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[Intervention Review]

Antiplatelet versus anticoagulation treatment for patients with heart failure in sinus rhythm

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ABSTRACT

Background

Morbidity in patients with chronic heart failure is high, and this predisposes them to thrombotic complications, including stroke and thromboembolism, which in turn contribute to high mortality. Oral anticoagulants (e.g. warfarin) and antiplatelet agents (e.g. aspirin) are the principle oral antithrombotic agents. Many heart failure patients with sinus rhythm take aspirin because coronary artery disease is the leading cause of heart failure. Oral anticoagulants have become a standard in the management of heart failure with atrial fibrillation. However, a question remains regarding the appropriateness of oral anticoagulants in heart failure with sinus rhythm. This update of a review previously published in 2012 aims to address this question.

Objectives

To assess the effects of oral anticoagulant therapy versus antiplatelet agents for all-cause mortality, non-fatal cardiovascular events and risk of major bleeding in adults with heart failure (either with reduced or preserved ejection fraction) who are in sinus rhythm.

Search methods

We updated the searches in September 2015 on CENTRAL (*The Cochrane Library*), MEDLINE and Embase. We searched reference lists of papers and abstracts from cardiology meetings and contacted study authors for further information. We did not apply any language restrictions. Additionally, we searched two clinical trials registers: ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal apps.who.int/trialsearch/) (searched in July 2016).

Selection criteria

We included randomised controlled trials comparing antiplatelet therapy versus oral anticoagulation in adults with chronic heart failure in sinus rhythm. Treatment had to last at least one month. We compared orally administered antiplatelet agents (aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor, dipyridamole) versus anticoagulant agents (coumarins, warfarin, non-vitamin K oral anticoagulants).

Data collection and analysis

Two review authors independently assessed trials for inclusion and assessed the risks and benefits of antithrombotic versus antiplatelet therapy using relative measures of effects, such as risk ratios (RR), accompanied with 95% confidence intervals (CI). The data extracted included data relating to the study design, patient characteristics, study eligibility, quality, and outcomes. We used GRADE criteria to assess the quality of the evidence.

Main results

This update identified one additional study for inclusion, adding data for 2305 participants. This addition more than doubled the overall number of patients eligible for the review. In total, we included four randomised controlled trials (RCTs) with a total of 4187 eligible participants. All studies compared warfarin with aspirin. One RCT additionally compared warfarin with clopidogrel. All included RCTs studied patients with heart failure with reduced ejection fraction.

Analysis of all outcomes for warfarin versus aspirin was based on 3663 patients from four RCTs. All-cause mortality was similar for warfarin and aspirin (RR 1.00, 95% CI 0.89 to 1.13; 4 studies; 3663 participants; moderate quality evidence). Oral anticoagulation was associated with a reduction in non-fatal cardiovascular events, which included non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism (RR 0.79, 95% CI 0.63 to 1.00; 4 studies; 3663 participants; moderate quality evidence). The rate of major bleeding events was twice as high in the warfarin groups (RR 2.00, 95% CI 1.44 to 2.78; 4 studies; 3663 participants; moderate quality evidence). We generally considered the risk of bias of the included studies to be low.

Analysis of warfarin versus clopidogrel was based on a single RCT (N = 1064). All-cause mortality was similar for warfarin and clopidogrel (RR 0.93, 95% CI 0.72 to 1.21; 1 study; 1064 participants; low quality evidence). There were similar rates of non-fatal cardiovascular events (RR 0.85, 95% CI 0.50 to 1.45; 1 study; 1064 participants; low quality evidence). The rate of major bleeding events was 2.5 times higher in the warfarin group (RR 2.47, 95% CI 1.24 to 4.91; 1 study; 1064 participants; low quality evidence). Risk of bias for this study can be summarised as low.

Authors' conclusions

There is evidence from RCTs to suggest that neither oral anticoagulation with warfarin or platelet inhibition with aspirin is better for mortality in systolic heart failure with sinus rhythm (high quality of the evidence for all-cause mortality and moderate quality of the evidence for non-fatal cardiovascular events and major bleeding events). Treatment with warfarin was associated with a 20% reduction in non-fatal cardiovascular events but a twofold higher risk of major bleeding complications (high quality of the evidence). We saw a similar pattern of results for the warfarin versus clopidogrel comparison (low quality of the evidence). At present, there are no data on the role of oral anticoagulation versus antiplatelet agents in heart failure with preserved ejection fraction with sinus rhythm. Also, there were no data from RCTs on the utility of non-vitamin K antagonist oral anticoagulants compared to antiplatelet agents in heart failure with sinus rhythm.

PLAIN LANGUAGE SUMMARY

Antiplatelet versus anticoagulation treatment for patients with heart failure in sinus rhythm

Background

Blood clots can be formed by clotting proteins (coagulation factors) and sticky blood cells (platelets). Oral anticoagulants such as warfarin are drugs that can prevent clot formation by blocking the clotting proteins. Other drugs, like aspirin, can also reduce clotting by blocking the platelets. Warfarin is better than aspirin in patients with heart failure who have abnormal heart rhythm (atrial fibrillation). Aspirin is known to be helpful in patients with heart failure with normal (sinus) rhythm, whose heart arteries are narrowed. This condition is a common cause of heart failure, so doctors often advise patients with a normal rhythm to take aspirin. Arguably, people with heart failure with a normal rhythm are at increased risk of clotting due to slower blood flow in the heart, similarly to people with an abnormal rhythm. Also, blood clots (thromboembolism) in the lungs, legs and brain (ischaemic stroke) lead to disability and death of patients with heart failure. Several studies have tried to find out whether all heart failure patients should receive oral anticoagulants, but the debate is still open.

Study characteristics

This is an update of an earlier review. The evidence is current to September 2015. We only identified one new study with 2305 participants. In total, we analysed four randomised controlled studies with 4187 participants.

Key results

The comparison of warfarin with aspirin was based on a large number of patients from four high-quality studies. The analysis showed an almost identical risk of death with both drugs. There was not enough evidence to prove benefits of warfarin over aspirin to reduce the possibility of clotting complications, such as a heart attack or stroke. However, patients receiving warfarin experienced serious bleeding twice as often as those taking aspirin. A comparison of warfarin with another antiplatelet drug, clopidogrel, was based on a single medium size study, and it showed similar results: no difference in occurrence of death or clotting complications, but a higher chance of developing of a serious bleed.

Conclusions

There is currently no evidence to suggest advantages of warfarin over antiplatelet drugs in heart failure with a normal rhythm. Moreover, treatment with warfarin leads to more bleeding events than aspirin or clopidogrel. It is unlikely that further studies will change these conclusions unless new, more effective and safe drugs become available.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings: warfarin versus aspirin for heart failure with sinus rhythm

Warfarin versus aspirin for heart failure with sinus rhythm

Patient or population: patients with heart failure with sinus rhythm

Settings: outpatient clinics

Intervention: warfarin

Comparison: aspirin

Outcomes	Illustrative comparative risks* (95% CI) ^a		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Aspirin	Warfarin			
All-cause mortality Mean follow-up: 18.5-42 months	219 per 1000	219 per 1000 (195 to 247)	RR 1.00 (0.89 to 1.13)	3663 (4)	⊕⊕⊕⊖ ^b Moderate
Non-fatal cardiovascular events (non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism) Mean follow-up: 18.5-42 months	83 per 1000	66 per 1000 (52 to 83)	RR 0.79 (0.63 to 1.00)	3663 (4)	⊕⊕⊕⊖ ^b Moderate
Major bleeding events Mean follow-up: 18.5-42 months	28 per 1000	56 per 1000 (40 to 78)	RR 2.00 (1.44 to 2.78)	3663 (4)	⊕⊕⊕⊖ ^b Moderate

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aAll results are presented for the whole population analyses. The assumed risk is provided based on the aspirin group as aspirin is often used in patients with heart failure with sinus rhythm due to background ischaemic heart disease.

^bDowngraded due to imprecision.

Summary of findings 2. Summary of findings: warfarin versus clopidogrel for heart failure with sinus rhythm

Warfarin versus clopidogrel for heart failure with sinus rhythm

Patient or population: patients with heart failure with sinus rhythm

Settings: outpatient clinics

Intervention: warfarin

Comparison: clopidogrel

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Clopidogrel	Warfarin			
All-cause mortality Mean follow-up: 1.9 years	183 per 1000	170 per 1000 (132 to 221)	RR 0.93 (0.72 to 1.21)	1064 (1)	⊕⊕⊕⊖ Low^a
Non-fatal cardiovascular events (non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism) Mean follow-up: 1.9 years	54 per 1000	46 per 1000 (27 to 78)	RR 0.85 (0.50 to 1.45)	1064 (1)	⊕⊕⊕⊖ Low^a
Major bleeding events Mean follow-up: 1.9 years	20 per 1000	49 per 1000 (25 to 98)	RR 2.47 (1.24 to 4.91)	1064 (1)	⊕⊕⊕⊖ Low^a

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by two due to imprecision.

BACKGROUND

Description of the condition

Chronic heart failure is a major clinical and social problem and a significant cause of morbidity, with almost 60% five-year mortality despite modern treatments (Stewart 2010). Heart failure poses an increased risk of thrombotic complications, which occur in a third of patients with the disease (Lip 2012). Mild to moderate heart failure is associated with an annual stroke risk of approximately 1.5% (Witt 2007), compared to less than 0.5% in the general population, while the annual risk of stroke increases to almost 4% in severe heart failure (Packer 1991). Indeed, the SAVE study reported an inverse relationship between stroke risk and the left ventricular ejection fraction (LVEF), with an 18% increase in stroke risk for every 5% reduction in LVEF in severe heart failure (SAVE 1997). People with heart failure are also prone to developing venous thromboembolism (Khoury 2011; Piazza 2011). Pulmonary embolism and peripheral arterial embolism clearly contribute to the high morbidity in heart failure (Alberts 2010; Witt 2007). Multiple factors predispose patients with heart failure to prothrombotic risk, including diastolic dysfunction, blood flow congestion and a hypercoagulable shift in pro- versus haemostatic factor balance (Shantsila 2016). For these reasons, patients with heart failure are expected to benefit from antithrombotic therapy, and it is essential to have evidence to support the best treatment options for prevention of thrombotic complications.

Description of the intervention

All heart failure patients who have atrial fibrillation have a CHA₂DS₂-VASc score (a measure of stroke risk for patients with atrial fibrillation) of 1 or more and benefit from oral anticoagulation according to the current guidelines (Camm 2012). Choice of an antithrombotic agent in heart failure patients with sinus rhythm is more controversial, but antiplatelet therapy is common. Its use is based on its general efficacy as an antithrombotic agent, as it has been shown to reduce the incidence of myocardial infarction and death in men and women over the age of 50, in patients with unstable angina and myocardial infarction, and in patients with atherosclerotic cerebrovascular disease (APT Collab I 1994; ATT 2009), whilst the administration of aspirin improves the patency rates of saphenous-vein aorto-coronary bypass grafts (APT Collab I 1994; ATT 2009; Stein 1998). Aspirin also reduces the incidence of stroke and death in patients with recurrent episodes of cerebral ischaemia (Sze 1988). Given that ischaemic cardiomyopathy is a major aetiological factor of heart failure, clinicians routinely use aspirin. Furthermore, research has shown aspirin to be moderately effective in reducing venous thrombosis and thromboembolism in patients undergoing hip surgery and possibly in preventing these occurrences in general surgical patients (APT Collab I 1994).

Investigators have also studied antiplatelet agents such as dipyridamole and clopidogrel in cardiovascular disease. Studies have shown that dipyridamole reduces the incidence of thromboembolism when added to warfarin in high-risk patients with prosthetic heart valves (APT Collab I 1994; Stein 1998), and others have reported that it reduces the risk of stroke when added to aspirin in patients with a history of cerebrovascular disease (APT Collab I 1994; APT Collab II 1994; Klimt 1986). However, dipyridamole appears to have little antithrombotic effect, and studies have indicated that the addition of dipyridamole adds little to aspirin therapy alone in most cardiovascular diseases.

In contrast, the newer platelet-active agent clopidogrel has been studied in the large Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, with evidence of a reduction in the composite outcome of vascular death, ischaemic stroke and myocardial infarction in patients with a history of cardiovascular disease (CAPRIE 1996).

There have been few prospective studies of oral anticoagulants or antiplatelet agents in patients with heart failure in sinus rhythm. Given the evident prothrombotic state in such patients, it is plausible that use of oral anticoagulants can be beneficial. The previous version of this Cochrane review was not able to conclude that oral anticoagulation was better than antiplatelet therapy, but the analysis was limited by the paucity of high-quality studies. A joint consensus document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis in 2012, 'Thromboembolism and antithrombotic therapy for heart failure in sinus rhythm', concluded that "[w]hilst there is the potential for a reduction in ischaemic stroke, there is currently no compelling reason to routinely use warfarin for these patients" (Lip 2012). We performed a new literature search for this Cochrane review update to reflect recent advances in the field.

How the intervention might work

The efficacy of antithrombotic therapy in arterial fibrillation (including in people with heart failure) and of oral anticoagulation versus placebo for heart failure in sinus rhythm are the subjects of related Cochrane reviews (Aguilar 2005; Lip 2014), and we will not address these topics in the present review, which focuses on heart failure with sinus rhythm.

There is compelling evidence that aspirin reduces the short term risk of death after myocardial infarction, although the mortality benefits are less impressive during long-term treatment or following the late initiation of aspirin (APT Collab I 1994; ATT 2009). This evidence supports the use of aspirin in heart failure patients with ischaemic heart disease, although many of these patients have only a distant history of myocardial infarction, and the magnitude of any potential long-term benefits is not conclusively established.

Antithrombotic agents (i.e. oral anticoagulants or antiplatelet agents) might reduce thrombotic complications, such as myocardial infarction and stroke, and improve survival in heart failure with sinus rhythm. Bleeding complications are not uncommon with these agents, an important consideration during assessment of their overall benefits.

Why it is important to do this review

This review addresses an important problem, and it calls for the best evidence-based antithrombotic therapy in heart failure without arterial fibrillation. The studies available at the time of the previous version of the review produced conflicting results. The new study included in this update contributes more participants for the analysis than the three older studies combined, thus significantly improving the power and validity of the analysis.

OBJECTIVES

To assess the effects of oral anticoagulant therapy versus antiplatelet agents for all-cause mortality, non-fatal cardiovascular

events and risk of major bleeding in adults with heart failure (either with reduced or preserved ejection fraction) who are in sinus rhythm.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT) comparing antiplatelet therapy with oral anticoagulation.

Types of participants

People aged 16 years or older with clinically defined heart failure and if possible, with objective evidence of left ventricular systolic dysfunction, diastolic dysfunction (e.g. echocardiography, radionuclide ventriculography) or both. Patients with heart failure with reduced or preserved ejection fraction were eligible. We excluded studies in participants with arterial fibrillation only and studies that did not perform a separate analysis for a subgroup of participants with heart failure.

Types of interventions

Orally administered antiplatelet agents (aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor or dipyridamole) compared with oral anticoagulants (coumarins, warfarin, dabigatran, apixaban, edoxaban or rivaroxaban). We considered studies administering treatment for at least one month. We excluded studies with additional simultaneously tested active treatments in the intervention arm (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, etc.).

Types of outcome measures

Primary outcomes

- All-cause mortality
- Non-fatal cardiovascular events (non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism)

Secondary outcomes

- Major bleeding events

We excluded studies without recorded or available clinical events.

Search methods for identification of studies

Electronic searches

We updated the searches from 2005 (Appendix 1) and re-ran them in February 2010 (Appendix 2), June 2013 (Appendix 3) and September 2015 (Appendix 4).

- The Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 8) in *The Cochrane Library*.
- MEDLINE (Ovid, 1946 to September week 1 2015).
- Embase (Ovid, 1980 to 2015 week 37).
- Database of Abstracts of Reviews of Effects (DARE) (Issue 1, 2010) in *The Cochrane Library* (not updated in 2015).

We used the Cochrane sensitivity-maximising RCT filters to search MEDLINE and Embase (Lefebvre 2011), applying no language or date restrictions. We would have had relevant foreign language

papers translated and we handsearched the reference lists of papers.

We searched two clinical trials registers on 29 July 2016: ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/). See Appendix 4 for the search terms used.

Searching other resources

We searched abstracts from national and international cardiology meetings (American Heart Congress, American College of Cardiology Congress, European Society of Cardiology Congress, Congress of the International Society on Thrombosis and Haemostasis, European Stroke Conference, International Stroke Conference, World Stroke Congress, UK Stroke Forum Conference and the Heart Failure Congress) from 1980 (or the date the resource became available) to September 2015 to identify unpublished studies, and we contacted relevant authors of these studies to obtain further details, if required.

Data collection and analysis

Selection of studies

The authors (ES, GYHL) independently selected suitable trials for inclusion in the review, resolving disagreements by discussion.

Data extraction and management

The review authors (ES and GYHL) screened studies for inclusion and retrieved all potentially relevant studies. Later the authors independently reviewed characteristics of the preselected studies to identify studies eligible for this review. The authors were not blinded to any aspect of the studies (for example, journal type, authors' names, institution). There was no disagreement regarding the selection of eligible studies. Both authors extracted information on study populations, interventions, pre-specified outcomes, methodology, and quality of the eligible trials.

Assessment of risk of bias in included studies

Using the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we assessed six domains related to risk of bias: randomisation sequence generation, allocation concealment, incomplete outcome data, selective reporting, blinding of participants and personnel, and blinding of outcome assessors.

Measures of treatment effect

We expressed dichotomous data on outcomes as Mantel-Haenszel risk ratios (RR) with 95% confidence intervals (CI).

Dealing with missing data

For unpublished studies or where data were incomplete in published papers, we made attempts to contact authors or researchers to obtain further details. Where relevant, we contacted pharmaceutical companies to attempt to obtain unpublished trial data on newer antiplatelet drugs that may have been used in patients with heart failure.

Assessment of heterogeneity

We assessed statistical heterogeneity appropriately in each meta-analysis using the I^2 and χ^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 50% or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity.

Data synthesis

We considered whether an overall summary was meaningful and used a fixed-effects model to conduct meta-analysis.

Subgroup analysis and investigation of heterogeneity

Heterogeneity was low across the included studies. If it were high, we would have investigated it through subgroup analyses.

Sensitivity analysis

We would have conducted sensitivity analyses to explore the effect of trial quality for each comparison by restricting the analysis to those trials rated as being at low risk of bias for random sequence generation and allocation concealment. However, all included trials were of low risk of bias in these domains.

Summary of findings table

We created a 'Summary of findings' table using the following outcomes: all-cause mortality, non-fatal cardiovascular events (non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism), and major bleeding events. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies contributing data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software. We justified all decisions to downgrade the quality of studies using footnotes, and we made comments to aid readers' understanding of the review where necessary.

RESULTS

Description of studies

Results of the search

The initial search in 2005 yielded 1647 records, of which we excluded 1631 after screening titles and abstracts. We assessed the full text of the remaining 16 records. [WASH 2004](#) met our inclusion criteria. We excluded 12 studies, and the other 3 were ongoing ([HELAS 2006](#); [WATCH 2009](#); [WARCEF 2000](#)).

The updated search in 2010 yielded 1219 new records, of which we excluded 1203 after screening the titles and abstracts. We assessed 16 full-text records and included two previously ongoing studies ([HELAS 2006](#); [WATCH 2009](#)).

The updated search in 2013 yielded 1460 new records, of which we excluded 1452 after screening the titles and abstracts. Four records were abstracts of interest based on two retrospective analyses. However, they did not specify the proportion of participants with atrial fibrillation and did not provide information on adverse outcomes, so we excluded them. We reviewed four full-text records, one of which met the inclusion criteria ([WARCEF 2012](#)).

The updated search in 2015 yielded 975 new records; we excluded 971 after screening the titles and abstracts and examined four records in detail. [Pullicino 2013](#) was a journal publication with a subanalysis of the [WARCEF 2012](#) study, looking at different types of stroke. The analysis did not add any new information relevant to this review. The three remaining records were abstracts of conference presentations of two small randomised studies ([ASAP-HF 2013](#); [CACHE-EHF 2014](#); [CACHE-EJHF 2014](#)), which did not meet all inclusion criteria for this analysis.

In total, this review includes four studies ([HELAS 2006](#); [WARCEF 2012](#); [WASH 2004](#); [WATCH 2009](#)). We present the reasons for excluding studies that closely missed the inclusion criteria in [Characteristics of excluded studies](#).

In the two clinical trials registers, we checked all the retrieved entries but found no additional studies meeting review requirements.

We show the flow of studies, combined for all searches, in [Figure 1](#).

Figure 1. PRISMA flow chart.

Included studies

We included four RCTs that met the review criteria for assessing the effectiveness of antiplatelet therapy ([HELAS 2006](#); [WARCEF 2012](#); [WASH 2004](#); [WATCH 2009](#); see [Characteristics of included studies](#)).

All studies recruited patients with heart failure with reduced LVEF only. Arterial fibrillation was not an absolute exclusion criterion in [WASH 2004](#), but 92% of the study participants had no history of it at the time of recruitment. Other studies only included patients with sinus rhythm. The range of ages for the trials was 18 years and older with a mean age of 61 years across the trials. Most participants were men (61% to 93% across trials). We analysed all outcomes based on the intention-to-treat principle.

The studies were international (involving the USA, the UK, countries in Western and Eastern Europe, Canada and Argentina). The pharmaceutical industry provided some funding and support to the studies. The WASH trial was partly supported by the Bristol-Myers Squibb, which manufactures warfarin in the USA. The Bristol-Myers Squibb, Sanofi-Synthelabo, and Dupont pharmaceutical companies partly supported the WATCH trial through unrestricted grants and provision of the study drugs. [HELAS 2006](#) did not specify sources of funding, but Greece-based centres led and coordinated

the study, and Greece-based companies manufactured all study agents.

[WASH 2004](#) was a pilot study in 279 participants recruited from 17 centres in the UK and 3 centres in the USA. This review analysed only the 180 patients randomised to warfarin (target international normalised ratio (INR) 2.0 to 3.0) versus aspirin (300 mg once daily). The remaining patients were randomised to no antithrombotic therapy and thus were outside the scope of the analysis. Investigators recorded baseline data on all participants by telephone at the data centre before randomisation using prospectively constructed blocks of random numbers.

Participants had to have a clinical diagnosis of heart failure requiring treatment with diuretics and evidence of left ventricular systolic dysfunction on echocardiography within six months before entry ([WASH 2004](#)). Echocardiographic criteria of left ventricular dysfunction included an increased left ventricular end-diastolic internal dimension (≥ 56 mm or ≥ 30 mm/m² body surface area) combined with a fractional shortening of at least 28% or LVEF of at least 35%. Investigators were encouraged to use warfarin in participants who developed arterial fibrillation and to reduce the dose of aspirin or use any appropriate antidiyspeptic medication if dyspepsia occurred. This trial was limited by open-label treatment

with warfarin, small numbers and relatively short follow-up (27 ± 1 months). Also, from the study manuscript it is not clear whether any patients had incomplete outcome data.

HELAS 2006 recruited 197 participants in centres in Greece, Cyprus, Yugoslavia, Romania, Bulgaria, Poland and Georgia. We excluded the participants with dilated cardiomyopathy who were randomised to warfarin versus placebo, but we included participants with underlying ischaemic heart disease ($n = 115$) who were randomised to warfarin versus aspirin. The trial was double-blinded and included participants with the New York Heart Association (NYHA) class II to IV and LVEF of more than 35% assessed by echocardiography, or by radionuclide or angiocardigraphic ventriculography. The University coordination centre conducted computerised randomisation by fax or telephone. Investigators were blinded to therapy, and warfarin doses were recommended according to sham results where appropriate. However, the study manuscript does not provide details on the sham procedures, and it is unclear how robust they were. The participants were regularly followed up with a recording of any clinical outcomes. As with **WASH 2004**, **HELAS 2006** is limited by the small number of participants and short follow-up period (mean follow-up time of 18.5 months for those taking aspirin and 18.7 months for those taking warfarin). It is not clear whether there was an independent assessment of study outcomes.

WATCH 2009 included 1587 participants from 142 centres in the USA, Canada and the UK. Patients were eligible if they had NYHA class II to IV heart failure for more than three months, LVEF of less than 35%, were in sinus rhythm and on a diuretic and ACE inhibitor (unless not tolerated). Patients were randomised into three arms: aspirin 162 mg once daily, clopidogrel 75 mg once daily in a double-blind, double-dummy manner, or open label warfarin (target INR 2.5 to 3.0). The Cooperative Studies Program Coordinating Center (CSPCC) generated randomisation sequences for each site and allocated treatment. The main outcome measures were adjudicated by a blinded committee. The mean duration of follow-up was 1.9 years, for a total of 3073 patient-years of follow-up. Due to slow enrolment, the study failed to recruit the pre-specified target of 4500 participants. The study was limited by open-label management of warfarin. Also, similar to **WASH 2004**, it is not clear whether any participants in **WATCH 2009** had incomplete outcome data.

WARCEF 2012 was a large RCT conducted at 168 centres in 11 countries. The trial recruited 2305 participants with LVEF of 35% or less and sinus rhythm who were randomised to warfarin (target INR of 2.0 to 3.5) or aspirin (325 mg once daily). Investigators reported the primary outcomes of the first event in a composite endpoint of ischaemic stroke, intracerebral haemorrhage or death from any cause during a mean follow-up period of 3.5 ± 1.8 years. Two independent core echocardiography laboratories, which were unaware of the study treatment, assessed the accuracy of LVEF measurement. An independent endpoint adjudication committee blinded to the treatment assignments adjudicated all primary and secondary outcomes and cases of major haemorrhage. The WARCEF trial was a well-designed, adequately powered study with low risk of the assessed bias types.

Excluded studies

We excluded 40 references and present our reasons for excluding 9 studies that most closely missed the inclusion criteria in **Characteristics of excluded studies**.

Four RCTs of ACE inhibitors assessed the use of antithrombotic therapy in participants with heart failure and/or left ventricular systolic dysfunction (**Al-Khadra 1998a**; **SAVE 1997**; **SOLVD 1997**; **V-HeFT II 1992**). These analyses were done outside the randomisation scheme. **V-HeFT II 1992** included participants with symptomatic heart failure and radiological, echocardiographic or radionuclide evidence of left ventricular systolic dysfunction. The SOLVD trials included participants with left ventricular systolic dysfunction, defined as a LVEF of 35% or less, who were either symptomatic and enrolled into the treatment trial (**SOLVD-treatment 1991**), or asymptomatic and enrolled into the prevention trial (**SOLVD-prevent 1992**). **SAVE 1997** included participants post-myocardial infarction with an LVEF of 40% or more and no overt heart failure (i.e. asymptomatic participants). **PROMISE 1993** presented limited information from a retrospective analysis of one trial in abstract form only.

In one recent retrospective, observational, non-randomised study, investigators used aspirin in 32% of 417 participants (warfarin in 28%) with an average follow-up of five years (**EPICAL 2002**). Treatment with antithrombotic agents (either aspirin, warfarin or both) was associated with better survival at five years (40.4% versus 31% with no antithrombotic treatment, $P = 0.01$). However, we excluded this study because 24% of the participants had concomitant arterial fibrillation, investigators reported only survival rates, and they did not report event rates separately for the sinus rhythm group or those treated with aspirin, warfarin or no therapy.

Two almost identical abstracts presented results of the randomised open-label clopidogrel versus aspirin in chronic heart failure (CACHE) study that compared 75 mg daily doses of the two drugs in 87 participants with heart failure in sinus rhythm and an N-terminal-pro-brain natriuretic peptide (NT-proBNP) of 400 ng/L (mostly NYHA II) (**CACHE-EHF 2014**; **CACHE-EJHF 2014**). By six months, treatment with aspirin was associated with worse renal function and higher diastolic blood pressure compared with clopidogrel, but investigators did not report any major adverse outcomes. The study did not have a comparator other than another antiplatelet agent (i.e. placebo or oral anticoagulant), so we excluded it from the analysis.

No adequately powered prospective studies have specifically examined the role of the antiplatelet agent dipyridamole in heart failure participants. There was a small randomised pilot study of dipyridamole plus aspirin (aggrenox) versus placebo in 18 participants with congestive heart failure (NYHA class II to IV) and LVEF of less than 40%, presented as a conference abstract in 2013 (**ASAP-HF 2013**). After six months of therapy, there were no reported changes in haemodynamic characteristics in either group. BNP levels were reduced in the treatment group, but not in the placebo group (the report did not include a between-group comparison). More participants in the treatment group showed improvement in six-minute walking distance than in the placebo group. We excluded the study because no clinical events were recorded (although investigators mentioned the absence of bleeding events in both groups). There were two active treatments

in the intervention arms, and investigators provided no information on whether the participants were in arterial fibrillation or sinus rhythm.

The ongoing [COMMANDER HF trial](#) ([COMMANDER HF trial](#)) compares rivaroxaban versus placebo in participantpatients with heart failure of ischaemic aetiology with sinus rhythm.

Risk of bias in included studies

We summarize the 'Risk of bias' assessment in [Figure 2](#) and [Figure 3](#). Because there were only four studies and all had a low risk of selection bias, we did not perform a sensitivity analysis.

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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
HELAS 2006	+	+	+	+	?	?
WARCEF 2012	+	+	+	+	+	+
WASH 2004	+	+	?	+	-	+
WATCH 2009	+	+	?	+	-	+

Allocation

All studies used central randomisation with low risk of bias in relation to random sequence generation and allocation concealment.

Blinding

For blinding of participants and personnel, we assessed two studies as being at high risk ([WASH 2004](#); [WATCH 2009](#)), one study as being at low risk ([WARCEF 2012](#)), and one study as being at unclear risk of blinding of participants and personnel ([HELAS 2006](#)).

We considered [HELAS 2006](#) to be at unclear risk of detection bias in relation to the blinding of outcome assessors, while the other three studies were at low risk ([WARCEF 2012](#); [WASH 2004](#); [WATCH 2009](#)).

Incomplete outcome data

Two studies were also at unclear risk of incomplete outcome bias ([WASH 2004](#); [WATCH 2009](#)), while two studies were at low risk of bias in this domain ([HELAS 2006](#); [WARCEF 2012](#)).

Selective reporting

We deemed all four included studies to be at low risk of selective reporting bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Summary of findings: warfarin versus aspirin for heart failure with sinus rhythm; [Summary of findings 2](#) Summary of findings: warfarin versus clopidogrel for heart failure with sinus rhythm

All-cause mortality

Four trials involving 3663 participants reported all-cause mortality for warfarin versus aspirin ([HELAS 2006](#); [WARCEF 2012](#); [WASH 2004](#); [WATCH 2009](#)). Participants in both groups were at a similar risk of all-cause death (219 events per 1000 for both agents, Mantel-Haenszel RR 1.00, 95% CI 0.89 to 1.13; $I^2 = 0\%$; [Analysis 1.1](#)). The quality of the evidence was moderate.

[WATCH 2009](#) (N = 1064) reported on all-cause mortality for warfarin versus clopidogrel, but there was no evidence that either treatment was superior to the other (RR 0.93, 95% CI 0.72 to 1.21; participants = 1064; low quality of evidence; [Analysis 2.1](#)).

Non-fatal cardiovascular events

Four trials with 3663 participants also reported non-fatal cardiovascular events (such as non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism) for warfarin versus aspirin ([HELAS 2006](#); [WARCEF 2012](#); [WASH 2004](#); [WATCH 2009](#)). Treatment with warfarin was associated with a reduction in non-fatal cardiovascular events (66 per 1000 for warfarin, 83 per 1000 for aspirin, Mantel-Haenszel RR 0.79, 95% CI 0.63 to 1.00; $I^2 = 0\%$; [Analysis 1.2](#)). The quality of the evidence was moderate.

[WATCH 2009](#) (N = 1064) reported non-fatal cardiovascular events for warfarin versus clopidogrel. Patients in both groups were at similar risk (46 per 1000 for warfarin, 54 per 1000 for aspirin, Mantel-Haenszel RR 0.85, 95% CI 0.50 to 1.45; [Analysis 2.2](#)). The quality of the evidence was low.

Major bleeding events

Four trials (N = 3663) reported rates of major bleeding events ([HELAS 2006](#); [WARCEF 2012](#); [WASH 2004](#); [WATCH 2009](#)). In the pooled analysis warfarin use was associated with a twofold increase in the risk of major bleeding compared to aspirin (56 per 1000 for warfarin, 28 per 1000 for aspirin, Mantel-Haenszel RR 2.00, 95% CI 1.44 to 2.78; $I^2 = 4\%$; [Analysis 1.3](#)). The quality of the evidence was moderate.

[WATCH 2009](#) (N = 1064) reported major bleeding events for warfarin versus clopidogrel. The rate of major bleeding events was 2.5 times higher in the warfarin group (49 per 1000 for warfarin, 20 per 1000 for aspirin, Mantel-Haenszel RR 2.47, 95% CI 1.24 to 4.91; [Analysis 2.3](#)). The quality of the evidence was low.

DISCUSSION

Summary of main results

The analysis of warfarin versus aspirin is based on four RCTs with a large overall number of participants. More than half of the participants were from the well-designed, double-blind WARCEF trial. Despite some limitations of other studies (e.g. open-label treatment with warfarin in two trials), the analysis shows low heterogeneity of the outcomes, and we judged the quality of the evidence to be high for all-cause mortality and moderate for non-fatal cardiovascular events and major bleeding events. Despite the availability of different oral anticoagulants and antiplatelet agents, the main analysis is limited to the long-established agents warfarin and aspirin. The analysis did not provide evidence that either was better for all-cause mortality, and further studies are unlikely to change these conclusions.

The risk of non-fatal cardiovascular events tended to be lower in the warfarin group, but this was offset by the twofold rise in risk of major haemorrhage. The reduction in non-fatal cardiovascular events is likely due to undiagnosed/silent arterial fibrillation and deep vein thrombosis in some patients. Again, further research of these two agents is unlikely to prove the clinical superiority of either.

Comparison of warfarin with clopidogrel was limited to a single trial with open-label warfarin management ([WATCH 2009](#)). Slow recruitment restricted the statistical power, and as a result the trial was stopped early. The quality of the evidence for these analyses was low. However, the outcomes of these analyses were broadly similar to those of warfarin versus aspirin, with results that did not favour either drug for the primary outcome, but with 2.5 times higher major bleeding rates in the warfarin arm of the study. Further trials are unlikely to add more to the conclusions in relation to role of warfarin versus clopidogrel in heart failure in sinus rhythm.

Overall completeness and applicability of evidence

Non-vitamin K antagonist oral anticoagulants (e.g. direct thrombin inhibitor, dabigatran, and factor Xa inhibitors, apixaban, edoxaban and rivaroxaban) have now been approved for clinical use in patients with arterial fibrillation and venous thromboembolism. These agents show good efficacy and a favourable safety profile and may become a suitable alternative to warfarin to be tested in future trials in heart failure with sinus rhythm. No such data are available at present. The ongoing [COMMANDER HF trial](#) compares rivaroxaban versus placebo in participants with heart failure of ischaemic aetiology with sinus rhythm. The non-vitamin K antagonist oral anticoagulants are used as fixed-dose agents as opposed to warfarin, and this would facilitate easier concealment of the study treatments.

Given the fact that all four included RCTs focused on heart failure with reduced ejection fraction, it is not possible to extrapolate their conclusions to patients with heart failure with preserved ejection fraction. Admittedly, the specific prothrombotic risk in heart failure with preserved ejection fraction and sinus rhythm has not been firmly established, and further research would be essential in this field.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate quality evidence demonstrating no difference in all-cause mortality between warfarin and aspirin in patients with heart failure in sinus rhythm. Warfarin was associated with a slightly lower risk of non-fatal cardiovascular events but a higher risk of major bleeding complications (moderate quality of the evidence). We saw a similar pattern of results for the warfarin versus clopidogrel comparison (low quality evidence). At the time of writing, there were no data on the role of oral anticoagulants versus antiplatelet agents in heart failure with preserved ejection fraction with sinus rhythm. Likewise, there were no data from RCTs on the utility of non-vitamin K oral anticoagulants compared to antiplatelet agents in heart failure with sinus rhythm.

Implications for research

Current evidence is based on four randomised controlled trials ([HELAS 2006](#); [WASH 2004](#); [WATCH 2009](#), [WARCEF 2012](#)), and further

similar studies are unlikely to change the conclusions regarding comparisons of warfarin with aspirin. Although comparison of warfarin with clopidogrel is only based on a single, medium-size study, it generally agrees with the conclusions of the aspirin studies, and new studies are unlikely to lead to new clinically relevant conclusions.

Several non-vitamin K antagonist oral anticoagulants have now been approved for clinical practice. They show good efficacy and a favourable safety profile in other clinical settings, including heart failure with arterial fibrillation. Future trials should establish the potential utility of these agents in patients with heart failure with sinus rhythm.

The role of antithrombotic agents in heart failure with preserved ejection fraction remains unclear. It would be important to obtain contemporary data on thrombotic risk specific to this condition, and if the risk is confirmed, high-quality RCTs would be necessary to establish optimal management of such patients.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

HELAS 2006

Methods	<p>Randomised controlled trial</p> <p>Multicentre trial: centres in Greece, Cyprus, Yugoslavia, Romania, Bulgaria, Poland and Georgia</p> <p>Setting: outpatient clinics</p> <p>Period of trial: between January 1998 and August 1999</p>
Participants	<p>Heart failure, sinus rhythm</p> <p>Entire cohort was 197 participants, of whom 115 had ischaemic aetiology of heart failure and were randomised to warfarin or aspirin. These 115 participants were included in the present analysis (aspirin group: n = 61, age 61.0 ± 8.9 years, 93% men; warfarin group: n = 54, age 62.3 ± 9.7 years, 85% men). The remaining 82 participants had dilated cardiomyopathy and they were randomised to warfarin vs placebo (not included in this review). Among the 61 participants in the aspirin group, 1 developed atrial fibrillation and was withdrawn and excluded from the final analysis.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Aged 20-75 years • Symptomatic heart failure (NYHA class II-IV) • LVEF < 35% by echocardiographically by the area-length method or Simpson's rule, or by radionuclide or angiographic ventriculography • Ischaemic heart disease established as previous myocardial infarction (> 2 months from date of enrolment) or by coronary arteriography, to be eligible for warfarin vs aspirin randomisation and analysis <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Evidence of reversible ischaemia • Mitral valvular disease • Hypertrophic cardiomyopathy • Atrial fibrillation • Left ventricular thrombi on echocardiography • Other severe life-threatening diseases that might limit survival or compliance with the 2-year study period • Contraindication to aspirin or warfarin • Uncontrolled hypertension (> 160/100 mm Hg) • Pregnancy
Interventions	<p>Warfarin (target INR 2.0-3.0) vs aspirin 325 mg once daily (ischemic etiology of heart failure);</p>

HELAS 2006 (Continued)

Warfarin vs placebo (idiopathic dilated cardiomyopathy)

Only the warfarin vs aspirin trial arm was used in this review

Outcomes	Primary outcome: composite of non-fatal stroke, peripheral or pulmonary embolism, myocardial (re)infarction, re-hospitalisation, exacerbation of heart failure, or death from any cause Safety endpoints: major haemorrhage
Follow-up duration	Mean duration: 18.5 months in the aspirin group; 18.7 months in the warfarin group
Funding source	Not reported
Declarations of interest	Not reported
Notes	Planned as a definite trial to recruit 6000 participants but stopped early due to actual recruitment being < 5% of the target recruitment; reported as a pilot trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computerised randomization was conducted by fax or by phone to the Athens University Coordinating Centre"
Allocation concealment (selection bias)	Low risk	"Computerised randomization was conducted by fax or by phone to the Athens University Coordinating Centre"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in follow-up analysis, and an independent data committee conducted interim analyses.
Selective reporting (reporting bias)	Low risk	Predefined primary and secondary outcomes were used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The investigator-supervisor was blinded to the study in the same manner as in the CAFA study and regulated the study medication dose according to the prothrombin time results to maintain an INR of 2–3. The dose was then administered to the patient by a second physician. In the placebo arm, the supervisor recommended the dose according to sham results." and further, "Warfarin (Panwarfin, Abbot, Greece) was supplied as 5-mg tablets. The daily dose was 2.5–10mg, with a target INR of 2–3. ASA (Salospir A, Uni-Pharma, Greece) was supplied as 325-mg tablets and was given once daily or according to sham adjustment." Comment: The study used sham medications to conceal the study drug, but it is not clear how robust the system was. The provided reference refers to a study not related to warfarin.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The occurrence of clinical endpoints [end-points listed] was recorded."

WARCEF 2012

Methods	Randomised double-blind double-dummy controlled trial
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WARCEF 2012 (Continued)

Multicentre trial: 168 centres in 11 countries

Setting: outpatient clinics

Period of trial: recruitment between October 2002 and January 2010 with a minimum follow-up of 1 year

Participants
Heart failure, sinus rhythm

Randomised 2305: warfarin group $n = 1142$, mean age 61 ± 11.6 years, 79.3% men; aspirin group $n = 1163$, mean age 61 ± 11.1 years, 80.7% men.

34 participants (1.5%) withdrew consent, and 35 (1.5%) were lost to follow-up

All 2305 randomised patients were included into the analysis:

Inclusion criteria

- Age ≥ 18 years
- Sinus rhythm
- No contraindication to warfarin therapy
- LVEF $\leq 35\%$ by echocardiography (or a wall-motion index of ≤ 1.2) or as assessed by radionuclide or contrast ventriculography within 3 months before randomisation
- Participants in any NYHA functional class were eligible, but participants in NYHA class I could account for no more than 20% of the total number of participants undergoing randomisation
- Additional eligibility criteria
 - * A modified Rankin score of ≤ 4
 - * Planned treatment with a beta-blocker, an angiotensin-converting-enzyme inhibitor, or hydralazine and nitrates

Exclusion criteria

- A clear indication for warfarin or aspirin
- A condition with a high risk of cardiac embolism (e.g. arterial fibrillation, a mechanical cardiac valve, endocarditis, or an intracardiac mobile or pedunculated thrombus)

Interventions

Warfarin (target INR 2.0-3.5) vs aspirin 325 mg once daily

Outcomes

Primary outcome: composite of ischaemic stroke, intracerebral haemorrhage, or death from any cause.

Secondary outcome: composite of the primary outcome, myocardial infarction or hospitalisation for heart failure

Follow-up duration

Mean 3.5 ± 1.8 years

Funding source

Supported by grants (U01-NS-043975 (to Dr Homma) and U01-NS-039143 (to Dr Thompson)) from the National Institute of Neurological Disorders and Stroke

Declarations of interest

Dr Homma reports receiving payment from AGA Medical (now St. Jude Medical) for his work as a member of a data and safety monitoring board and consulting fees from Boehringer Ingelheim; Dr Levin received consulting fees from United Healthcare; Dr Teerlink, received consulting fees from Amgen and grant support from Amgen, Cytokinetics, and Novartis on behalf of himself and from NovaCardia/Merck on behalf of himself and his institution; Dr. Graham, owning stock in March Pharmaceuticals, Medtronic, and Pfizer; Dr Labovitz received grant support from Boehringer Ingelheim on behalf of his institution, lecture fees from Boehringer Ingelheim, and fees for the development of educational presentations from the American College of Cardiology; Dr Anker received consulting fees from Amgen, Bosch Healthcare, GlaxoSmithKline, Helsinn, LoneStar Heart, Novartis, Professional Dietetics, PsiOxus, Relypsa, SHL Telemedicine, and Thermo Fisher, grant support from Vifor Pharma, and lecture fees from Novartis, holding patents with Brahms AG and Charit Berlin, and royalties from Imperial College; Dr Ponikowski received consulting fees from Bayer, Boehringer Ingelheim, Coridea, Corthera, Johnson & Johnson, Pfizer, Respicardia, and Vifor Pharma, grant support from Vifor Pharma on behalf of himself

WARCEF 2012 (Continued)

and his institution, and lecture fees from Abbott, Boehringer Ingelheim, Merck Serono, Pfizer, Respicardia, Sanofi-Aventis, Servier, and Vifor Pharma; and Dr Lip received consulting fees from Astellas, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Merck, Portola, and Sanofi-Aventis, speakers bureau fees from Bayer, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, and Sanofi-Aventis, and payment for the development of educational presentations from Bayer, Boehringer Ingelheim, and Merck. Authors did not report any other potential conflict of interest relevant to this article.

Notes

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were (randomly) assigned to . . ."; the study protocol specifies that randomisation occurred centrally
Allocation concealment (selection bias)	Low risk	Quote: "Patients were (randomly) assigned to . . ."; the study protocol specifies that randomisation occurred centrally
Incomplete outcome data (attrition bias) All outcomes	Low risk	Survival status available for 97% of the participants
Selective reporting (reporting bias)	Low risk	Predefined primary and secondary outcomes were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"In the double-blind, double-dummy design, patients who were assigned to active warfarin received warfarin and placebo aspirin, and patients assigned to active aspirin received aspirin and placebo warfarin."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An independent end-point adjudication committee, whose members were unaware of the treatment assignments, adjudicated all primary and secondary outcomes and major hemorrhages."

WASH 2004

Methods	<p>Randomised open-label controlled trial</p> <p>Multicentre trial: 17 centres in the UK and 3 centres in the USA.</p> <p>Setting: outpatient clinics</p> <p>Period of trial: recruitment between November 1995 and September 1998</p>
Participants	<p>Heart failure (sinus rhythm in 94% of the participants)</p> <p>Randomised 279 participants (180 participants eligible for this review, another 99 participants were randomised for no antithrombotic therapy): warfarin group n = 89, mean age 62 years, 76% men; aspirin group n = 91, mean age 65 years, 75% men</p> <p>Analysed: 180 participants randomised for warfarin vs. aspirin</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> Clinical diagnosis of heart failure requiring treatment with diuretics

WASH 2004 (Continued)

- Left ventricular systolic dysfunction on echocardiography performed within the 6 months prior to entry: end-diastolic internal dimension (≥ 56 mm or ≥ 30 mm/m² body surface area) plus a fractional shortening of $\leq 28\%$ or ejection fraction $\leq 35\%$.

Exclusion criteria

- Definite indication for or contraindication to aspirin and warfarin (included mitral stenosis or mechanical valve prosthesis, increased risk of haemorrhage due to defects in haemostasis, deranged liver function, active peptic ulcer, and vascular malformation)
- Uncontrolled hypertension
- Evidence of poor drug compliance
- Alcohol abuse
- History of frequent falls

Interventions	Warfarin (target INR 2.0-3.0) vs aspirin (300 mg once daily) vs no antithrombotic therapy Only the warfarin vs aspirin arm was used in this review
Outcomes	Primary outcome: composite of all-cause death, non-fatal myocardial infarction and non-fatal stroke Secondary outcomes: death or cardiovascular hospitalisation (including worsening heart failure, myocardial infarction, stroke, other thromboembolic events, and major haemorrhage); death or all-cause hospitalisation, total number of hospitalisations; the composite of death, cardiovascular hospitalisation, and increase in diuretic therapy for worsening heart failure
Follow-up duration	Mean 27 ± 1 months (for all trial participants)
Funding source	Supported in part by the NHS R&D Cardiovascular Disease and Stroke Programme Executive and Bristol-Myers Squibb, who manufacture warfarin in the USA
Declarations of interest	Not reported in the trial manuscript
Notes	Arterial fibrillation was not an absolute exclusion criterion, but 92% of participants had no history of it at the time of recruitment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Data on patients recorded by telephone at data centre before randomisation using prospectively constructed blocks of random numbers"
Allocation concealment (selection bias)	Low risk	"Data on patients recorded by telephone at data centre before randomisation using prospectively constructed blocks of random numbers"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided on presence of incomplete outcome data
Selective reporting (reporting bias)	Low risk	Predefined primary and secondary outcomes were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias)	Low risk	Blinded endpoint design

WASH 2004 (Continued)

All outcomes

WATCH 2009

Methods	<p>Randomised controlled trial</p> <p>Aspirin and clopidogrel given in double blind, double-dummy manner; open label warfarin</p> <p>Multicentre trial: 142 centres in the United States, Canada, and the United Kingdom</p> <p>Setting: outpatient clinics</p> <p>Period of trial: between October 1999 and June 2003</p>
Participants	<p>Heart failure, sinus rhythm</p> <p>Randomised 1587 participants: warfarin group n = 540, mean age 63 ± 11 years, 85% male; aspirin group n = 523, aged 63 ± 11 years, 85% men; clopidogrel group n = 524, aged 62 ± 11 years, 86% men.</p> <p>Loss to follow-up in warfarin group n = 35; aspirin group n = 24; clopidogrel n = 30;</p> <p>Analysed: 1585 patients: 1063 participants for the warfarin vs aspirin comparison and 1064 patients for the warfarin vs clopidogrel comparison:</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age ≥ 18 years • Symptomatic heart failure (NYHA class II to IV) for > 3 months before entry • LVEF ≤ 35% measured within 3 months by any standard technique • Sinus rhythm • Treated with a diuretic and an ACE inhibitor for ≥ 60 days (unless not tolerated) <p>Principle exclusion criteria:</p> <ul style="list-style-type: none"> • Contraindications or specific indications for any of the study medications • Imminent procedures necessitating withdrawal or use of the study medications • Heart failure from correctable causes • Serious comorbid conditions expected to limit life expectancy • Other conditions that would interfere with protocol adherence
Interventions	Warfarin (target INR 2.5-3.0) vs aspirin 162 mg once daily or clopidogrel 75 mg once daily
Outcomes	<p>Primary outcome: composite of all-cause death, non-fatal myocardial infarction and non-fatal stroke.</p> <p>Secondary outcomes: all-cause mortality; non-fatal myocardial infarction; non-fatal stroke; hospitalisations for heart failure</p> <p>Primary safety outcome: major bleeding episodes</p>
Follow-up duration	Mean 1.9 years, median 21 months
Funding source	This trial was supported and administered by the Cooperative Studies Program of the Office of Research and Development, Department of Veterans Affairs. Study drugs and unrestricted grants were provided by Bristol Myers Squibb, Sanofi-Synthelabo, and Dupont pharmaceutical companies.
Declarations of interest	Dr Massie received research grants from Bristol-Myers Squibb and Sanofi-Aventis. Dr Schulman received research grants from Bristol-Myers Squibb, and Sanofi-Aventis and does consulting for Sanofi-

WATCH 2009 (Continued)

Aventis. Dr Ezekowitz served as a consultant to Bristol-Myers Squibb and Sanofi-Aventis. The other authors of the reporting manuscript reported no conflicts of interest.

Notes	Terminated early due to slow recruitment, 4500 participants planned for randomisation, 1587 participants randomised	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The Cooperative Studies Program Coordinating Center generated a randomization sequence for each site separately using varying block sizes of 3 or 6. The site coordinator/site investigator called the Cooperative Studies Program Coordinating Center to obtain a randomization number and treatment allocation." Comment: Central randomisation
Allocation concealment (selection bias)	Low risk	"The Cooperative Studies Program Coordinating Center generated a randomization sequence for each site separately using varying block sizes of 3 or 6. The site coordinator/site investigator called the Cooperative Studies Program Coordinating Center to obtain a randomization number and treatment allocation." Comment: Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Low risk	Predefined primary and secondary outcomes were used All results were reported, including negative results
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants assigned to aspirin or clopidogrel were blinded although those receiving warfarin were unblinded, which may lead to some performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint committee reviewed outcomes and were blinded to the therapies

ACE: angiotensin converting enzyme; **CAFA:** Canadian Atrial Fibrillation Anticoagulation [study]; **INR:** international normalised ratio; **LVEF:** left ventricular ejection fraction; **NYHA:** New York Heart Association.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Al-Khadra 1998a	Post hoc retrospective, non-randomised analysis of ACE inhibitor trial
ASAP-HF 2013	This is a study of a dipyridamole plus aspirin vs placebo. Oral anticoagulants not been tested in the study
CACHE-EHF 2014	Comparator not of interest (a study of two antiplatelet agents)

Study	Reason for exclusion
EPICAL 2002	Retrospective, observational, non-randomised study
PROMISE 1993	Post hoc retrospective, non-randomised analysis of inotrope trial
SAVE 1997	Post hoc retrospective, non-randomised analysis of ACE inhibitor trial
SOLVD 1997	Post hoc retrospective, non-randomised analysis of ACE inhibitor trial
V-HeFT II 1992	Post hoc retrospective, non-randomised analysis of ACE inhibitor trial

ACE: angiotensin converting enzyme.

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

COMMANDER HF trial

Trial name or title	A randomized, double-blind, event-driven, multicenter study comparing the efficacy and safety of rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an episode of decompensated heart failure
Methods	Randomised controlled trial
Participants	Estimated enrolment: 5000

Inclusion criteria

- Symptomatic heart failure for at least 3 months prior to screening
- An episode of decompensated heart failure (index event) requiring: an overnight stay (that is, staying past midnight) in a hospital, emergency department, or medical facility with the capability of treating with intravenous medications and observing heart failure participants before randomisation; or an unscheduled outpatient visit to a heart failure management centre, where parenteral therapy is required for heart failure stabilisation. An episode of decompensated heart failure is defined as symptoms of worsening dyspnea or fatigue, objective signs of congestion such as peripheral oedema or ascites, and/or adjustment of pre-hospitalisation/outpatient visit heart failure medications. Participants are eligible for randomisation at discharge from the facility treating the index event and up to 30 days after discharge if they are in stable condition
- Documented LVEF of $\leq 40\%$ within 1 year before randomisation
- Evidence of significant coronary artery disease
- Medically stable in terms of their heart failure clinical status at the time of randomisation
- Brain natriuretic peptide (BNP) level of ≥ 200 pg/mL or N-terminal-proBNP (NT-proBNP) level ≥ 800 pg/mL (preferred assay) during the screening period and before randomisation

Exclusion criteria

- Any condition that, in the opinion of the investigator, contraindicates anticoagulant therapy or would imply an unacceptable risk of bleeding, such as, but not limited to, active internal bleeding, clinically significant bleeding, bleeding at a noncompressible site, or bleeding diathesis within 28 days of randomisation
- Severe concomitant disease such as atrial fibrillation (AFib) or another condition that requires chronic anticoagulation (participants with isolated transient may be allowed at the discretion of the treating physician investigator) and documented acute myocardial infarction during index event
- Prior stroke within 90 days of randomisation
- Has been hospitalised for longer than 21 days during the index event

COMMANDER HF trial (Continued)

- Planned intermittent outpatient treatment with positive inotropic drugs administered intravenously

Interventions	Experimental: rivaroxaban 2.5 mg Placebo comparator
Outcomes	Primary outcome measures: time to the first occurrence (day 1 up to approximately month 30) of any of the following: death from any cause, myocardial infarction, stroke, fatal bleeding or bleeding into a critical space with potential for permanent disability Secondary outcome measures: time to the first occurrence (day 1 up to approximately month 30) of the following: either death due to a cardiovascular cause or re-hospitalisation for worsening of heart failure (if both re-hospitalisation and death occur, they will be separately counted as per outcome measures below), death due to a cardiovascular cause, re-hospitalisation for worsening of heart failure, re-hospitalisation for cardiovascular events, bleeding requiring hospitalisation
Starting date	—
Contact information	—
Notes	Estimated study completion date: May 2018

LVEF: left ventricular ejection fraction.

DATA AND ANALYSES

Comparison 1. Warfarin vs aspirin in heart failure with sinus rhythm

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	4	3663	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.89, 1.13]
2 Non-fatal cardiovascular events (non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism)	4	3663	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.63, 1.00]
3 Major bleeding events	4	3663	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.44, 2.78]

Analysis 1.1. Comparison 1 Warfarin vs aspirin in heart failure with sinus rhythm, Outcome 1 All-cause mortality.

Study or subgroup	Warfarin n/N	Aspirin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WASH 2004	22/89	27/91		6.67%	0.83[0.51,1.35]
WATCH 2009	92/540	94/523		23.87%	0.95[0.73,1.23]
WARCEF 2012	275/1142	272/1163		67.35%	1.03[0.89,1.19]
HELAS 2006	11/54	9/61		2.11%	1.38[0.62,3.08]
Total (95% CI)	1825	1838		100%	1[0.89,1.13]

Favours warfarin 0.1 0.2 0.5 1 2 5 10 Favours aspirin

Analysis 1.2. Comparison 1 Warfarin vs aspirin in heart failure with sinus rhythm, Outcome 2 Non-fatal cardiovascular events (non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism).

Analysis 1.3. Comparison 1 Warfarin vs aspirin in heart failure with sinus rhythm, Outcome 3 Major bleeding events.

Comparison 2. Warfarin vs clopidogrel in heart failure with sinus rhythm

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1	1064	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Non-fatal cardiovascular events (non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism)	1	1064	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.50, 1.45]
3 Major bleeding events	1	1064	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.24, 4.91]

Analysis 2.1. Comparison 2 Warfarin vs clopidogrel in heart failure with sinus rhythm, Outcome 1 All-cause mortality.

Analysis 2.2. Comparison 2 Warfarin vs clopidogrel in heart failure with sinus rhythm, Outcome 2 Non-fatal cardiovascular events (non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism).

Analysis 2.3. Comparison 2 Warfarin vs clopidogrel in heart failure with sinus rhythm, Outcome 3 Major bleeding events.

APPENDICES

Appendix 1. Search strategies 2005

CENTRAL

- 1 HEART-FAILURE-CONGESTIVE*:ME
- 2 (CARDIAC near FAILURE)
- 3 (HEART near FAILURE)
- 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 DICOUMAROL
- 15 (#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)
- 16 (#4 and #15)

MEDLINE

- 1 exp Heart Failure, Congestive/
- 2 heart failure.tw.
- 3 cardiac failure.tw.
- 4 or/1-3
- 5 exp ANTICOAGULANTS/
- 6 exp Coumarins/
- 7 warfarin.tw.
- 8 dicoumarol.tw.
- 9 coumarin\$.tw.
- 10 or/5-9
- 11 4 and 10
- 12 exp Platelet Aggregation Inhibitors/
- 13 antiplatelet\$.tw.
- 14 anti-platelet\$.tw.
- 15 ticlopidine.tw.
- 16 clopidogrel.tw.
- 17 dipyridamole.tw.
- 18 or/12-17
- 19 18 and 4
- 20 11 or 19
- 21 randomized controlled trial.pt.
- 22 controlled clinical trial.pt.
- 23 Randomized controlled trials/
- 24 random allocation.sh.
- 25 double blind method.sh.
- 26 single-blind method.sh.
- 27 or/21-26
- 28 (animal not human).sh.
- 29 27 not 28
- 30 clinical trial.pt.
- 31 exp Clinical trials/
- 32 (clin\$ adj25 trial\$).ti,ab.
- 33 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ti,ab.
- 34 placebos.sh.
- 35 placebo\$.ti,ab.

36 random\$.ti,ab.
37 research design.sh.
38 or/30-37
39 38 not 28
40 39 not 29
41 comparative study.sh.
42 exp evaluation studies/
43 follow up studies.sh.
44 prospective studies.sh.
45 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
46 or/41-45
47 46 not 28
48 47 not (29 or 40)
49 29 or 40 or 48
50 20 and 49

Embase

1 exp Heart Failure/
2 heart failure.tw.
3 cardiac failure.tw.
4 or/1-3
5 Anticoagulant Agent/
6 exp Coumarin Anticoagulant/
7 warfarin.tw.
8 dicoumarol.tw.
9 coumarin\$.tw.
10 or/5-9
11 4 and 10
12 exp Antithrombocytic Agent/
13 antiplatelet\$.tw.
14 anti-platelet\$.tw.
15 ticlopidine.tw.
16 clopidogrel.tw.
17 dipyridamole.tw.
18 or/12-17
19 18 and 4
20 11 or 19
21 random\$.ti,ab.
22 factorial\$.ti,ab.
23 (crossover\$ or cross over\$ or cross-over\$).ti,ab.
24 placebo\$.ti,ab.
25 (double\$ adj blind\$).ti,ab.
26 (singl\$ adj blind\$).ti,ab.
27 assign\$.ti,ab.
28 allocat\$.ti,ab.
29 volunteer\$.ti,ab.
30 Crossover Procedure/
31 Double Blind Procedure/
32 Randomized Controlled Trial/
33 Single Blind Procedure/
34 or/21-33
35 exp animal/
36 nonhuman/
37 exp animal experiment/
38 or/35-37
39 exp human/
40 38 not 39
41 34 not 40
42 20 and 41

Appendix 2. Search strategies 2010

CENTRAL and DARE (the Cochrane Library)

#1 MeSH descriptor heart failure explode all trees
#2 heart next failure in All Text
#3 cardiac next failure in All Text
#4 (#1 or #2 or #3)
#5 MeSH descriptor anticoagulants this term only
#6 MeSH descriptor coumarins this term only
#7 MeSH descriptor 4-Hydroxycoumarins explode all trees
#8 warfarin in All Text
#9 dicoumarol in All Text
#10 dicumarol in All Text
#11 coumarin* in All Text
#12 anticoagulant* in All Text
#13 anti-coagulant* in All Text
#14 (#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)
#15 MeSH descriptor platelet aggregation inhibitors explode all trees
#16 antiplatelet* in All Text
#17 anti-platelet* in All Text
#18 aspirin in All Text
#19 ticlopidine in All Text
#20 clopidogrel in All Text
#21 dipyridamole in All Text
#22 antithrombocytic in All Text
#23 "acetyl salicylic acid" in All Text
#24 acetylsalicylic in All Text
#25 (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24)
#26 (#14 or #25)
#27 (#4 and #26)

MEDLINE Ovid

1 exp Heart Failure/
2 heart failure.tw.
3 cardiac failure.tw.
4 or/1-3
5 Anticoagulants/
6 Coumarins/
7 exp 4-Hydroxycoumarins/
8 warfarin.tw.
9 dicoumarol.tw.
10 dicumarol.tw.
11 coumarin\$.tw.
12 or/5-11
13 exp Platelet Aggregation Inhibitors/
14 antiplatelet\$.tw.
15 anti-platelet\$.tw.
16 aspirin.tw.
17 ticlopidine.tw.
18 clopidogrel.tw.
19 dipyridamole.tw.
20 or/13-19
21 4 and (12 or 20)
22 randomized controlled trial.pt.
23 controlled clinical trial.pt.
24 randomized.ab.
25 placebo.ab.
26 exp Clinical Trials as Topic/
27 randomly.ab.
28 trial.ti.
29 or/22-28

30 exp animal/ not humans/
31 29 not 30
32 21 and 31

Embase Ovid

1 exp Heart Failure/
2 heart failure.tw.
3 cardiac failure.tw.
4 or/1-3
5 anticoagulant agent/
6 exp coumarin anticoagulant/
7 warfarin.tw.
8 dicoumarol.tw.
9 dicumarol.tw.
10 coumarin\$.tw.
11 or/5-10
12 exp antithrombotic agent/
13 antiplatelet\$.tw.
14 anti-platelet\$.tw.
15 aspirin.tw.
16 ticlopidine.tw.
17 clopidogrel.tw.
18 dipyridamole.tw.
19 or/12-18
20 4 and (11 or 19)
21 random\$.tw.
22 factorial\$.tw.
23 (crossover\$ or cross-over\$).tw.
24 placebo\$.tw.
25 (doubl\$ adj blind\$).tw.
26 (singl\$ adj blind\$).tw.
27 assign\$.tw.
28 allocat\$.tw.
29 volunteer\$.tw.
30 Crossover Procedure/
31 Double-blind Procedure/
32 Randomized Controlled Trial/
33 Single-blind Procedure/
34 or/21-33
35 (animal/ or nonhuman/) not human/
36 34 not 35
37 20 and 36

Appendix 3. Search strategies 2013

CENTRAL

#1MeSH descriptor: [Heart Failure] explode all trees
#2heart near/2 failure*
#3cardiac near/2 failure*
#4myocardial near/2 failure*
#5heart near/2 decompensat*
#6#1 or #2 or #3 or #4 or #5
#7MeSH descriptor: [Anticoagulants] this term only
#8MeSH descriptor: [Coumarins] this term only
#9MeSH descriptor: [4-Hydroxycoumarins] explode all trees
#10warfarin
#11dicoumarol
#12dicumarol
#13coumarin*
#14anticoagulant* or anti-coagulant*
#15indirect next thrombin next inhibitor*

#16benzopyron* or benzopyran*
 #17#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
 #18MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees
 #19antiplatelet* or anti-platelet*
 #20antithrombocytic or "acetyl salicylic acid" or acetylsalicylic
 #21aspirin
 #22ticlopidine
 #23clopidogrel
 #24dipyridamole
 #25platelet near/2 (antagonist* or inhibit* or antiaggregant*)
 #26#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
 #27#17 or #26
 #28#6 and #27

MEDLINE Ovid

1. exp Heart Failure/
 2. (heart adj2 failure*).tw.
 3. (cardiac adj2 failure*).tw.
 4. (myocardial adj2 failure*).tw.
 5. (heart adj2 decompensat*).tw.
 6. heart failure.tw.
 7. cardiac failure.tw.
 8. 1 or 6 or 7
 9. 1 or 2 or 3 or 4 or 5
 10. Anticoagulants/
 11. Coumarins/
 12. exp 4-Hydroxycoumarins/
 13. warfarin.tw.
 14. dicoumarol.tw.
 15. dicumarol.tw.
 16. coumarin\$.tw.
 17. anticoagulant*.tw.
 18. indirect thrombin inhibitor*.tw.
 19. benzopyr?n*.tw.
 20. 10 or 11 or 12 or 13 or 14 or 15 or 16
 21. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
 22. exp Platelet Aggregation Inhibitors/
 23. antiplatelet\$.tw.
 24. anti-platelet\$.tw.
 25. aspirin.tw.
 26. ticlopidine.tw.
 27. clopidogrel.tw.
 28. dipyridamole.tw.
 29. (platelet adj2 (antagonist* or inhibit* or antiaggregant*)).tw.
 30. 22 or 23 or 24 or 25 or 26 or 27 or 28
 31. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
 32. 20 or 30
 33. 21 or 31
 34. 8 and 32
 35. 9 and 33
 36. randomized controlled trial.pt.
 37. controlled clinical trial.pt.
 38. randomized.ab.
 39. placebo.ab.
 40. drug therapy.fs.
 41. randomly.ab.
 42. trial.ab.
 43. groups.ab.
 44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
 45. exp animals/ not humans.sh.
 46. 44 not 45

47. 34 and 46
48. 35 and 46
49. ((2010* or 2011* or 2012* or 2013*) not 201001*).ed.
50. 47 and 49
51. 48 not 47
52. 50 or 51

Embase Ovid

1. exp heart failure/
2. heart failure.tw.
3. cardiac failure.tw.
4. (heart adj2 failure*).tw.
5. (cardiac adj2 failure*).tw.
6. (myocardial adj2 failure*).tw.
7. (heart adj2 decompensat*).tw.
8. 1 or 2 or 3
9. 1 or 4 or 5 or 6 or 7
10. anticoagulant agent/
11. exp coumarin anticoagulant/
12. warfarin.tw.
13. dicoumarol.tw.
14. dicumarol.tw.
15. coumarin\$.tw.
16. anticoagulant*.tw.
17. indirect thrombin inhibitor*.tw.
18. benzopyr?n*.tw.
19. 10 or 11 or 12 or 13 or 14 or 15
20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
21. exp antithrombocytic agent/
22. antiplatelet\$.tw.
23. anti-platelet\$.tw.
24. aspirin.tw.
25. ticlopidine.tw.
26. clopidogrel.tw.
27. dipyridamole.tw.
28. (platelet adj2 (antagonist* or inhibit* or antiaggregant*)).tw.
29. 21 or 22 or 23 or 24 or 25 or 26 or 27
30. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
31. 19 or 29
32. 20 or 30
33. 8 and 31
34. 9 and 32
35. random\$.tw.
36. factorial\$.tw.
37. crossover\$.tw.
38. cross over\$.tw.
39. cross-over\$.tw.
40. placebo\$.tw.
41. (doubl\$ adj blind\$).tw.
42. (singl\$ adj blind\$).tw.
43. assign\$.tw.
44. allocat\$.tw.
45. volunteer\$.tw.
46. crossover procedure/
47. double blind procedure/
48. randomized controlled trial/
49. single blind procedure/
50. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. (animal/ or nonhuman/) not human/
52. 50 not 51
53. 33 and 52

54. 34 and 52
55. ((2010* or 2011* or 2012* or 2013*) not 201001*).dd.
56. 53 and 55
57. 54 not 53
58. 56 or 57
59. limit 58 to embase

Appendix 4. Search strategies 2015

CENTRAL

- #1MeSH descriptor: [Heart Failure] explode all trees
- #2heart near/2 failure*
- #3cardiac near/2 failure*
- #4myocardial near/2 failure*
- #5heart near/2 decompensat*
- #6#1 or #2 or #3 or #4 or #5
- #7MeSH descriptor: [Anticoagulants] this term only
- #8MeSH descriptor: [Coumarins] this term only
- #9MeSH descriptor: [4-Hydroxycoumarins] explode all trees
- #10warfarin
- #11dicumarol
- #12dicumarol
- #13coumarin*
- #14anticoagulant* or anti-coagulant*
- #15indirect next thrombin next inhibitor*
- #16benzopyron* or benzopyran*
- #17#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
- #18MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees
- #19antiplatelet* or anti-platelet*
- #20antithrombocytic or "acetyl salicylic acid" or acetylsalicylic
- #21aspirin
- #22ticlopidine
- #23clopidogrel
- #24dipyridamole
- #25platelet near/2 (antagonist* or inhibit* or antiaggregant*)
- #26#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
- #27#17 or #26
- #28#6 and #27

MEDLINE Ovid

1. exp Heart Failure/
2. (heart adj2 failure*).tw.
3. (cardiac adj2 failure*).tw.
4. (myocardial adj2 failure*).tw.
5. (heart adj2 decompensat*).tw.
6. heart failure.tw.
7. cardiac failure.tw.
8. 1 or 6 or 7
9. 1 or 2 or 3 or 4 or 5
10. Anticoagulants/
11. Coumarins/
12. exp 4-Hydroxycoumarins/
13. warfarin.tw.
14. dicumarol.tw.
15. dicumarol.tw.
16. coumarin\$.tw.
17. anticoagulant*.tw.
18. indirect thrombin inhibitor*.tw.
19. benzopyr?n*.tw.
20. 10 or 11 or 12 or 13 or 14 or 15 or 16
21. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

22. exp Platelet Aggregation Inhibitors/
23. antiplatelet\$.tw.
24. anti-platelet\$.tw.
25. aspirin.tw.
26. ticlopidine.tw.
27. clopidogrel.tw.
28. dipyridamole.tw.
29. (platelet adj2 (antagonist* or inhibit* or antiaggregant*)).tw.
30. 22 or 23 or 24 or 25 or 26 or 27 or 28
31. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
32. 20 or 30
33. 21 or 31
34. 8 and 32
35. 9 and 33
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomized.ab.
39. placebo.ab.
40. drug therapy.fs.
41. randomly.ab.
42. trial.ab.
43. groups.ab.
44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. exp animals/ not humans.sh.
46. 44 not 45
47. 34 and 46
48. 35 and 46
49. ((2010* or 2011* or 2012* or 2013* or 2014* or 2015*) not 201001*).ed.
50. 47 and 49
51. 48 not 47
52. 50 or 51

Embase Ovid

1. exp heart failure/
2. heart failure.tw.
3. cardiac failure.tw.
4. (heart adj2 failure*).tw.
5. (cardiac adj2 failure*).tw.
6. (myocardial adj2 failure*).tw.
7. (heart adj2 decompensat*).tw.
8. 1 or 2 or 3
9. 1 or 4 or 5 or 6 or 7
10. anticoagulant agent/
11. exp coumarin anticoagulant/
12. warfarin.tw.
13. dicoumarol.tw.
14. dicumarol.tw.
15. coumarin\$.tw.
16. anticoagulant*.tw.
17. indirect thrombin inhibitor*.tw.
18. benzopyr?n*.tw.
19. 10 or 11 or 12 or 13 or 14 or 15
20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
21. exp antithrombocytic agent/
22. antiplatelet\$.tw.
23. anti-platelet\$.tw.
24. aspirin.tw.
25. ticlopidine.tw.
26. clopidogrel.tw.
27. dipyridamole.tw.
28. (platelet adj2 (antagonist* or inhibit* or antiaggregant*)).tw.

29. 21 or 22 or 23 or 24 or 25 or 26 or 27
 30. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
 31. 19 or 29
 32. 20 or 30
 33. 8 and 31
 34. 9 and 32
 35. random\$.tw.
 36. factorial\$.tw.
 37. crossover\$.tw.
 38. cross over\$.tw.
 39. cross-over\$.tw.
 40. placebo\$.tw.
 41. (doubl\$ adj blind\$).tw.
 42. (singl\$ adj blind\$).tw.
 43. assign\$.tw.
 44. allocat\$.tw.
 45. volunteer\$.tw.
 46. crossover procedure/
 47. double blind procedure/
 48. randomized controlled trial/
 49. single blind procedure/
 50. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
 51. (animal/ or nonhuman/) not human/
 52. 50 not 51
 53. 33 and 52
 54. 34 and 52
 55. ((2010* or 2011* or 2012* or 2013*) not 201001*).dd.
 56. 53 and 55
 57. 54 not 53
 58. 56 or 57
 59. limit 58 to embase

ClinicalTrials.gov (www.ClinicalTrials.gov)

(searched on 29/07/2016). Key words:

heart failure AND warfarin (24 entries)

heart failure AND dabigatran (5 entries)

heart failure AND apixaban (4 entries)

heart failure AND edoxaban (1 entry)

heart failure AND rivaroxaban (9 entries)

cardiac failure AND warfarin (24 entries)

cardiac failure AND dabigatran (5 entries)

cardiac failure AND apixaban (4 entries)

cardiac failure AND edoxaban (1 entry)

cardiac failure AND rivaroxaban (9 entries)

The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/)

(searched on 29/07/2016). Key words:

heart failure AND warfarin (4 entries)

heart failure AND dabigatran (1 entry)

heart failure AND apixaban (0 entries)

heart failure AND edoxaban (1 entry)

heart failure AND rivaroxaban (3 entries)

cardiac failure AND warfarin (4 entries)

cardiac failure AND dabigatran (1 entry)

cardiac failure AND apixaban (0 entries)

cardiac failure AND edoxaban (1 entry)

cardiac failure AND rivaroxaban (3 entries)

FEEDBACK

Cochrane Editorial Unit's report on feedback on anticoagulants reviews, 15 February 2011

Summary

Feedback received on this review, and other reviews and protocols on anticoagulants, is available on the Cochrane Editorial Unit website at www.editorial-unit.cochrane.org/anticoagulants-feedback.

Reply

NA

Contributors

NA

WHAT'S NEW

Date	Event	Description
2 March 2020	Amended	Clarification message from the Co-ordinating Editor added to the Declarations of interest Declarations of interest statement about the review's compliance with the Cochrane conflict of interest policy , which includes the relevant parts of the Cochrane Commercial Sponsorship Policy .

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 4, 2001

Date	Event	Description
16 September 2015	New citation required but conclusions have not changed	One new study, adding data for 2305 participants, is included in this update but conclusions remain unchanged.
16 September 2015	New search has been performed	An updated search has been performed up until 16 September 2015.
6 January 2014	New search has been performed	New author added. An updated search has been performed up until 14 June 2013 with the addition of one new studies to the previous review. However, the overall conclusion of the review remains unchanged.

Date	Event	Description
15 February 2011	Feedback has been incorporated	Added a link to the Cochrane Editorial Unit's report on feedback on anticoagulants reviews.
11 February 2010	Amended	Error in dates: 'assessed as up-to-date' and 'date of search' from the RevMan conversion has been corrected.
22 May 2009	Amended	Author details error due to RevMan conversion has been corrected.
8 September 2008	Amended	Converted to new review format.
5 December 1999	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Prof GYH Lip: conceived the review and obtained funding. Helped to interpret data and provided a methodological, policy and clinical perspective on the data. Participated in writing the review and the current update. For purposes of dual data collection, screened papers for inclusion or exclusion and extracted data from papers that were included. Coordinated the review process. He is the guarantor of the review.

Dr E Shantsila: revised and updated the current version of the review. For purposes of dual data collection, screened papers for inclusion or exclusion and extracted data from papers that were included.

DECLARATIONS OF INTEREST

The study unit was a centre for the WATCH Study, which received drugs and unrestricted grants from the pharmaceutical companies Bristol-Myers Squibb, Sanofi-Synthelabo, and Dupont. The centre also participates in other trials of antithrombotic therapy in cardiovascular disease and stroke.

Dr Lip has served as a Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo; and Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo.

Dr E Shantsila reported no conflict of interest.

Clarification statement added from the Co-ordinating Editor on 2 March 2020: This review was found by the Cochrane Funding Arbiters, post-publication, to be noncompliant with the [Cochrane conflict of interest policy](#), which includes the relevant parts of the [Cochrane Commercial Sponsorship Policy](#). It will be updated within a year. The update will have a majority of authors and lead author free of conflicts.

SOURCES OF SUPPORT

Internal sources

- Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [*therapeutic use]; Heart Failure [*complications] [mortality]; Platelet Aggregation Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Thromboembolism [*drug therapy] [etiology]

MeSH check words

Humans