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META-ANALYSIS

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

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.

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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.

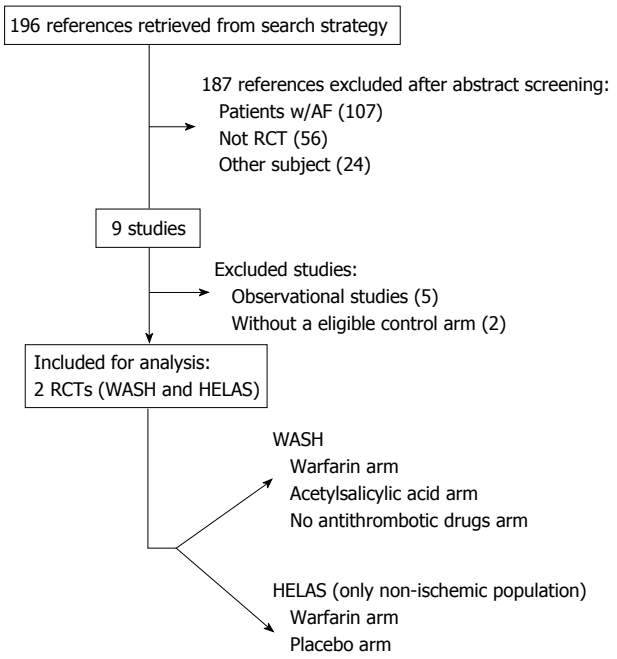

Figure 1 Flowchart of studies' selection. AF: Atrial fibrillation; RCT: Randomized controlled trial; WASH: Warfarin/Aspirin Study in Heart failure; HELAS: Heart failure Long-term Antithrombotic Study.

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[15]. 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 χ^2 test and quantified with Higgins I^2 test[16]. Pooled results estimates were based on the random or fixed effects model according to the existence ($I^2 \geqslant 50\%$) 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[23-27]. 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/Ⅵ. 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[22].

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.

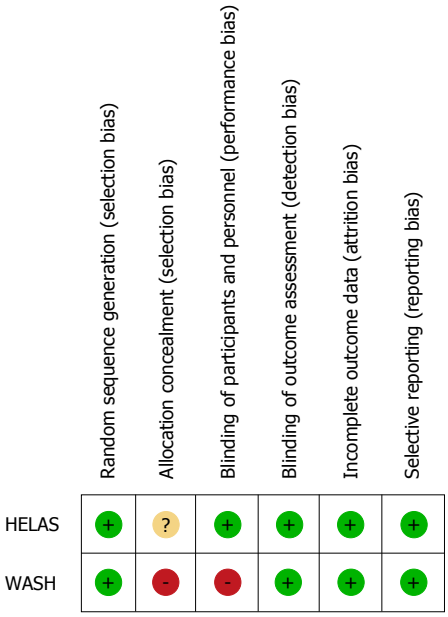

Figure 2 Studies quality of reporting. WASH: Warfarin/Aspirin Study in Heart failure; HELAS: Heart failure Long-term Antithrombotic Study.

Quantitative evaluation

Meta-analysis was performed for the following comparisons: antiplatelet drugs *vs* control, anticoagulant drugs *vs* control, and antithrombotic drugs (antiplatelet plus anticoagulant drugs) *vs* control.

While anticoagulation *vs* control data was derived from both WASH and HELAS studies[21,22], WASH study was the only that provided data for antiplatelet (acetylsalicylic acid) *vs* placebo[21]. For quantitative evaluation of overall antithrombotic treatment in this population, we considered both oral anticoagulation and antiplatelet from WASH study as a single arm and efficacy was directly obtained from WASH study[21].

Primary outcome

Antithrombotic drugs did not reduce stroke risk against placebo or no treatment, with RR = 1.18 (95%CI: 0.17-8.15) for antiplatelet drugs, RR = 0.30 (95%CI: 0.03-2.65) for anticoagulants, and RR = 0.52 (95%CI: 0.10-2.74) for overall antithrombotic drugs.

Secondary outcomes

Antithrombotic drugs showed an increased risk of CHF worsening (RR = 1.61, 95%CI: 1.04-2.48), mainly due to the single antiplatelet drug studied, acetylsalicylic acid, which had RR = 1.78 (95%CI: 1.08-2.92), while oral anticoagulants were not different from controls (RR = 1.03, 95%CI: 0.61-1.75).

Warfarin showed a significant increased risk of major bleeding (RR = 9.00, 95%CI: 1.14-70.90) and acetylsalicylic acid showed a non-significant trend (RR = 3.26, 95%CI: 0.13-79.04). The RR for overall major bleeding risk with antithrombotic drugs was 6.99 (95%CI: 0.89-54.64).

None of the antithrombotic drugs or overall antithrombotic treatment 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[28].

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 an important bleeding risk. Furthermore, our attempt to perform a bayesian mixed treatment comparison meta-analysis, with data from clopidogrel arm from WATCH study[20], and warfarin *vs* acetylsalicylic acid presented in multiple systematic reviews and meta-analyses, failed due to high inconsistency in the statistical analysis of the network (data not shown). Although this inconsistence strongly compromises the results of such exercise, it is worth to report that placebo had a high probability of being the best treatment option. This reinforces the need of further trials to elucidate whether these interventions do/do not interfere with the prognosis, rather than have contradictory signs.

Accordingly, the 2012 consensus document of the HF Association of the European Society of Cardiology (ESC) and the ESC Working Group on Thrombosis corroborates our conclusions[29]. This consensus document stated that 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).

Safety concerns regarding acetylsalicylic acid and HF (in patients with previously optimized background therapy with drugs such as angiotensin-converting enzyme inhibitors) were previously mentioned[30-32]. However if we

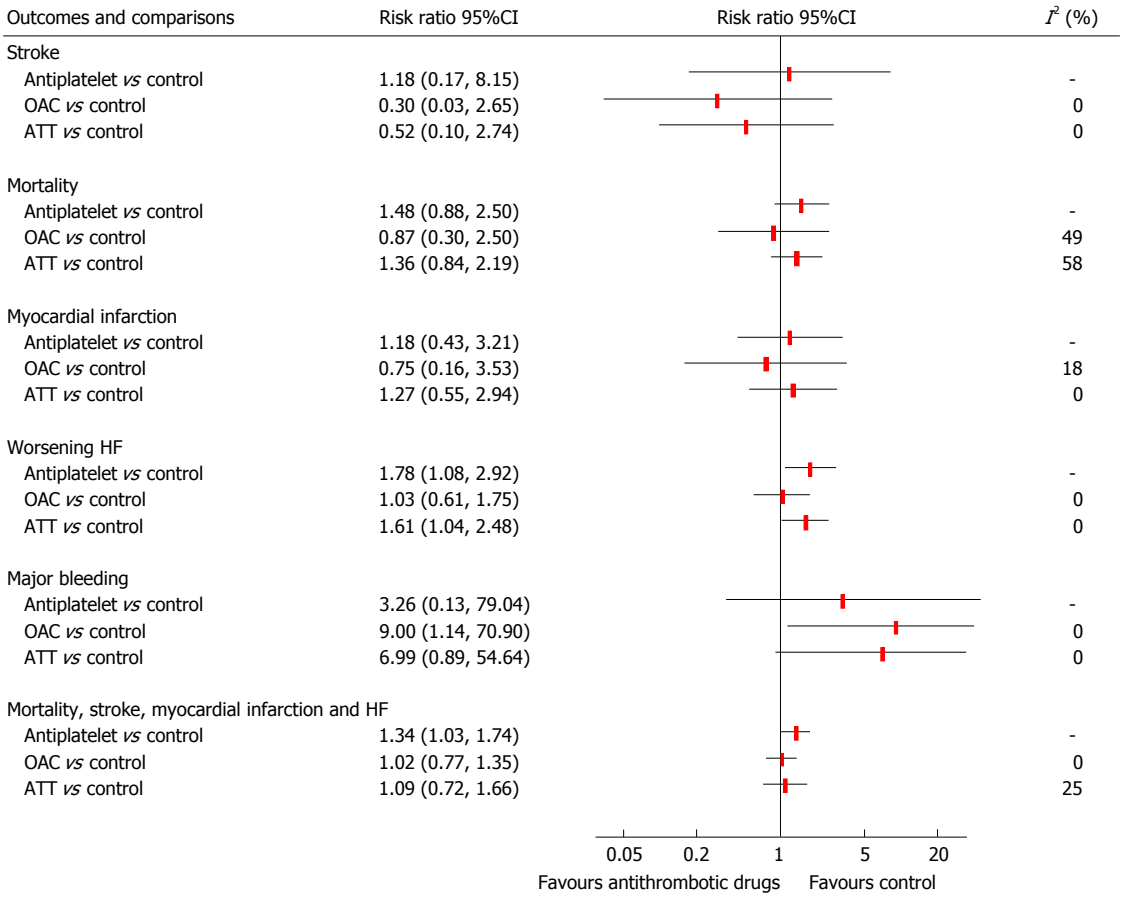

Figure 3 Forest plot evaluating antithrombotic drugs *vs* control. Data for "Antiplatelet *vs* control" comparison derived from WASH study. ATT: Antithrombotic treatment; OAC: Oral anticoagulation; HF: Heart failure; WASH: Warfarin/Aspirin Study in Heart failure.

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

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 have an prognosis impact in patients with CHF in sinus rhythm (*i.e.*, without history of AF) is still very debated.

Research frontiers

Anticoagulation has been established as the gold standard treatment of stroke and embolism prevention in AF. The WARCEF trial did not show differences between warfarin and acetylsalicylic acid concerning major cardiovascular events in patients with CHF and sinus rhythm. Warfarin reduced the risk of ischemic stroke in this trial. However the efficacy of any of these drugs compared should be evaluated before drawing any conclusions and recommendations.

Innovations and breakthroughs

Based on the best available evidence (2 randomized controlled trials Warfarin/Aspirin Study in Heart failure and Heart failure Long-term Antithrombotic Study), this systematic review emphasizes the lack of efficacy of any antithrombotic drugs (individually or pooled together) in patients with CHF and sinus rhythm. In addition should be considered that these drugs increase significantly the risk of major bleeding.

Applications

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.

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