Antithrombotic treatment in chronic heart failure and sinus rhythm: Systematic review

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Abstract

AIM: To assess the efficacy and safety of antithrombotic drugs (antiplatelet or anticoagulant drugs) compared to no antithrombotic treatment or placebo in patients with heart failure (HF) and sinus rhythm.

METHODS: We searched Medline and Cochrane Library for randomized controlled trials evaluating antithrombotic treatment and no antithrombotic treatment in patients with HF and sinus rhythm. Risk ratio (RR) and 95% CIs were estimated performing meta-analysis with random effects method.

RESULTS: Two studies met the inclusion criteria: Heart failure Long-term Antithrombotic Study and Warfarin/Aspirin Study in Heart failure, with 336 patients and mean follow-up 1.8-2.25 years. Stroke risk was not reduced by acetylsalicylic acid (RR = 1.18, 95%CI: 0.17-8.15), oral anticoagulation (RR = 0.30, 95%CI: 0.03-2.65) or overall antithrombotic drugs (RR = 0.52, 95%CI: 0.10-2.74). Acetylsalicylic acid showed a significant increased risk of worsening HF (RR = 1.78, 95%CI: 1.08-2.92), while oral anticoagulation had no impact in this outcome (RR = 1.03, 95%CI: 0.61-1.75). Overall antithrombotic drugs showed a significant risk increase of major bleeding (RR = 6.99, 95%CI: 0.89-54.64).

CONCLUSION: Best available evidence does not support the routine use of antithrombotic drugs in patients with HF and sinus rhythm. These drugs, particularly oral anti-
coagulation has the hazard of increase significantly major bleeding risk.

**Key words:** Heart failure; Sinus rhythm; Platelet aggregation inhibitors; Anticoagulants

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Core tip: In patients with atrial fibrillation, chronic heart failure (CHF) increases thromboembolic risk and oral anticoagulation is essential to decrease the risk of thromboembolic complications. Evidence suggests a positive association between CHF, impaired hemostasis and thromboembolic events. Whether antithrombotic drugs should be recommended for these patients (in sinus rhythm) is still debated. We looked for the best available evidence and we found 2 studies fulfilling the inclusion criteria. We performed a meta-analysis of antithrombotic drugs vs placebo and strengthened that antithrombotic drugs do not decrease the risk of stroke (fatal or non-fatal) and increase the risk of major bleeding.


**INTRODUCTION**

Chronic heart failure (CHF) is an increasingly prevalent cardiovascular disease with significant associated morbidity and mortality,[1] CHF constitutes a significant economic burden,[2,3], which is expected to increase over the next decades due to increasing prevalence of associated diseases and risk factors as well as population aging. Former observational studies suggest a positive association between CHF, impaired hemostasis and thromboembolic events.[4,5] In patients with atrial fibrillation (AF), CHF increases thromboembolic risk and oral anticoagulation is the cornerstone of AF treatment aiming to decrease the risk of thromboembolic complications.[6] The results from the WARCEF trial (Warfarin vs Aspirin in Reduced Cardiac Ejection Fraction) has highlighted the role of antithrombotic treatment in patients with CHF and sinus rhythm.[7] There were no differences between warfarin and acetylsalicylic acid in the primary outcome (time to the first event in a composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause). However, warfarin was associated with fewer stroke events (2.5% vs 4.7%) but also with a higher rate of major bleeding events (5.8% vs 2.7%). The clinical interpretation of these findings was that the choice between warfarin and aspirin should be made on the basis of the individual patient.[8]

Previous systematic reviews with meta-analyses comparing oral anticoagulation (namely warfarin) and acetylsalicylic acid in patients with CHF and sinus rhythm reached conclusions overlapping those from the WARCEF study.[9-13]

Although much effort have been done comparing and discussing the relative effectiveness of oral anticoagulation vs acetylsalicylic acid in patients with CHF and sinus rhythm, significantly less is known about the true efficacy of the overall antithrombotic treatment. Therefore, we aimed to perform a systematic review to better estimate the true clinical benefit of antithrombotic treatments (oral anticoagulation or antiplatelet drugs) against placebo, standard care or no treatment, in patients with CHF and sinus rhythm.

**MATERIALS AND METHODS**

**Guidance**

This work followed PRISMA guidelines for systematic reviews and meta-analyses promoted by the EQUATOR network.[14]

**Eligibility criteria**

We have searched for all randomized controlled trials (RCTs) evaluating patients with CHF and sinus rhythm treated with oral antithrombotic therapy or control. We considered for antithrombotic treatments both oral anticoagulants (such as vitamin K antagonists, like warfarin, acenocoumarol or phenprocoumon) and antiplatelet drugs [such as acetylsalicylic acid (ASA), clopidogrel or ticlopidine]. We allowed controls under placebo, standard care or no antithrombotic treatment. Studies had to report clinical and/or echocardiographic features for the enrolled CHF patients, such as impaired left ventricle ejection fraction or shortening fraction.

**Database and search method**

Medline and Cochrane Library (CENTRAL) databases were searched from inception to November 2013 for eligible studies. The search strategy details are available at the Online Supplementary Material. We considered all studies irrespective of language. References of obtained studies were also comprehensively searched and cross-checked to identify possible missing studies.

**Studies and data selection**

Citations obtained from electronic search were independently screened by two authors, followed by full-text assessment of potentially eligible studies for inclusion in accordance with previously mentioned criteria.

Primary outcome was stroke (fatal or non-fatal). Secondary outcomes were all-cause mortality, myocardial infarction, worsening heart failure (HF), major bleeding and a composite of major adverse clinical events, defined as the combination of mortality, stroke, myocardial infarction and HF.
We extracted detailed data about demographics, comorbidities, interventions, follow-up and outcomes. Data extraction and data entry into software was double-checked. Disagreements were resolved by consensus.

**Quality reporting assessment**

Quality of reporting was analysed by using a qualitative classification according to risk of bias (high, unclear or low risk), adapted from Cochrane Collaboration’s Tool[13]. Studies were not excluded based on quality of reporting.

**Statistical analysis**

Outcomes data were summarized as frequencies. Statistical analyses were performed using the RevMan version 5.2.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) to derive forest plots with pooled estimates of risk ratios (RR) and their 95%CI. Statistical heterogeneity was assessed with $\chi^2$ test and quantified with Higgins $I^2$ test[19]. Pooled results estimates were based on the random or fixed effects model according to the existence ($I^2 \geq 50\%$) or not ($I^2 < 50\%$) of significant heterogeneity[17]. Publication bias was assessed through visual inspection of funnel plots symmetry and Peters’ regression tests[18,19]. Pooled results were evaluated for the overall antithrombotic treatment, as well separately for antiplatelet and anticoagulation groups.

**RESULTS**

**Search**

After title and abstract screening of citations obtained in Medline and Cochrane Library, 196 citations were retrieved. One-hundred and eighty seven studies did not meet inclusion criteria through initial assessment: 107 included AF patients; 56 studies were not randomized and 24 did not address the pretended topic (either different population and/or other interventions).

The remaining 9 studies were fully-evaluated, of which 7 were further excluded: 5 were observational studies, and 2 RCTs did not include a placebo, standard care or no antithrombotic treatment arm (WARCEF and WATCH trials)[5,20]. Therefore, 2 RCTs were eligible for the purpose of this systematic review[21,22]. The search of reference lists of review articles and included studies failed to identify any additional eligible study[21,22]. Figure 1 shows the flowchart of studies’ selection.

**Characteristics of obtained studies and quality of reporting**

Studies Warfarin/Aspirin Study in Heart failure (WASH) and Heart failure Long-term Antithrombotic Study (HELAS) met the outlined inclusion criteria[21,22].

WASH study was an open-label RCT with blinded endpoint assessment, published in 2004. WASH enrolled 254 patients (80 warfarin; 80 ASA; 94 no anti-thrombotic treatment) with CHF and sinus rhythm and followed them for a mean period of 2.25 years. About 60% had CHF of ischemic etiology, 75% of the patients were male, mean age was 63 years old, and 30% were in New York Heart Association class III/IV. About 34% of the patients had hypertension, and 20% had diabetes. In terms of echocardiography mean parameters, patients had a fractional shortening of 15% and a left-ventricular end-diastolic diameter of 66 mm. Regarding treatments, the daily dosage of acetylsalicylic acid was 300 mg and international normalized ratio (INR) target for warfarin-treated patients was 2.5 (range 2-3). Primary outcome was the composite of all-cause death, non-fatal myocardial infarction, or non-fatal stroke[21].

HELAS study was published in 2006 and included two comparisons: warfarin vs acetylsalicylic acid in patients with CHF of ischemic etiology (not evaluated in this review due to absence of a placebo/no treatment control arm); and warfarin vs placebo in 82 patients (38 vs 44) with dilated non-ischemic CHF in sinus rhythm. Study’s mean follow was 1.8 years. Most of the patients were male and mean age was 55 years. Hypertension was present in 25% of the patients, and diabetes in 11%. No significant differences were noticed in the main baseline characteristics. Echocardiographic features of these patients were remarkable for a baseline ejection fraction of 28%, left ventricle end-systolic diameter of 58 mm and end-diastolic diameter of 70 mm. Target INR for warfarin treatment was 2.3. Primary outcome was the composite of all-cause mortality, non-fatal stroke, non-fatal myocardial infarction, peripheral or pulmonary embolism, hospitalisation, or HF worsening[23].

Quality of reporting assessment is available in Figure 2. The main methodological flaws were the open-label design of WASH and the unknown method of allocation concealment in HELAS.
A quantitative evaluation of antithrombotic drugs showed reduction of mortality and myocardial infarction risk in patients with systolic HF and sinus rhythm.

Antiplatelet drug/acetylsalicylic acid, but not warfarin, showed increased risk of the composite outcome of mortality, stroke, myocardial infarction, and worsening HF, most probably due to the increased risk of CHF worsening. Statistical heterogeneity was present in the evaluation of mortality when comparing antithrombotic drugs with control ($I^2 = 58\%$). Figure 3 shows the pooled results. Publication bias was not evaluated due to the scarcity of studies.

**DISCUSSION**

Our main findings were the lack of proven efficacy of antithrombotic treatments, in patients with systolic HF and sinus rhythm, in the risk reduction of clinically important outcomes such as stroke, mortality and myocardial infarction; moreover, warfarin is associated to a significant 9-fold increased risk of major bleeding and acetylsalicylic acid was associated with increased risk of CHF worsening.

The spotlight of this theme looks for Warfarin vs Acetylsalicylic acid comparison. By conducting this systematic review, the authors aimed to move back to the original problem and ask the question of whether antithrombotic treatments are, in the first place, effective in the treatment of CHF with sinus rhythm. If we accept that RCTs are the unique type of clinical studies that can prove causality with a reasonable margin of error, our results show that these interventions still have to prove their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe their efficacy in this population, knowing that they owe...
consider warfarin as a “negative control”, the pooled rates of HF worsening (after the WARCEF trial) were similar between acetylsalicylic acid and warfarin [7].

Along this century, antithrombotic treatment has gone forward in many therapeutic indications, but in patients with systolic HF and sinus rhythm the evidence to determine the prognostic importance of antithrombotic treatment (individually or globally) remained stationary and unsatisfactory for those who have to deal with CHF patients with sinus rhythm.

**Limitations**

This systematic review with meta-analysis has limitations attributed to included studies and analysis method.

As for included studies, WASH study had an open-label design; the control arm of this study was a no-antithrombotic treatment group (i.e., not a placebo controlled trial), and included 7% of patients with AF that could not be excluded in the analyses. Furthermore the dosage of acetylsalicylic acid used in this trial was considerably higher than recommended [33].

Both studies had different proportions of HF etiologies. Although it can be important, particularly in ischemic HF cases where acetylsalicylic acid may play recognized prognostic role, here we aimed evaluate the thrombotic and embolic risk of patients with clinically important left ventricle impairment.

Major bleeding definitions were not common along the included trials. Worsening HF was defined by the investigator in WASH and no definition was provided in HELAS.

Periods of unrecognized paroxysmal AF could have biased of results. However it would bias favouring the antithrombotic drugs, which did not occur.

In conclusions, current evidence does not support the routine use of antithrombotic drugs (anticoagulant or antiplatelet drugs) for thromboprophylaxis in patients with systolic HF and sinus rhythm, as it carries a well known and documented bleeding risk without proven benefits compared to placebo or no antithrombotic treatment.

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**COMMENTS**

**Background**

In patients with atrial fibrillation (AF), chronic heart failure (CHF) increases...
Warfarin and acetylsalicylic acid should not be routinely used for thromboprophylaxis in patients with systolic HF and sinus rhythm, in the absence of concomitant comorbidities with clear indications for anticoagulation (e.g., AF) or acetylsalicylic acid (e.g., documented coronary artery disease).

**Peer review**

A systematic review and meta-analysis of two studies addressing antithrombotic drugs in patients with CHF and sinus rhythm. The manuscript is well written and adds new points to the discussion of anticoagulation.

**REFERENCES**


P- Reviewer: Aronow WS, Rauch B, Skobel E
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