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Antiplatelet agents and anticoagulants for hypertension (Review)

Shantsila E, Kozieł-Siołkowska M, Lip GYH

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TABLE OF CONTENTS

[Intervention Review]

Antiplatelet agents and anticoagulants for hypertension

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ABSTRACT

Background

The main complications of elevated systemic blood pressure (BP), coronary heart disease, ischaemic stroke, and peripheral vascular disease, are related to thrombosis rather than haemorrhage. Therefore, it is important to investigate if antithrombotic therapy may be useful in preventing thrombosis-related complications in patients with elevated BP.

Objectives

To conduct a systematic review of the role of antiplatelet therapy and anticoagulation in patients with elevated BP, including elevations in systolic or diastolic BP alone or together.

To assess the effects of antiplatelet agents on total deaths or major thrombotic events or both in these patients versus placebo or other active treatment.

To assess the effects of oral anticoagulants on total deaths or major thromboembolic events or both in these patients versus placebo or other active treatment.

Search methods

The Cochrane Hypertension Information Specialist searched the following databases for randomised controlled trials (RCTs) up to January 2021: the Cochrane Hypertension Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 12), Ovid MEDLINE (from 1946), and Ovid Embase (from 1974). The World Health Organization International Clinical Trials Registry Platform and the US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) were searched for ongoing trials.

Selection criteria

RCTs in patients with elevated BP were included if they were ≥ 3 months in duration and compared antithrombotic therapy with control or other active treatment.

Data collection and analysis

Two review authors independently extracted data for inclusion criteria, our prespecified outcomes, and sources of bias. They assessed the risks and benefits of antiplatelet agents and anticoagulants by calculating odds ratios (OR), accompanied by the 95% confidence intervals (CI). They assessed risks of bias and applied GRADE criteria.

Main results

Six trials (61,015 patients) met the inclusion criteria and were included in this review.

Four trials were primary prevention (41,695 patients; HOT, JPAD, JPPP, and TPT), and two secondary prevention (19,320 patients, CAPRIE and Huynh). Four trials (HOT, JPAD, JPPP, and TPT) were placebo-controlled and two studies (CAPRIE and Huynh) included active comparators.

Four studies compared acetylsalicylic acid (ASA) versus placebo and found no evidence of a difference for all-cause mortality (OR 0.97, 95% CI 0.87 to 1.08; 3 studies, 35,794 participants; low-certainty evidence). We found no evidence of a difference for cardiovascular mortality (OR 0.98, 95% CI 0.82 to 1.17; 3 studies, 35,794 participants; low-certainty evidence). ASA reduced the risk of all non-fatal cardiovascular events (OR 0.63, 95% CI 0.45 to 0.87; 1 study (missing data in 3 studies), 2540 participants; low-certainty evidence) and the risk of all cardiovascular events (OR 0.86, 95% CI 0.77 to 0.96; 3 studies, 35,794 participants; low-certainty evidence). ASA increased the risk of major bleeding events (OR 1.77, 95% CI 1.34 to 2.32; 2 studies, 21,330 participants; high-certainty evidence).

One study (CAPRIE; ASA versus clopidogrel) included patients diagnosed with hypertension (mean age 62.5 years, 72% males, 95% Caucasians, mean follow-up: 1.91 years). It showed no evidence of a difference for all-cause mortality (OR 1.02, 95% CI 0.91 to 1.15; 1 study, 19,143 participants; high-certainty evidence) and for cardiovascular mortality (OR 1.08, 95% CI 0.94 to 1.26; 1 study, 19,143 participants; high-certainty evidence). ASA probably reduced the risk of non-fatal cardiovascular events (OR 1.10, 95% CI 1.00 to 1.22; 1 study, 19,143 participants; high-certainty evidence) and the risk of all cardiovascular events (OR 1.08, 95% CI 1.00 to 1.17; 1 study, 19,143 participants; high-certainty evidence) when compared to clopidogrel. Clopidogrel increased the risk of major bleeding events when compared to ASA (OR 1.35, 95% CI 1.14 to 1.61; 1 study, 19,143 participants; high-certainty evidence).

In one study (Huynh; ASA verus warfarin) patients with unstable angina or non–ST-segment elevation myocardial infarction, with prior coronary artery bypass grafting (CABG) were included (mean age 68 years, 79.8% males, mean follow-up: 1.1 year). There was no evidence of a difference for all-cause mortality (OR 0.98, 95% CI 0.06 to 16.12; 1 study, 91 participants; low-certainty evidence). Cardiovascular mortality, non-fatal cardiovascular events, and all cardiovascular events were not available. There was no evidence of a difference for major bleeding events (OR 0.13, 95% CI 0.01 to 2.60; 1 study, 91 participants; low-certainty evidence).

Authors' conclusions

There is no evidence that antiplatelet therapy modifies mortality in patients with elevated BP for primary prevention. ASA reduced the risk of cardiovascular events and increased the risk of major bleeding events.

Antiplatelet therapy with ASA probably reduces the risk of non-fatal and all cardiovascular events when compared to clopidogrel. Clopidogrel increases the risk of major bleeding events compared to ASA in patients with elevated BP for secondary prevention.

There is no evidence that warfarin modifies mortality in patients with elevated BP for secondary prevention.

The benefits and harms of the newer drugs glycoprotein IIb/IIIa inhibitors, clopidogrel, prasugrel, ticagrelor, and non-vitamin K antagonist oral anticoagulants for patients with high BP have not been studied in clinical trials.

Further RCTs of antithrombotic therapy including newer agents and complete documentation of all benefits and harms are required in patients with elevated BP.

PLAIN LANGUAGE SUMMARY

Antiplatelet agents and anticoagulants for high blood pressure (hypertension)

Review question

We reviewed the evidence that examined whether antiplatelet agents reduced total deaths or major thrombotic events or both in patients with elevated blood pressure (BP) when compared to placebo or other active treatment. We also assessed whether oral anticoagulants reduced total deaths or major thrombotic events or both in these patients when compared to placebo or other active treatment.

Background

Although systemic (arterial) elevations in BP result in high intravascular pressure, the main complications of elevated BP, coronary heart disease events, ischaemic stroke, and peripheral vascular disease, are associated with thrombosis.

We wanted to discover whether the use of antithrombotic or antiplatelet therapy may be of particular benefit for primary prevention in reducing total deaths or major thrombotic events or both in patients with elevated BP. Moreover, we tried to determine whether antithrombotic or antiplatelet therapy may be beneficial for secondary prevention in reducing total deaths or major thrombotic events or both in patients with elevated BP.

Search date

This update of a previously published systematic review is current to January 2021.

Study characteristics

We included six trials with a combined total of 61,015 patients in this review. Four trials were primary prevention (41,695 patients; HOT, JPAD, JPPP, and TPT) and two were secondary prevention (19,320 patients; CAPRIE and Huynh). Four trials were placebo-controlled (HOT, JPAD, JPPP, and TPT) and two trials included active comparators (CAPRIE and Huynh). CAPRIE 1996 included patients from 16 countries in Europe and USA with recent ischaemic stroke, recent myocardial infarction (MI) or symptomatic peripheral vascular disease (PVD). Mean patients' age was 62.5 years. 72% of the patients were males, and 95% of the patients were Caucasians. HOT 1998 included patients from 26 countries, aged 50 to 80 years (mean 61.5 years) with hypertension. In TPT 1998, men aged between 45 and 69 years (mean 57.5 years) at high risk of ischaemic heart disease were recruited from 108 practices in the UK. Huynh 2001 included patients from Canada with mean age of 67 and with unstable angina or non-ST-segment elevation MI, with prior coronary artery bypass grafting (CABG), and who were poor candidates for a revascularisation procedure. JPAD 2012 included patients from Japan with type 2 diabetes, mean age 65 years and 55% male. JPPP 2019 included Japanese patients with atherosclerotic risk factors (hypertension, diabetes mellitus, or dyslipidaemia). Median age was 70 years and 42% of patients were men.

Key results

Antiplatelet therapy with acetylsalicylic acid (ASA), also known as aspirin, for primary prevention in patients with elevated BP did not modify mortality and increased the risk of major bleedings.

Antiplatelet therapy with aspirin probably reduces the risk of non-fatal and all cardiovascular events when compared to clopidogrel. Clopidogrel increases the risk of major bleeding events when compared to aspirin in patients with elevated BP for secondary prevention.

There is no evidence that oral anticoagulation with warfarin modifies mortality in patients with elevated BP for secondary prevention.

Ticlopidine, clopidogrel, and newer antiplatelet agents, such as prasugrel and ticagrelor have not been sufficiently evaluated in patients with elevated BP. Newer antithrombotic oral drugs (dabigatran, rivaroxaban, apixaban, and edoxaban) are yet to be tested in patients with high BP.

Certainty of the evidence

Most evidence in this review is associated with low-certainty evidence. The high risk of bias seemed to be associated with incomplete outcome data and selective reporting in two studies (Huynh and JPPP).

SUMMARY OF FINDINGS

Summary of findings 1. Aspirin compared to placebo for adults with hypertension

ASA compared to placebo for adults with hypertension

Patient or population: adults with hypertension (patients with atrial fibrillation, congestive heart failure, pre-eclampsia or pulmonary hypertension were excluded)
Settings: outpatients and hospitalised **(primary prevention)**
Intervention: ASA **(75 mg, 81 mg, or 100 mg)**
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI) Study population		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	ASA			
Total mortality Follow-up: mean 3.8 years	**40.1 per 1000 patients-year**	**38.8 per 1000 patients-year**	**OR 0.97** (0.87 to 1.08)	35,794 (3 studies)	⊕⊕⊖⊖ **low**[b]
Cardiovascular mortality Follow-up: mean 3.8 years	**13.7 per 1000 patients-years**	**13.4 per 1000 patients-years**	**OR 0.98** (0.82 to 1.17)	35,794 (3 studies)	⊕⊕⊖⊖ **low**[b]
Non-fatal cardiovascular events Follow-up: mean 4.4 years	**77.0 per 1000 patients-years**	**49.7 per 1000 patients-years**	**OR 0.63** (0.45 to 0.87)	2540 (1 study)	⊕⊕⊖⊖ **low**[c]
Major bleeding[a] Follow-up: mean 3.8 years	**7.7 per 1000 patients-years**	**13.4 per 1000 patients-years**	**OR 1.77** (1.34 to 2.32)	21,330 (2 studies)	⊕⊕⊕⊕ **high**
All cardiovascular events Follow-up: mean 3.8 years	**42.8 per 1000 patients-years**	**37.1 per 1000 patients-years**	**OR 0.86** (0.77 to 0.96)	35,794 (3 studies)	⊕⊕⊖⊖ **low**[d]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ASA: acetylsalicylic acid; **BP:** blood pressure; **CI:** confidence interval; **OR:** odds ratio.

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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[a]A major bleeding was defined as haemorrhagic stroke, or major blood loss defined as a drop in haemoglobin of > 2 g/dl with adequate hydration, or urgent transfusion with final haemoglobin after equilibration of less than pre-bleed level, or orthostatic hypotension, or supine BP < 90/60 mmHg.
[b]Total mortality and cardiovascular mortality have been downgraded twice (for imprecision, and unclear or high risk of bias).
[c]Non-fatal cardiovascular events have been downgraded twice (for unclear or high risk of bias and outcome reported in only 1 out of 4 included studies).
[d]All cardiovascular events have been downgraded twice (for imprecision, and for unclear or high risk of bias).

BACKGROUND

Description of the condition

Although systemic (arterial) elevations in blood pressure (BP) result in high intravascular pressure, the main complications of elevated BP, coronary heart disease (CHD), ischaemic stroke and peripheral vascular disease (PVD), are related to thrombosis. The association between elevated BP and risk for stroke and CHD has a linear relationship, with increasing risk for higher BP (Collins 1990a; Collins 1990b; Collins 1994). An increase in the diastolic BP by 10 millimetres of mercury (mmHg) is associated with a 33% increase in CHD events and a 50% increase in stroke events (Collins 1990a; Collins 1994). In middle and old age, there appears to be a direct relationship between the level of BP and the risk of cardiovascular death without any evidence of a threshold down to a BP as low as 115/75 mmHg (PSC 2002). In accordance with the observational data, BP reduction trials have shown a 16% reduction in CHD and 38% reduction in stroke (Collins 1990b).

Description of the intervention

Some complications related to elevated BP, heart failure (HF) or atrial fibrillation (AF), are themselves associated with thromboembolism (Lip 2001b). Evidence also points towards a prothrombotic or hypercoagulable state conferred by elevated BP, as evident by abnormalities of coagulation (Lee 1997; Lip 1994), platelet activation (Lee 1997; Lip 1994), and endothelial dysfunction (Lip 1997; Lip 2000; Vanhoutte 1996) in such patients. It therefore seems plausible that use of antithrombotic therapy may be of particular benefit in preventing the thrombosis-related complications of elevated BP (Lip 2001b).

How the intervention might work

The antithrombotic agent, acetylsalicylic acid (ASA), is established as an effective agent for secondary prevention in patients with proven occlusive vascular disease. However, it is not recommended for primary prevention, and it is unclear whether it has a role in patients with an increased risk of thrombotic complications such as those with elevated BP. Warfarin has also been found to be useful as thromboprophylaxis in patients with elevated BP and AF, but if BP remains uncontrolled, such therapy carries significant risk, especially from intracranial haemorrhage (Aguilar 2009; SPAF-II 1994).

Why it is important to do this review

The debate over the role of antiplatelet therapy and anticoagulation in patients with high BP in clinical practice is still ongoing. The JPAD 2012 and JPPP 2019 focused on Japanese patients in primary prevention.

OBJECTIVES

To conduct an update of a previously published systematic review of the role of antiplatelet therapy and anticoagulation in patients with elevated blood pressure (BP), including elevations in systolic or diastolic BP alone or together:

1. to determine whether antiplatelet agents (acetylsalicylic acid (ASA), non-steroidal anti-inflammatory drugs (NSAIDs), dipyridamole, clopidogrel, ticlopidine, prasugrel, ticagrelor) reduce total deaths or major thrombotic events or both in these patients when compared to placebo or other active treatment; and
2. to determine whether oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban or edoxaban or other vitamin K antagonist anticoagulants) reduce total deaths or major thromboembolic events or both in these patients when compared to placebo or other active treatment.

It should be noted that patients with atrial fibrillation (AF), heart failure (HF), and pre-eclampsia are excluded, as they are the subjects of separate Cochrane Reviews (Aguilar 2009; Duley 2004; Lip 2001a).

METHODS

Criteria for considering studies for this review

Types of studies

Single or double-blind randomised controlled trials (RCTs) comparing antiplatelet drugs or oral anticoagulation with placebo or active treatment **of at least 3 months in duration** were included. Cohort-studies, non-RCTs, and open-label studies were excluded.

The presence or absence of elevated blood pressure (BP) related target organ damage at baseline, was analysed separately if possible. For example, participants who have had a stroke and have elevated BP represented secondary prevention as compared to studies in individuals who have elevated BP but have no prior vascular disease.

Definitions of elevated blood pressure

The reader should note that all definitions of elevated BP, including that used in this review, are arbitrary. The crucial question concerns the question 'who benefits from this treatment?' Whilst the absolute benefit may be expected to increase with the level of BP, since BP is a risk factor for the events to be prevented, the iatrogenic risk (haemorrhage) is also expected to increase with increasing BP.

Types of participants

We included patients with at least mild increases in BP or isolated systolic or diastolic increases in BP as defined (for practical reasons) by the WHO-ISH Guidelines for Management of Hypertension 1999, British Society of Hypertension Guidelines for Management of Hypertension 2004, and/or 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Guidelines for the management of hypertension (WHO-ISHGMH 1999; Williams 2004; Williams 2018). In trials prior to 1999, WHO-ISH guidelines valid at the time of the study/publication were used and noted in the review (WHO-ISH 1993). Generally, a systolic BP ≥ 140 mmHg or a diastolic BP ≥ 90 mmHg or both were considered to be elevated and fitted the criteria.

We excluded patients with atrial fibrillation (AF), congestive heart failure (HF), pre-eclampsia, eclampsia, and pulmonary hypertension.

Types of interventions

Treatment duration of at least 3 months with antiplatelet agents (acetylsalicylic acid (ASA), non-steroidal anti-inflammatory

drugs (NSAIDs), dipyridamole, clopidogrel, ticlopidine, prasugrel, ticagrelor) or oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban or edoxaban or other vitamin K antagonist anticoagulants) were included. Available data on concomitant treatment were collected, where available.

Types of outcome measures

Primary outcomes

All-cause mortality and **cardiovascular mortality** (stroke, myocardial infarction (MI), sudden death, thromboembolic events).

Secondary outcomes

All non-fatal cardiovascular events (stroke, MI, thromboembolic events such as acute coronary syndrome, acute limb ischaemia, pulmonary embolism, deep vein thrombosis), as a composite endpoint.

All major bleeding events (fatal, non-fatal) as a composite endpoint. A major bleed was defined as haemorrhagic stroke, or major blood loss defined as a drop in haemoglobin of > 2 g/dl with adequate hydration, or urgent transfusion with final haemoglobin after equilibration of less than pre-bleed level, or orthostatic hypotension, or supine BP < 90/60 mmHg.

Tertiary outcomes

All cardiovascular events (sudden death, fatal, non-fatal: stroke, MI, thromboembolic events, coronary revascularization) as a composite endpoint. Any interaction between risk factors for cardiovascular disease or bleeding, and concomitant treatment were analysed if appropriate data were available. Further details were obtained from trial authors, if possible.

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist conducted systematic searches in the following databases for RCTs without language or publication status restrictions:

- the Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (to 8 January 2021);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 12) via the Cochrane Register of Studies;
- MEDLINE Ovid (1946 to 8 January 2021);
- Embase Ovid (1974 to 8 January 2021);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (to 8 January 2021);
- World Health Organization International Clinical Trials Registry Platform via the Cochrane Register of Studies (to 8 January 2021).

The Information Specialist modelled subject strategies for databases on the search strategy designed for MEDLINE. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We presented search strategies for major databases in Appendix 1.

Searching other resources

Other sources.

- We checked abstracts from national and international hypertension meetings to identify unpublished studies and relevant authors of these studies were contacted to obtain further details.
- The Cochrane Hypertension Information Specialist searched the Hypertension Specialised Register segment (which includes searches of MEDLINE, Embase, and Epistemonikos for systematic reviews) to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials.
- We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.
- Where necessary, we contacted authors of key papers and abstracts to request additional information about their trials.

Data collection and analysis

- Two review authors (Eduard Shantsila (ES) and Monika Kozieł-Siołkowska (MKS)) independently selected trials that met the inclusion criteria.
- The data extracted included information such as patient characteristics, concomitant treatments, study eligibility, quality, and outcomes.
- Trial quality criteria: assessment of quality for each trial was made in accordance with guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* based on adequacy of randomisation, degree of blinding, incomplete outcome reporting, selective outcome reporting, loss to follow-up, and other bias (Higgins 2011).
- Contacting trialists: for unpublished studies or where data were incomplete in published papers, attempts were made to contact authors or researchers to obtain further details. Where relevant, the drug company was contacted to attempt to obtain unpublished trial data on newer antiplatelet drugs that may have been used in patients with hypertension.
- Resolution of differences: in the rare instances where the two review authors (ES and MKS) disagreed over the grading and inclusion of the studies, they consulted a third person (Gregory Lip (GL)).
- Appropriate statistical analyses were used (e.g. fixed-effect or random-effects model, testing for heterogeneity, etc.). The outcome measures are reported as odds ratio with 95% confidence intervals. Due to lack of sufficient data, funnel-plot analyses could not be done for the correction for publication bias. At present, we do not intend to use individual patient data.

Selection of studies

Two review authors (ES and MKS) independently analysed for inclusion the titles and abstracts of all the potential studies we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there were any doubts, the third author was asked to arbitrate. We retrieved the full-text study reports/publication and two review authors independently screened the full-text and identified studies for inclusion. They also identified and recorded reasons for exclusion of the ineligible studies. We resolved any

disagreement through discussion or, if required, we consulted a third person (GL). We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram.

Data extraction and management

We used a data collection form for study characteristics and outcome data which was piloted on at least one study in the review. One review author (MKS) extracted study characteristics from included studies. We extracted the following study characteristics.

- Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, and date of study.
- Participants: number (N) randomised, N lost to follow-up/ withdrawn, N analysed, mean age, age range, gender, inclusion and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications, and excluded medications.
- Outcomes: primary, secondary, and tertiary outcomes specified and collected, and time points reported.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (ES and MKS) independently extracted outcome data from included studies. We resolved disagreements by consensus with a provision of involving a third person (GL) would it be required. One review author (MKS) transferred data into the Review Manager (Review Manager 2020) file. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (ES) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (ES and MKS) independently evaluated risk of bias for individual studies using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another author (GL). We evaluated the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective reporting (reporting bias).
- Other bias.

We graded each source of bias as high, low, or unclear, and included a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias was related to unpublished data or correspondence with a trialist, we reported this in the risk of bias table.

When analysing treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

We analysed dichotomous data using the Mantel-Haenszel method. The above mentioned data were presented as odds ratios (OR) with 95% confidence intervals (CIs).

Unit of analysis issues

The unit of analysis was individual participants in RCTs with parallel design. Participants were individually randomised to intervention groups. Studies with multiple time points or more than two arms were not included.

Dealing with missing data

We communicated with investigators or study sponsors in order to verify principal study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). Where this was not possible, and the missing data might introduce serious bias, we examined the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We inspected forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We used the I^2 statistic to measure heterogeneity among the trials in each analysis, but acknowledged that there was substantial uncertainty in the value of I^2 when there was only a small number of studies. We also considered the P value from the Chi^2 test. If we identified substantial heterogeneity we reported it and explored possible causes by prespecified subgroup analysis. We defined substantial heterogeneity using a threshold of I^2 50% or above.

Assessment of reporting biases

If we were able to pool more than 10 trials, we would have designed and evaluated a funnel plot to explore possible small study biases for the primary outcomes.

Data synthesis

We undertook meta-analyses only where this was meaningful i.e. if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

We used a fixed-effect model as the previous updates of the analysis indicated a relatively small number of eligible trials and the same intervention effect could be assumed.

Subgroup analysis and investigation of heterogeneity

Heterogeneity among trial participants could be related to age or comorbidities. There were insufficient data to carry out subgroup analyses.

Sensitivity analysis

Due to the small number of included studies, these planned sensitivity analyses were not performed.

Summary of findings and assessment of the certainty of the evidence

We designed a summary of findings table using the following outcomes: total mortality, cardiovascular mortality, non-fatal cardiovascular events, major bleedings, and all cardiovascular events. The five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) were used to evaluate the certainty of a body of evidence as it relates to the studies which contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017) using GRADEpro software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of studies using footnotes, and we left comments to aid reader's understanding of the review where necessary.
Judgements about evidence certainty were made by two review authors (ES and MKS) working independently, with disagreements resolved by discussion or involving a third author (GL). Judgements were justified, documented, and incorporated into reporting of results for each outcome.
We extracted study data, formatted our comparisons in data tables, and prepared a summary of findings table before writing the results and conclusions of our review.

RESULTS

Description of studies

See Characteristics of included studies.

Results of the search

The January 2021 search identified 3728 potentially relevant publications, of which 2398 records remained after de-duplication. Of the 2398, 1712 were removed by the Information Specialist after comparison with previously excluded records and the remaining 686 records were screened by the author team (Figure 1).

Figure 1. Flow diagram corresponding to the search update (2021).

91 studies were assessed for eligibility in this review. Nine potentially appropriate randomised controlled trials (RCTs) remained. One study had two publications, with two different definitions for elevated blood pressure (BP) used: patients with systolic BP > 145 mmHg (2000 publication), and patients treated with antihypertensive drugs at entry or during the trial (1998 publication) (TPT 1998). Both sets of data reported on different outcomes in hypertensive subgroups. These data were included as much as possible without duplication.

Among the other included studies, we tried to obtain further information from the authors. In most studies we were unable to retrieve the data, which was largely due to the length of time since publication of the original trials. However, details were successfully retrieved from two studies (CAPRIE 1996; Huynh 2001). One study had a duplicate publication including a subgroup analysis with a different definition of hypertension, systolic BP > 145 mmHg (2000 publication), than in the data set provided from the original trial, patients on antihypertensive medication at entry or during study (1998 publication) (TPT 1998). Both sets of data have been considered separately.

Included studies

We included six studies (CAPRIE 1996; HOT 1998; Huynh 2001; JPAD 2012; JPPP 2019; and TPT 1998). Two of the trials (JPAD 2012; JPPP 2019) were new in this update.

Participants

CAPRIE 1996 included patients from 16 countries in Europe and USA with recent ischaemic stroke, recent myocardial infarction (MI) or symptomatic peripheral vascular disease (PVD). Mean patients' age was 62.5 years. 72% of the patients were males, and 95% of the patients were Caucasians.

In HOT 1998, patients from 26 countries, aged 50 to 80 years (mean 61.5 years) with hypertension and diastolic BP between 100 mmHg and 115 mmHg were enrolled.

In TPT 1998, men aged between 45 and 69 years (mean 57.5 years) at high risk of ischaemic heart disease were recruited from 108 practices in the UK.

Huynh 2001 included patients from Canada with unstable angina or non-ST-segment elevation MI, with prior coronary artery bypass grafting (CABG), and who were poor candidates for a revascularisation procedure. Mean age of patients was 67 years.

JPAD 2012 included patients from Japan with type 2 diabetes, aged 30 to 85 years (mean age 65 years) with 55% males.

In the JPPP 2019, Japanese patients with atherosclerotic risk factors (hypertension, diabetes mellitus, or dyslipidaemia) were enrolled. Median age was 70 years. 42% of patients were men.

Interventions

CAPRIE 1996 - acetylsalicylic acid (ASA) versus clopidogrel.

HOT 1998 - ASA versus placebo.

TPT 1998 - ASA versus placebo or warfarin versus placebo.

Huynh 2001 - ASA versus placebo or warfarin versus placebo or ASA versus warfarin.

JPAD 2012 - ASA versus placebo.

JPPP 2019 - ASA versus placebo.

Outcomes

CAPRIE 1996 - all-cause mortality (vascular death, MI, ischaemic or haemorrhagic stroke), all-cause rehospitalisation (hospitalisation for ischaemic events (unstable angina, transient ischaemic attack (TIA), limb ischaemia) or for bleeding events). Non-fatal events (ischaemic stroke, MI, primary intracranial haemorrhage and leg amputation).

HOT 1998 - major cardiovascular events were defined as fatal and non-fatal MI, fatal and non-fatal stroke, and other cardiovascular

deaths. Silent MI was defined as new Q or QS waves without clinical signs of MI.

TPT 1998 - fatal and non-fatal events (i.e. coronary death and fatal and non-fatal MI). Stroke was a secondary endpoint.

Huynh 2001 - composite endpoint of all-cause mortality, MI or unstable angina requiring hospital admission. Other endpoints were coronary revascularisation.

JPAD 2012 - primary endpoint: any atherosclerotic event (a composite of sudden death from coronary, cerebrovascular, and aortic causes; non-fatal acute MI; unstable angina; newly developed exertional angina; non-fatal ischaemic and haemorrhagic stroke; transient ischaemic attack; or non-fatal aortic and PVD (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis). Secondary endpoints: each primary endpoint and combinations of primary endpoints and death from any cause.

JPPP 2019 - primary outcome: composite of death from cardiovascular causes (MI, stroke, and other cardiovascular causes), non-fatal stroke (ischaemic or haemorrhagic, including undefined cerebrovascular events), and non-fatal MI. The first secondary endpoint: a composite that included the same events as the primary endpoint, plus TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention. Other secondary endpoints: death from cardiovascular disease, death from non-cardiovascular causes, non-fatal stroke (ischaemic or haemorrhagic), non-fatal MI, TIA, angina pectoris, arteriosclerotic disease requiring surgery or intervention, and serious extracranial haemorrhage requiring transfusion or hospitalisation.

Funding and conflicts of interest

CAPRIE 1996 - the study was funded by Sanofi and Bristol-Myers Squibb.

HOT 1998 - the principal sponsor of the HOT Study was Astra AB, Sweden.

TPT 1998 - funding: Medical Research Council, British Heart Foundation, DuPont Pharma, and Bayer Corporation. GlaxoWellcome and Boehringer-Ingelheim provided warfarin free of charge during the pilot stage. DuPont Pharma provided warfarin, and Bayer Corporation provided ASA free of charge during the main trial.

Huynh 2001 - no information regarding funding of this study was provided.

JPAD 2012 - the study was supported by the Ministry of Health, Labour, and Welfare of Japan.

JPPP 2019 - the study was supported by the funds from the Japanese Ministry of Health, Labour, and Welfare, and the Wacksman Foundation of Japan.

Excluded studies

See Figure 1.

516 studies were excluded because of the coexistence of atrial fibrillation (AF) or generally lack of suitability of the study and due to lack of randomisation.

Among the studies evaluating non-steroidal anti-inflammatory drugs (NSAIDs) (including ASA), clopidogrel and ticlopidine, 67 studies were not included for further analysis for various reasons: 39 because of short duration of the studies (less than 3 months) and 12 due to inability to obtain data for the hypertensive subgroup (see Characteristics of excluded studies).

Three studies evaluating warfarin were excluded, since detailed data on the hypertensive patients were not available (CARS 2001; SPIRIT 1997; WARS 2001). One study evaluating rivaroxaban was also excluded due to lack of hypertensive group (ATLAS ACS 2-TIMI 51 2012). Two trials investigating rivaroxaban or ASA or both in secondary prevention had no information on the hypertensive patients despite inclusion of the majority of patients with elevated BP (COMPASS 2017; NAVIGATE ESUS 2018). Five studies investigating glycoprotein IIb/IIIa inhibitors or ticlopidine and their impact on cardiovascular and haemorrhagic events lacked sufficient follow-up data (EPIC 1999; EPILOG 1998; Finelli 1991; Novo 1996; Schuhlen 2001). A further publication was excluded due to the inability to acquire the relevant data (TASS 1998).

The CHANCE study (CHANCE 2017) compared two drugs (ASA and clopidogrel) versus one drug (ASA) which was not the aim of this review.

The APTC meta-analysis included mostly secondary prevention trials (142 out of 145) and compared the effects of antiplatelet therapy (at least 1 month duration) to placebo on a composite outcome measure, major vascular events (defined as non-fatal MI, non-fatal stroke or vascular deaths). Individual patient data for patients with baseline diastolic BP > 90 mmHg was reported from 29 of the trials (APTC 1994). These trials must have been mostly secondary prevention trials and probably would have met the inclusion criteria of this review. However, several attempts were made to obtain more information from the APTC authors as to the identity of and data from these 29 trials, but no replies were received.

Most of the excluded trials were less than 1 month duration, in particular the 5 GPIIb/IIIa inhibitor and ticlopidine trials were only observing the effects over a few days. We did not think that this observational period would be sufficient to make any meaningful statements about the prevention of thromboembolic events in hypertensive patients. Furthermore, the NSAID trials assessed the effects on BP itself rather than thromboembolic complications.

Risk of bias in included studies

Risk of bias has been assessed in the corresponding tables and figures (Figure 2; Figure 3) section, evaluating the internal validity of each included study.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

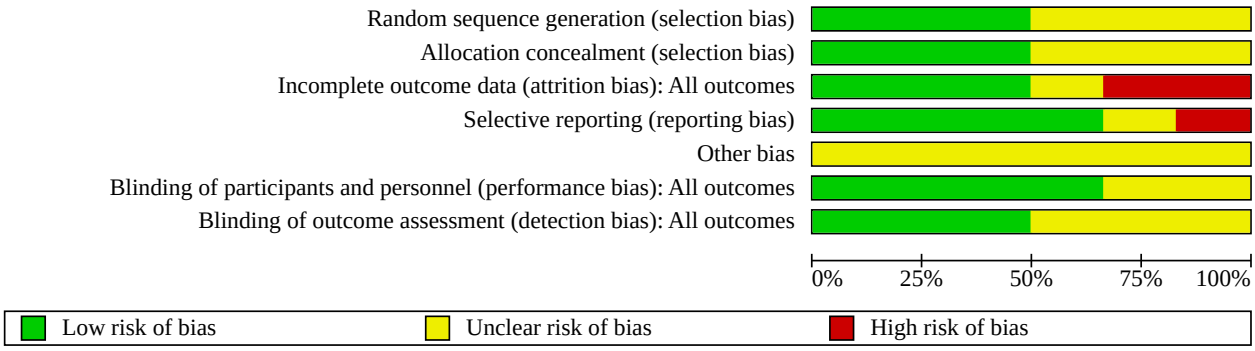
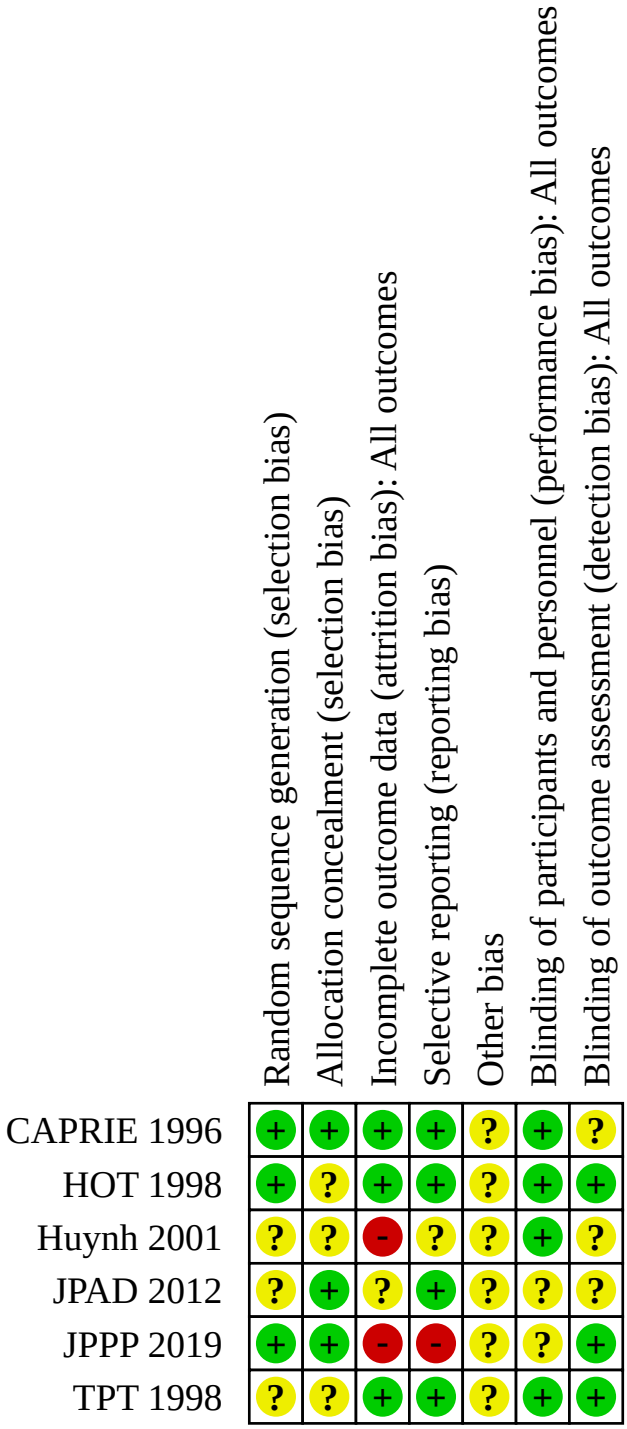


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Three studies (HOT 1998; JPAD 2012; JPPP 2019) gave information about how the randomisation sequence was generated.

CAPRIE 1996 had low risk of selection bias. Randomisation: computer-generated balanced blocks of four treatments with random sequential allocation of drug supplies packaged in predetermined order, each carton containing tablets for four patients.

HOT 1998 had also a low risk of selection bias. Computer-generated randomisation on the basis of baseline characteristics. Patients were stratified for a number of geographic variables.

TPT 1998 had unclear risk of bias. Randomised controlled trial, although the randomisation sequence generation technique used is not fully described.

Huynh 2001 had unclear risk of bias because of no information regarding the randomisation method.

JPAD 2012 had also unclear risk of bias. The randomisation was performed as non-stratified randomisation from a random number table. Other details are lacking. The sealed envelopes with random assignments were prepared, and they were sent by email to the physicians from the trial.

JPPP 2019 had low risk of bias. Pseudo-random numbers were generated using the Mersenne Twister method with a seed of 4989. The study statistician generated the random allocation sequence using a central computerised system and study physicians were sent the information about treatment via the study website or by fax. A placebo-controlled study design was not performed because the Japan Pharmaceutical Affairs Law limits the use of placebo in large, physician-led studies of approved products such as aspirin.

Blinding

CAPRIE 1996 had low risk of performance bias. Participants blinded. Blinding procedure is described (blisters packs with placebo tablets were given to patients, and platelet aggregation testing was forbidden). No information is given regarding personnel blinding. A central validation committee validated the reported outcome events unaware of randomisation code and independent statistical centre performed the analysis before randomisation scheme was provided. It had unclear risk of detection bias. Obtained from medical records; review authors do not believe this would introduce bias. However, no information about blinding of outcome assessor is given.

HOT 1998 had low risk of performance and detection bias. Patients were randomised in a double-blinded way to ASA or identical-looking placebo tablets. Patients randomised in the Study Co-ordinating Centre (blinded for trial personnel). A clinical event committee evaluated events masked to treatment allocation: review authors do not believe this would introduce bias.

TPT 1998 had low risk of performance and detection bias. Dose changes were matched on placebo warfarin. Patients were reviewed by their general practitioner (unaware of the allocated study group), records flagged in the NHS central register. Independent assessment of endpoints was carried out. Obtained from medical records: review authors do not believe this would introduce bias. Independent reviewer was unaware of treatment group.

Huynh 2001 had low risk of performance bias. Unblinded pharmacists or physicians, not otherwise involved in the study and patient care, adjusted warfarin to a targeted international normalised ratio (INR) (2.0 to 2.5). To maintain the double-blinded integrity, patients assigned to placebo therapy had also regular blood tests and mock adjustments. It had an unclear risk of detection bias. Obtained from medical records: review authors do not believe this would introduce bias. However, no information about blinding of outcome assessor is given.

JPAD 2012 had unclear risk of performance and detection bias. Open-label trial. Study participants were unblinded. Patients were randomly assigned to the ASA group or the non-ASA group. The randomisation was performed as non-stratified randomisation from a random number table. The details about study centre and explanation of the term non-aspirin groups are not provided. The trial is designed with blinded endpoint assessment. However, the way of blinding of outcome assessment is not described.

JPPP 2019 had unclear risk of performance bias and a low risk of detection bias. Patients were reviewed by their general practitioner (unaware of the allocated study group), records flagged in the NHS central register. Independent assessment of endpoints was carried out. Obtained from medical records: review authors do not believe this would introduce bias. Study endpoints were evaluated centrally and biannually by an expert, multidisciplinary event adjudication committee that was blinded to treatment assignments in accordance with the Prospective Randomized Open Blinded Endpoint (PROBE) trial design.

Incomplete outcome data

Three studies (CAPRIE 1996; HOT 1998; TPT 1998) had low risk of attrition bias.

In CAPRIE 1996, 0.3% of patients were lost to follow-up in each group.

In TPT 1998 only 1.1% of patients were lost to follow-up.

JPAD 2012 had unclear risk of attrition bias. There was a lack of planned statistical power due to the lower than expected incidence of atherosclerotic events. All-cause mortality was not reported. 193 patients (7.6%) were lost to follow-up.

Huynh 2001 had high risk of attrition bias. The study was terminated prematurely due to difficulty in recruiting because of high rate conventional and investigative procedures although only three patients (2.2% of 135 patients) were lost to follow-up.

JPPP 2019 had also high risk of attrition bias. 10.5% of patients were lost to follow-up.

Selective reporting

Four studies (CAPRIE 1996; HOT 1998; JPAD 2012; TPT 1998) had low risk of bias. All predetermined outcomes were reported. One study (Huynh 2001) had unclear risk of bias and one (JPPP 2019) had a high risk of reporting bias.

Even if they lack selective reporting (all predetermined outcomes were reported), we must keep in mind that we reviewed only

published articles. However, studies achieving inconclusive results are unlikely published.

Moreover, interpretation and comparisons among trials are difficult as they differ on the defined endpoints. Indeed, endpoints are usually a composite outcome, in which each study group includes different definition. Among the included studies, we tried to obtain further information from the authors. In most studies we were unable to obtain data, which was largely due to the length of time since publication of the original trials. However, details were successfully retrieved from two studies (CAPRIE 1996; Huynh 2001).

Other potential sources of bias

Huynh 2001 was underpowered by a low event rate to detect a difference between treatment groups. Patients with uncontrolled systemic hypertension were excluded. Moreover, no information is given about how financial support was provided.

In JPPP 2019 results might have been confounded by a decreasing level of adherence with daily low-dose ASA in the ASA group (dropping to 76% in year 5) and increasing uptake of daily ASA in the no ASA group (reaching 10% in year 5). Results are limited to Japanese population.

Financial support is listed in the 'Included studies' section.

Effects of interventions

See: **Summary of findings 1** Aspirin compared to placebo for adults with hypertension

1. Primary prevention trials of ASA versus placebo

(HOT 1998; JPAD 2012; JPPP 2019; TPT 1998)

Primary outcome measures

All-cause mortality

All-cause mortality was reported in three trials (HOT 1998; JPPP 2019; TPT 1998). We were unable to obtain data relating to all-cause mortality from JPAD 2012. The HOT 1998; JPPP 2019; and TPT 1998 studies showed no evidence of a difference for all-cause mortality (odds ratio (OR) 0.97, 95% confidence interval (CI) 0.87 to 1.08; 3 studies, 35,794 participants; low-certainty evidence).

Cardiovascular mortality

Cardiovascular mortality was reported in three trials (HOT 1998; JPPP 2019; TPT 1998). We were unable to obtain data relating to cardiovascular mortality from JPAD 2012. The HOT 1998; JPPP 2019; and TPT 1998 studies showed no evidence of a difference for cardiovascular mortality (OR 0.98, 95% CI 0.82 to 1.17; 3 studies, 35,794 participants; low-certainty evidence).

Secondary outcome measures

All non-fatal cardiovascular events

Total non-fatal cardiovascular events were reported in one trial (TPT 1998). They were not reported in HOT 1998; JPAD 2012; and JPPP 2019. In the TPT 1998 study, ASA reduced the risk of all non-fatal cardiovascular events (OR 0.63, 95% CI 0.45 to 0.87; 1 study, 2540 participants; low-certainty evidence).

Major bleeding events

Major bleeding events were reported in two trials (CAPRIE 1996; TPT 1998). They were not reported in HOT 1998; JPAD 2012; and JPPP 2019. In the CAPRIE 1996 and TPT 1998 trials, aspirin increased the risk of major bleeding events (OR 1.77, 95% CI 1.34 to 2.32; 2 studies, 21,330 participants; high-certainty evidence).

Tertiary outcome measures

All cardiovascular events

Cardiovascular events were evaluated in three studies (HOT 1998; JPPP 2019; TPT 1998). They were not reported in JPAD 2012.

In the HOT 1998; JPPP 2019; and TPT 1998 studies, aspirin reduced the risk of all cardiovascular events (OR 0.86, 95% CI 0.77 to 0.96; 3 studies, 35,794 participants; low-certainty evidence).

2. ASA versus clopidogrel; secondary prevention trial

(CAPRIE 1996)

Primary outcome measures

All-cause mortality

In the CAPRIE 1996 trial, there was no evidence of a difference for all-cause mortality (OR 1.02, 95% CI 0.91 to 1.15; 1study, 19,143 participants; high-certainty evidence).

Cardiovascular mortality

In the CAPRIE 1996 trial, there was no evidence of a difference for cardiovascular mortality (OR 1.08, 95% CI 0.94 to 1.26; 1 study, 19,143 participants; high-certainty evidence).

Secondary outcome measures

All non-fatal cardiovascular events

In the CAPRIE 1996 trial, ASA probably reduces the risk of non-fatal cardiovascular events when compared to clopidogrel (OR 1.10, 95% CI 1.00 to 1.22; 1 study, 19,143 participants; high-certainty evidence).

Major bleeding events

Clopidogrel increases the risk of major bleeding events when compared to ASA (OR 1.35, 95% CI 1.14 to 1.61; 1 study, 19,143 participants; high-certainty evidence).

Tertiary outcome measures

All cardiovascular events

In the CAPRIE 1996 trial, ASA probably reduces the risk of all cardiovascular events when compared to clopidogrel (OR 1.08, 95% CI 1.00 to 1.17; 1 study, 19,143 participants; high-certainty evidence).

3. ASA versus warfarin; secondary prevention trial

(Huynh 2001)

Primary outcome measures

Data on cardiovascular mortality were not available.

All-cause mortality

In the Huynh 2001 trial, there was no evidence of a difference for all-cause mortality (OR 0.98, 95% CI 0.06 to 16.12; 1 study, 91 participants; low-certainty evidence).

Secondary outcome measures

Data on all non-fatal cardiovascular events were not available.

Major bleeding events

In the Huynh 2001 trial, there was no evidence of a difference for major bleeding events (OR 0.13, 95% CI 0.01 to 2.60; 1 study, 91 participants; very low-certainty evidence).

Tertiary outcome measures

Data on all cardiovascular events were not reported.

DISCUSSION

Summary of main results

We included six studies (61,015 patients). Four studies were primary (41,695 patients, HOT 1998; JPAD 2012; JPPP 2019; TPT 1998), and two secondary prevention (19,320 patients, CAPRIE 1996; Huynh 2001). Four trials (HOT 1998; JPAD 2012; JPPP 2019; TPT 1998) were placebo-controlled, and two studies (CAPRIE 1996; Huynh 2001) included active comparators. The primary analysis in the present review is based on four high-quality, prospective, randomised, double-blinded, controlled trials and two prospective, randomised, open-label, controlled trials with blinded endpoint assessment. Four of these trials evaluated the effects of acetylsalicylic acid (ASA) as compared to placebo (HOT 1998; JPAD 2012; JPPP 2019; TPT 1998), whilst one trial compared the effects of ASA, warfarin and ASA plus warfarin (Huynh 2001). A further trial investigated the outcome of ASA versus clopidogrel (CAPRIE 1996).

The HOT 1998; JPPP 2019; and TPT 1998 studies showed no evidence of a difference for all-cause mortality. The HOT 1998; JPPP 2019; and TPT 1998 studies showed no evidence of a difference for cardiovascular mortality. In the TPT 1998 study, ASA reduced the risk of all non-fatal cardiovascular events. In the TPT 1998 trial, ASA increased the risk of major bleeding events. In the HOT 1998; JPPP 2019; and TPT 1998 studies, ASA reduced the risk of all cardiovascular events. See Summary of findings 1.

In the CAPRIE 1996 trial, there was no evidence of a difference for all-cause mortality, and cardiovascular mortality. In the CAPRIE 1996 trial, ASA probably reduces the risk of non-fatal cardiovascular events when compared to clopidogrel. Clopidogrel increases the risk of major bleeding events when compared to ASA. ASA probably reduces the risk of all cardiovascular events when compared to clopidogrel.

In the Huynh 2001 trial, there was no evidence of a difference for all-cause mortality, and major bleeding events.

The benefits and harms of the newer drugs glycoprotein IIb/IIIa inhibitors, clopidogrel, prasugrel, ticagrelor and oral antithrombotic agents (dabigatran, apixaban, edoxaban, and rivaroxaban) for patients with high blood pressure (BP) have not been studied in clinical trials.

Further randomised controlled trials (RCTs) of antithrombotic therapy including newer agents and complete documentation of all benefits and harms are required in patients with elevated BP.

Overall completeness and applicability of evidence

Antiplatelet data were mostly limited to ASA. There were no data available from subgroup analyses of patients with elevated BP treated with glycoprotein IIb/IIIa inhibitors. However, oral glycoprotein IIb/IIIa inhibitors have failed to demonstrate an advantage over ASA after percutaneous coronary revascularisation (EXCITE 2000). These patients are at high risk of thromboembolic events.

There are no data available with newer antiplatelets (i.e. prasugrel, ticagrelor) or oral anticoagulants (i.e. dabigatran, rivaroxaban, apixaban, edoxaban) as these have not been tested as yet in patients with elevated BP.

Quality of the evidence

Six studies were RCTs, but contributed to the certainty of the evidence with some limitations.

For ASA versus placebo, we downgraded total mortality and cardiovascular mortality twice (once for imprecision, and once for risk of bias due to incomplete outcome and reporting bias).

Non-fatal cardiovascular events have been downgraded twice (for risk of bias due to small sample size and reported only in one study). All cardiovascular events have been downgraded twice (for imprecision, and for risk of bias due to incomplete outcome and reporting bias).

For ASA versus clopidogrel, we assessed GRADE as high certainty for all-cause mortality, cardiovascular mortality, all non-fatal cardiovascular events, major bleeding events, and all cardiovascular events.

For ASA versus warfarin we downgraded all-cause mortality, and major bleeding events thrice (for imprecision due to low event rate, high risk of attrition bias, study terminated early, and small sample size).

Potential biases in the review process

The probability that all used methods (e.g. searching, study selection, data collection, and analysis) could have introduced bias is low.

Agreements and disagreements with other studies or reviews

The Antithrombotic Trialists (ATT) Collaboration 2009 (ATT Collaboration 2009) assessed the benefits and risks of ASA in the primary and secondary prevention of vascular disease. The analysis involved 18,790 men and women with diastolic BP 100 to 115 mmHg who received 75 mg ASA daily or placebo. The main outcomes were defined as vascular event (myocardial infarction, stroke, or death from a vascular cause including sudden death, pulmonary embolism, haemorrhage). In the primary prevention trials, ASA was associated with a 12% proportional reduction in vascular events (0.51% ASA versus 0.57% control per year, P = 0.0001), due to a reduction of about a fifth in non-fatal myocardial infarction (0.18% versus 0.23% per year, P < 0.0001). ASA did not

reduce the risk of stroke (0.20% versus 0.21% per year, P = 0.4: haemorrhagic stroke 0.04% versus 0.03%, P = 0.05; other stroke 0.16% versus 0.18% per year, P = 0.08).
ASA did not modify vascular mortality. ASA increased major gastrointestinal and extracranial bleeds (0.10% versus 0.07% per year, P < 0.0001).

AUTHORS' CONCLUSIONS

Implications for practice

Antiplatelet therapy with acetylsalicylic acid (ASA) for primary prevention in patients with elevated blood pressure (BP) provides a benefit, reduction of the risk of cardiovascular events, which is negated by a harm of similar magnitude: increase in major haemorrhage.

For secondary prevention in patients with elevated BP, ASA probably reduces the risk of non-fatal and all cardiovascular events when compared to clopidogrel. Clopidogrel increases the risk of major bleeding events when compared to aspirin in patients with elevated BP for secondary prevention.

There is no evidence that oral anticoagulation with warfarin modifies mortality when compared to ASA in patients with elevated BP for secondary prevention. There was no evidence of a difference for major bleeding events when warfarin was compared to ASA.

Ticlopidine, clopidogrel and newer antiplatelet agents such as prasugrel and ticagrelor have not been sufficiently evaluated in patients with high BP. Newer antithrombotic oral drugs such as dabigatran, rivaroxaban, apixaban, and edoxaban are yet to be tested in patients with high BP.

Implications for research

Further trials of antiplatelet therapies in patients with elevated BP are required to identify subgroups in whom benefits outweigh the harms and to determine whether there are differences in the effectiveness of different drugs. Specific attention to the standardised documenting of haemorrhagic events is essential. All strokes should be investigated with computerised tomography to differentiate between those of ischaemic and haemorrhagic origin. There should be standard definition of outcomes and complete reporting of all clinically relevant outcomes (mortality, fatal and non-fatal cardiovascular events, and major and minor bleeding).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

CAPRIE 1996

Study characteristics	
Methods	Randomised, double-blinded, multicentre**,** international (16 countries) study
Participants	19,185 patients with previous ischaemic stroke (onset > 1 week and < 6 months before randomisation), MI (onset < 35 days before randomisation) or symptomatic PVD Mean age (SD): 62.5 years (11.1), 72% males, 95% Caucasians. 9880 included patients diagnosed with hypertension at inclusion No information regarding blood pressure at baseline. Mean follow-up: 1.91 years
Interventions	ASA 325 mg vs clopidogrel 75 mg
Outcomes	All-cause mortality included vascular death, myocardial infarction, ischaemic or haemorrhagic stroke All-cause rehospitalisation: hospitalisation for ischaemic events (unstable angina, TIA, limb ischaemia) or for bleeding events Non-fatal events were ischaemic stroke, myocardial infarction, primary intracranial haemorrhage, and leg amputation
Notes	CAPRIE study (CAPRIE 1996): a secondary prevention trial in 19,185 patients with recent ischaemic stroke, recent MI or symptomatic peripheral arterial disease

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	No information is given regarding the randomisation process Randomisation: computer-generated balanced blocks of 4 treatments with random sequential allocation of drug supplies packaged in predetermined order, each carton containing tablets for 4 patients
Allocation concealment (selection bias)	Low risk	No information is given about allocation sequence before assignment Randomisation: computer-generated balanced blocks of 4 treatments with random sequential allocation of drug supplies packaged in predetermined order, each carton containing tablets for 4 patients
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 22 in clopidogrel group, 20 in ASA group; withdrawn nil
Selective reporting (reporting bias)	Low risk	Reported all predetermined endpoints
Other bias	Unclear risk	Financial support provided by Sanofi and Bristol-Myers Squibb
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded. Blinding procedure is described (blisters packs with placebo tablets were given to patients, and platelet aggregation testing was forbidden). No information is given regarding personnel blinding. A central validation committee validated the reported outcome events unaware of ran-

CAPRIE 1996 *(Continued)*

		domisation code and independent statistical centre performed the analysis before randomisation scheme was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Obtained from medical records; review authors do not believe this would introduce bias. However, no information about blinding of outcome assessor is given

HOT 1998

Study characteristics	
Methods	Prospective, randomised, open with blinded endpoint evaluation, multicentre, international (26 countries) DBP < 90 mmHg; DBP < 85 mmHg; DBP < 80 mmHg
Participants	19,193 patients with DBP 105 to 115 mmHg; age 50 to 80 (mean 61.5 years), with 53% males Average follow-up time was 3.8 years (range 3.3 to 4.9)
Interventions	ASA vs placebo Antihypertensive therapy was given to all patients, in a progressive way in order to reach the randomised target blood pressure: - step 1: felodipine (5 mg daily to all patients) - step 2: ACE inhibitor or beta-blocker (no dose information) - step 3: felodipine 10 mg daily - step 4: doubling the dose of either the ACE inhibitor or the beta-blocker (no exact dose information) - step 5: addition of diuretic (no information regarding dose or drug type)
Outcomes	Major cardiovascular events, + silent MI, all MI, all MI + silent MI, all CVA, cardiovascular mortality, total mortality Fatal bleed, non-fatal bleed, minor bleed
Notes	Had access to protocol or multiple publication to assess risk of bias for this study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation on the basis of baseline characteristics
Allocation concealment (selection bias)	Unclear risk	No information is given about allocation sequence before assignment. Only randomisation procedure is described
Incomplete outcome data (attrition bias) All outcomes	Low risk	245 patients (2.60%) from the ASA group and 246 (2.62%) from the placebo group were lost Review authors do not believe that this was large enough to introduce bias
Selective reporting (reporting bias)	Low risk	Reported all predetermined endpoints, similar loss in follow-up for both placebo and ASA groups. Silent MI analysed separately as 14% ECGs not obtained

HOT 1998 *(Continued)*

Other bias	Unclear risk	Financial support provided by Astra AB (Sweden), Astra Merck Inc. (USA), TEVA (Israel), and Hoechst (Argentina)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were randomised in a double-blinded way to ASA or identical-looking placebo tablets. Patients randomised in the Study Coordinating Centre (blinded for trial personnel)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A clinical event committee evaluated events masked to treatment allocation: review authors do not believe this would introduce bias

Huynh 2001

Study characteristics	
Methods	Double-blinded, randomised trial
Participants	135 patients with prior coronary artery bypass grafting (CABG) with unstable angina or non-ST elevation MI
Interventions	ASA + placebo or warfarin + placebo or ASA + warfarin
Outcomes	All-cause mortality, MI, unstable angina, reperfusion procedure
Notes	INR 2 to 2.5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information regarding the randomisation method
Allocation concealment (selection bias)	Unclear risk	No information regarding the randomisation method
Incomplete outcome data (attrition bias) All outcomes	High risk	The study was terminated prematurely due to difficulty in recruiting because of high rate conventional and investigative procedures although only 3 patients (2.2% of 135 patients) were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	The study was terminated prematurely due to difficulty in recruiting because of high rate conventional and investigative procedures. However, only 3 patients (2.2% of 135 patients) were lost to follow-up
Other bias	Unclear risk	Underpowered by a low event rate to detect a difference between treatment groups. The sample size was suboptimal, providing 60% power to detect a 15% risk difference, 70% power to detect a 20% risk difference, and 80% power to detect a 25% risk difference (at $P < 0.05$). Patients with uncontrolled systemic hypertension were excluded. Moreover, no information is given about how financial support was provided
Blinding of participants and personnel (performance bias)	Low risk	Unblinded pharmacists or physicians, not otherwise involved in the study and patient care, adjusted warfarin to a targeted INR (2 to 2.5). To maintain the

Huynh 2001 *(Continued)*

All outcomes		double-blinded integrity, patients assigned to placebo therapy had also regular blood tests and mock adjustments
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Obtained from medical records: review authors do not believe this would introduce bias. However, no information about blinding of outcome assessor is given

JPAD 2012

Study characteristics

Methods	Prospective, randomised, open-label, controlled trial with blinded endpoint assessment, multicentre with 163 centres in Japan. Patients divided according to BP at enrolment: SBP ≥ 140 mmHg DBP ≥ 90 mmHg in the unattained group and SBP < 140 mmHg and DBP < 90 mmHg in the attained group
Participants	2539 patients with type 2 diabetes, age 30 to 85 (mean age 65 ± 10 years) with 55% males. Average follow-up time was 4.37 years (95% CI 4.35 to 4.39)
Interventions	ASA 81 mg or 100 mg once daily vs placebo
Outcomes	Primary endpoint: any atherosclerotic event (a composite of sudden death; death from coronary, cerebrovascular, and aortic causes; non-fatal acute MI; unstable angina; newly developed exertional angina; non-fatal ischaemic and haemorrhagic stroke; TIA; or non-fatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis) Secondary endpoints: each primary endpoint and combinations of primary endpoints and death from any cause Adverse events: gastrointestinal (GI) events and any haemorrhagic events other than haemorrhagic stroke
Notes	'Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes' - published in 2008 'ASA reduces cerebrovascular events in type 2 diabetic patients with poorly controlled blood pressure' - subanalysis from the JPAD trial, published in 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomisation was performed as non-stratified randomisation from a random number table. Other details are lacking
Allocation concealment (selection bias)	Low risk	The study centre prepared the sealed envelopes with random assignments and sent them by email to the physicians in charge at the study sites
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lack of planned statistical power due to the lower than expected incidence of atherosclerotic events. All-cause mortality not reported. 193 patients (7.6%) were lost to follow-up
Selective reporting (reporting bias)	Low risk	All predetermined endpoints reported
Other bias	Unclear risk	Trial with blinded endpoint assessment which did not have the advantages of a double-blinded, randomised trial The Japanese Pharmaceutical Affairs Law limits the use of placebo in studies because it is not classified as an unapproved medicine

JPAD 2012 *(Continued)*

		The findings of the study concern Japanese population only
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial. Study participants were unblinded. Patients were randomly assigned to the aspirin group or the non-aspirin group. The randomisation was performed as non-stratified randomisation from a random number table. The details about study centre and explanation of the term non-aspirin groups are not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial is designed with blinded endpoint assessment. However, the way of blinding of outcome assessment is not described

JPPP 2019

Study characteristics	
Methods	Primary prevention, prospective, open-label, randomised, parallel-group trial. Multicentre study with centres (1007) in Japan
Participants	14,464 patients with atherosclerotic risk factors (hypertension, diabetes mellitus, or dyslipidaemia). Median age of 70 ± 6.2 years. 42% of men. Median follow-up of 5.02 years
Interventions	Enteric-coated ASA 100 mg/day vs placebo
Outcomes	The primary outcome: composite of death from cardiovascular causes (MI, stroke, and other cardiovascular causes), non-fatal stroke (ischaemic or haemorrhagic, including undefined cerebrovascular events), and non-fatal myocardial infarction. The first secondary endpoint: a composite that included the same events as the primary endpoint, plus TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention. Other secondary endpoints: death from cardiovascular disease, death from non-cardiovascular causes, non-fatal stroke (ischaemic or haemorrhagic), non-fatal MI, TIA, angina pectoris, arteriosclerotic disease requiring surgery or intervention, and serious extracranial haemorrhage requiring transfusion or hospitalisation
Notes	2014 'Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors' 2019 subgroup analysis 'Influence of blood pressure on the effects of low-dose aspirin in elderly patients with multiple atherosclerotic risks'

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Pseudo-random numbers were generated using the Mersenne Twister method
Allocation concealment (selection bias)	Low risk	The study statistician generated the random allocation sequence with a central computerised system and study physicians were informed of treatment assignments via the study website or by fax
Incomplete outcome data (attrition bias) All outcomes	High risk	10.5% of patients were lost to follow-up
Selective reporting (reporting bias)	High risk	All predetermined endpoints were reported. 10.5% of patients were lost to follow-up

JPPP 2019 *(Continued)*

Other bias	Unclear risk	Results might have been confounded by a decreasing level of adherence with daily low-dose aspirin in the aspirin group (dropping to 76% in year 5) and increasing uptake of daily aspirin in the no aspirin group (reaching 10% in year 5). Results limited to Japanese population
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients were reviewed by their general practitioner (unaware of the allocated study group), records flagged in the NHS central register. Independent assessment of endpoints was carried out. Obtained from medical records: review authors do not believe this would introduce bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study endpoints were evaluated centrally and biannually by an expert, multidisciplinary event adjudication committee that was blinded to treatment assignments in accordance with the Prospective Randomized Open Blinded Endpoint (PROBE) trial design

TPT 1998

Study characteristics	
Methods	Primary prevention, double-blinded, placebo-controlled, multicentre, single-country, trial. No information is given regarding the length of follow-up. Patients with current or recent history of possible peptic ulceration or history of possible or definite MI or stroke were excluded
Participants	5499 men, aged 45 to 69 years (mean (SD): 57.5 (6.7)); increased risk of ischaemic heart disease mean (SD) systolic blood pressure: 139 (18) mmHg; 245 patients under antihypertensive drug treatment at inclusion Patients with current or recent history of possible peptic ulceration or history of possible or definite MI or stroke were excluded
Interventions	ASA 75 mg vs placebo + warfarin vs placebo
Outcomes	Definition of endpoints: fatal and non-fatal events (i.e. coronary death and fatal and non-fatal MI) Stroke was a secondary endpoint, with results for thrombotic and haemorrhagic events to be distinguished as far as possible. Definition of all events was based on WHO criteria
Notes	1998 publication: on antihypertensive medications during trial 2000 publication: subgroup analysis of ASA group, according to BP: < 130, 130 to 145, > 145 Multiple publications to assess risk of bias

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised controlled trial, although the randomisation sequence generation technique used is not fully described
Allocation concealment (selection bias)	Unclear risk	No information is given about allocation sequence before assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: only 58 (1.1%) of the 5499 patients

TPT 1998 *(Continued)*

Selective reporting (reporting bias)	Low risk	All predetermined endpoints (coronary heart disease and stroke) were reported Losses to follow-up: 58 (1.1% of 5499 patients) Beneficial effects of low-dose aspirin demonstrated following subgroup analyses Data for subgroup analysis of patients treated with antihypertensive medication at entry or during trial was reported in a subsequent publication Definition of all events was based on WHO criteria
Other bias	Unclear risk	Financial support provided by Medical Research Council, British Heart Foundation, DuPont Pharma and Bayer corporation. GlaxoWellcome, Boeehringer-Intelgheim and Bayer corporation provided drugs free of charge
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Dose changes were matched on placebo warfarin
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients were reviewed by their general practitioner (unaware of the allocated study group), records flagged in the NHS central register. Independent assessment of endpoints was carried out. Obtained from medical records: review authors do not believe this would introduce bias independent reviewer unaware of treatment group

ASA: acetylsalicylic acid; ACE: angiotensin converting enzyme; CI: confidence interval; CVA: cerebrovascular accident; DBP: diastolic blood pressure; ECG: electrocardiogram; INR: international normalised ratio; MI: myocardial infarction; mmHg: millimetres of mercury; PVD: peripheral vascular disease; SBP: systolic blood pressure; SD: standard deviation; TIA: transient ischaemic attack; vs: versus; WHO: World Health Organization.

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

Study	Reason for exclusion
Ahn 2019	Data from registry
Ajani 2000	Unable to obtain data from hypertensive group
APTC 1994	Unable to obtain data from hypertensive subgroup (paper contains on 1 figure [Figure 7] of a subgroup of 'high risk' patients from 29 trials who had recorded diastolic blood pressure > 90 mmHg only, with no information on the individual trials)
ATLAS ACS 2-TIMI 51 2012	Unable to obtain data from hypertensive group
Bhatt 2000	Unable to obtain data from hypertensive subgroup (subgroup analysis of CAPRIE)
Bhatt 2001	Unable to obtain data from hypertensive subgroup (subgroup analysis of CAPRIE)
Califf 2000	Observational study
Caravaca 1995	Retrospective study
CARS 2001	Unable to obtain data of hypertensive subgroup

Study	Reason for exclusion
CHANCE 2017	Compares 2 drugs versus 1 drug
COMPASS 2017	Data from hypertensive group not available
Cook 1997	Self-selected post-trial ASA use
Cusson 1992	Treatment duration only 7 days
Drapkin 1972	Unable to obtain data from hypertensive subgroup
EPIC 1999	Unable to obtain data from hypertensive subgroup
EPILOG 1998	Abciximab treatment only 12-hour duration
ESPS-2 1998	Unable to obtain data from hypertensive subgroup
Ferri 1993	Treatment duration of only 5 days
Finelli 1991	Treatment duration of only 60 days
Fisher 2001	Calculation of the effect of "clopidogrel vs placebo"
Forbes 1999	Duration of treatment only 7 days
Furey 1993	Duration of treatment only 7 days
Gurwitz 1996	Duration of treatment only 4 weeks
Harker 1999	Subgroup analysis of CAPRIE study, no data available from hypertensive subgroup
Harpaz 2000	ASA not randomised, retrospective analysis of bezafibrate infarction prevention study of women who were not randomised to bezafibrate
Hartmann 1995	Duration of treatment only 15 days
Harvey 1995	Duration of treatment only 4 weeks
Hermida 1997	Duration of treatment only 7 days
Herskovits 1985	Unable to obtain data from hypertensive subgroup
Hess 1985	Unable to obtain data from hypertensive subgroup
Houston 1995	Duration of treatment only 3 weeks
Houtsmuller 1984	Cardiovascular events and cerebrovascular accident were not evaluated
Johnson 1996	Duration of treatment only 1 month
Klassen 1993	Duration of 4 weeks
Klassen 1995	Duration of 4 weeks
Lee 1999	Prospective cohort study

Study	Reason for exclusion
Lemak 1986	Unable to obtain required data
Magagna 1991	Duration of NSAID therapy only 1 month
Magagna 1994	Duration of NSAID therapy only 1 month
Maggioni 1992	ASA not randomised
Mehta 2001	Duration of treatment only 4 weeks
Mills 1982	Duration of aspirin treatment only 7 days Duration of indomethacin treatment only 7 days
Minuz 1990	Duration of NSAID therapy only 2 weeks
Minuz 1995	Duration of NSAID therapy only 3 days
Morgan 1993	Duration of NSAID therapy too short
Morgan 2000	Treatment duration 3 weeks
NAVIGATE ESUS 2018	Data for hypertensive group not available
Nawarskas 1999	Treatment duration 2 weeks
Novo 1996	No suitable endpoints reported
Oosterga 1998	ASA not randomised
Pancera 1996	Treatment duration 3 days
Peto 1998	Not placebo-controlled, not blinded (avoid ASA)
PHS 1989	Unable to obtain data from hypertensive subgroup
Polonia 1995	Treatment duration: ASA 2 weeks, indomethacin 1 week
Polonia 1996	Treatment duration 1 week
PPP 2001	Unable to obtain data from hypertensive subgroup
Pritchard 1997	Treatment duration 3 weeks
Proudman 2000	Control group treated with corticosteroids, methotrexate and cyclosporin - unsuitable for this analysis as effecting blood pressure and other variables
Puranen 1998	Unable to obtain relevant endpoint data of hypertensive subgroup
PURSUIT 1999	Duration of treatment only up to 96 hours
Saloheimo 2001	Not randomised, only observational study
Schreiber 1992	Open-label ASA, treatment duration, unable to retrieve data
Schuhlen 2001	Not randomised, duration of treatment only 4 weeks

Study	Reason for exclusion
Sivenius 1993	Unable to obtain data from hypertensive subgroup
Smith 1993	Duration of aspirin treatment only 2 weeks
SPIRIT 1997	Unable to obtain data from hypertensive subgroup
Sturrock 1994	Treatment duration only 4 days
Takeuchi 1991	Treatment duration only 1 week
TASS 1998	Unable to obtain data from hypertensive subgroup
Thakur 1999	Treatment duration only 1 month
Tison 1994	Treatment duration 8 weeks
Tsuji 2000	Single injection of ASA
UK-TIA 1991	Unable to obtain data from hypertensive subgroup
Walter 1981	Patients on antihypertensives excluded, remaining patients SBP 119.4 (3.9) mmHg and DBP 73.5 (2.4) mmHg, ASA (n = 17), warfarin (n = 14)
WARS 2001	Unable to obtain data
Whelton 2001	Treatment duration 6 weeks

ASA: acetylsalicylic acid; DBP: diastolic blood pressure; mmHg: millimetres of mercury; NSAID: non-steroidal anti-inflammatory drug; SBP: systolic blood pressure.

DATA AND ANALYSES

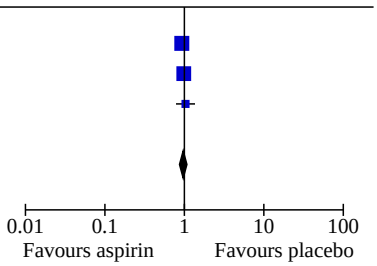
Comparison 1. ASA vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Total mortality	3	35794	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.08]
1.2 Cardiovascular mortality	3	35794	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.17]
1.3 Non-fatal cardiovascular events	1	2540	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.45, 0.87]
1.4 Major bleedings	2	21330	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [1.34, 2.32]
1.5 All cardiovascular events	3	35794	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.77, 0.96]

Analysis 1.1. Comparison 1: ASA vs placebo, Outcome 1: Total mortality

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
HOT 1998	284	9399	305	9391	43.1%	0.93 [0.79 , 1.09]
JPPP 2019	297	7220	303	7244	42.3%	0.98 [0.83 , 1.16]
TPT 1998	113	1268	110	1272	14.6%	1.03 [0.79 , 1.36]
Total (95% CI)		**17887**		**17907**	**100.0%**	**0.97 [0.87 , 1.08]**
Total events:	694		718			

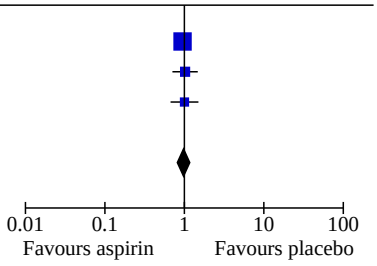
Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: ASA vs placebo, Outcome 2: Cardiovascular mortality

Study or Subgroup	ASA Events	ASA Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
HOT 1998	133	9399	140	9391	57.2%	0.95 [0.75 , 1.20]
JPPP 2019	58	7220	57	7244	23.4%	1.02 [0.71 , 1.47]
TPT 1998	49	1268	49	1272	19.5%	1.00 [0.67 , 1.50]
Total (95% CI)		**17887**		**17907**	**100.0%**	**0.98 [0.82 , 1.17]**
Total events:	240		246			

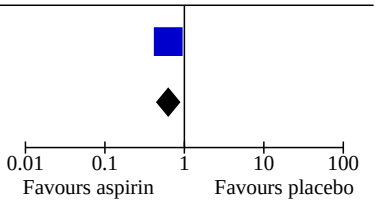
Heterogeneity: Chi² = 0.13, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: ASA vs placebo, Outcome 3: Non-fatal cardiovascular events

Study or Subgroup	ASA Events	ASA Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
TPT 1998	63	1268	98	1272	100.0%	0.63 [0.45 , 0.87]
Total (95% CI)		**1268**		**1272**	**100.0%**	**0.63 [0.45 , 0.87]**
Total events:	63		98			

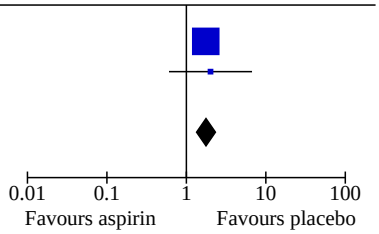
Heterogeneity: Not applicable
Test for overall effect: Z = 2.81 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: ASA vs placebo, Outcome 4: Major bleedings

Study or Subgroup	ASA Events	ASA Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
HOT 1998	136	9399	78	9391	95.1%	1.75 [1.33 , 2.32]
TPT 1998	8	1268	4	1272	4.9%	2.01 [0.60 , 6.70]
Total (95% CI)		**10667**		**10663**	**100.0%**	**1.77 [1.34 , 2.32]**
Total events:	144		82			

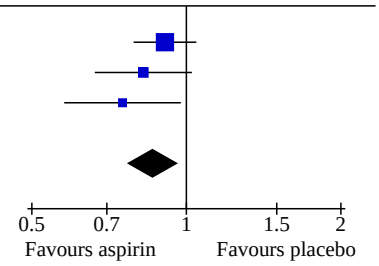
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 4.09 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: ASA vs placebo, Outcome 5: All cardiovascular events

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
HOT 1998	388	9399	425	9391	56.8%	0.91 [0.79 , 1.05]
TPT 1998	176	1268	208	1272	24.9%	0.82 [0.66 , 1.03]
JPPP 2019	100	7220	133	7244	18.3%	0.75 [0.58 , 0.98]
Total (95% CI)		**17887**		**17907**	**100.0%**	**0.86 [0.77 , 0.96]**
Total events:	664		766			

Heterogeneity: Chi² = 1.76, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.77 (P = 0.006)
Test for subgroup differences: Not applicable



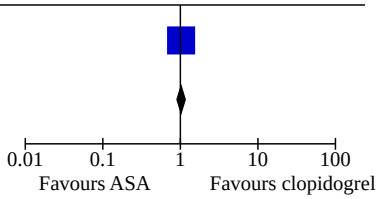
Comparison 2. ASA vs clopidogrel

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Total mortality	1	19143	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.91, 1.15]
2.2 Cardiovascular mortality	1	19143	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.94, 1.26]
2.3 Non-fatal cardiovascular events	1	19143	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [1.00, 1.22]
2.4 All cardiovascular events	1	19143	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [1.00, 1.17]
2.5 Major bleeding events	1	19143	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [1.14, 1.61]

Analysis 2.1. Comparison 2: ASA vs clopidogrel, Outcome 1: Total mortality

Study or Subgroup	ASA Events	ASA Total	Clopidogrel Events	Clopidogrel Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CAPRIE 1996	571	9566	560	9577	100.0%	1.02 [0.91 , 1.15]
Total (95% CI)		**9566**		**9577**	**100.0%**	**1.02 [0.91 , 1.15]**
Total events:	571		560			

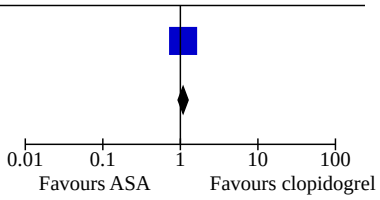
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: ASA vs clopidogrel, Outcome 2: Cardiovascular mortality

Study or Subgroup	ASA Events	ASA Total	Clopidogrel Events	Clopidogrel Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CAPRIE 1996	378	9566	350	9577	100.0%	1.08 [0.94 , 1.26]
Total (95% CI)		**9566**		**9577**	**100.0%**	**1.08 [0.94 , 1.26]**
Total events:	378		350			

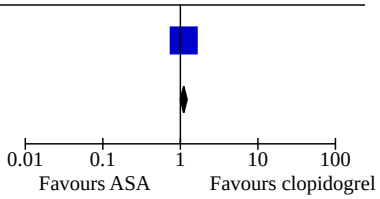
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: ASA vs clopidogrel, Outcome 3: Non-fatal cardiovascular events

Study or Subgroup	ASA Events	ASA Total	Clopidogrel Events	Clopidogrel Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CAPRIE 1996	852	9566	779	9577	100.0%	1.10 [1.00 , 1.22]
Total (95% CI)		**9566**		**9577**	**100.0%**	**1.10 [1.00 , 1.22]**
Total events:	852		779			

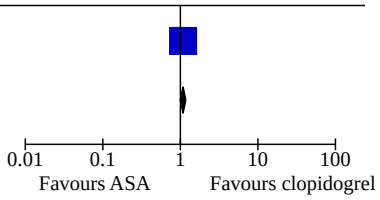
Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: ASA vs clopidogrel, Outcome 4: All cardiovascular events

Study or Subgroup	ASA Events	ASA Total	Clopidogrel Events	Clopidogrel Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CAPRIE 1996	1447	9566	1353	9577	100.0%	1.08 [1.00 , 1.17]
Total (95% CI)		**9566**		**9577**	**100.0%**	**1.08 [1.00 , 1.17]**
Total events:	1447		1353			

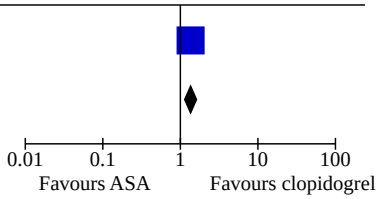
Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: ASA vs clopidogrel, Outcome 5: Major bleeding events

Study or Subgroup	ASA Events	ASA Total	Clopidogrel Events	Clopidogrel Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CAPRIE 1996	302	9566	225	9577	100.0%	1.35 [1.14 , 1.61]
Total (95% CI)		**9566**		**9577**	**100.0%**	**1.35 [1.14 , 1.61]**
Total events:	302		225			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.40 (P = 0.0007)
Test for subgroup differences: Not applicable



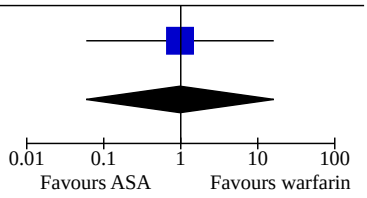
Comparison 3. ASA vs warfarin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Total mortality	1	91	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 16.12]
3.2 Major bleedings	1	91	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.60]

Analysis 3.1. Comparison 3: ASA vs warfarin, Outcome 1: Total mortality

Study or Subgroup	ASA + placebo Events	ASA + placebo Total	Warfarin + placebo Events	Warfarin + placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Huynh 2001	1	46	1	45	100.0%	0.98 [0.06 , 16.12]
Total (95% CI)		**46**		**45**	**100.0%**	**0.98 [0.06 , 16.12]**
Total events:	1		1			

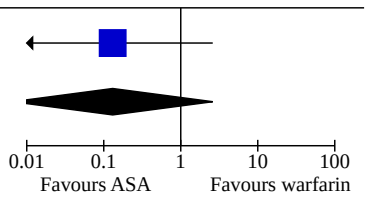
Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: ASA vs warfarin, Outcome 2: Major bleedings

Study or Subgroup	ASA + placebo Events	ASA + placebo Total	Warfarin + placebo Events	Warfarin + placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Huynh 2001	0	46	3	45	100.0%	0.13 [0.01 , 2.60]
Total (95% CI)		**46**		**45**	**100.0%**	**0.13 [0.01 , 2.60]**
Total events:	0		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies from 2021 version of review

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 07, 2021>
Search date: 8 January 2021

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1 exp Anticoagulants/
2 (anticoagul$ or anti-coagul$).tw,kf.
3 exp Antithrombins/
4 (antithromb$ or anti-thromb$).tw,kf.
5 (abciximab$ or apixaban or argatroban or dabigatran or eftifibatid$ or endosaban or olysaccharide sulphate$ or rivaroxaban or tirofiban $).tw,kf.
6 exp Coumarins/
7 (acenocoumarol$ or ancrod$ or coumarin$ or chromonar$ or coumestro$ or dermatan?sul$ or dextran$ or dicoumarol$ or ethyl biscoumacetate$ or esculi$ or isocoumarin$ or phenprocoumon$ or psoralens or pyranocoumarin$ or umbelliferone$).tw,kf.
8 (aldocumar or citrate$ or citric acid$ or coumadin or coumadine or edetic acid$ or enoxaparin$ or fragmin$ or fraxiparin$ or gabexate $ or heparin$ or hirudin or klexane or LMWH or lomoparan or marevan or mesoglycan or nadroparin$ or ochratoxin$ or parnaparin or pentosan sulfuric polyester$ or phenindione$ or pipecolic acid$ or reviparin$ or tedelparin$ or tedicumar or tinzaparin or TSC or UFH or warfant or warfarin$).tw,kf.
9 or/1-8
10 exp Platelet Aggregation Inhibitors/
11 (clopidogrel or dipyridamol$ or prasugrel or ticagrelor or ticlopidine$).tw,kf.
12 (antiplatelet adj2 (agent$ or drug$ or intervention$ or regime$ or therap$ or treatment$)).tw,kf.
13 (antiplatelet$ or anti-platelet$ or antiaggrega$ or anti-aggrega$ or (platelet$ adj4 inhibit$) or (thrombocyt$ adj4 inhibit$)).tw,kf. (54996)
14 exp Anti-Inflammatory Agents, Non-Steroidal/
15 nsaid$.tw,kf.
16 ((non-steroid$ or nonsteroid$) adj2 (antiinflammat$ or anti-inflammat$)).tw,kf.
17 (ampyrone or antipyrine or apazone or bufexamac or clofazimine or clonixin or curcumin or diclofenac or diflunisal or dipyrone or epirizole or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or etoprofen or ketorolac or meclofenamic acid or mefenamic acid or mesalamine or naproxen or niflumic acid or oxyphenbutazone or phenylbutazone or piroxicam or prenazone or sulfasalazine or sulindac or suprofen or tolmetin).tw,kf.
18 Aspirin/
19 (aspirin$ or acetylsalicylic acid or salicylat$ or salicylic$).tw,kf.
20 or/10-19
21 hypertension/
22 essential hypertension/
23 (antihypertens$ or hypertens$).tw,kf.
24 exp blood pressure/
25 ((elevat$ or high or rais$) adj2 (arterial pressur$ or blood pressur$ or diastolic pressur$ or systolic pressur$)).tw,kf.
26 ((elevat$ or high or rais$) adj2 (bp or dbp or sbp)).tw,kf.
27 or/21-26
28 randomized controlled trial.pt.
29 controlled clinical trial.pt.
30 randomi?ed.ab.
31 placebo.ab.
32 drug therapy.fs.
33 randomly.ab.
34 trial.ab.
35 groups.ab.
36 or/28-35
37 animals/ not (humans/ and animals/)
38 (preeclamp$ or eclamp$ or congestive heart failure or chf).ti.
39 36 not (37 or 38)
40 (9 or 20) and 27 and 39

Database: Cochrane Hypertension Specialised Register via Cochrane Register of Studies
Search date: 8 January 2021

#1 (anticoag* or "anti-coag*" or antithromb* or "anti-throm*" or abciximab* or apixaban or argatroban or dabigatran or eftifibatid* or endosaban or olysaccharide sulphate* or rivaroxaban or tirofiban*) AND INSEGMENT
#2 (acenocoumarol* or ancrod* or coumarin* or chromonar* or coumestro* or dermatan*sul* or dextran* or dicoumarol* or ethyl biscoumacetate* or esculi* or isocoumarin* or phenprocoumon* or psoralens or pyranocoumarin* or umbelliferone*) AND INSEGMENT
#3 (aldocumar or citrate* or citric acid* or coumadin or coumadine or edetic acid* or enoxaparin* or fragmin* or fraxiparin* or gabexate* or heparin* or hirudin or klexane or LMWH or lomoparan or marevan or mesoglycan or nadroparin* or ochratoxin* or parnaparin or pentosan sulfuric polyester* or phenindione* or pipecolic acid* or reviparin* or tedelparin* or tedicumar or tinzaparin or TSC or UFH or warfant or warfarin*) AND INSEGMENT
#4 (antiplatelet* OR "anti-platelet*" OR antiaggrega* OR "anti-aggrega" OR platelet inhibitor* OR platelet antagonist* OR clopidogrel OR dipyridamol* OR prasugrel OR ticagrelor OR ticlopidine*) AND INSEGMENT
#5 (nonsteroidal antiinflammator* OR "non-steroidal anti-inflammator*" OR "nonsteroidal anti-inflammator*" OR "nonsteroidal anti-inflammator*") AND INSEGMENT
#6 (ampyrone or antipyrine or apazone or bufexamac or clofazimine or clonixin or curcumin or diclofenac or diflunisal or dipyrone or epirizole or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or etoprofen or ketorolac or meclofenamic acid or mefenamic acid or mesalamine or naproxen or niflumic acid or oxyphenbutazone or phenylbutazone or piroxicam or prenazone or sulfasalazine or sulindac or suprofen or tolmetin) AND INSEGMENT
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 RCT:DE AND INSEGMENT
#9 Review:ODE AND INSEGMENT
#10 (#8 OR #9)
#11 #7 AND #10

Database: Cochrane Central Register of Controlled Trials (CENTRAL 2021, Issue 1) via Cochrane Register of Studies
Search date: 8 January 2021

#1 MESH DESCRIPTOR Anticoagulants EXPLODE ALL AND CENTRAL:TARGET
#2 (anticoag* OR "anti-coag*"):TI,AB AND CENTRAL:TARGET
#3 MESH DESCRIPTOR Antithrombins EXPLODE ALL AND CENTRAL:TARGET
#4 (antithromb* OR "anti-throm*"):TI,AB AND CENTRAL:TARGET
#5 (abciximab* or apixaban or argatroban or dabigatran or eftifibatid* or endosaban or olysaccharide sulphate* or rivaroxaban or tirofiban*):TI,AB AND CENTRAL:TARGET
#6 MESH DESCRIPTOR Coumarins EXPLODE ALL AND CENTRAL:TARGET
#7 (acenocoumarol* or ancrod* or coumarin* or chromonar* or coumestro* or dermatan*sul* or dextran* or dicoumarol* or ethyl biscoumacetate* or esculi* or isocoumarin* or phenprocoumon* or psoralens or pyranocoumarin* or umbelliferone*):TI,AB AND CENTRAL:TARGET
#8 (aldocumar or citrate* or citric acid* or coumadin or coumadine or edetic acid* or enoxaparin* or fragmin* or fraxiparin* or gabexate* or heparin* or hirudin or klexane or LMWH or lomoparan or marevan or mesoglycan or nadroparin* or ochratoxin* or parnaparin or pentosan sulfuric polyester* or phenindione* or pipecolic acid* or reviparin* or tedelparin* or tedicumar or tinzaparin or TSC or UFH or warfant or warfarin*):TI,AB AND CENTRAL:TARGET
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) AND CENTRAL:TARGET
#10 MESH DESCRIPTOR Platelet Aggregation Inhibitors EXPLODE ALL AND CENTRAL:TARGET
#11 (clopidogrel OR dipyridamol* OR prasugrel OR ticagrelor OR ticlopidine*):TI,AB AND CENTRAL:TARGET
#12 antiplatelet NEAR2 (agent* OR drug* OR intervention* OR regime* OR therap* OR treatment*):TI,AB AND CENTRAL:TARGET
#13 (antiplatelet* OR "anti-platelet*" OR antiaggrega* OR "anti-aggrega*"):TI,AB AND CENTRAL:TARGET
#14 (platelet* NEAR4 inhibit*) OR (thrombocyt* NEAR4 inhibit*) AND CENTRAL:TARGET
#15 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL AND CENTRAL:TARGET
#16 nsaid*:TI,AB AND CENTRAL:TARGET
#17 (nonsteroidal antiinflammator* OR "non-steroidal anti-inflammator*" OR "nonsteroidal anti-inflammator*" OR "nonsteroidal anti-inflammator*"):TI,AB AND CENTRAL:TARGET
#18 (ampyrone or antipyrine or apazone or bufexamac or clofazimine or clonixin or curcumin or diclofenac or diflunisal or dipyrone or epirizole or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or etoprofen or ketorolac or meclofenamic acid or mefenamic acid or mesalamine or naproxen or niflumic acid or oxyphenbutazone or phenylbutazone or piroxicam or prenazone or sulfasalazine or sulindac or suprofen or tolmetin):TI,AB AND CENTRAL:TARGET
#19 MESH DESCRIPTOR Aspirin AND CENTRAL:TARGET
#20 (aspirin* OR "acetylsalicylic acid" OR salicylat* OR salicylic*):TI,AB AND CENTRAL:TARGET
#21 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20) AND CENTRAL:TARGET
#22 (#9 OR #21)
#23 MESH DESCRIPTOR Hypertension AND CENTRAL:TARGET
#24 MESH DESCRIPTOR Essential Hypertension AND CENTRAL:TARGET
#25 (antihypertens* OR hypertens*) AND CENTRAL:TARGET
#26 MESH DESCRIPTOR BLOOD PRESSURE EXPLODE ALL AND CENTRAL:TARGET

#27 ((elevat* OR high OR rais*) NEAR2 (arterial pressur* OR blood pressur* OR diastolic pressur* OR systolic pressur*)) AND CENTRAL:TARGET
#28 ((elevat* OR high OR rais*) NEAR2 (bp OR dbp OR sbp)) AND CENTRAL:TARGET
#29 (#23 OR #24 OR #25 OR #26 OR #27 OR #28)
#30 #22 AND #29

Database: Embase <1974 to 2021 January 07>
Search date: 8 January 2021

---

1 exp Anticoagulant Agent/
2 Anticoagulant Therapy/
3 (anticoagul$ or anti-coagul$).tw.
4 Antithrombin/
5 (antithromb$ or anti-thromb$).tw.
6 (abciximab$ or apixaban or argatroban or dabigatran or eftifibatid$ or endosaban or olysaccharide sulphate$ or rivaroxaban or tirofiban $).tw.
7 (acenocoumarol$ or ancrod$ or coumarin$ or chromonar$ or coumestro$ or dermatan?sul$ or dextran$ or dicoumarol$ or ethyl biscoumacetate$ or esculi$ or isocoumarin$ or phenprocoumon$ or psoralens or pyranocoumarin$ or umbelliferone$).tw.
8 (aldocumar or citrate$ or citric acid$ or coumadin or coumadine or edetic acid$ or enoxaparin$ or fragmin$ or fraxiparin$ or gabexate $ or heparin$ or hirudin or klexane or LMWH or lomoparan or marevan or mesoglycan or nadroparin$ or ochratoxin$ or parnaparin or pentosan sulfuric polyester$ or phenindione$ or pipecolic acid$ or reviparin$ or tedelparin$ or tedicumar or tinzaparin or TSC or UFH or warfant or warfarin$).tw.
9 or/1-8
10 exp Antithrombocytic Agent/
11 (clopidogrel or dipyridamol$ or prasugrel or ticagrelor or ticlopidine$).tw.
12 (antiplatelet adj2 (agent$ or drug$ or intervention$ or regime$ or therap$ or treatment$)).tw.
13 (antiplatelet$ or anti-platelet$ or antiaggrega$ or anti-aggrega$ or (platelet$ adj4 inhibit$) or (thrombocyt$ adj4 inhibit$)).tw.
14 exp Nonsteroid AntiInflammatory Agent/
15 nsaid$.tw.
16 ((non-steroid$ or nonsteroid$) adj2 (antiinflammat$ or anti-inflammat$)).tw.
17 (ampyrone or antipyrine or apazone or bufexamac or clofazimine or clonixin or curcumin or diclofenac or diflunisal or dipyrone or epirizole or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or etoprofen or ketorolac or meclofenamic acid or mefenamic acid or mesalamine or naproxen or niflumic acid or oxyphenbutazone or phenylbutazone or piroxicam or prenazone or sulfasalazine or sulindac or suprofen or tolmetin).tw.
18 (aspirin$ or acetylsalicylic acid or salicylat$ or salicylic$).mp.
19 or/10-18
20 exp hypertension/
21 (antihypertens$ or hypertens$).tw.
22 exp *blood pressure/
23 ((elevat$ or high or rais$) adj2 (arterial pressur$ or blood pressur$ or diastolic pressur$ or systolic pressur$)).tw.
24 ((elevat$ or high or rais$) adj2 (bp or dbp or sbp)).tw.
25 or/20-24
26 randomized controlled trial/
27 crossover procedure/
28 double-blind procedure/
29 (randomi?ed or randomly).tw.
30 (crossover$ or cross-over$).tw.
31 placebo$.tw.
32 (doubl$ adj blind$).tw.
33 assign$.ab.
34 allocat$.ab.
35 or/26-34
36 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
37 (preeclamp$ or eclamp$ or congestive heart failure or chf).ti.
38 35 not (36 or 37)
39 (9 or 19) and 25 and 38

Database: ClinicalTrials.gov Search date: 8 January 2021

Condition or disease: hypertension
Other terms: randomized
Study type: Interventional Studies (Clinical Trials)
Study results: All Studies
Intervention/treatment: anticoagulants OR antiplatelets OR apixaban OR aspirin OR clopidogrel OR dabigatran OR dipyridamole OR endosaban OR vitamin K OR NSAIDS OR prasugrel OR rivaroxaban OR ticagrelor OR ticlopidine OR warfarin

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Database: WHO International Clinical Trials Registry Platform (ICTRP)

Searched via CRS as part of CCTR search as ICTRP platform was not available for direct searching

Appendix 2. Search strategies from 2008 version of review

The Cochrane Controlled Trials Register (CENTRAL) was searched using the strategy with the keywords outlined below. This was updated by searching MEDLINE 2000-2001 on Ovid using a standard randomised controlled trial (RCT) filter (Dickersin 1996) and EMBASE 1998 to 2001 using an EMBASE RCT filter (Lefebvre 1996). The NHS Database of Abstracts of Reviews of Effectiveness and other relevant databases were searched to identify eligible studies and review articles. Relevant foreign papers were translated. Abstracts from national and international hypertension meetings were studied to identify unpublished studies and relevant authors of these studies were contacted to obtain further details. Searches of reference lists of papers were made.

CENTRAL search strategy (2008 review):
1 HYPERTENSION
2 HIGH BLOOD PRESSURE
3 BLOOD PRESSURE
4 ((#1 or #2) or #3)
5 ANTICOAGULANTS*:ME
6 ANTICOAGULANT*
7 ANTI-COAGULANT*
8 ANTITHROMBINS*:ME
9 ANTITHROMB*
10 ANTI-THROM*
11 COUMARINS*:ME
12 COUMARIN*
13 WARFARIN
14 WARFARIN*:ME
15 (((((((((#5 or #6) or #7) or #8) or #9) or #10) or #11) or #12) or #13) or #14)
16 PLATELET-AGGREGATION-INHIBITORS*:ME
17 PLATELET*
18 ANTI-PLATELET*
19 ASPIRIN*:ME
20 ASPIRIN
21 ANTI-INFLAMMATORY-AGENTS-NON-STEROIDAL*:ME
22 (NONSTEROID* near ANTIINFLAMM*)
23 (NON-STEROID* near ANTIINFLAM*)
24 (NONSTEROID* near ANTIINFLAM*)
25 (NON-STEROID* near ANTI-INFLAM*)
26 (NONSTEROID* near ANTI-INFLAM*)
27 NSAID*
28 TICLOPIDINE
29 CLOPIDOGREL
30 DIPYRIDAMOL
31 ((((((((((((((#16 or #17) or #18) or #19) or #20) or #21) or #22) or #23) or #24) or #25) or #26) or #27) or #28) or #29) or#30)
32 (#4 and #15)
33 (#31 and #32)

FEEDBACK

Hypertension and the ATC meta-analysis, October 2007

Summary

This review concludes that acetylsalicylic acid (ASA) is efficacious for secondary prevention of cardiovascular events in people with elevated blood pressure based on the ATC meta-analysis (29 trials, 10,600 patients). However, the Cochrane authors were unable to obtain the data for their own analysis of the subgroup of high-risk patients with hypertension. Additionally, haemorrhagic events were not reported and may have altered the risk/benefit ratio. Cleland challenged the validity of the ATC meta-analysis, making the following points:
- the Antiplatelet Trialists' Collaboration meta-analysis was state-of-the-art for its time but not robust by modern standards;
- the findings of the meta-analysis were driven largely by data from small positive trials, with a dearth of small negative trials;
- most clinicians agree that meta-analysis is useful for confirming robust clinical trial results - which are lacking for long-term aspirin therapy - or calculating the size of trial required to provide a robust result; however, proof depending on meta-analysis alone is now generally considered weak.[a]

The Cochrane review authors argue that, since (1) the ATC meta-analysis included 100,000 high-risk patients with or without elevated blood pressure and (2) there was an overall reduction in mortality demonstrated, consequently, the benefit of antiplatelet therapy for secondary prevention extends to patients both with or without elevated blood pressure. This is a logical fallacy. All of the benefit might have occurred in the subgroup of non-hypertensive patients.

For all these reasons, the benefit of antiplatelet therapy for secondary prevention in patients with elevated blood pressure should not be considered established.

The primary endpoint, which determines the main conclusions of the review, should have included safety endpoints rather than just efficacy endpoints. Fatal bleeding and intracranial bleeding are particularly important and should be separately included in the primary or secondary endpoints rather than using all major bleeding events (fatal, disabling, and other non-fatal) as a composite endpoint.

Because of excluding observational and population-based studies from consideration in the safety analysis of the small warfarin trials (Huynh and Throm Prev Trial '98), the bleeding complications were very likely understated. Adding the safety data concerning vitamin K inhibitors from previous randomised controlled trials (RCTs), observational studies, and population-based studies to the safety and efficacy results of the two warfarin RCTs reviewed here, the implications for practice should state: "Vitamin K inhibitors should be contraindicated as an antithrombotic therapy approach to improving clinical outcomes in patients with elevated blood pressure."

Likewise, the implications for research section should state: "Because of the bleeding risk and lack of efficacy in published RCTs, further trials with vitamin K inhibitors as antithrombotic treatment to improve clinical outcome in patients with hypertension would be unethical."

[a]Cleland JG. Chronic aspirin therapy for the prevention of cardiovascular events: a waste of time, or worse? *Nature Clinical Practice Cardiovascular Medicine* 2006;3(5):234-5.

Reply

We thank Dr Cundiff for his comments. Many patients with hypertension have associated vascular disease or comorbidities, e.g. previous myocardial infarction (MI) or stroke, and thus, many are currently treated with aspirin as secondary prevention. He claims that the benefit of antiplatelet therapy for 'secondary prevention' in patients with elevated blood pressure should not be considered established. Given that 'secondary prevention' implies those patients who are post-event, this point is invalid.

Dr Cundiff also has concerns over the general interpretation of the Antiplatelet (now Antithrombotic) Trialists' Collaboration meta-analysis. All meta-analyses are limited by the studies included (or not, as the case may be), but the counter-arguments to John Cleland's stance have been repeatedly debated in detail, with many concerns raised regarding his views and interpretation of the Antithrombotic Trialists' Collaboration meta-analysis[a,b] Indeed, many early trials of antiplatelet treatment were rather small to detect moderate benefits reliably, which is why meta-analyses were needed. Dr Cundiff's suggestion that "all of the benefit might have occurred in the subgroup of non-hypertensive patients" is not supported by the detailed subgroup data provided in the earlier Antiplatelet Trialists' Collaboration meta-analysis manuscript.[c]

We agree that bleeding is an important consideration in antithrombotic therapy, and have already included discussion of this aspect in our review. However, the objective was to assess the impact of antithrombotic therapy on major adverse events in hypertension (i.e. mortality, vascular events, etc.), as reported as primary endpoints in various trials, and this was agreed when we submitted our Cochrane Review protocol. Our objective was not to redefine primary endpoints in the various trials, especially bleeding definitions were variable between the different trials.

Dr Cundiff comments on our inclusion of the small warfarin trials (Huynh 2001 and TPT 1998), and the bleeding complications were very likely understated. We already recognise the limitations of these small studies in our review, and by its nature, many randomised trials only include a small selection of those screened. There are inadequate data on warfarin in hypertension per se.

Although one may presume that warfarin is associated with more bleeding, this was not seen in the recent BAFTA clinical trial amongst elderly atrial fibrillation patients in the primary care setting, where warfarin (INR2-3) was superior to aspirin 75 mg for stroke prevention but the rates of major bleeding were no different between warfarin and aspirin.[d]

[a]Baigent C, Collins R, Peto R. Article makes simple errors and could cause unnecessary deaths. *BMJ* 2002;324(7330):167.
[b]Sudlow C, Sandercock P, Warlow C. Antiplatelet therapy and atherosclerotic events. Commentary is inaccurate. *BMJ* 2002;324(7342):917.

[c]Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
[d]Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370(9586):493-503.

Contributors

David K Cundiff, MD, Occupation Physician
Submitter agrees with default conflict of interest statement: "I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback."

WHAT'S NEW

Date	Event	Description
7 June 2022	New citation required but conclusions have not changed	New citation, conclusions unchanged. Two new co-authors added, two previous authors removed.
8 January 2021	New search has been performed	Two additional trials with 17,003 participants were included in this update.

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 3, 2004

Date	Event	Description
11 October 2011	New citation required but conclusions have not changed	One new author added: Girish Dwivedi.
11 October 2011	New search has been performed	Updated search (no new trials found), included Risk of Bias Tables, edited Abstract and Plain Language Summary to improve readability.
13 August 2008	Amended	Converted to new review format.
14 November 2007	New search has been performed	Minor update.
31 October 2007	Feedback has been incorporated	Response to feedback added.
15 October 2007	Feedback has been incorporated	Feedback added.
25 May 2004	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Professor Lip and Dr Felmeden contributed to the protocol design and jointly undertook the first version of this review, published in 2004. Dr Dwivedi joined them as an author for the 2011 update of this review. Dr Gallego-Hernanz joined them as an author for the 2013 update of this review. Dr Kozieł-Siołkowska and Dr Shantsila joined Dr Lip as authors for the current update of this review.

DECLARATIONS OF INTEREST

Professor Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi-Aventis, BMS/Pfizer, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, and Sanofi-Aventis.

Dr Kozieł-Siołkowska and Dr Shantsila declared no conflicts of interest.

The Haemostasis, Thrombosis and Vascular Biology Unit with which all the authors are affiliated undertakes clinical trials of antithrombotic therapy in cardiovascular disease and stroke, and has received research funding from various pharmaceutical companies involved in thrombosis and antithrombotic therapy.

SOURCES OF SUPPORT

Internal sources

- University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

  The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme.
- Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool Heart and Chest Hospital, Liverpool, UK

  The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme.
- 1st Department of Cardiology and Angiology, Silesian Centre for Heart Diseases, Zabrze, Poland

  The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme.

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences between protocol and review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Anticoagulants [adverse effects] [*therapeutic use]; Aspirin [adverse effects] [therapeutic use]; Clopidogrel; Hypertension [*complications]; Myocardial Infarction [prevention & control]; Platelet Aggregation Inhibitors [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Thromboembolism [etiology] [*prevention & control]; Ticlopidine [analogs & derivatives] [therapeutic use]; Warfarin [therapeutic use]

MeSH check words

Humans