Anticoagulation for heart failure in sinus rhythm: a Cochrane systematic review

G.Y.H. Lip and C.R. Gibbs

From the Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK

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Summary

Background: Patients with chronic heart failure (heart failure) are at risk of thromboembolic events, and coronary ischaemic events also contribute to the progression of heart failure. Long-term oral anticoagulation is established in certain groups, including patients with heart failure and atrial fibrillation, but there is wide variation in the use of oral anticoagulation in the broader heart failure population.

Objective: To determine whether long-term oral anticoagulation reduces total deaths and/or major thromboembolic events in patients with heart failure.

Design: Systematic review.

Data sources: Reference lists of papers resulting from this search, electronic database searching (MEDLINE, EMBASE, DARE), and abstracts from national and international cardiovascular meetings were studied to identify unpublished studies. Relevant authors of these studies were contacted to obtain further data.

Selection criteria: Randomized controlled trials (RCTs) comparing oral anticoagulants with control or placebo. Non-randomized studies were included, as they may help in assessing side-effects. Other inclusion criteria included duration of treatment ≥1 month, and adults with heart failure due to any underlying cause. Inclusion decisions were duplicated, and disagreement resolved by discussion or a third party.

Results: One recent pilot RCT compared warfarin, aspirin and no antithrombotic therapy, but no definitive data have yet been published. Three small prospective studies of warfarin in heart failure were also identified, but were over 50 years old, with methods considered unreliable today: in these, anticoagulation was more efficacious than control in reducing all-cause death (OR 0.64; 95%CI 0.45–0.90) and cardiovascular events (OR 0.26; 95%CI 0.16–0.43). Four retrospective non-randomized cohort analyses and three small observational studies of oral anticoagulation in heart failure included differing populations of heart failure patients, and reported contradictory results.

Conclusions: Limited evidence from randomized trials and observational studies found a reduction in mortality and cardiovascular events with anticoagulants compared to controls. This evidence should be interpreted with caution. Although oral anticoagulation is indicated in certain groups of patients with heart failure (e.g. atrial fibrillation), the available data do not support its routine use in heart failure patients who remain in sinus rhythm.

Introduction

Chronic heart failure (heart failure) is an increasing clinical and social problem, and is associated with high morbidity rates and annual mortality rates of >30% in patients with severe symptoms.1

Heart failure has long been recognized to predispose to stroke and thromboembolism, including pulmonary embolism and peripheral arterial embolism, and these thromboembolic
events contribute to the high morbidity in heart failure. In addition, ischaemic and thromboembolic events, particularly stroke, myocardial ischaemia and myocardial infarction, contribute to the high hospital admission rates in these patients. The incidence of ischaemic and thromboembolic events, and the risk factors associated with a high thromboembolic risk, have been addressed in numerous small- and large-scale studies, although the reported incidence of these events appears to vary, depending on study methodologies and populations. Nevertheless, mild-to-moderate heart failure, for example, appears to be associated with an annual stroke risk of approximately 1.5%, compared with an annual stroke risk in the general population of <0.5%, while the annual risk of stroke increases to almost 4% in severe heart failure.

Although there is evidence of benefit from long-term oral anticoagulation in certain groups of patients (oral anticoagulation has been proven to be extremely effective in reducing stroke and other embolic events in patients with atrial fibrillation and heart failure), the role of anticoagulation in the broader heart failure population (in sinus rhythm) is less well established. Indeed, there is a wide variation in the use of oral anticoagulants in patients with heart failure. In addition, although oral anticoagulation has been associated with a reduction in the number of thromboembolic events in various cardiovascular disease states, the potential risks of bleeding must also be considered. Importantly, the control of anticoagulation is reported to be more difficult, and bleeding complications more frequent, in heart failure, as a result of hepatic congestion and potential drug interactions which occur in these patients.

Our objective was to perform a systematic review addressing the role of long-term oral anticoagulation in patients with heart failure, with the hypothesis that oral anticoagulation reduces total deaths, cardiovascular deaths and/or major thromboembolic events in patients with heart failure, when compared to placebo. The efficacy of antithrombotic therapy in atrial fibrillation (including atrial fibrillation with heart failure) is not addressed.

Methods
Criteria for considering studies for this review
We considered randomized parallel group placebo or controlled trials comparing (low-dose and full-dose) oral anticoagulants with control or placebo, in adults with heart failure due to any underlying cause, with a duration of treatment at least 1 month. Patients with heart failure were defined clinically and if possible, by more objective evidence (e.g. echocardiography, radionuclide ventriculography) of left ventricular systolic dysfunction. Studies were excluded if only participants with atrial fibrillation only were studied, if no clinical events were recorded or available, or if the trial was of only short duration (<1 month). We excluded studies if there were additional active treatments in the intervention arm (e.g. beta-blockers, ACE inhibitors), or if participants of various diagnoses and diagnostic subgroups were not distinguished in analyses or not available from investigators.

To assess any adverse effects, we also examined cohort studies and non-randomized controlled studies, as well as decision analysis studies. Data from the non-randomized studies have been included to provide additional information to aid interpretation of data on the effectiveness of therapy. Complications of active therapy (when compared to placebo) were also recorded.

We included the following outcome measures: all-cause deaths; cardiovascular deaths (stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism) and sudden deaths; non-fatal cardiovascular events (non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism); revascularization procedures (e.g. coronary angioplasty, embolectomy); and major bleeding events (fatal, non-fatal).

We identified studies from the following sources: (i) The Cochrane Controlled Trials Register (CENTRAL), which was updated by searching MEDLINE 2000 on Ovid using a standard RCT filter and EMBASE 1998 to 2000 using an EMBASE RCT filter (Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomized controlled trials in EMBASE. *Fourth International Cochrane Colloquium*, Adelaide, Australia; 20–24 Oct 1996). Other citations between 1966–2000 were obtained as follows: (i) the NHS Database of Abstracts of Reviews of Effectiveness and any other relevant databases were searched to identify potentially eligible studies and review articles, relevant foreign language papers being translated; (ii) abstracts from national and international cardiology meetings were studied to identify unpublished studies and relevant authors of these studies were contacted to obtain further details; and (iii) reference lists of papers were searched.

Analysis of data
We analysed the data using Review Manager (RevMan version 4.1) statistical software. The two
reviewers (GYHL and CRG) independently selected suitable trials for inclusion in the review. There was a review of the inclusion criteria for each question; the search strategies; the methodology criteria; and methods for pooling the data. The data extracted included information relating to the complexities of the topic area, such as patient characteristics and concomitant treatments, as well as data relating to study eligibility, quality, and outcomes. Non-randomized studies would not usually be helpful in a review of the effects of these drugs as any estimates of treatment effects are likely to be biased, but they have been included as they may help in assessing side-effects of anticoagulants.

Assessment of trial quality was made in accordance with guidelines in the Cochrane Handbook, including adequacy of randomization, degree of blinding and losses to follow-up for each trial.

Results
We identified 34 references from our search strategy. From these we excluded 21 references after examining the title and abstract because they were not relevant. Full reprints of the remaining 13 references were obtained for more detailed examination (Figure 1).

One case series, conducted over 50 years ago in heterogeneous heart failure population ($n = 61$), was excluded, but it did report that the prevalence of thromboembolism on dicumarol (6.5%) was lower than in previously published reports (22%). Of the 12 remaining trials, one is awaiting

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**Figure 1.** Flow diagram of systematic review (Quorom statement flow diagram) of anticoagulation for heart failure in sinus rhythm.

- Potentially relevant publications identified and screened for retrieval: 34
- Papers excluded on the basis of title and abstract (generally due to lack of suitability of study design or intervention): 21
- Excluded, reasons—Inappropriate study methods: 1
- Papers coalesced into RCT studies (further publications of single studies grouped): 0
- RCTs included in systematic review, but with no usable outcome data: 0

- Papers retrieved for more detailed evaluation: 13
- Papers included: 12
- Potentially appropriate RCTs (with or without appropriate outcome data): 12
- RCTs with outcome data useful in the systematic review:
  - 1 randomized controlled trial
  - 3 non-randomized controlled trials and performed $>50$ years ago
  - 8 posthoc analyses of RCTs of other treatments
<table>
<thead>
<tr>
<th>(a) Included studies</th>
<th>Patients</th>
<th>n</th>
<th>Intervention(s)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-randomized controlled trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersen et al.²⁰</td>
<td>CHF</td>
<td>297</td>
<td>Dicoumarol</td>
<td>Death, stroke, pulmonary and peripheral embolism</td>
</tr>
<tr>
<td>Griffith et al.²¹</td>
<td>CHF</td>
<td>465</td>
<td>Tromexan, Dicoumarol +/- heparin</td>
<td>Death, stroke, pulmonary and peripheral embolism</td>
</tr>
<tr>
<td>Harvey et al.¹⁹</td>
<td>CHF</td>
<td>180</td>
<td>Warfarin</td>
<td>Death, stroke, pulmonary and peripheral embolism</td>
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<tr>
<td>Post-hoc analyses of trials in heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS⁸</td>
<td>Retrospective cohort analysis of patients with severe CHF</td>
<td></td>
<td>Warfarin (at investigators' discretion)</td>
<td>Death, stroke, pulmonary and peripheral embolism</td>
</tr>
<tr>
<td>SOLVD⁷</td>
<td>Retrospective cohort analysis; heart failure (ejection fraction &lt; 35%)</td>
<td>6767 patients enrolled in SOLVD</td>
<td>Warfarin (at investigators' discretion, n = 861)</td>
<td>Death, sudden death, cardiovascular events</td>
</tr>
<tr>
<td>V-HeFT⁶</td>
<td>Retrospective cohort analysis; Heart failure (ejection fraction &lt; 40%)</td>
<td>V-HeFT I: n = 642</td>
<td>Warfarin (at investigators' discretion)</td>
<td>Death, sudden death, cardiovascular events</td>
</tr>
<tr>
<td>SAVE²³</td>
<td>Cohort analysis; post MI, with asymptomatic left ventricular systolic dysfunction</td>
<td>V-HeFT II: n = 804</td>
<td>Warfarin, aspirin</td>
<td>Death, stroke</td>
</tr>
<tr>
<td>Falk et al.⁹</td>
<td>Retrospective cohort analysis of patients with severe CHF (NYHA III or IV)</td>
<td>1088 patients with CHF enrolled in RCT of milrinone</td>
<td>Warfarin (at investigators' discretion)</td>
<td>Death, stroke</td>
</tr>
<tr>
<td>Observational studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fuster et al.²</td>
<td>Observational retrospective series of patients with dilated cardiomyopathy</td>
<td>104 participants</td>
<td>Warfarin</td>
<td>Death, stroke, pulmonary and peripheral embolism</td>
</tr>
<tr>
<td>Kyrle et al.³</td>
<td>Observational retrospective series of patients with dilated cardiomyopathy</td>
<td>38 patients</td>
<td>Warfarin</td>
<td>Death, stroke, pulmonary and peripheral embolism</td>
</tr>
<tr>
<td>Natterson et al.²²</td>
<td>Observational retrospective study in patients with heart failure (awaiting cardiac transplantation)</td>
<td>224 participants</td>
<td>Warfarin</td>
<td>Death, stroke, pulmonary and peripheral embolism</td>
</tr>
</tbody>
</table>
CHF, congestive heart failure; RCT, randomized controlled trial.

(b) Excluded studies
Wishart et al.17

Case series, conducted over 50 years ago in heterogeneous CHF population (n = 61), and methodology considered inappropriate

(c) RCTs awaiting further assessment and/or ongoing studies

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Population</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin Aspirin Study in CHF (WASH)18</td>
<td>CHF (70% NYHA II)</td>
<td>279</td>
</tr>
<tr>
<td>Warfarin-Antiplatelet Trial in Chronic Heart Failure (WATCH)</td>
<td>NYHA Class II–IV heart failure</td>
<td>4500</td>
</tr>
</tbody>
</table>

Pilot study for WATCH. Full paper awaited
All-cause mortality, non-fatal myocardial infarction and non-fatal stroke, in addition to ischaemic events and thromboembolism

Anticoagulation for heart failure in sinus rhythm

In summary, we could distinguish three kinds of study in this systematic review, investigating anticoagulation in heart failure in sinus rhythm: (i) randomized controlled trials (RCTs), (ii) non-randomized controlled trials, and (iii) post hoc analyses of trials investigating ACE inhibition in heart failure or left ventricular systolic dysfunction. The SAVE study included patients post-myocardial infarction with left ventricular systolic dysfunction of ≤35% and no overt heart failure, that is, asymptomatic patients.23 In summary, we could distinguish three kinds of study in this systematic review, investigating anticoagulation in heart failure in sinus rhythm: (i) randomized controlled trials (RCTs), (ii) non-randomized controlled trials, and (iii) post hoc analyses of trials investigating ACE inhibition in heart failure or left ventricular systolic dysfunction. The SAVE study included patients post-myocardial infarction with left ventricular systolic dysfunction of ≤35% and no overt heart failure, that is, asymptomatic patients.23 In summary, we could distinguish three kinds of study in this systematic review, investigating anticoagulation in heart failure in sinus rhythm: (i) randomized controlled trials (RCTs), (ii) non-randomized controlled trials, and (iii) post hoc analyses of trials investigating ACE inhibition in heart failure or left ventricular systolic dysfunction. The SAVE study included patients post-myocardial infarction with left ventricular systolic dysfunction of ≤35% and no overt heart failure, that is, asymptomatic patients.23
Randomized and non-randomized controlled trials of anticoagulation versus placebo in heart failure

The only randomized controlled data on anticoagulation for heart failure in sinus rhythm are the preliminary data from the WASH study, which found no significant difference in the composite endpoint of death/myocardial infarction/stroke in patients treated with anticoagulation compared to no antithrombotic therapy (24% vs. 27%). The patients in the warfarin group spent 200 fewer days in hospital, compared to those treated with aspirin or no antithrombotic therapy.

A metaanalysis of the four controlled studies of oral anticoagulation in patients with heart failure was performed. Based on the data from the four prospective controlled studies, anticoagulation was more efficacious than control for the reduction of all-cause death (aggregate OR 0.64, 95% CI 0.45–0.90) based on a combined dataset of 594 patients treated with anticoagulants who were compared to 493 controls; and the reduction of cardiovascular events (aggregate OR 0.26, 95% CI 0.16–0.43), based on a combined dataset of 616 patients treated with anticoagulants who were compared to 514 controls. However, it should be emphasized that only 24% of the weight was contributed by the one contemporary randomized controlled trial. Complete information on bleeding complications was available in two studies, with a trend towards more bleeding in patients treated with warfarin (OR 1.52, 95% CI 0.56–4.10). Preliminary information from the WASH study reported four haemorrhages in the warfarin group.

Three small observational studies met the criteria for inclusion. The first, a retrospective study of 104 patients with idiopathic dilated cardiomyopathy, followed-up for a total of 725 patient-years, observed an 18% incidence of thromboembolic events (including those demonstrated at post mortem) in patients who were not receiving chronic oral anticoagulation (624 patient-years with an estimated annual incidence of 3.5%), although no events were recorded in those who were anticoagulated (101 patient-years). In the second, a study of 38 patients with non-ischaemic cardiomyopathy followed for a total of 72 patient-years, the estimated incidence of thromboembolic events was 45 per 100 patient-years in patients not receiving oral anticoagulation, while no events were recorded in patients who were anticoagulated. In contrast a third, more recent study of 224 patients awaiting cardiac transplantation, which reported an annual incidence of thromboembolism of 3.2%, failed to demonstrate a statistically significant difference in the rate of thromboembolism in the 37% of patients receiving (non-randomized) warfarin therapy. The latter study reported an actuarial 1-year survival for patients receiving warfarin of 78%, compared with 86% for patients not receiving warfarin (p = 0.30). Based on these observational series, anticoagulation therapy was associated with a reduction in thromboembolism (OR 0.15, 95% CI 0.06–0.36), with an associated increase in bleeding. Nevertheless, data on the latter were based on two studies.

Post hoc analyses of the effects of warfarin in non-randomized comparisons

Four large-scale non-randomized post hoc analyses of the effects of warfarin in non-randomized comparisons were found (Table 1). No information on bleeding complications was available.

In the largest, which included a high proportion of patients with ischaemic heart disease as the cause of left ventricular dysfunction, warfarin therapy was associated with a significantly lower risk of all cardiovascular and sudden deaths. However, in a multivariate analysis, the point estimate for the overall risk reduction of sudden death was 32% for warfarin, when compared to 25% for beta blockers, 24% for aspirin, and 11% for enalapril. In addition, multivariate analysis in patients considered to have non-ischaemic heart failure also demonstrated a 70% risk reduction. Similarly, observations in CONSENSUS, suggested that (non-randomized) long-term anticoagulation with warfarin was associated with a 40% lower mortality. Interestingly, 75% of the deaths in CONSENSUS were classified as due to progressive heart failure.

The Vasodilator Heart Failure Studies (V-HeFT) also provided detailed observational data regarding the effects of long-term oral anticoagulation. In V-HeFT I, during 1068 patient-years of follow-up without antithrombotic therapy (aspirin or warfarin), there were 21 strokes, four recorded events of pulmonary embolism and four recorded events of peripheral embolism, with an overall an incidence of 2.7 events in 100 patient-years. In 208 patient-years of follow-up in patients receiving chronic oral anticoagulation with warfarin, there were four strokes, one recorded pulmonary embolism and one recorded peripheral embolism, with an incidence of 2.9 events in 100 patient-years. There was no significant difference in the rates of thromboembolism between patients on long-term
warfarin therapy, compared to those not on anticoagulation.

In V-HeFT II, during 1188 patient-years of follow-up without antithrombotic therapy, there were 23 strokes, one pulmonary embolism and one peripheral embolism, with an incidence of 2.1 events in 100 patient-years. In the 247 patient-years of follow-up in patients receiving warfarin, there were seven strokes, four pulmonary embolic events and one peripheral embolism, with an overall incidence of 4.9 events per 100 patient-years. Interestingly, the difference between the incidence of thromboembolic events in patients with and without warfarin was significantly higher in those receiving warfarin (p<0.01). In addition, although data from the SOLVD trials suggest that anticoagulation was associated with a reduction in sudden cardiovascular deaths and all-cause deaths, long-term warfarin was not, however, associated with a reduction in the total number of (fatal and non-fatal) thromboembolic events.

Similarly, in the SAVE trial, warfarin use was associated with a 81% reduction in stroke risk (RR 0.19, 95% CI 0.13–0.27), but no direct comparison against aspirin (56% reduction) was made. One retrospective analysis of limited data from one trial of milrinone in severe heart failure found that warfarin was used in 324 patients with a significant reduction in stroke only in those who had very severe heart failure (ejection fraction ≤20%, 0.6% vs. 3.3% in controls, p<0.05).

Discussion

The only prospective randomized controlled trial which passed our trial selection criteria for estimation of the effectiveness of anticoagulation is the WASH study. This was a pilot study of 279 patients with heart failure randomized to anticoagulation (target INR 2.5), aspirin (300 mg) or no antithrombotic therapy. It should be noted that this study reported better results in controls than the other trials did with warfarin—the reasons for this are uncertain, pending publication of the full paper, but may be a reflection of changes in the contemporary management of heart failure, as well as the possibility of bias due to the size and selection of the trial.

The earlier prospective studies were performed over 50 years ago, in hospitalized patients with a high prevalence of rheumatic disease and atrial fibrillation, and the trial methodology in these studies cannot be seen as reliable by modern standards (e.g. method of randomization, monitoring, patient inclusion/exclusion criteria, etc.). For example, patients with heart failure in the study by Harvey et al. were allocated to dicumarol or control depending on whether their hospital admission was on an even or odd day. In the study by Andersen et al., the first 61 patients were alternatively allocated to treated and control groups, and for the rest, the treated and control groups were alternated weekly between different medical units and rotated between the wards; thus, there was patient alternation, service alternation and ward rotation in allocating patients to anticoagulation or control. In the study by Griffith et al. during the first year of the study, all patients with heart failure admitted were serially allocated to control, dicumarol or depo-heparin; although in the second year of the study, all patients ‘on certain designated wards’ were used as controls, while others were assigned anticoagulants. In these three controlled studies from the 1950s, randomization is thus inadequate, and it is possible that allocation to anticoagulation in the study by Griffiths et al. could be biased. Thus, these early non-randomized trials do not pass our trial selection criteria for inclusion in estimating the effectiveness of anticoagulation, but they are included as they fulfil our criteria for examining the adverse effects of anticoagulation. Analysis of their results show that a trend is present for a reduction in mortality and cardiovascular events with anticoagulants compared to control, although this is based on a small dataset. A trend towards increased bleeding with warfarin is also noted.

Anticoagulation monitoring in the older studies was performed using prothrombin activity but was variable in different studies: 30% by Quick’s method, 10–30% by an unstated method, and 20% by variable methods. The data from the non-randomized observational studies are potentially confounded by a number of factors, including confounding, selection and information biases, the substantial and uncontrolled use of anticoagulation in these patients, and the influence of time on the risk of embolization following thrombus development, particularly post-MI.

In addition, the observational data from the large heart failure trials and small studies are conflicting. Indeed, four large-scale non-randomized cohort analyses and three small observational studies of oral anticoagulation in heart failure met the criteria for inclusion, although these included differing populations of heart failure patients (including asymptomatic left ventricular dysfunction), and reported contradictory results. Nevertheless, it is important to note that data from the SOLVD and VeHeFT studies were observational, without randomization or control with respect to oral anticoagulation. The decision to treat with warfarin was made by the study investigator, while the
target INR, the average degree of anticoagulation, and the INR at the time of thromboembolic events was not reported in either of these studies. In addition, interpretation of these data are potentially confounded, as it is possible that patients who were considered to be at the highest risk of thromboembolism were treated with warfarin and that this substantially reduced the long-term risk of thromboembolic events in these patients.

Importantly, the positive early small studies, which suggested an overall benefit from oral anticoagulation, were limited to patients with non-ischaemic cardiomyopathy, while approximately half of the patients in both V-HeFT studies and 70–80% of those in SOLVD had definite coronary artery disease. It is, therefore, possible that the efficacy of oral anticoagulation may differ according to the cause of heart failure, as patients with idiopathic cardiomyopathy may have a greater risk of cardiogenic thromboembolism, while patients with atherosclerosis are also at risk of other vascular events, including in situ coronary artery thrombosis. Clearly, substantial problems exist in interpreting data from non-randomized studies.

Implications for practice

As anticoagulation therapy is itself not without risk, clinicians contemplating antithrombotic therapy for prophylaxis against stroke and thromboembolic events in patients with heart failure have to balance the benefit of risk reduction against the risks of potentiating haemorrhage with warfarin therapy.

Based on current evidence, patients with heart failure with poor cardiac function or idiopathic dilated cardiomyopathy, atrial fibrillation and a protruding, mobile left ventricular thrombus on cardiac imaging are probably at highest risk, requiring anticoagulant therapy. If patients are in sinus rhythm, anticoagulants should perhaps be reserved especially for patients with severe cardiac impairment, the presence of intracardiac thrombus, and previous thromboembolism or stroke. Thus, until more evidence becomes available, clinical decisions to treat patients with heart failure with anticoagulants must be made on an individual basis, based upon individual benefits and risks.

Implications for research

A large-scale randomized controlled trial in ambulant patients with heart failure to evaluate the effectiveness of anticoagulant therapy and antiplatelet therapy is long overdue, and one is in progress: The Veterans Administration is currently conducting the large Warfarin-Antiplatelet Trial in Chronic Heart Failure (WATCH) in 4500 patients with NYHA Class II-IV heart failure and ejection fraction ≤30%, who will be randomized to warfarin or antiplatelet therapy (blinded aspirin or clopidogrel). The primary outcomes in WATCH will be all-cause mortality, non-fatal myocardial infarction and non-fatal stroke, in addition to ischaemic events and thromboembolism.

In conclusion, although oral anticoagulation is indicated in certain groups of patients with heart failure (e.g. atrial fibrillation), the present (limited) data do not support its routine use in heart failure patients who remain in sinus rhythm.

Acknowledgements

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References