Title: Anticoagulation therapy in heart failure and sinus rhythm: A systematic review and meta-analysis

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ABSTRACT

OBJECTIVE - Heart failure is a prothrombotic state and it has been hypothesized that thrombosis and embolism cause non-fatal and fatal events in heart failure and reduced ejection fraction (HFrEF). We sought to determine the effect of anticoagulant therapy on clinical outcomes in patients with HFrEF who are in sinus rhythm.

METHODS - We conducted an updated systematic review and meta-analysis to examine the effect of anticoagulation therapy in patients with HFrEF in sinus rhythm. Our analysis compared patients randomized to anticoagulant therapy with those randomized to antiplatelet therapy, placebo or control, and examined the endpoints of all-cause mortality, (re)hospitalization for worsening heart failure, non-fatal myocardial infarction, non-fatal stroke of any aetiology, and major haemorrhage.

RESULTS - Five trials were identified that met the prespecified search criteria. Compared with control therapy, anticoagulant treatment did not reduce all-cause mortality (RR 0.99, 95%CI 0.90-1.08), (re)hospitalisation for heart failure (RR 0.97, 95%CI 0.82-1.13) or non-fatal myocardial infarction (RR 0.92, 95%CI 0.75-1.13). Anticoagulation did reduce the rate of non-fatal stroke (RR 0.63, 95%CI 0.49-0.81, p=0.001), but this was offset by an increase in the incidence of major haemorrhage (RR 1.88, 95%CI 1.49-2.38, p=0.001), but this was offset by an increase in the incidence of major haemorrhage (RR 1.88, 95%CI 1.49-2.38, p <0.001).

CONCLUSIONS - Our meta-analysis provides evidence to oppose the hypothesis that thrombosis or embolism plays an important role in the morbidity and mortality associated with HFrEF, with the exception of stroke-related morbidity.

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KEY QUESTIONS

What is already known about this subject?

A benefit of anticoagulation in patients with heart failure in sinus rhythm has not been established, despite the fact that heart failure is a prothrombotic syndrome. Older trials in these patients suggested that warfarin reduced stroke at the expense of an increased haemorrhagic risk, but without a discernible effect on all-cause mortality.

What does this study add?

Our meta-analysis and critical review includes the COMMANDER-HF trial, which more than doubles the number of patients available for analysis. Our results confirm that anticoagulation does not reduce all-cause mortality, readmission for heart failure or myocardial infarction in patients with heart failure and sinus rhythm. From a pathophysiological perspective, our analysis provides evidence to oppose the hypothesis that unidentified thrombosis or embolism commonly underlie the morbidity and mortality associated with heart failure.

How might this impact on clinical practice?

This meta-analysis strengthens current guideline recommendations that heart failure with reduced ejection fraction is not by itself an indication for anticoagulation.

INTRODUCTION

There has been a long-standing hypothesis that both arterial and venous thrombosis and embolism might contribute to fatal as well as non-fatal events in patients with heart failure even when in sinus rhythm. This hypothesis reflected the view that heart failure is a prothrombotic state due to endothelial dysfunction, inflammation and increased thrombin production.[1-5] The logical proof of this hypothesis would be demonstration of reduced morbidity and mortality with an oral anticoagulant. Crucially, any such benefit must clearly outweigh the risk of clinically important bleeding. Although trials have been conducted to try and determine the balance between the benefit and risk of anticoagulation in heart failure (with reduced ejection fraction, in all cases), most have been insufficiently powered to give a definitive answer to this question. The largest, the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, did suggest potential benefit of warfarin but at the expense of unacceptable bleeding risk. Consequently, the recent completion of the Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER-HF) is a critical additional (and probably final) contribution to the evidence base related to this question. The non-vitamin K oral anticoagulants (NOACs) have proven to be at least as effective as warfarin and safer, in terms of major bleeding, even in patients with heart failure,[6] and this trial had the potential to replicate the benefit of anticoagulation seen in WARCEF with acceptable safety.

Accordingly, we conducted a meta-analysis of all relevant trials to determine the effect of anticoagulant treatment on death and other major clinical events in patients with heart failure and reduced ejection fraction (HFrEF) who were not in atrial fibrillation.

METHODS

Selection of outcomes

The main outcomes of interest were (1) death from any cause; (2) (re)hospitalisation due to worsening heart failure; (3) non-fatal stroke of any cause; (4) major haemorrhage; (5) non-fatal myocardial infarction.

Search strategy and study selection

We systematically identified published randomised controlled trials (RCTs) testing oral anticoagulation therapy against oral antiplatelet therapy (ATT) and/or placebo therapy and/or no therapy (collectively referred to from hereon in as control therapy), in adult patients with heart failure who were in sinus rhythm. Since the subject of interest was chronic heart failure, studies were excluded if they involved patients who were in hospital with acute heart failure, or in the acute phase of recovery following a myocardial infarction. Eligible studies were required to report at least one of the outcome measures detailed above. We performed searches of Medline (via PubMed) and the Cochrane Controlled Register of Trials (CENTRAL) (from 1966 to August 2018), using search terms including “anticoagulant”, “warfarin”, “apixaban”, “rivaroxaban”, “dabigatran”, “edoxaban”, “heart failure” and “left ventricular systolic dysfunction” as search terms in the abstract, MeSH subject heading, keyword heading or title fields. Prospective RCTs conducted in adults that were published in English were considered. Studies identified via conference presentation and bibliographic search were also considered for inclusion. Unpublished data were not sought. We restricted our search to RCTs enrolling >100 patients. Additional information regarding our method of study selection is presented in the supplementary appendix, along with model search strategies employed. Included trials were assessed for bias using the Cochrane Risk of Bias Tool (see supplementary appendix). A

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart detailing the selection process is presented in Figure 1. No protocol is available.

FIGURE 1 HERE [PRISMA]

Data extraction

Two authors (SB and RR) independently assessed trial eligibility and extracted data from included trials. Data in relation to the main outcomes of interest (1 to 5, detailed above) were collected. Differentiation between ischaemic or haemorrhagic stroke was not made consistently across studies, and for this reason all strokes were combined in a single efficacy outcome.

Statistical analysis

We utilised summary statistics from the individual trials because patient-level data were not available. Hazard ratios and 95% confidence intervals (CIs) from original trial results papers were used as the principal summary measures where available. Where hazard ratios were not available, rate ratios were used instead, and where neither of these measures were stated, risk ratios were generated using available data. These metrics were considered equivalent and are henceforth referred to identically as risk ratios (RRs). Single-study estimates were combined using inverse variance-weighted averages of logarithmic RRs in both fixed- and random-effects analysis. Heterogeneity between studies was assessed using the I^2 statistic and Cochran's Q statistic. The I^2 statistic has limited power when applied to a small number of studies; we considered the presence of heterogeneity when I^2 exceeded 50%, wherein we planned to utilise a random-effect model. We considered heterogeneity to be present at a significance level of 10% for Cochran's Q statistic. The fixed-effect model was otherwise employed preferentially. Where either the fixed-effect or random-effect model was used, the

result derived from the alternative model is additionally reported in the supplementary appendix. A weighting was derived from the number of events that occurred in each study. We performed pre-specified sensitivity analyses for each outcome measure to assess the contribution of any single trial to the pooled estimate by recalculating the pooled estimate after excluding single trials one by one. Publication bias was sought using Eggers's test for small-study effects. Analyses were performed using Stata version 14 (StataCorp, College Station, Texas).

RESULTS

Characteristics of studies included in meta-analysis

A total of 1040 titles were screened. Of these, 1035 were excluded (see Figure 1). Five RCTs were identified that met the pre-specified search criteria. These were: (1) the Warfarin/Aspirin Study in Heart failure (WASH) trial;[7] (2) the HEart failure Long term Antithrombotic Study (HELAS);[8] (3) the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial;[9] (4) WARCEF;[10] and (5) COMMANDER-HF.[11] In total these trials contributed up to 9390 patients to our meta-analysis, more than half of whom came from the recent COMMANDER-HF trial.

The design and population characteristics of these trials are summarised in Table 1. Event rates from individual trials for the clinical outcome measures evaluated in this meta-analysis are presented in Table 2. An assessment of the risk of bias among these trials is presented in the supplementary appendix. In summary, all individual trials were deemed either of low risk (WARCEF and COMMANDER-HF) or unclear risk (WASH, HELAS and WATCH), with none deemed high risk; bias across studies was deemed either low or unclear risk. WASH utilised a Prospective Randomized Open-label Blinded End point (PROBE) trial design,

randomising patients to open-label anticoagulation with warfarin, antiplatelet therapy with aspirin, or no therapy. For the purposes of this meta-analysis, we compared patients randomised to anticoagulation in WASH with those patients receiving ATT or no therapy. A small number of patients in WASH were in atrial fibrillation (AF) at enrolment or developed it during the trial. Where data were available for patients in sinus rhythm exclusively, these were used preferentially. WATCH randomised patients to open-label anticoagulation (warfarin) or one of aspirin or clopidogrel, which were provided in a double blind, double-dummy design. We compared patients randomised to anticoagulation in WATCH with patients assigned to any antiplatelet agent. HELAS was a double-blind trial involving stratification of treatment assignment according to aetiology of heart failure. Patients with HFrEF of ischaemic aetiology were randomised to receive either warfarin or aspirin; patients with idiopathic dilated cardiomyopathy were randomised to receive either warfarin or placebo. We compared all patients receiving warfarin to a control arm including all patients randomised to either aspirin or placebo. WARCEF and COMMANDER-HF were both double-blind RCTs involving random allocation to either anticoagulation (warfarin in WARCEF and rivaroxaban in COMMANDER-HF) or placebo. All studies employed satisfactory randomisation.

Effect of anticoagulation therapy on all-cause mortality

Among the 4361 patients randomized to anticoagulation and 5004 patients randomized to control therapy, there were 946 and 1076 all-cause deaths respectively. Compared with the control group, anticoagulation was not associated with a reduction in all-cause mortality (RR 0.99, 95%CI 0.90-1.08). The point estimates were similar in all five RCTs (RR ranging from 0.94 to 1.03) indicating a consistent lack of effect across the trials. In a sensitivity analysis, there was no significant difference in the effect on all-cause mortality after the removal of any single study from the pooled analysis. We did not detect evidence of significant heterogeneity between the trials (I^2 statistic = 0%; Cochran's Q = 0.40; p = 0.98)

FIGURE 2 HERE

Effect of anticoagulation therapy on (re)hospitalisation for heart failure

The effect of anticoagulation therapy was assessed using a random-effects model because of the likelihood of heterogeneity between the studies (I^2 = 52%; Cochran's Q = 8.41; p = 0.078). Among 4370 patients randomized to anticoagulation and 5020 patients randomized to control therapy, (re)hospitalisation for worsening heart failure occurred in 1040 and 1164 patients respectively. Compared with the control group, anticoagulation was not associated with a significant reduction in this outcome (RR 0.97, 95%CI 0.82-1.13). The magnitude of treatment effect failed to cross unity in any individual RCT, although there was a trend towards reduced rehospitalisation for heart failure with anticoagulation when compared to aspirin or clopidogrel in WATCH (RR 0.81, 95%CI 0.65-1.01) and a trend towards increased rehospitalisation with anticoagulation compared to aspirin in WARCEF (RR 1.21, 95%CI 1.00-1.47). Sensitivity analysis demonstrated no significant difference in the effect on (re)hospitalisation for heart failure after the removal of any single study from the pooled analysis.

FIGURE 3 HERE

Effect of anticoagulation therapy on non-fatal stroke from any cause

Stroke of ischaemic aetiology was not clearly defined/available for WASH, HELAS or COMMANDER-HF. Consequently, stroke of any cause was used in this analysis. Among 4361 patients randomized to anticoagulation and 5004 patients randomized to control therapy, non-fatal stroke occurred in 94 and 163 patients respectively. Compared with the control group, there was a significant reduction in stroke with anticoagulation compared to control (RR 0.63, 95%CI 0.49-0.81, p = 0.001). This effect appears consistent across all five RCTs, although only WARCEF and COMMANDER-HF (which together contribute >75% of the patients in this meta-analysis) were individually statistically significant. There was no suggestion of publication bias when the RCTs were examined using Egger's test for small-study effects (p = 0.63). It should be noted that the power to detect publication bias using Egger's test is limited when only a small number of studies are available for analysis, such as is the case here. Sensitivity analysis demonstrated no significant difference in the effect on stroke after the removal of any single study from the pooled analysis. We did not detect evidence of significant heterogeneity between the trials (I^2 statistic = 0%; Cochran's Q = 0.45; p = 0.98).

FIGURE 4 HERE

Effect of anticoagulation therapy on non-fatal MI

Among 4361 patients randomized to anticoagulation and 5004 patients randomized to control therapy, non-fatal MI occurred in 150 and 184 patients respectively. Compared with the control group, anticoagulation therapy did not reduce the risk of non-fatal MI (RR 0.92, 95%CI 0.75-1.13). There was no suggestion of benefit from anticoagulation compared to the control group

in any individual trial. Sensitivity analysis demonstrated no significant difference in the effect on non-fatal MI after the removal of any single study from the pooled analysis. We did not detect evidence of significant heterogeneity between the trials (I^2 statistic = 36%; Cochran's Q = 6.28; p = 0.179).

FIGURE 5 HERE

Effect of anticoagulation therapy on major haemorrhage

Among 4370 patients randomized to anticoagulation and 5020 patients randomized to control therapy, major haemorrhage occurred in 187 and 112 patients respectively. There was a significant increase in the risk of a major haemorrhage with anticoagulant therapy, compared with control therapy (RR 1.88, 95%CI 1.49-2.38, p <0.001). This effect was consistent across the three largest trials (WATCH, WARCEF and COMMANDER-HF), which together contributed >90% of events in the anticoagulation group. Sensitivity analysis demonstrated no significant difference in the effect on major haemorrhage after the removal of any single study from the pooled analysis. We did not detect evidence of significant heterogeneity between the trials (I^2 statistic = 16%; Cochran's Q = 4.74; p = 0.315).

FIGURE 6 HERE

DISCUSSION

Implicit in the "thrombosis/embolism" hypothesis of heart failure is the notion that many such events must be unidentified, because the rates of recognised MI and stroke in patients with this syndrome are low compared with the dominant drivers of morbidity and mortality which are cardiovascular death and heart failure hospitalisation.[1-5] However, it is plausible that coronary thrombotic occlusion might cause sudden cardiac death and even pump failure death in patients with electrically unstable and already failing left ventricles. Alternatively, non-fatal coronary thrombotic occlusion could lead to admission with worsening heart failure associated with a raised troponin. Similarly, embolization of cardiac thrombus, or even thrombosis resulting from cerebral hypoperfusion, might lead to fatal stroke classified as a "sudden death". Lastly, venous thromboembolism could also lead to sudden death or be an unrecognized cause of presentation with worsening dyspnoea or the development of pulmonary hypertension in patients with heart failure.

Accepting the assumption that anticoagulation is effective at preventing thrombosis and embolism, the completely neutral effect of anticoagulant therapy on both death and heart failure hospitalisation demonstrated in our meta-analysis suggests that *unidentified* thrombosis or embolism do not, after all, play an important role in the pathogenesis of the major causes of mortality in HFrEF.

In terms of morbidity resulting from *identified* thrombotic/embolic events - namely stroke and MI - there is somewhat more to say. One unequivocal finding of this meta-analysis is that anticoagulant therapy decreases the incidence of stroke with a substantial relative risk reduction of 37% when compared to control therapy. Whether this reflects a benefit in patients with clinically unidentified atrial fibrillation or new-onset atrial fibrillation (which is associated with a very high risk of stroke in HFrEF [17]), prevention of cardiac embolism even in sinus rhythm, or cerebral arterial thrombosis is unknown. Because the incidence of stroke in the trials

conducted was low, large numbers of patients had to be exposed to anticoagulant therapy to prevent one stroke; consequently, the beneficial effect on stroke was matched by similar harm related to bleeding, even with a NOAC. Specifically, in COMMANDER-HF, rivaroxaban reduced the risk of stroke from a rate of 3.0 to 2.0 events per 100 person-years which was counterbalanced by an increase in the risk of major haemorrhage from 2.0 to 3.3 events per 100 person-years (although it should be noted that most patients in both treatment groups were receiving concomitant anti-platelet therapy). Clearly, the totality of evidence does not support the general use of anticoagulation in patients with HFrEF to reduce the risk of stroke (or any other event). It may be possible, using risk scores, to identify a subset of patients with HFrEF (and heart failure with preserved ejection fraction), not in atrial fibrillation, who are at a substantially increased risk of stroke.[18-20] Further refinement of stroke risk prediction, perhaps using biomarkers,[21-22] seems a worthwhile effort, given the possibility of targeting an undoubtedly effective treatment at the prevention of such a devastating cardiovascular complication. Selective use of anticoagulation therapy in such patients might have a more favourable benefit-to-risk profile but this needs to be tested prospectively in clinical trials.

In contrast to the reduction in stroke with anticoagulation, however, it was not possible to demonstrate a benefit of anticoagulant therapy on clinically recognised acute coronary events, even despite the substantial cumulative number of MIs in this meta-analysis. In this context, examination of the COMMANDER-HF trial is instructive. Participants in the trial were required to have coronary artery disease (CAD), based on the supposition both that thrombin plays a fundamental role in deleterious pathophysiological processes which occur in patients with CAD following a recent heart failure decompensation, and that rivaroxaban - a specific inhibitor of activated Factor Xa which interrupts thrombin production – would be more efficacious in this setting than conventional vitamin K antagonists. Patients were also required both to have experienced a recent exacerbation of heart failure symptoms, and to have an

elevated natriuretic peptide concentration, further enriching the risk profile of the trial cohort. Despite these measures, the results of COMMANDER-HF were similar to those of the preceding RCTs that trialled warfarin in populations with HFrEF of mixed ischaemic and non-ischaemic aetiology, in that anticoagulation did not result in a lower rate of MI. This may seem a surprising finding, given the clear evidence from older trials with warfarin, and two more recent trials with NOACs, that anticoagulants, both alone and in combination with antiplatelet therapy, can reduce the risk of MI.[12-15] There are several potential explanations for this anomaly. Most likely is the probability that many MIs in patients with HFrEF are "type 2" events, caused by myocardial ischaemia due to increased oxygen demand (e.g. due to tachycardia, bradycardia, arrhythmias, myocardial hypertrophy, increased wall stress), decreased supply (e.g. due to anaemia, increased left ventricular end-diastolic pressure, microvascular dysfunction, hypotension, hypoxaemia) or both.[16] Where MI does play a precipitant role in morbidity and mortality in HFrEF, the pathogenesis of "type 2" events is unlikely to be altered by anticoagulation. Less likely is the possibility that coronary thrombus in heart failure is more resistant to anticoagulant therapy than in other conditions – however the lack of treatment effect in a risk-enriched population, and this despite the therapeutic potency of the drug employed, argues against this. Indeed, such was the targeted design of COMMANDER-HF – wherein rivaroxaban seemed ideally suited to preventing coronary thrombosis/emboli in a population at high risk of these events – that it is improbable that this hypothesis will, or indeed should, be retested in further RCTs. Thus COMMANDER-HF likely represents the final instalment in this suite of trials.

The evidence reviewed here pertains to patients with HFrEF and the potential value of anticoagulant therapy in patients with HFpEF (but without atrial fibrillation) has not been studied. However, it is difficult to imagine the results would be different, especially as

underlying coronary artery disease is less common in HFpEF than HFrEF (meaning the risk of myocardial infarction is lower) and because the risk of embolic stroke in heart failure may be greatest in patients with severely reduced ejection fraction.[23-24]

In summary, in this comprehensive meta-analysis of 5 prospective randomised controlled trials including over 9000 patients, anticoagulant therapy was unequivocally demonstrated to have no effect on mortality, heart failure hospitalisation or myocardial infarction when compared to control therapy. Conversely, there was equally clear evidence that anticoagulant therapy reduced the risk of stroke compared to control therapy, but this benefit was completely offset by a similar increase in risk of absolute rates of major bleeding, even with a NOAC. In clinical terms, any future efforts to establish a role for anticoagulant therapy in heart failure should focus on targeted treatment of patients at high risk of stroke where the benefit-to-risk balance might be more favourable. From a mechanistic perspective, these trials suggest that, excepting clinically recognised stroke, thrombosis and embolism that are amenable to treatment are unlikely to play a major role in the pathogenesis of major morbidity or mortality in heart failure.

Study limitations

We conducted a meta-analysis of large randomized trials, with this method of analysis carrying limitations that merit consideration. The main limitation was that our analysis using trial-level data rather than patient-level data, which were unavailable. This limits the possibility of adjustment for individual patient characteristics. We pooled the effects of two different types of anticoagulant therapy (i.e. a vitamin K antagonist (warfarin) and non-vitamin K antagonists) but assumed a class 'anticoagulant' effect. In addition, the intensity of warfarin-induced anticoagulation varied between the trials using that agent. It is possible that these differences may have introduced heterogeneity into the analysis, although this is more likely to have

influenced the adverse-effect profile (particularly bleeding rates), rather than efficacy. Other potential sources of heterogeneity include differences between the trials in relation to patient inclusion and exclusion criteria, and geographical location (see Table 1). It was not possible to differentiate between ischaemic and haemorrhagic stroke consistently across the included trials. At a study level, one limitation is that a small number of patients in WARCEF and WASH had previously experienced atrial fibrillation or developed this condition during the trial. Study level limitations relating to bias are detailed in Appendix 2. As stated above, the utility of Egger's test to detect publication bias is limited when only a small number of studies are available for analysis.

Contributorship statement

The authors have reviewed and approved the submission of this manuscript. This manuscript is original and is not under consideration for publication elsewhere. Specifically, SB and RR undertook the data extraction and SB performed the analysis. SB and JMcM drafted the manuscript. SB, RR, RG and JMcM reviewed and revised the manuscript. JMcM is responsible for the overall content as guarantor.

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Competing interests

No competing interests to declare.

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Table 1: Baseline characteristics of patients with heart failure in sinus rhythm randomised to anticoagulation therapy or control

Characteristic	WASH [7]	HELAS [8]	WATCH [9]	WARCEF [10]	COMMANDER-HF [11]
Year of publication	2004	2006	2009	2012	2018
Study design	Open-label, randomised, controlled trial	Double-blind, randomised, placebo-controlled trial	Double-blind, randomised trial. Double-dummy controlled for ATT, or open-label warfarin	Double-blind, randomised, double-dummy controlled trial	Double-blind, randomised, placebo-controlled trial
Main inclusion criteria	HF requiring diuretic	HF (NYHA II - IV)	i) Symptomatic HF ii) Sinus rhythm iii) Diuretic + ACE-inhibitor ≥60 days	i) HF (NYHA I - IV) ii) Sinus rhythm	i) HF ≥3 months duration ii) CAD iii) recent WHF iv) elevated natriuretic peptide concentration*
LVEF inclusion criterion	≤ 35%	< 35%	≤ 35%	≤ 35%	≤ 40%
Location	US & UK	Greece, Cyprus, Yugoslavia, Romania, Bulgaria, Poland and Georgia	US, UK & Canada	North America, Europe & Argentina	Europe, North America, Latin America, Asia-Pacific & South Africa
No. randomised	279	197	1587	2305	5022
Therapies evaluated	Warfarin vs aspirin vs no ATT	Warfarin vs aspirin vs placebo	Warfarin vs aspirin vs clopidogrel	Warfarin vs aspirin	Rivaroxaban vs placebo
Target INR	2.0 - 3.0	2.0 - 3.0	2.5 - 3.0 §	2.0 - 3.5	N/A
Aspirin dose	300mg/day	325mg/day	162mg/day	325mg/day	N/A
Other antiplatelet dose	N/A	N/A	Clopidogrel 75mg/day	N/A	N/A
Follow-up, mean (SD), mo	27 (1)	19 (NR)	23 (NR)	42 (22)	21 (NR) ◊
Demographics					
Age, mean (SD), y	63 (NR)	55 - 62	63 (11)	61 (11)	66 (10)
Female, %	26	15	15	20	23
Race or ethnic group					
White, %	NR	NR	77	75	82
Black, %	NR	NR	13	14	1
Other, %	NR	NR	10	10	17
BMI, mean (SD), kg/m2	NR	NR	NR	29 (6)	28 (5)
NYHA functional class					
NYHA class I, %	NR	0	0	14	3
NYHA class II, %	NR	NR	44	55	44
NYHA class III, %	27%	NR	54	30	49
NYHA class IV, %	2%	NR	2	1	4
Smoking status					
Current, %	NR	49	17	18	NR

		Former, %	NR	NR	60	51	NR
		Never smoked, %	NR	NR	23	31	NR
	Hypertension		34	37	48	61	75
	Diabetes mellitus		20	21	34	31	41
	Atrial fibrillation		6	0	0	4	0
	Myocardial infarction		46	49	58	48	76
	Ischaemic cardiomyopathy		60	58	73	43	NR
	Pulmonary or other embolism		NR	0	NR	2%	NR
	Prior stroke or TIA		NR	0	5	13	9
	Blood pressure at baseline	SBP, mean (SD), mmHg	126 (NR)	NR	119 (18)	124 (19)	NR
		DBP, mean (SD), mmHg	77 (NR)	NR	NR	74 (11)	NR
	LVEF, mean (SD), %		NR ‖	27 - 29	25 (6)	25 (8)	34 @
Medications at baseline, %							
	Aspirin†		48	NR	NR	59	93
	Other antiplatelet†		NR	NR	NR	8	40
	Warfarin / other oral anticoagulant*		5	NR	1	8	0
	ACE inhibitor / ARB		91	61	97	98	93
	Beta-blocker		11	12	70	90	92
	MRA		NR	NR	28	60	77
	Nitrate		NR	32	NR	24	20
	Diuretic		96 #	59	99	81	96
	Statin		NR	NR	NR	83	NR
Device at baseline, %							
	Pacemaker		NR	NR	NR	12	4
	ICD		NR	NR	NR	18	9
	CRT		NR	NR	NR	NR	2
Design	Primary endpoint		Composite outcome of death, nonfatal MI, and nonfatal stroke.	Composite of non-fatal stroke, peripheral or pulmonary embolism, MI, re-hospitalisation, WHF, or ACM;	Composite of ACM, nonfatal MI and nonfatal stroke	Time to first event in a composite end point of ischemic stroke, intracerebral haemorrhage, or ACM	Composite of ACM, nonfatal MI and nonfatal stroke
Internal validity							
	INR achieved in warfarin group		Mean INR was 2.3 after excluding patients who discontinued treatment.	NR	Median INR was 2.5; 70% of actual INRs were 2.0 - 3.5	After initial 6-week titration phase, mean INR was 2.6 +/- 0.9 ^	N/A
	Follow-up, %		NR	NR	94.4	98.5	99.8
	Crossovers to A/C, % (No.)		NR Δ	NR	NR ¶	NR ‡	NR
	Crossovers to control % (No.)		NR Δ	NR	NR ¶	34% of total follow-up time ‡	28
	Blinded endpoint committee		Yes	NR	Yes	Yes	No $

Abbreviations: ACE, angiotensin converting enzyme; ACM, all-cause mortality; ATT, antiplatelet therapy; CAD, coronary artery disease; HF, heart failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; UK, United Kingdom; US, United States; WHF, worsening heart failure

* After the enrolment of 1155 patients (23.0%), a protocol amendment required patients to also have a plasma concentration of brain natriuretic peptide (BNP) ≥200 pg/ml or N-terminal pro–brain natriuretic peptide (NT-proBNP) ≥800 pg/ml measured at any time during the screening period before randomization

† Data on aspirin and other antiplatelet agents and warfarin or other oral anticoagulants are for the use of these medications before the patients underwent randomization

‡ Patients in the warfarin group did not receive the randomly assigned medication (and instead received open-label therapy) for 34% of the total follow-up time, and patients in the aspirin group did not receive the assigned medication for 32% of the time

§ INR of 2.0 - 3.5 designated acceptable

‖ Mean fractional shortening = 16%

¶ Crossover rates unknown. Number of patients discontinuing study drug were 100 in aspirin group and 110 in warfarin groups respectively.

Only patients prescribed a loop diuretic included

^ 70.4% of measurements falling within the acceptable range (2.0 to 3.5), 20.3% falling below 2.0, and 9.3% falling above 3.5. The median INR was 2.5.

Δ At 12 months, among patients initially assigned to aspirin or no ATT, 88% and 79% remained taking aspirin and without ATT respectively. Of those assigned to warfarin, 75% remained on warfarin at 12 months.

◊ Median (cf mean)

$ Outcome events reported by investigators and not independently adjudicated

Table 2: Reported clinical events and event rates

All-cause mortality

	Anticoagulation			Control arm		
Trial	Participants	Events	Event rate (per 100 person years)	Participants	Events	Event rate (per 100 person years)
WASH	80	22	NR	174	48	NR
HELAS	92	13	13.3 (d); 3 (e)	105	15	9.6 (f); 8.9 (g)
WATCH	540	92	NR	1047	190	NR
WARCEF	1142	275	6.6 (c)	1163	272	6.5 (c)
COMMANDER	2507	546	11.4	2515	556	11.6

Rehospitalisation for heart failure

	Anticoagulation			Control arm		
Trial	Participants	Events	Event rate (per 100 person years)	Participants	Events	Event rate (per 100 person years)
WASH	89	18	20	190	50	17 (a); 29 (b)
HELAS	92	5	2.4 (d); 4.4 (e)	105	7	3.2 (f); 5.9 (g)
WATCH	540	89	NR	1047	213	NR
WARCEF	1142	239	6.8	1163	203	5.7
COMMANDER	2507	689	17.2	2515	691	17.5

Non-fatal stroke

	Anticoagulation			Control arm		
Trial	Participants	Events	Event rate (per 100 person years)	Participants	Events	Event rate (per 100 person years)
WASH	80	0	NR	174	3	NR
HELAS	92	2	2.4 (d); 0 (e)	105	3	2.1 (f); 1.5 (g)
WATCH	540	7	NR	1047	24	1.0 (h)
WARCEF	1142	34	NR	1163	57	NR
COMMANDER	2507	51	1.1	2515	76	1.6

Non-fatal MI

	Anticoagulation			Control arm		
Trial	Participants	Events	Event rate (per 100 person years)	Participants	Events	Event rate (per 100 person years)
WASH	80	1	NR	174	8	NR
HELAS	92	2	1.2 (d); 1.5 (e)	105	0	0
WATCH	540	21	NR	1047	27	NR

WARCEF	1142	28	0.8	1163	31	0.9
COMMANDER	2507	98	2.1	2515	118	2.5

	Major haemorrhage					
	Anticoagulation			Control arm		
Trial	Participants	Events	Event rate (per 100 person years)	Participants	Events	Event rate (per 100 person years)
WASH	89	4	NR	190	1	NR
HELAS	92	7	4.8 (d); 4.4 (e)	105	0	0
WATCH	540	28	NR	1047	30	NR
WARCEF	1142	66	NR	1163	31	NR
COMMANDER	2499	82	2.0	2509	50	1.2

NR = not reported

(a) Patients randomised to no antithrombotic therapy in WASH

(b) Patients randomised to aspirin in WASH

(c) Reported rate is for deaths as a component of the composite primary outcome measure, thus excluding 7 deaths due to haemorrhage; the rate for total mortality was not reported

(d) Patients with ischaemic cardiomyopathy randomised to warfarin

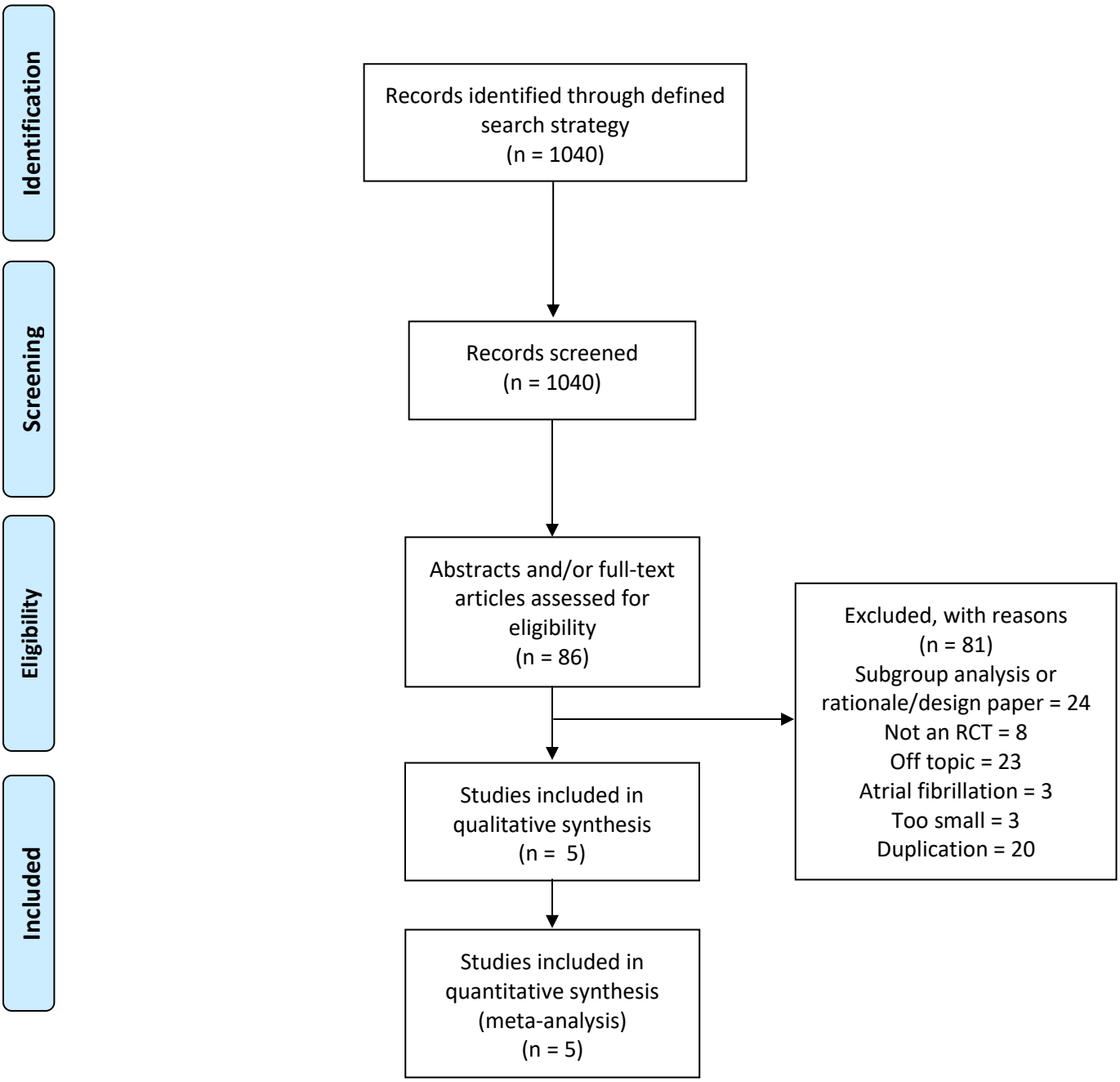
(e) Patients with dilated cardiomyopathy randomised to warfarin

(f) Patients with ischaemic cardiomyopathy randomised to aspirin

(g) Patients with dilated cardiomyopathy randomised to placebo

(h) For combination of aspirin and clopidogrel arms in WATCH; this figure may include fatal strokes

Figure 1 - PRISMA flow diagram of selection process for included studies



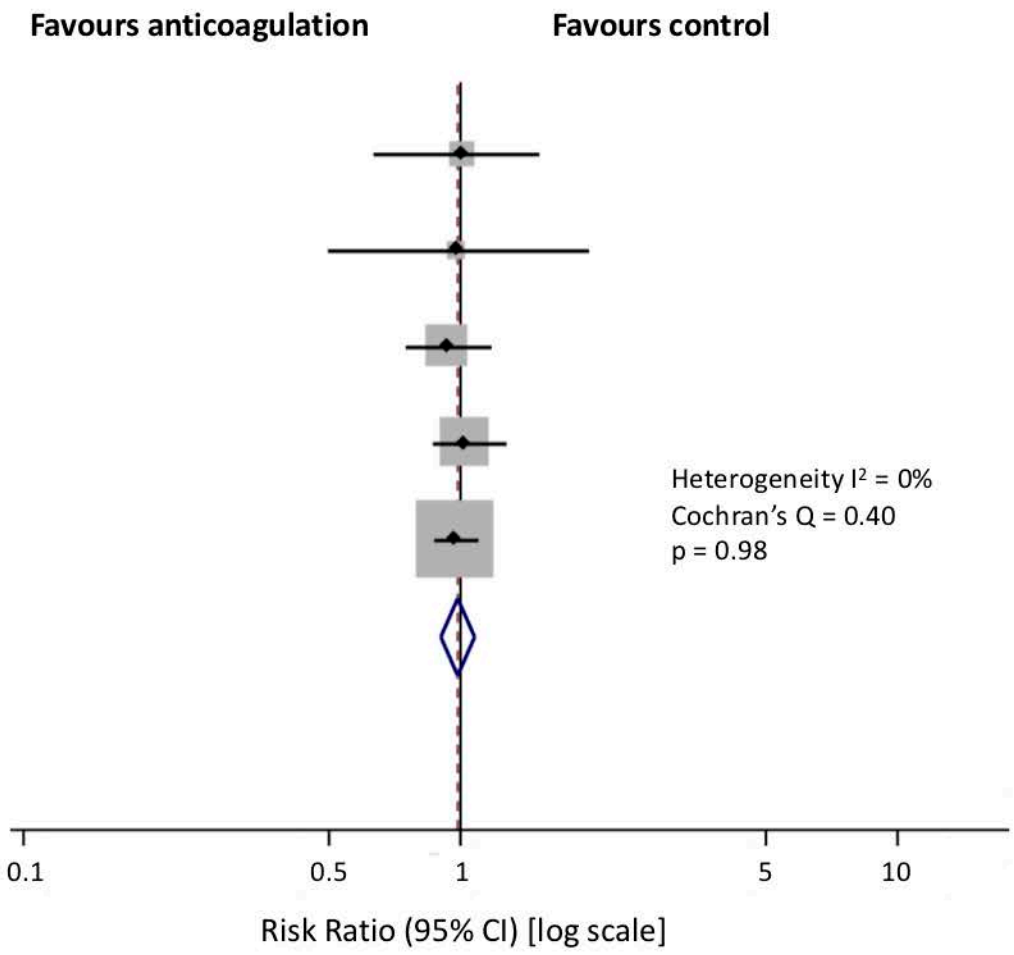
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2: All-cause mortality among patients randomized to anticoagulation or control

Study	Year of Publication	No. of Patients	Risk Ratio (95% CI)
WASH	2004	254	1.01 (0.63 – 1.52)
HELAS	2006	197	0.99 (0.50 – 1.97)
WATCH	2009	1587	0.94 (0.75 – 1.18)
WARCEF	2012	2305	1.03 (0.86 – 1.27)
COMMANDER	2018	5022	0.98 (0.87 – 1.10)
Combined		**9365**	**0.99 (0.90 – 1.08)**

p = 0.742

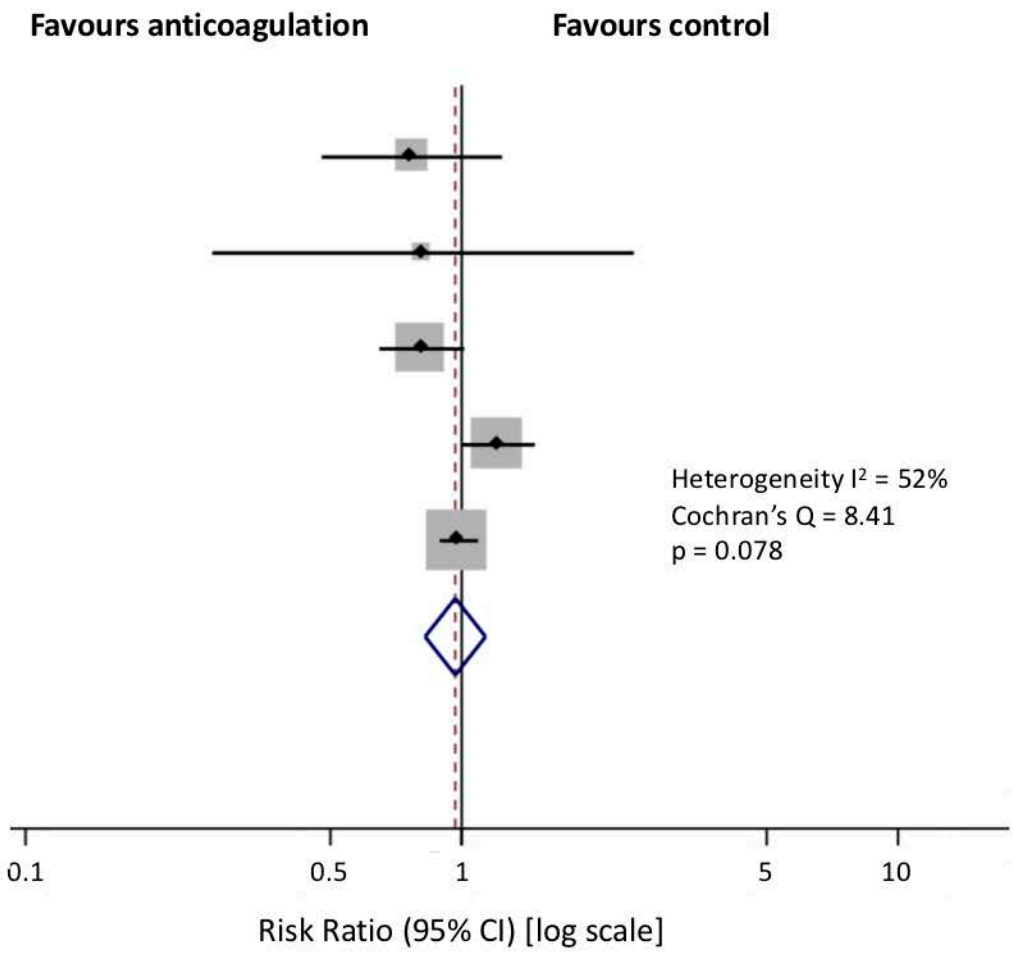


Size of the data marker corresponds to the relative weight assigned in the pooled analysis using fixed-effects models

Figure 3: (Re)hospitalisation for worsening heart failure among patients randomized to anticoagulation or control

Study	Year of Publication	No. of Patients	Risk Ratio (95% CI)
WASH	2004	279	0.77 (0.48 – 1.24)
HELAS	2006	197	0.82 (0.27 – 2.48)
WATCH	2009	1587	0.81 (0.65 – 1.01)
WARCEF	2012	2305	1.21 (1.00 – 1.47)
COMMANDER	2018	5022	0.98 (0.89 – 1.09)
Combined		**9390**	**0.97 (0.82 – 1.13)**

p = 0.677

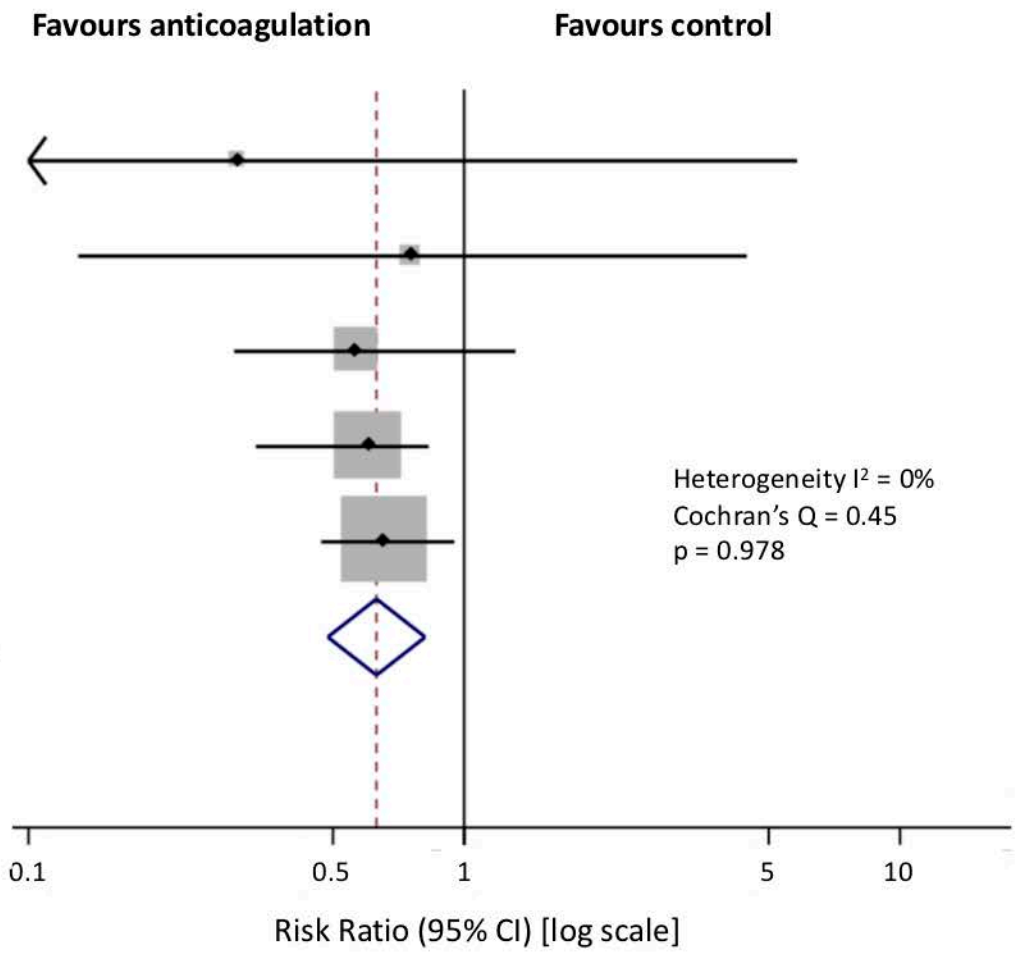


Size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models

Figure 4: Non-fatal strokes among patients randomized to anticoagulation or control

Study	Year of Publication	No. of Patients	Risk Ratio (95% CI)
WASH	2004	254	0.30 (0.02 – 5.81)
HELAS	2006	197	0.76 (0.13 – 4.46)
WATCH	2009	1587	0.57 (0.30 – 1.31)
WARCEF	2012	2305	0.61 (0.33 – 0.83)
COMMANDER	2018	5022	0.66 (0.47 – 0.95)
Combined		**9365**	**0.63 (0.49 – 0.81)**

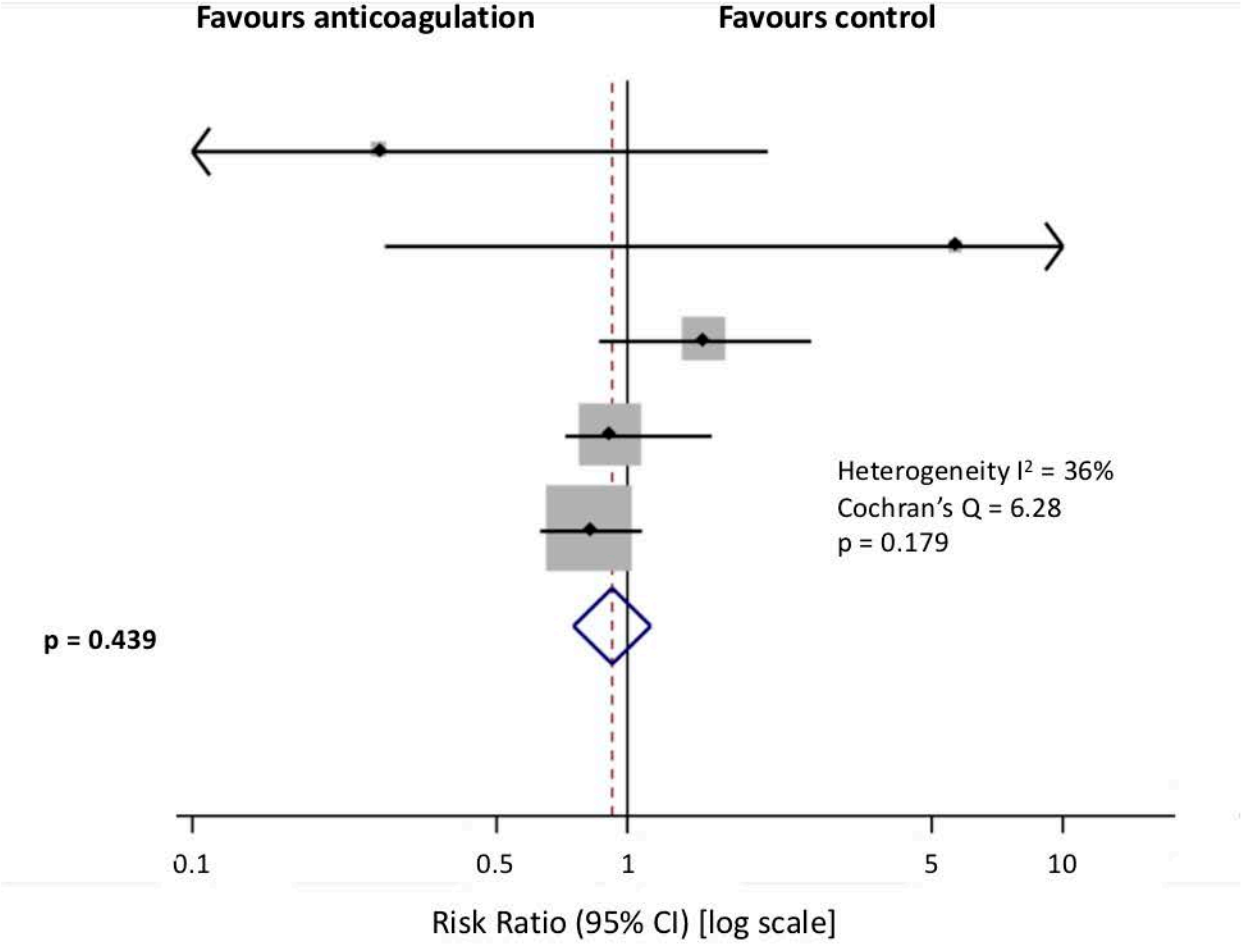
p = 0.001



Size of the data marker corresponds to the relative weight assigned in the pooled analysis using fixed-effects models

Figure 5: Non-fatal myocardial infarction among patients randomized to anticoagulation or control

Study	Year of Publication	No. of Patients	Risk Ratio (95% CI)
WASH	2004	254	0.27 (0.03 – 2.10)
HELAS	2006	197	5.70 (0.28 – 117)
WATCH	2009	1587	1.51 (0.86 – 2.64)
WARCEF	2012	2305	0.92 (0.72 – 1.56)
COMMANDER	2018	5022	0.83 (0.63 – 1.08)
Combined		**9365**	**0.92 (0.75 – 1.13)**

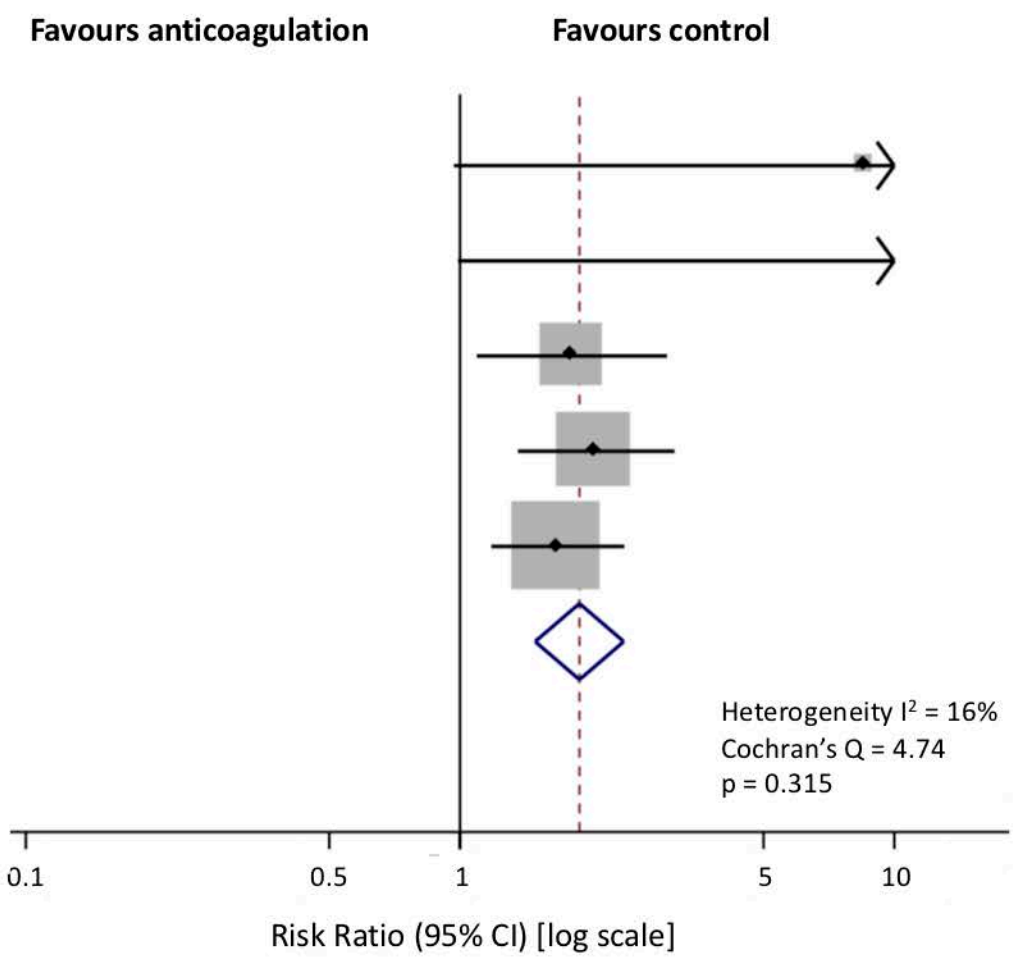


Size of the data marker corresponds to the relative weight assigned in the pooled analysis using fixed-effects models

Figure 6: Major haemorrhage among patients randomized to anticoagulation or control

Study	Year of Publication	No. of Patients	Risk Ratio (95% CI)
WASH	2004	279	8.54 (0.97 – 75.3)
HELAS	2006	197	17.10 (0.99 – 295)
WATCH	2009	1587	1.81 (1.09 – 3.00)
WARCEF	2012	2305	2.05 (1.36 – 3.12)
COMMANDER	2018	5022	1.68 (1.18 – 2.39)
Combined		**9390**	**1.88 (1.49 – 2.38)**

p <0.001



Size of the data marker corresponds to the relative weight assigned in the pooled analysis using fixed-effects models