronary artery disease or vascular risk factors the combination was not superior to aspirin alone (CHARISMA 2006). However, there were promising results for the combination from the subgroup of patients randomised within a week of onset of ischaemic stroke or transient ischaemic attack in the MATCH trial of aspirin plus clopidogrel versus clopidogrel alone (MATCH 2004), from a small randomised pilot trial of clopidogrel plus aspirin versus aspirin alone started within 24 hours of minor ischaemic stroke or transient ischaemic attack (FASTER), and from a randomised trial showing that adding clopidogrel to aspirin reduced transcranial Doppler ultrasound signals (thought to represent asymptomatic emboli) in patients with severe carotid stenosis (CARESS). Together these suggest that the combination may be beneficial very early after ischaemic stroke or TIA when the recurrence risk is particularly high.

Newer thienopyridine derivatives are now becoming available that may improve on the benefits of clopidogrel by producing a more consistent antiplatelet effect. Recent randomised trials have shown superiority of the combination of the new thienopyridine drug, prasugrel, plus aspirin compared with clopidogrel plus aspirin in patients with acute coronary syndromes, although at the expense of a higher haemorrhage risk (TRITON-TIMI 38 2007). However, there are no direct randomised comparisons of any thienopyridine other than ticlopidine or clopidogrel with aspirin, and no current evidence base to support the use of prasugrel as antiplatelet monotherapy.

Current guidelines for prevention of further vascular events after ischaemic stroke or TIA suggest that the combination of aspirin with modified release dipyridamole 200 mg twice daily is the antiplatelet regimen of choice, based on the results of

two randomised trials comparing these two regimens in a total of about 6000 patients ([ESPRIT](#); [ESPS-2](#); [NICE Guidelines](#); [RCP Guidelines](#); [SIGN Guidelines](#)). However, a subsequent large trial in about 20,000 patients with a prior ischaemic stroke or TIA compared this combination with clopidogrel alone and found no difference in effects on vascular events ([PRoFESS](#)). When the available data from randomised trials of all three relevant comparisons (aspirin versus clopidogrel, aspirin versus aspirin plus modified release dipyridamole, and clopidogrel versus aspirin plus modified release dipyridamole) were considered together in a network meta-analysis ([PRoFESS Editorial](#)), there were no overall significant differences, suggesting that there is still no antiplatelet regimen that is clearly superior to aspirin alone in long-term prevention in high vascular risk patients.

Finally, there remains the question of what to do about antiplatelet treatment when high vascular risk patients have further events while taking aspirin alone. This will to some extent be determined by the ASCET study, in which 1000 patients with documented coronary heart disease will be randomised to either continued treatment with aspirin 160 mg daily or change to clopidogrel 75 mg daily and followed for two years after initial determination of their platelet reactivity while on aspirin treatment ([ASCET](#)). However, further large trials addressing this question will be needed to generate reliable answers.

A further randomised trial, in which around 1000 patients with heart failure (mainly due to ischaemic heart disease) were randomised between aspirin and clopidogrel and followed for about two years, was published after the searches for the current version of this review had been completed ([WATCH](#)). It found no significant differences in the effects of the two antiplatelet drugs on the trial's stated primary outcome of all-cause mortality, non-fatal MI or non-fatal stroke (hazard ratio clopidogrel versus aspirin 1.08, 95% CI 0.83 to 1.40), on any of the separate components of this primary outcome, or on intracranial or extracranial haemorrhages. From these results, it seems very unlikely that the formal inclusion of this trial in our systematic review would materially alter the results or conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

The role of thienopyridines in clinical practice should be determined by the proportional reduction in risk of serious vascular

events compared with alternative antiplatelet drugs, the absolute benefit they confer, their cost, and safety. Thienopyridines are at least as effective as aspirin and possibly somewhat more so. Ticlopidine and clopidogrel appear to be very similar in terms of efficacy and safety, except that ticlopidine is associated with more skin rash and diarrhoea as well as a risk of bone marrow suppression and thrombotic thrombocytopenic purpura, making clopidogrel the thienopyridine of choice on safety and tolerability grounds. However, since clopidogrel is substantially more expensive than aspirin and the magnitude of any additional benefit over aspirin is uncertain, it should generally only be used as monotherapy in patients who are genuinely intolerant of or allergic to aspirin.

Implications for research

Future large trials are needed to address two important, unresolved issues.

1. What clinicians should do about antiplatelet treatment when high vascular risk patients have further vascular events while taking aspirin alone. It remains unclear whether increasing the daily dose of aspirin, substituting aspirin with an alternative antiplatelet drug (eg. a thienopyridine such as clopidogrel) or adding another antiplatelet drug to aspirin are of net benefit in this situation.
2. Whether combining a thienopyridine derivative, such as clopidogrel, with aspirin is safe and more effective than either alone in the early very high risk period after acute ischaemic stroke or TIA when the recurrence risk is particularly high and the benefits may outweigh the risks. Despite this being a potentially promising strategy, at present there is no clear evidence to support the use of the combination in such patients.

ACKNOWLEDGEMENTS

We are very grateful to Hazel Fraser, Cochrane Stroke Group Managing Editor, for her help in preparing this review, to the referees, Professors Charles Warlow and Peter Sandercock (Cochrane Stroke Group Editors) and Dr Daniel Bereczki, for their helpful comments on previous versions of the review, and to Professors Mike Gent and Robin Roberts for providing additional unpublished data from the [CAPRIE](#) trial, and for their helpful comments on previous versions of the review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by year of study]

Japanese-B

Methods	R = randomised but method not stated C = not stated

Japanese-B (Continued)

Blinding: clinician, patient, assessor

Participants	101 centres in Japan 340 patients randomised; 1981 to 1983 Recent (within 3 months) TIA Balanced prognostic factors
Interventions	Ticlopidine (2 x 100 mg tablets) and 1 placebo tablet versus aspirin (1 x 500 mg tablet) and 2 placebo tablets Mean duration of treatment: 17 months
Outcomes	Frequency, duration and severity of TIA, RIND, cerebral and MI
Notes	Co: "About half" discontinued medication before completing the 12-month follow up (due to expiry of study period for patients who were entered late, lost to follow up, and adverse reactions) 59 patients (34 ticlopidine, 25 aspirin) were not included in analysis of efficacy; 6 patients (5 ticlopidine and 1 aspirin) excluded post-randomisation because of questionable diagnosis of TIA or incorrect medication (the meaning of the latter requires clarification; does it mean that treatment was unblinded?); 39 were not considered to have had a TIA within 3 months (21 ticlopidine, 18 aspirin), and 14 discontinued medication within 2 weeks after entry (8 ticlopidine, 6 aspirin) Follow up: 12 months

Schoop 1983

Methods	R = randomised, but method not stated C = not stated Blinding: described as 'open' (and presumed that neither patients nor investigators blinded)
Participants	Single centre, Germany January 1979 to January 1983 Peripheral leg arteriopathy with unilateral femoral artery stenosis or occlusion, or the beginning of stenosis of the femoral or popliteal artery on the side opposed to the occlusion All male (62 men) Ex crit: thrombocytosis, diabetes, pulmonary insufficiency, thyroid dysfunction, severe hepatic or renal insufficiency, malignant hypertension, acute gastric or recurring ulcers, malignant tumours, or long-term treatment with drugs modifying platelet functions
Interventions	Ticlopidine 250 mg twice daily versus aspirin 500 mg 3 times daily Duration of Rx: 2 years
Outcomes	Primary outcome (not included in this review): thrombosis/occlusion of the contralateral femoral artery Secondary outcomes (included in this review): death, fatal MI, diarrhoea, nausea and gastric pain, skin rash
Notes	Co: withdrawals on ticlopidine: 8 (3 due to adverse drug reaction, 5 other, 0 deaths), withdrawals on aspirin: 23 (11 due to adverse drug reactions, 7 other, 5 deaths) Follow up: 36 patients (23 ticlopidine, 13 aspirin) completed 2 years in the trial, 27 per protocol (17 ticlopidine, 10 aspirin) 62 patients (31 ticlopidine, 31 aspirin) were analysed by intention to treat, and 44 patients (23 ticlopidine and 21 aspirin) were analysed per protocol, according to the inclusion criteria; the remaining 18 patients (8 ticlopidine and 10 aspirin) had bilateral femoral artery stenosis

TASS

Methods	R = central office, stratified by gender, previous TIA or stroke, previous severe stroke Blinding: treating clinician, patient, and assessor Medications in identical capsules and containers 12 patients (3 ticlopidine, 9 aspirin) judged ineligible after randomisation
Participants	56 centres in USA and Canada 3069 patients randomised (8814 screened), 1982 to 1986 TIA, RIND, or minor ischaemic stroke (at least 80% recovery within 3 weeks) due to presumed atherothromboembolism CT scan: 75% of patients (50% abnormal) Mean time from qualifying event to treatment: 21 days Mean age: 63 years Gender: 64% male Race: 80% white Comparability of groups: age, gender, vascular risk factors Ex crit: < 40 years; women of childbearing potential; history of carotid artery surgery or a moderate-to-major stroke < 3 months before a qualifying event; symptoms due to migraine, cardiogenic embolism, or haematological disorders; history of peptic ulcer, upper GI bleeding; life-threatening disease such as cancer; aspirin hypersensitivity or intolerance; aspirin or anticoagulant use required
Interventions	Ticlopidine 250 mg twice daily versus aspirin 650 mg twice daily Duration of Rx: mean 29 months ticlopidine, 26 months aspirin
Outcomes	Primary: non-fatal stroke or death from all causes Secondary: fatal and non-fatal stroke and MI
Notes	Co: 89% took at least 75% of medication more than 90% of the time; 24 (11 ticlopidine, 13 aspirin) never took drug Duration of follow up: 24 to 72 months (mean 40 months) Lost to follow up: 84 (3%) patients (46 ticlopidine, 38 aspirin)

Sadowski 1995

Methods	R = randomised but method not stated C = not stated Blinding = double blinded
Participants	320 patients Unstable angina type increasing angina (204) or rest angina (116)
Interventions	Ticlopidine and metoprolol, ticlopidine and gallopamil, aspirin and metoprolol, aspirin and gallopamil
Outcomes	Angina recurrence, MI and death
Notes	Duration of follow up: 3 months

CAPRIE

Methods	R = computer-generated balanced blocks of 4 with random allocation to indistinguishable blister packs containing either clopidogrel plus aspirin placebo or aspirin plus clopidogrel placebo tablets, stratified by clinical centre and the 3 disease subgroups; the initial supply of study drug had a sealed treatment code label attached which once opened could not be resealed C = access to code restricted to Independent Statistical Centre, Chairman of Safety and Efficacy Monitoring Committee and 2 companies responsible for preparing the study drugs

CAPRIE (Continued)

	Blinding: patients, clinicians (testing and assessing) Results available for all patients
Participants	384 centres in USA, Europe, and Australia 19,185 patients randomised, 1992 to 1995 6431 patients with recent ischaemic stroke (including retinal and lacunar infarction) likely to be of atherothrombotic origin 1 week to 6 months before randomisation; 6302 patients with recent MI < 35 days before randomisation; and 6452 patients with atherosclerotic peripheral arterial disease manifest as intermittent claudication and either ankle/arm systolic BP ratio < 0.85 in either leg at rest or previous peripheral artery surgery/angioplasty Mean age: 62.5 years Gender: 72% male Race: 95% white Comparability of groups: age, gender, and vascular risk factors Ex. crit: < 21 years, severe cerebral deficit, carotid endarterectomy after qualifying stroke, qualifying stroke induced by carotid endarterectomy or angiography, poor life expectancy (< 3 years), uncontrolled hypertension, contraindications to study drugs (aspirin sensitivity, bleeding diathesis, other antiplatelet drugs), women of childbearing potential not using contraception
Interventions	Clopidogrel 75 mg once daily versus aspirin 325 mg once daily
Outcomes	Primary: ischaemic stroke, MI, or vascular death Secondary: ischaemic stroke, MI, leg amputation, or vascular death; vascular death; stroke, MI or death from any cause; death from any cause
Notes	Co: mean compliance was 91% for clopidogrel and also for aspirin 86 patients (0.4%) never took any study drug (46 in clopidogrel group and 40 in aspirin group) 4059 patients (21.2%) permanently discontinued study drug early for reasons other than occurrence of an outcome event; 21.3% in the clopidogrel and 21.1% in the aspirin group Reasons for stopping drug early were: adverse events (11.4%), withdrawn consent (4.7%), contraindicated medications (2.4%), non-compliance (1.8%), and other (0.8%) Duration of follow up: mean follow up was 1.91 years Lost to follow up: 42 patients (0.22%), (22 in clopidogrel and 20 in aspirin groups) but were included in the analyses with their follow up censored at the time of last contact

AAASPS

Methods	R = randomisation sequence in blocks varying randomly in size from 2 to 8 Ratio of those receiving ticlopidine to aspirin was 1:1 Study participants registered by local study site personnel via a dedicated automated telephone registration system C = access to code restricted to chief study statistician Blinding: patients and all study personnel with exception of study statistician Ticlopidine and aspirin tablets dispensed with physically identical placebo from plastic bottles
Participants	62 centres in the USA 1809 patients randomised, 1995 to 2001 Black (African-American race, 29 to 85 years of age, noncardioembolic ischaemia stroke onset 7 to 90 days before randomisation CT or MRI image consistent with cerebral infarct and measurable neurological deficit correlating with infarct Mean age: 61 years Gender: 47% male Race: 100% Black Comparability of groups: age, gender and vascular risk factors Ex crit: TIA, SAH, cardiac source embolism, iatrogenic stroke, non-atherosclerotic stroke, post-operative stroke, carotid endarterectomy as primary treatment measure, mean arterial blood pressure > 130 mmHg on 3 consecutive days, modified Barthel index < 10, dementia or neurodegenerative disease, se-

AAASPS (Continued)

vere co-morbid condition such as cancer, allergy or insensitivity to study drugs, woman of childbearing potential, GI tract bleeding, bleeding diathesis, platelet or other haematological abnormality, haematuria, positive faecal occult blood test, prolonged prothrombin time or partial thromboplastin time, blood urea > 40mg/dL, serum creatinine > 2mg/dL, thrombocytopenia, neutropenia, liver function tests > 2 times upper limit of normal

Interventions	Ticlopidine 250 mg twice daily versus aspirin 325 mg twice daily
Outcomes	Primary: composite of recurrent stroke, MI or vascular death Secondary: stroke, MI, vascular death, any death
Notes	Co: median compliance was 90% for ticlopidine and 92% for aspirin Duration of follow up: mean follow up was 1.54 years Lost to follow up: 137 patients (15.2%) in the ticlopidine group and 121 (13.3%) in aspirin group were either lost to follow-up or voluntarily withdrew Most of these were due to voluntary withdrawals but it is uncertain whether follow-up data was available for these patients

De Lucia 2000

Methods	R = randomised but method not stated C = not stated Blinding = double blind but methods not stated
Participants	100 patients randomised Hx TIA, < 45 years old Mean age: 36 years Gender: 72% male
Interventions	Aspirin 100 mg daily versus ticlopidine 500 mg daily
Outcomes	Ischaemic stroke, MI, cancer and all causes of vascular death
Notes	No data available

Li 2000

Methods	R = randomised but method not stated C = not stated Blinding = described as 'open'
Participants	329 patients randomised Inclusion criteria according to Chinese standards of acute cerebral vascular disease classification and diagnosis Mean age: 64 years Gender: 70% male
Interventions	Aspirin 100 mg daily versus ticlopidine 500 mg daily
Outcomes	Primary: stroke and MI
Notes	Co: no information available Duration of follow up: 6 to 18 months Lost to follow up: 21 in the ticlopidine and 10 in aspirin group; they were not included in the analyses

Zhu 2001

Methods	R = randomised but method not stated C = not stated Not blinded
Participants	181 patients randomised Inclusion criteria according to Chinese stroke diagnosis standards Ex crit: Intolerance to antiplatelets or anticoagulant drugs, presence of bleeding disorder, low platelet count, cardiac source embolism, infarction induced by tumour, haemorrhagic stroke
Interventions	Aspirin (3 doses: 25 mg, 50 mg, 100 mg) versus ticlopidine 250 mg daily versus lumbrokinase 600 mg
Outcomes	Primary: recurrent stroke
Notes	Co: No information available Duration of follow up: 12 months Lost to follow up: 16 patients were not included in the analyses; of these 6 were lost to follow up, 7 suffered brain haemorrhage and 3 had low white cell count; the number in each treatment arm was not available

STAMI

Methods	R= randomised but method not stated C = not stated Blinding: patients, clinicians and outcome assessors Patients allocated to indistinguishable blister packs containing either ticlopidine or aspirin
Participants	Multicentre, number not stated 1470 patients randomised > 18 years old with MI (treated with thrombolytic therapy) ≤ 30 days before randomisation Mean age: 59 years Gender: 84% male Race: not stated Comparability of groups: age, gender, vascular risk factors Ex crit: contraindications to the study drugs including haemopoietic or haemostatic disorders, Hx thrombocytopenia, leucopenia or peptic ulcer, need for oral anticoagulant therapy, scheduled major or bypass surgery, severe co-morbidity likely to limit life-expectancy, uncontrolled hypertension, geographic or other factors likely to make participation impractical
Interventions	Ticlopidine 250 mg twice daily versus aspirin 80 mg twice daily
Outcomes	Primary: non-fatal MI, non-fatal stroke, angina with objective evidence of cardiac ischaemia, vascular death Secondary: vascular death, non-vascular death, non-fatal stroke, non-fatal MI, angina
Notes	Co: 333 (22.6%) patients permanently discontinued the study drug early; 152 in the aspirin group and 181 in the ticlopidine group Reasons for stopping the treatment early were adverse events (35 in aspirin group and 53 in ticlopidine group) Of these, 26 in the aspirin group and 21 in the ticlopidine group withdrew because of occurrence of a primary end point Duration of follow up: mean follow up was 6 months Lost to follow up: 32 (4.4%) in the ticlopidine group and 30 (4.1%) in the aspirin group

B: blood pressure

C: concealment of allocation
Co: compliance
Ex crit: exclusion criteria
GI: gastrointestinal
Hx: history
MI: myocardial infarction
R: randomisation method
RIND: reversible ischaemic neurological deficit
Rx: treatment
SAH: subarachnoid haemorrhage
TIA: transient ischaemic attack

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abe 1981	Outcome measure (platelet aggregation) was not a serious vascular event
Akyuz 1999	Non-randomised and outcome measure (platelet aggregation) was not a serious vascular event
Apollonio 1989	Non-randomised Comparison confounded for question of interest (ticlopidine and pentoxifylline versus aspirin, dipyridamole and buflomedil versus buflomedil)
Aramendi 1998	Non-randomised
Bergamasco 1997	Ticlopidine compared with indobufen, not aspirin
Cooke 2006	Outcome measures (platelet function) were not serious vascular events; follow up only 10 days
Dorr 2004	Outcome measures (platelet glycoprotein expression and aggregation) were not serious vascular events
Droste 1996	Duration of treatment was only 2 weeks (with cross over to 2 weeks of treatment with the alternative agent), and outcomes (haematological parameters, and asymptomatic cerebral emboli detected by transcranial doppler) were not important vascular events
Eder 2007	Outcome measure (platelet function) not serious vascular events
Fork 2000	Outcome measure (detection of macroscopic differences in the gastric mucosa) was not a serious vascular event
Jagroop 2004	Outcome measures (platelet function indices) were not serious vascular events
Kindsvater 2003	Outcome measure exercise tolerance, not serious vascular events; follow up several hours only
KTS 1999	Uncertain if randomised Presumably healthy participants
Lim 2004	Primary outcome measure (platelet aggregation) was not a serious vascular event
Nomura 1996	Outcome measure (platelet aggregation) was not a serious vascular event
Ozalp 1997	Uncertain if randomised; outcome measure (plasma fibrinogen) not a serious vascular event
Rebrov 2001	Outcome measures (haemostasis and platelet aggregation) were not serious vascular events
Rey 1996	Not randomised

Study	Reason for exclusion
Rupprecht 1998	Outcome measure (platelet aggregation) not serious vascular events; follow up for 14 days only
Singh 1999	Outcome measure (platelet aggregation) not serious outcome events; follow up 10 days only
Tokyo 1993	Comparison confounded for question of interest (ticlopidine versus ticlopidine plus aspirin)
Vyshlov 2000	Outcome measures (platelet aggregation) not serious vascular events; follow up only 21 days
Woodward 2004	Outcome measures (clotting factors and C reactive protein) were not serious vascular events
Zucca 1992	Not randomised Outcome measure (carotid restenosis demonstrated by carotid doppler) not a serious vascular event

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bokarev 1998

Methods	Uncertain
Participants	Patients with unstable angina
Interventions	Aspirin versus ticlopidine
Outcomes	Uncertain
Notes	Full paper awaited

WATCH

Methods	Randomised = centrally generated randomisation sequence for each site using varying block sizes of 3 or 6 Concealment of treatment allocation - centralised, telephone randomisation Blinding: of patients and clinicians to aspirin versus clopidogrel (warfarin arm open label); of end-point adjudication committee to allocated treatment Results available for all patients
Participants	1587 patients (523 aspirin, 524 clopidogrel) with symptomatic heart failure, in sinus rhythm, with left ventricular ejection fraction $\leq 35\%$ Mean age: 63 years Gender: 85% male Race: 77% white; 13% black Cause of heart failure ischaemic heart disease in 73% Comparability of groups: age, gender, cause and duration of heart failure, medications, vascular risk factors Ex crit: contraindications to or specific indications for study drugs, imminent procedures necessitating withdrawal or use of study drugs, heart failure from correctable causes, serious co-morbidity likely to limit life-expectancy, conditions likely to interfere with protocol adherence
Interventions	Aspirin 162 mg daily versus clopidogrel 75 mg daily versus warfarin (INR 2.5 to 3.0)
Outcomes	Primary: all-cause mortality, non-fatal MI or non-fatal stroke

WATCH (Continued)

Secondary: components of primary outcome, hospitalisations for heart failure

Notes	Trial stopped early due to slow enrolment Planned sample size originally 4500 patients Compliance: on the basis of returned tablet counts, 80% of prescribed aspirin and clopidogrel (or matching placebo) tablets taken 100 (19%) aspirin and 102 (19%) clopidogrel patients discontinued study drug early Duration of follow up: mean follow up was 1.9 years Lost to follow up: aspirin 24 (5%), 6 (1%) for vital status; clopidogrel 30 (6%), 8 (2%) for vital status

Ex crit: exclusion criteria

INR: International normalized ratio

MI: myocardial infarction

Characteristics of ongoing studies [ordered by study ID]

ASCET

Trial name or title	ASpirin non-responsiveness and Clopidogrel Endpoint Trial (ASCET)
Methods	Randomised, open label
Participants	1000 patients with documented coronary heart disease
Interventions	Continued treatment with aspirin 160 mg daily versus or change to clopidogrel 75 mg daily
Outcomes	Composite of unstable angina, myocardial infarction, stroke or death
Starting date	April 2003
Contact information	http://clinicaltrials.gov/ct2/show/NCT00222261
Notes	

DATA AND ANALYSES

Comparison 1. Thienopyridine versus aspirin in high vascular risk patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stroke, MI or vascular death during follow up	7	26255	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.85, 0.99]
2 Stroke, MI or vascular death (thienopyridine subgroups)	7	26255	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.85, 0.99]
2.1 Ticlopidine versus aspirin	6	7070	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.82, 1.07]
2.2 Clopidogrel versus aspirin	1	19185	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.83, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Stroke (of all types) during follow up	7	26244	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.82, 1.01]
4 Ischaemic/unknown stroke during follow up	5	22778	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.79, 0.99]
5 Haemorrhagic stroke (symptomatic intracranial haemorrhage) during follow up	4	22645	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.59, 1.35]
6 Myocardial infarction (MI) during follow up	7	26244	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.78, 1.02]
7 Vascular death during follow up	7	26255	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.84, 1.07]
8 Death from any cause during follow up	7	26255	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.87, 1.06]
9 Extracranial haemorrhage during follow up	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Severe	2	19505	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.74, 1.29]
9.2 Any	3	22316	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.91, 1.09]
10 Gastrointestinal haemorrhage during follow up	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 Severe	3	21056	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.47, 0.95]
10.2 Any	2	22254	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.59, 0.86]
11 Indigestion/nausea/vomiting during follow up	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
11.1 Severe	2	20655	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.61, 1.04]
11.2 Any	4	23786	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.78, 0.90]
12 Neutropenia during follow up	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
12.1 Severe	3	24063	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [1.27, 3.21]
12.2 Any	2	22254	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [1.01, 2.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Any neutropenia (thienopyridine subgroups)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
13.1 Ticlopidine versus aspirin	1	3069	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.72 [1.53, 4.84]
13.2 Clopidogrel versus aspirin	1	19185	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.29, 1.36]
14 Thrombocytopenia during follow up	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
14.1 Severe	3	22464	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.67 [0.86, 3.25]
14.2 Any	2	20655	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.61, 1.76]
15 Any thrombocytopenia (thienopyridine subgroups)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
15.1 Ticlopidine versus aspirin	1	1470	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.26, 8.66]
15.2 Clopidogrel versus aspirin	1	19185	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.57, 1.74]
16 Skin rash during follow up	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
16.1 Severe	1	19185	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.36 [1.21, 4.57]
16.2 Any	5	25595	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [1.32, 1.64]
17 Any skin rash (thienopyridine subgroups)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
17.1 Ticlopidine versus aspirin	4	6410	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [1.66, 2.61]
17.2 Clopidogrel versus aspirin	1	19185	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [1.17, 1.50]
18 Diarrhoea during follow up	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
18.1 Severe	1	19185	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [0.98, 3.85]
18.2 Any	5	25595	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [1.45, 1.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 Any diarrhoea (thienopyridine subgroups)	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
19.1 Ticlopidine versus aspirin	4	6410	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.28 [1.89, 2.77]
19.2 Clopidogrel versus aspirin	1	19185	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [1.16, 1.55]

Analysis 1.1. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 1 Stroke, MI or vascular death during follow up.

Analysis 1.2. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 2 Stroke, MI or vascular death (thienopyridine subgroups).

Analysis 1.3. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 3 Stroke (of all types) during follow up.

Analysis 1.4. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 4 Ischaemic/unknown stroke during follow up.

Analysis 1.5. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 5 Haemorrhagic stroke (symptomatic intracranial haemorrhage) during follow up.

Analysis 1.6. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 6 Myocardial infarction (MI) during follow up.

Analysis 1.7. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 7 Vascular death during follow up.

Analysis 1.8. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 8 Death from any cause during follow up.

Analysis 1.9. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 9 Extracranial haemorrhage during follow up.

Analysis 1.10. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 10 Gastrointestinal haemorrhage during follow up.

Analysis 1.11. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 11 Indigestion/nausea/vomiting during follow up.

Analysis 1.12. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 12 Neutropenia during follow up.

Analysis 1.13. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 13 Any neutropenia (thienopyridine subgroups).

Analysis 1.14. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 14 Thrombocytopenia during follow up.

Analysis 1.15. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 15 Any thrombocytopenia (thienopyridine subgroups).

Analysis 1.16. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 16 Skin rash during follow up.

Analysis 1.17. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 17 Any skin rash (thienopyridine subgroups).

Analysis 1.18. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 18 Diarrhoea during follow up.

Analysis 1.19. Comparison 1 Thienopyridine versus aspirin in high vascular risk patients, Outcome 19 Any diarrhoea (thienopyridine subgroups).

Comparison 2. Thienopyridine versus aspirin in patients with TIA or ischaemic stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stroke, MI, or vascular death during follow up	4	11649	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.85, 1.03]
2 Ischaemic/unknown stroke during follow up	3	9829	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.75, 0.97]
3 Stroke (of all types) during follow up	5	11978	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.80, 1.00]
4 Haemorrhagic stroke (symptomatic intracranial haemorrhage) during follow up	3	9829	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.60, 1.55]

Analysis 2.1. Comparison 2 Thienopyridine versus aspirin in patients with TIA or ischaemic stroke, Outcome 1 Stroke, MI, or vascular death during follow up.

Analysis 2.2. Comparison 2 Thienopyridine versus aspirin in patients with TIA or ischaemic stroke, Outcome 2 Ischaemic/unknown stroke during follow up.

Analysis 2.3. Comparison 2 Thienopyridine versus aspirin in patients with TIA or ischaemic stroke, Outcome 3 Stroke (of all types) during follow up.

Analysis 2.4. Comparison 2 Thienopyridine versus aspirin in patients with TIA or ischaemic stroke, Outcome 4 Haemorrhagic stroke (symptomatic intracranial haemorrhage) during follow up.

Comparison 3. Thienopyridine versus aspirin in high vascular risk patients - sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious vascular events (sensible worst case scenario)	7	26255	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.86, 0.99]

Analysis 3.1. Comparison 3 Thienopyridine versus aspirin in high vascular risk patients - sensitivity analysis, Outcome 1 Serious vascular events (sensible worst case scenario).

APPENDICES

Appendix 1. MEDLINE search strategy

We used the following search strategy for MEDLINE (Ovid) and adapted it for CENTRAL

1. ticlopidine/
2. (ticlopidine or ticlid or tiklid or tiklyd or ticlodix or ticlodone or ticlodine or anagrel or panalidine).tw.
3. (clopidogrel or plavix or iscover).tw.
4. thienopyridine\$.tw.
5. ((adenosine diphosphate or adp) adj5 receptor adj5 antagonist\$.tw.
6. 1 or 2 or 3 or 4 or 5
7. aspirin/
8. (aspirin or acetylsalicylic acid or acetyl salicylic acid).tw.
9. 7 or 8
10. Randomized Controlled Trials as Topic/
11. random allocation/
12. Controlled Clinical Trials as Topic/
13. control groups/
14. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
15. Clinical Trials Data Monitoring Committees/
16. double-blind method/
17. single-blind method/
18. Placebos/
19. placebo effect/
20. Drug Evaluation/
21. Research Design/
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
25. meta analysis.pt.
26. meta-analysis as topic/
27. random\$.tw.
28. (controlled adj5 (trial\$ or stud\$)).tw.
29. (clinical\$ adj5 trial\$).tw.
30. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
31. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
32. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
33. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
34. (coin adj5 (flip or flipped or toss\$)).tw.
35. latin square.tw.

36. (aspirin versus or versus aspirin).tw.
37. placebo\$.tw.
38. (assign\$ or alternate or allocat\$ or counterbalance\$ or multiple baseline).tw.
39. (meta-analy\$ or metaanaly\$ or meta analy\$ or systematic review or systematic overview).tw.
40. or/10-39
41. 6 and 9 and 40
42. limit 41 to human

Appendix 2. EMBASE search strategy

We used the following search strategy for EMBASE (Ovid)

1. ticlopidine/
2. (ticlopidine or ticlid or tiklid or tiklyd or ticlodix or ticlodone or ticlodine or anagregal or panaldine).tw.
3. clopidogrel/
4. (clopidogrel or plavix or iscover).tw.
5. thienopyridine\$.tw.
6. ((adenosine diphosphate or adp) adj5 receptor adj5 antagonist\$).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. acetylsalicylic acid/
9. (aspirin or acetylsalicylic acid or acetyl salicylic acid).tw.
10. 8 or 9
11. Randomized Controlled Trial/
12. Randomization/
13. Controlled Study/
14. control group/
15. exp Clinical Trial/
16. Double Blind Procedure/
17. Single Blind Procedure/
18. latin square design/
19. Parallel Design/
20. drug comparison/
21. "types of study"/
22. "systematic review"/
23. Meta Analysis/
24. random\$.tw.
25. (controlled adj5 (trial\$ or stud\$)).tw.
26. (clinical\$ adj5 trial\$).tw.
27. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
28. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
29. ((control or experiment\$ or conservative) adj5 (treatment or therapy)).tw.
30. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
31. (coin adj5 (flip or flipped or toss\$)).tw.
32. latin square.tw.
33. (meta-analy\$ or metaanaly\$ or meta analy\$ or systematic review or systematic overview).tw.
34. (assign\$ or allocate\$).tw.
35. (aspirin versus or versus aspirin).tw.
36. or/11-35
37. 7 and 10 and 36
38. limit 37 to human

WHAT'S NEW

Date	Event	Description
9 July 2009	New search has been performed	The review has been updated to include six new trials involving 4209 participants, bringing the total number of included trials to 10 involving 26,865 participants. The Background and Discussion sections have been updated to include new material of rele-

Date	Event	Description
		vance. The main conclusions are essentially unchanged from the previous version of the review.
9 July 2009	New citation required but conclusions have not changed	The authorship of the review has changed.

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 1, 2000

Date	Event	Description
18 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Dr Cathie Sudlow is the guarantor of this version of the review and supervised and participated in all aspects of its development, including searching for studies, study selection, data extraction, analysis, interpretation and writing of the review.

Dr Gillian Mason performed update searches for this version of the review, selected studies, extracted data from new studies, performed analyses and assisted with writing the review.

Catherine Wedderburn and James Maurice performed update searches for this version of the review, selected studies for inclusion and exclusion, and assisted with writing the review.

Prof Graeme Hankey co-ordinated searches, study selection, data extraction, analysis and writing of the previous version of this review, and assisted with writing the current version.

DECLARATIONS OF INTEREST

Prof Graeme Hankey has received honoraria for lecturing at scientific symposia sponsored by Sanofi Aventis, Bristol Meyers Squibb, and Boehringer Ingelheim, and has received fees for consulting from Sanofi Aventis, Bristol Meyers Squibb, and Boehringer Ingelheim.

SOURCES OF SUPPORT

Internal sources

- Royal Perth Hospital Clinical Staff Education Fund, Australia.

External sources

- Wellcome Trust, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Aspirin [*therapeutic use]; Cardiovascular Diseases [*prevention & control]; Clopidogrel; Myocardial Infarction [prevention & control]; Platelet Aggregation Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Stroke [prevention & control]; Ticlopidine [analogs & derivatives] [*therapeutic use]

MeSH check words

Humans