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ORIGINAL RESEARCH ARTICLE

Major bleeding risk with non-vitamin K antagonist oral anticoagulant vs. aspirin in heart failure: network meta-analysis

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Abstract

Aims Relative bleeding risks of different antithrombotic agents in heart failure (HF) patients is an important consideration in treatment decision making, making detailed comparative analysis desirable. The aim of this study was to conduct a network meta-analysis to investigate the major bleeding risk for individual novel oral anticoagulants (NOACs) vs. aspirin among patients with HF.

Methods and results We searched Pubmed, EMBASE, Cochrane Collaboration Central Register of Controlled Clinical Trials, and Clinicaltrials.gov from 1966 to November 2019 to identify relevant randomized clinical trials. Studies comparing individual NOACs vs. aspirin were analysed using direct study-level meta-analysis. Studies comparing aspirin to warfarin and NOACs to warfarin were then additionally added using network (direct and indirect) study-level meta-analysis. Primary endpoint was major bleeding. Final analysis included nine trials with 34 367 participants, including one direct comparison trial (apixaban vs. aspirin) and eight indirect comparison trials against the shared warfarin comparator (four aspirin trials and one trial each of apixaban, dabigatran, rivaroxaban, and edoxaban). For apixaban, network meta-analysis combing direct and indirect comparison showed that major bleeding risk might not be different between apixaban and aspirin (odds ratio, 1.18 [95% confidence interval, 0.38 to 3.65]) in HF patients. In contrast, indirect-comparison meta-analysis showed dabigatran, rivaroxaban, and edoxaban compared with aspirin might be associated with a higher risk of major bleeding in HF patients.

Conclusions In network meta-analysis, apixaban might be associated with a comparable risk of major bleeding compared with aspirin in patients with HF, while other NOACs might be associated with a higher risk. However, such results were not strongly convincing because of lack of direct comparison in an original trial and small sample size of trials and participants. A clinical trial directly comparing apixaban vs. aspirin in patients with HF and sinus rhythm may be worth undertaking.

Keywords Heart failure; Aspirin; Meta-analysis; Major bleeding; Intracranial haemorrhage; NOACs

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Introduction

Patients with heart failure (HF) are at increased risk of falls[1] and potentially other causes of systemic and intracranial bleeding. Randomized clinical trials (RCTs) of warfarin vs. aspirin in sinus rhythm-HF patients showed no clear best agent, because higher bleeding complications with warfarin offset beneficial reduction in ischemic stroke.[2–6] Consequently, practice guidelines recognize both warfarin and antiplatelet therapy strategies as reasonable options.[7]

Non-vitamin K antagonist oral anticoagulants (NOACs) might favourably shift the benefit–risk ratio towards anticoagulation rather than antiplatelet therapy in sinus rhythm-HF patients by reducing the bleeding side effects.

However, NOAC agents differ by class (factor Xa inhibitors and direct thrombin inhibitors), within class by several features, including half-life and renal vs. hepatic clearance.[8] Analyses of trials largely performed in patients without HF have found safety differences between agents in those patient classes. A network meta-analysis comparing NOACs in patients with atrial fibrillation (AF) found safety differences.[8] Also, a pairwise meta-analysis in patients with AF, venous thromboembolisms, atherosclerotic disease, or embolic stroke of uncertain source suggested rivaroxaban at a dose of 15 to 20 mg once daily increased the risk of major bleeding and intracranial haemorrhage compared with aspirin, while apixaban at a dose of 5 mg twice daily conferred comparative risk.[9]

Direct RCTs of certain NOAC vs. acetylsalicylic acid (ASA) in sinus rhythm-HF patients[1]would be worth undertaking if there was suggestive evidence of a less incremental bleeding risk of certain NOACs in the HF population. The incremental bleeding risk in HF patients can usefully be evaluated in both HF patients in sinus rhythm and HF patients with AF. Therefore, we undertook this network meta-analysis to summarize current evidence of the relative bleeding risk of individual NOACs vs. aspirin in HF patients.

Methods

The study design was a network meta-analysis using a frequentist model.[10] The study was performed in accordance with the recommendations of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses statement.[11]

Data sources and searches

We systematically searched Pubmed, EMBASE, Cochrane Collaboration Central Register of Controlled Clinical Trials, and ClinicalTrials.gov from 1966 to 6 November 2019 using the search terms: heart failure or cardiac failure or heart decompensation or myocardial failure or congestive heart failure AND novel oral anticoagulants or non-vitamin K antagonist oral anticoagulants or direct oral anticoagulants or dabigatran or rivaroxaban or apixaban or edoxaban or warfarin or coumadin or vitamin K antagonist or aspirin or acetylsalicylic acid or ASA AND major bleeding or intracranial hemorrhage or brain hemorrhage or posterior fossa hemorrhage. We restricted our search to human and clinical trials. There were no language restrictions. We also reviewed the Introduction and Discussion sections of retrieved trials and relevant review articles to identify additional trials. Two investigators (WYH and YLW) independently conducted the literature search, screening of abstracts, and identification of eligible trials.

Study selection

Entry criteria for a study to be included in the meta-analysis were as follows: (i) the study design was an RCT; (ii) all or an identifiable subset of participants had HF (regardless whether there was or was not co-existing AF); (iii) the study included a comparison of NOACs with aspirin, NOACs with warfarin, or aspirin with warfarin; (iv) treatment duration was at least 6 months; (v) reported endpoints included major bleeding and/or intracranial bleeding; (vi) total number of patients and events were reported separately in each group. We only included trials with treatment duration of at least 6 months to avoid small trials with less rigorous methodology and very few major bleeding events.

Participants of any age or of either sex were included. Studies were excluded when (i) NOAC trials are not using one of four NOACs (i.e. dabigatran, rivaroxaban, apixaban, and edoxaban) because only these four NOACs are approved by regulatory authorities; (ii) combination of two or more antithrombotic agents as a treatment strategy in active or control arm; (iii) use of other antiplatelet agents rather than aspirin; (iv) most participants (>50%) had cancer; (v) most participants (>50%) had a mechanical heart valve (because use of a NOAC, dabigatran, in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding events, as compared with warfarin, and is thus not justified for these patients)[12]; (vi) most participants (>50%) had end stage renal disease; and (vii) either the active therapy or the comparator group received an additional treatment not administered to the other treatment arm.

Data abstraction

All data from eligible studies were independently abstracted by two investigators (ML and WYH). Any discrepant judgements were resolved by joint discussion. We abstracted data by treatment group about patient characteristics, including age, sex, duration of follow up, and proportion with AF or sinus rhythm at trial entry. Outcomes abstracted by treatment groups were (i) major bleeding (as defined in each study) and (ii) intracranial bleeding.

Quality assessment

The risk of bias for each trial was independently assessed by the two raters using the Cochrane risk of bias tool 1.0, assessing the six domains of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting, rating each as low, unclear, or high according to established criteria.[13]

Statistical analysis

The primary aim was to delineate the association of individual NOACs (compared with aspirin) with the endpoint major bleeding; the secondary aim was to delineate their association with intracranial haemorrhage. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to quantify the association of individual NOACs vs. aspirin with these outcomes. Two meta-analytic strategies were followed: first, a traditional pairwise meta-analysis with a random-effects model; and second, a random-effects network meta-analysis, assuming a common heterogeneity variable for all comparisons [the tau (τ) value].[14] To check for overall inconsistency, the command <network meta inconsistency> was used for the inconsistency model provided in Stata. In the network meta-analysis, effect estimates drew upon RCTs providing (i) a direct comparison of a NOAC with aspirin and (ii) an indirect comparison of NOACs vs. aspirin available by drawing upon RCTs directly comparing NOACs with warfarin and RCTs directly comparing aspirin with warfarin.[15] Network meta-analyses were performed for each NOAC separately. A subgroup analysis was performed in the subset of patients with diagnosis of HF who were additionally documented to have left ventricular ejection fraction <40% (or nearest equivalent). For all analyses, $P < 0.05$ was considered statistically significant. Software employed for meta-analyses was Revman 5.3 and Stata Version 15.

Table 1 Characteristics of included trials

Study, publication year, countries	Population and definition of heart failure at entry	Comparison	Sample size	Mean age (year)	Women (%)	History of atrial fibrillation (%)	Use of ACE inhibitor or ARB (%)
NOAC vs. aspirin							
AVERROES, 2011, Multiple countries	Subgroup of HF in AF patients unsuitable for warfarin	Apixaban 5 mg BID vs. aspirin 100 mg OD	2171	NA	NA	100	NA
Aspirin vs. warfarin							
WASH, 2004, UK and US	HF requiring treatment with diuretics, evidence of left ventricular systolic dysfunction on echocardiography; HF was defined as LVEF ≤35%	Aspirin 300 mg QD vs. warfarin	180	63.5	24.5	7	89
HELAS, 2006, European countries	Patients with symptomatic HF, defined as in NYHA Class II–IV and LVEF <35%	Aspirin 325 mg QD vs. warfarin	115	61.6	10.8	0	58
WATCH, 2009, US, Canada, and UK	Patients with symptomatic HF, defined as NYHA II–IV and LVEF ≤35%	Aspirin 162 mg QD vs. warfarin	1063	63	15	0	97
WARCEF, 2012, Multiple countries	Patients with HF, defined as NYHA II–IV and LVEF ≤35%	Aspirin 325 mg QD vs. warfarin	2305	61	20	3.7	98
NOAC vs. warfarin							
RE-LY, 2013, Multiple countries	Subgroup of symptomatic HF in an AF trial; HF was defined as presence of NYHA Class II or higher HF symptoms (fatigue, dyspnoea) in the 6 months before screening, in patients with a history of previous admission for congestive HF.	Dabigatran 150 mg BID or 110 mg BID vs. warfarin	4904	68.2	34.4	100	ACE inhibitor:57.3, ARB:22.1 \
ROCKET-AF, 2013, Multiple countries	Subgroup of HF in an AF trial; HF was defined a priori as a history of HF or a LVEF <40%	Rivaroxaban 20 mg QD vs. warfarin	9033	72	39.1	100	ACE inhibitor: 55.7
ARISTOTLE, 2013, Multiple countries	Subgroup of HF in an AF trial: HF was defined as patients with LVEF ≤40%, with or without symptomatic HF or patients with HF and preserved LVEF (>40%),	Apixaban 5 mg BID vs. warfarin	6451	68.5	32.6	100	78.7
ENGAGE AF-TIMI 48, 2016, Multiple countries	Subgroup of HF in an AF trial; HF was defined as the presence or history of HF Stage C or D according to the American College of Cardiology/American Heart Association definition	Edoxaban 60 mg QD vs. warfarin	8155	70	37.5	100	71

ACE inhibitor, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation, ARB, Angiotensin II receptor blocker; BID, twice daily; HF, heart failure; LVEF, left ventricular ejection fraction; NA, not available; NOAC, non-vitamin K antagonist oral anticoagulant; NYHA, New York Heart Association; QD, once daily

Trial names: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; AVERROES, Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; HELAS, Heart Failure Long-term Antithrombotic Study; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; WARCEF, the Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction; WASH, the Warfarin/Aspirin Study in Heart failure; WATCH, the Warfarin and Antiplatelet Therapy in Chronic Heart Failure.

Results

We identified 60 full articles for detailed assessment, of which 51 were excluded for taking placebo or no treatment in control group, taking another antiplatelet rather than aspirin in a comparator group, treatment duration less than 6 months, or not including identifiable HF patients (see Supporting Information *Figure S1*). The final analysis included nine RCTs enrolling 34 367 participants.[2–4,6,16–20] *Table 1* shows the trial design and patient characteristics of the studies. A direct comparison between a NOAC and aspirin in HF patients was available form one AF trial evaluating apixaban and aspirin.[16] Comparisons of each of the four NOACs with warfarin in HF patients were available from four trials enrolling patients with AF[17–20] while comparisons of aspirin with warfarin in HF patients was available from four trials enrolling patients with sinus rhythm.[2–4,6] Follow-up duration ranged from 1.1 to 3.5 years.

The Cochrane risk of bias assessment for the included trials is summarized in *Figure S2*. Three trials had potential performance bias because of non-blinding of intervention,[2,6,17] and one trial had potential detection bias because of non-blinding of outcome assessment.[6]

Major bleeding

Direct comparison showed that apixaban compared with aspirin was not associated with an increased risk of major bleeding in HF patients (OR, 0.88 [95% CI 0.44 to 1.76]; *Figure 1A*).

Figure 1 Odds ratio with 95% confidence interval (CI) of major bleeding in apixaban vs. aspirin: (A) direct comparison, (B) indirect comparison, (C) network meta-analysis combing direct and indirect comparison. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; AVERROES, Apixaban vs. Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who have Failed or are Unsuitable for Vitamin K Antagonist Treatment; HELAS, Heart Failure Long-Term Antithrombotic Study; M–H, Mantel–Haenszel; WARCEF, Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction; WASH, Warfarin/Aspirin Study in Heart Failure; WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart Failure.

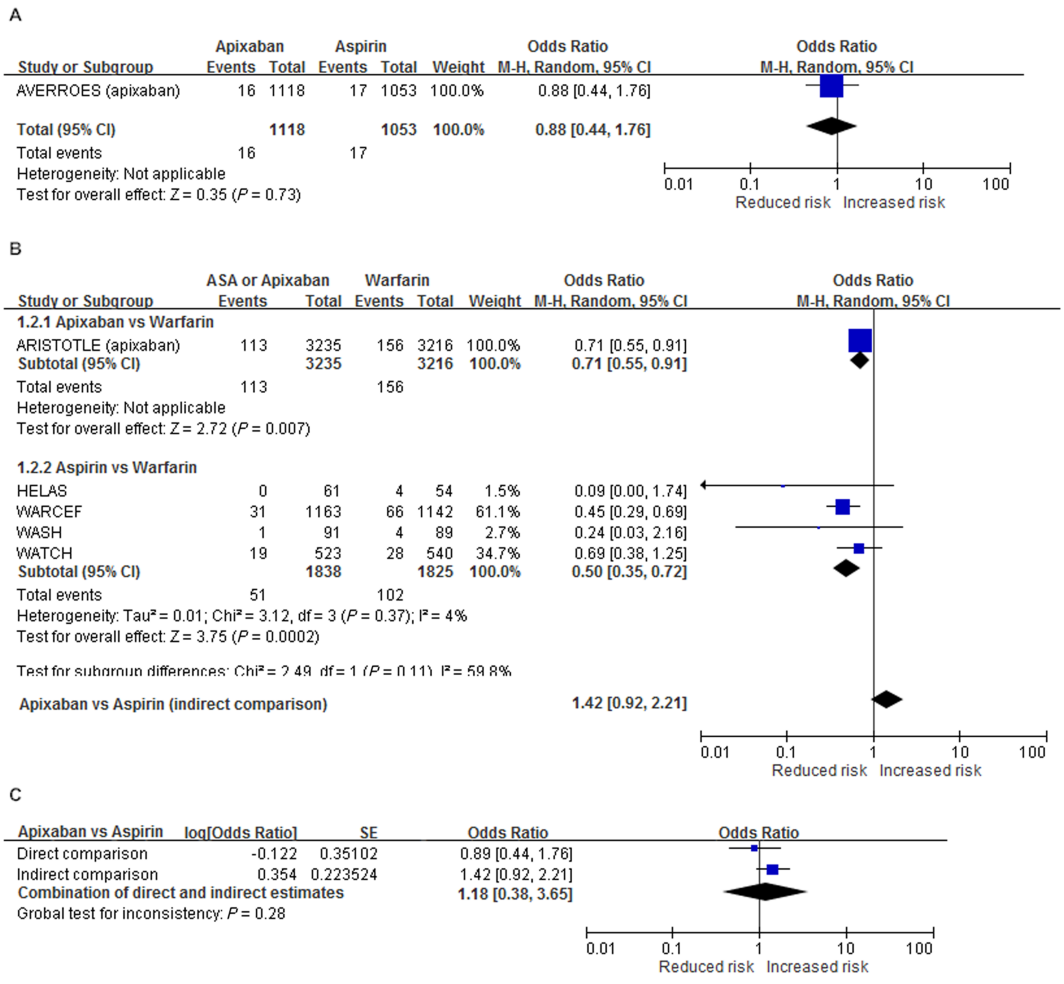

Table 2 Comparison of non-vitamin K antagonist oral anticoagulants vs. aspirin on major bleeding and intracranial haemorrhage in patients with heart failure, presented as odds ratio with 95% confidence interval

	Apixaban 5 mg twice daily vs. aspirin	Dabigatran 110 mg or 15 mg twice daily vs. aspirin	Rivaroxaban 20 mg once daily vs. aspirin	Edoxaban 60 mg once daily vs. aspirin
Major bleeding				
Direct comparison	0.88 (0.44–1.76)	NA	NA	NA
Indirect comparison	1.43 (0.92–2.21)	1.63 (1.06–2.51)	2.02 (1.39–2.95)	1.55 (1.04–2.33)
Combination of direct and indirect comparison	1.18 (0.38–3.65)	NA	NA	NA
Intracranial haemorrhage				
Direct comparison	NA	NA	NA	NA
Indirect comparison	0.24 (0.07–0.82)	0.40 (0.13–1.30)	0.66 (0.23–1.92)	0.46 (0.16–1.31)

NA, not available.

Indirect comparison based on apixaban vs. warfarin (OR, 0.71 [95% CI, 0.55 to 0.91]) and aspirin vs. warfarin (OR, 0.50 [95% CI, 0.35 to 0.72]) implied that there might be no significant difference in a risk of major bleeding between apixaban and aspirin in HF patients (OR, 1.43 [95% CI, 0.92 to 2.21]; *Figure 1B*). Network meta-analysis combing direct and indirect comparison accordingly found that major bleeding risk might not be different between 5 mg twice daily of apixaban and aspirin in HF patients (OR, 1.18 [95% CI, 0.38 to 3.65]; *Figure 1C*). The global test for inconsistency with the command <network meta inconsistency> provided in Stata obtained a *P* value of 0.28, giving no evidence of substantial statistical inconsistency. However, the point estimate point in the direct comparison suggested a lower risk for major bleeding associated with apixaban treatment, while the point estimate in the indirect comparison suggested the opposite. The difference between the two estimates corresponded to an OR of 1.63, which suggested that heterogeneity was not negligible.

We conducted analyses with a fixed-effect model for major bleeding endpoint between apixaban and aspirin as a sensitivity test and obtained similar results (direct comparison: OR, 0.89 [95% CI, 0.45 to 1.76]; indirect comparison: OR, 1.43 [95% CI, 0.93 to 2.18]; overall results: OR, 1.19 [95% CI 0.39 to 3.62]).

Indirect comparison based on dabigatran vs. warfarin and aspirin vs. warfarin showed 110 or 150 mg twice daily of dabigatran compared with aspirin might be associated with an increased risk of major bleeding in HF patients (OR, 1.63 [95% CI, 1.06 to 2.51]; *Figure S3*). Indirect comparison based on rivaroxaban vs. warfarin and aspirin vs. warfarin showed 20 mg once daily of rivaroxaban compared with aspirin might be associated with an increased risk of major bleeding in HF patients (OR, 2.02 [95% CI, 1.39 to 2.95]; *Figure S4*). Indirect comparison based on edoxaban vs. warfarin and aspirin vs. warfarin showed 60 mg once daily of edoxaban compared with aspirin might be associated with an increased risk of major bleeding in HF patients (OR, 1.55 [95% CI, 1.04 to 2.33]; *Figure S5*).

Intracranial haemorrhage

Indirect comparison based on apixaban vs. warfarin (OR, 0.22 [95% CI, 0.10 to 0.47]) and aspirin vs. warfarin (OR, 0.91 [95% CI, 0.35 to 2.37]) showed apixaban compared with aspirin might be associated with a reduced risk of intracranial haemorrhage in HF patients (OR, 0.24 [95% CI, 0.07 to 0.82]; *Figure S6*). Indirect comparison based on dabigatran vs. warfarin and aspirin vs. warfarin showed no significant difference in risk of intracranial haemorrhage between dabigatran and aspirin in HF patients (OR, 0.40 [95% CI, 0.13 to 1.30]; *Figure S7*). Indirect comparison based on rivaroxaban vs. warfarin and aspirin vs. warfarin showed no significant difference in risk of intracranial haemorrhage between rivaroxaban and aspirin in HF patients (OR, 0.66 [95% CI, 0.23 to 1.92]; *Figure S8*). Indirect comparison based on edoxaban vs. warfarin and aspirin vs. warfarin showed no significant difference in risk of intracranial haemorrhage between edoxaban and aspirin in HF patients (OR, 0.46 [95% CI, 0.16 to 1.31]; *Figure S9*).

Comparison of individual NOAC vs. aspirin in primary and secondary endpoints in patients with HF was presented in *Table 2*.

Sensitivity analyses

Sensitivity analyses in patients with HF and left ventricular ejection fraction less than 35% or nearest equivalent were done for major bleeding endpoint (*Table 3*).

Table 3 Indirect comparison of non-vitamin K antagonist oral anticoagulants vs. aspirin on major bleeding in patients with heart failure and left ventricular ejection fraction less than 40% or nearest equivalent

Endpoints	Apixaban 5 mg twice daily vs. aspirin	Dabigatran 110 mg or 15 twice daily vs. aspirin	Rivaroxaban 20 mg once daily vs. aspirin	Edoxaban 60 mg once daily vs. aspirin
Major bleeding	1.62 (0.98–2.68)	1.83 (1.06–3.16)	2.20 (1.46–3.32)	1.76 (1.11–2.80)

Indirect-comparison based on individual NOACs vs. warfarin and aspirin vs. warfarin showed that apixaban compared with aspirin might not be associated with a significantly increased risk of major bleeding (OR, 1.62 [95% CI, 0.98 to 2.68], *Figure S10*) whereas dabigatran (OR, 1.83 [95% CI, 1.06 to 3.16], *Figure S11*), rivaroxaban (OR, 2.20 [95% CI, 1.46 to 3.32], *Figure S12*), and edoxaban (OR, 1.76 [95% CI, 1.11 to 2.80], *Figure S13*) compared with aspirin might be associated with an increased risk of major bleeding.

Discussion

In this network meta-analysis of nine randomized controlled trials consisting over 30 000 participants, we found that 5 mg twice daily of apixaban compared with aspirin might not be associated with an increased risk of major bleeding in HF patients, whereas 150 or 110 mg twice daily of dabigatran, 20 mg once daily of rivaroxaban, and 60 mg once daily of edoxaban might be associated with an increased risk of major bleeding. Also, indirect comparison suggested that apixaban compared with aspirin might be associated with a lower risk of intracranial haemorrhage in HF patients. When we restricted analyses to patients with HF and left ventricular ejection fraction $<$35% or nearest equivalent, indirect comparison suggested apixaban compared with aspirin might not be associated with an increased risk of major bleeding.

HF and AF are both common heart diseases and frequently co-exist.[21] Among patients who have been diagnosed as congestive HF, 24% had a prior or concurrent diagnosis of AF, and 17% developed AF during the follow up period of 4.2 years.[22] Furthermore, some patients who are categorized as HF patients with sinus rhythm may have paroxysmal AF. While it is clear, a NOAC should be used in patients with co-existing HF and AF, an optimal antithrombotic strategy for HF with sinus rhythm remains inconclusive, and so in routine clinical practice, a more conservative approach (i.e. antiplatelet therapy), is usually applied. The novelty of our study lies in the comparisons of major bleeding risk of individual NOAC vs. aspirin in HF patients, regardless of whether AF co-existed. On the other hand, a meta-analysis of RCTs suggested that oral anticoagulant warfarin compared with aspirin was associated with a lower risk of ischemic stroke in HF with sinus rhythm.[5] Taken together, 5 mg twice daily of apixaban might be a viable alternative to aspirin in patients with HF, even when AF is not found.

A recently published clinical trial of patients in sinus rhythm, with a history of HF and coronary artery disease, and all receiving antiplatelet therapy showed that add-on rivaroxaban 2.5 mg twice daily vs. placebo reduced a risk of stroke, but increased a risk of major bleeding.[23] This benefit–risk profile is similar to that seen in trials comparing warfarin vs. aspirin in patients with HF and sinus rhythm.[5] As such, it is conceivable that adding a NOAC to baseline antiplatelet therapy, even at a lower dose, would likely raise a major bleeding risk compared with using antiplatelet therapy alone. Furthermore, 2.5 mg twice daily of rivaroxaban is unlikely to be an efficacious dose for preventing stroke in patients with unrecognized AF. Taken all together, 5 mg twice daily of apixaban monotherapy might be a more reasonable option for HF patients in sinus rhythm, given its comparable major bleeding risk with aspirin, and its greater efficacy in the prevention of cardioembolic stroke.

Direct comparison between NOACs and aspirin was only available between apixaban and aspirin and it was derived from a subgroup of HF in an AF trial.[16] However, this trial was not designed (i.e. not powered) to detect differences in major bleeding between the compared treatments in HF patients. Although the point estimate was 0.88, the 95% CIs ranged from 0.44 to 1.76, suggesting that the trial was not large enough to estimate the association with sufficient precision to get potential effects significant. Furthermore, in the direct comparison of apixaban vs. aspirin, the point estimate point towards a lower risk for major bleeding associated with apixaban treatment, while the point estimate in the indirect comparison indicates the opposite. The difference between the two estimates corresponds to an OR of 1.63. Although global test for inconsistency was not statistically significant between direct and indirect comparisons, tests for heterogeneity generally have poor statistical characteristics when applied in a meta-analysis with very few studies, mostly because of wide 95% CIs. Plausible reasons for the differences between estimates from direct and indirect comparisons, as well as wide CIs were (i) different demographics such as sex differences between included trials; (ii) different conditions such as AF or non-AF at baseline; (iii) different co-medication such as the proportion of angiotensin-converting-enzyme inhibitor use; and (iv) different dosing of the compared treatments such as different aspirin doses in included trials. Because this is a study-level meta-analysis and there was small number of the included trials, we were unable to further explore above-mentioned issues. Because the CIs were quite large and the point estimates of direct and indirect comparisons were in the opposite directions, the result of apixaban and aspirin having similar risk of major bleeding remains less convincing.

The aspirin doses using in the four warfarin vs. aspirin HF trials ranged from 162 to 325 mg once daily,[2–4,6] which were higher than the current recommended low-dose aspirin (75–100 mg daily).[24] Low-dose aspirin was associated with lower risk of bleeding complication when compared with high-dose aspirin.[25] As the current recommended dose of aspirin was low dose (75–100 mg daily), further trials comparing NOACs and low-dose aspirin are warranted.

Some previous studies revealed that women are at higher risk of bleeding after percutaneous coronary intervention and ST-elevation myocardial infarction treated with

fibrinolysis than men[26,27] while other studies revealed that the risk of bleeding events was lower in women than in men.[28] Also, one previous study suggested that an angiotensin-converting-enzyme inhibitor or an angiotensin receptor blocker therapy was associated with a protective effect of developing gastrointestinal bleeding in patients using continuous-flow left ventricular assist device[29] while other studies revealed that lisinopril therapy had a higher risk of hospitalized gastrointestinal haemorrhage when compared with amlodipine.[30] Because of the effects of sex difference and an angiotensin-converting-enzyme inhibitor use on bleeding risk remain inconclusive, we speculated that the observed differences between the populations (e.g. regarding sex or the proportion of patients receiving angiotensin-converting-enzyme inhibitors) did not affect the pooling of the effects.

Most of the patients in the four warfarin vs. aspirin trials were HF with sinus rhythm,[2–4,6] whereas the patients in the apixaban vs. aspirin trial[16] and NOACs vs. warfarin trials[17–20] were HF with AF. As no trial comparing NOACs vs. aspirin or NOACs vs. warfarin in HF with sinus rhythm patients is available currently, we assumed that the incremental bleeding risk in HF patients can usefully be evaluated in both sinus rhythm-HF patients and AF-HF patients with the assumption that no interaction between treatment and AF is present (regarding the risk of major bleeding).

Our study has several limitations. First, the literature search might be unable to identify all of the related trials. To reduce such risks, we performed exhaustive search across multiple trial and literature databases. Second, only one AF trial reported direct comparison between a NOAC and aspirin in subgroup of HF patients. Still, the comparable major bleeding risk between 5 mg twice daily of apixaban and aspirin was unlikely affected by the existence of AF in this trial; therefore, such results might be generalizable in sinus rhythm-HF patients. Third, given that the comparison of apixaban vs. aspirin suggesting that the direct and indirect comparisons are heterogeneous, this questions the other indirect comparisons. Because only indirect comparisons were available between dabigatran, rivaroxaban, and edoxaban vs. aspirin, such results should be interpreted with caution. Finally, definition of HF varied across trials. Still, sensitivity analyses focusing on patients with left ventricular ejection fraction $<$35% or nearest equivalent showed similar results.

Conclusions

The network meta-analysis of RCTs suggested that 5 mg twice daily of apixaban compared with aspirin might be associated with a comparable risk of major bleeding and a lower risk of intracranial haemorrhage in HF patients. Although the indirect comparison implied that dabigatran, rivaroxaban, and edoxaban compared with aspirin might be associated with increased risks of major bleeding, such result was not strongly convincing because of lack of direct comparison in an original trial and small sample size of trials and participants. As such, these results should be interpreted as signal generation rather than estimation of effects. Because an optimal antithrombotic strategy for patients with HF and sinus rhythm is not known to date, based on the results currently available, a clinical trial directly comparing 5 mg twice daily of apixaban vs. aspirin in these patients may be worth undertaking.

Conflict of interest

none declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Study selection.
Figure S2. Risk of Bias of Included Trial
Figure S3. Odds ratio with 95% confidence interval of major bleeding (dabigatran vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods. ASA indicates aspirin.
Figure S4. Odds ratio with 95% confidence interval of major bleeding (rivaroxaban vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods. ASA indicates aspirin.
Figure S5. Odds ratio with 95% confidence interval of major bleeding (edoxaban vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods. ASA indicates aspirin.
Figure S6. Odds ratio with 95% confidence interval of intracranial bleeding (apixaban 5 mg vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods. ASA indicates aspirin.
Figure S7. Odds ratio with 95% confidence interval of intracranial bleeding (dabigatran vs warfarin and aspirin vs

warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods. ASA indicates aspirin.

Figure S8. Odds ratio with 95% confidence interval of intracranial bleeding (rivaroxaban vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods. ASA indicates aspirin.

Figure S9. Odds ratio with 95% confidence interval of intracranial bleeding (edoxaban vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods.

Figure S10. Odds ratio with 95% confidence interval of major bleeding in LVEF <35% or nearest equivalent (apixaban vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods.

Figure S11. Odds ratio with 95% confidence interval of major bleeding in LVEF <35% or nearest equivalent (Dabigatran vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods.

Figure S12. Odds ratio with 95% confidence interval of major bleeding in LVEF< 35% or nearest equivalent (Rivaroxaban vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel–Haenszel methods.

Figure S13. Odds ratio with 95% confidence interval of major bleeding in LVEF<35% or nearest equivalent (Edoxaban vs warfarin and aspirin vs warfarin), by trial and pooled. M-H indicates Mantel-Haenszel methods.

References

1. Lee K, Pressler SJ, Titler M. Falls in patients with heart failure: a systematic review. *J Cardiovasc Nurs* 2016; **31**: 555–561.
2. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The warfarin/aspirin study in heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004; **148**: 157–164.
3. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK, Investigators H. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. *Eur J Heart Fail* 2006; **8**: 428–432.
4. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R, Investigators W. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012; **366**: 1859–1869.
5. Lee M, Saver JL, Hong KS, Wu HC, Ovbiagele B. Risk-benefit profile of warfarin versus aspirin in patients with heart failure and sinus rhythm: a meta-analysis. *Circ Heart Fail* 2013; **6**: 287–292.
6. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, Jafri SM, Krol WF, O'Connor CM, Schulman KA, Teo K, Warren SR, Investigators WT. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the warfarin and antiplatelet therapy in chronic heart failure (WATCH) trial. *Circulation* 2009; **119**: 1616–1624.
7. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA, American Heart Association Stroke Council CoC, Stroke Nursing CoCC, Council on Peripheral Vascular D. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; **45**: 2160–2236.
8. Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, Davies PA, Bodalia PN, Bryden PA, Welton NJ, Hollingworth W, Caldwell DM, Savovic J, Dias S, Salisbury C, Eaton D, Stephens-Boal A, Sofat R. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ* 2017; **359**: j5058.
9. Huang WY, Singer DE, Wu YL, Chiang CE, Weng HH, Lee M, Ovbiagele B. Association of intracranial hemorrhage risk with non-vitamin K antagonist oral anticoagulant use vs aspirin use: a systematic review and meta-analysis. *JAMA Neurol* 2018; **75**: 1511–1518.
10. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015; **15**: 58.
11. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catala-Lopez F, Gotzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; **162**: 777–784.
12. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmeyer MT, Maas H, Voigt JU, Simoons ML, Van de Werf F, Investigators R-A. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013; **369**: 1206–1214.
13. Higgins JPT. Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated 2011]. The Cochrane Collaboration; 2011.
14. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012; **3**: 80–97.
15. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997; **50**: 683–691.
16. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S, Committee AS, Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; **364**: 806–817.
17. Ferreira J, Ezekowitz MD, Connolly SJ, Brueckmann M, Fraessdorf M, Reilly PA, Yusuf S, Wallentin L, Investigators R-L. Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. *Eur J Heart Fail* 2013; **15**: 1053–1061.

18. Magnani G, Giugliano RP, Ruff CT, Murphy SA, Nordio F, Metra M, Moccetti T, Mitrovic V, Shi M, Mercuri M, Antman EM, Braunwald E. Efficacy and safety of edoxaban compared with warfarin in patients with atrial fibrillation and heart failure: insights from ENGAGE AF-TIMI 48. *Eur J Heart Fail* 2016; **18**: 1153–1161.
19. McMurray JJ, Ezekowitz JA, Lewis BS, Gersh BJ, van Diepen S, Amerena J, Bartunek J, Commerford P, Oh BH, Harjola VP, Al-Khatib SM, Hanna M, Alexander JH, Lopes RD, Wojdyla DM, Wallentin L, Granger CB, Committees A, Investigators. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Circ Heart Fail* 2013; **6**: 451–460.
20. van Diepen S, Hellkamp AS, Patel MR, Becker RC, Breithardt G, Hacke W, Halperin JL, Hankey GJ, Nessel CC, Singer DE, Berkowitz SD, Califf RM, Fox KA, Mahaffey KW. Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. *Circ Heart Fail* 2013; **6**: 740–747.
21. Nieuwlaat R, Eurlings LW, Cleland JG, Cobbe SM, Vardas PE, Capucci A, Lopez-Sendon JL, Meeder JG, Pinto YM, Crijns HJ. Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of atrial fibrillation: results of the Euro Heart Survey on atrial fibrillation. *J Am Coll Cardiol* 2009; **53**: 1690–1698.
22. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003; **107**: 2920–2925.
23. Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghiade M, Lam CSP, Mehra MR, Neaton JD, Nessel CC, Spiro TE, van Veldhuisen DJ, Greenberg B, Investigators CH. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med* 2018; **379**: 1332–1342.
24. Bermingham M, Shanahan MK, O'Connell E, Dawkins I, Miwa S, O'Hanlon R, Gilmer J, McDonald K, Ledwidge M. Aspirin use in heart failure: is low-dose therapy associated with mortality and morbidity benefits in a large community population? *Circ Heart Fail* 2014; **7**: 243–250.
25. Gorelick PB, Weisman SM. Risk of hemorrhagic stroke with aspirin use: an update. *Stroke* 2005; **36**: 1801–1807.
26. Daugherty SL, Thompson LE, Kim S, Rao SV, Subherwal S, Tsai TT, Messenger JC, Masoudi FA. Patterns of use and comparative effectiveness of bleeding avoidance strategies in men and women following percutaneous coronary interventions: an observational study from the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2013; **61**: 2070–2078.
27. Mehta RH, Stebbins AS, Lopes RD, Califf RM, Pieper KS, Armstrong PW, Van de Werf F, Hochman JS, White HD, Topol EJ, Alexander JH, Granger CB. Comparison of incidence of bleeding and mortality of men versus women with ST-elevation myocardial infarction treated with fibrinolysis. *Am J Cardiol* 2012; **109**: 320–326.
28. Penttila T, Lehto M, Niiranen J, Mehtala J, Khanfir H, Lassila R, Raatikainen P. Differences in the risk of stroke, bleeding events, and mortality between female and male patients with atrial fibrillation during warfarin therapy. *Eur Heart J Cardiovasc Pharmacother* 2019; **5**: 29–36.
29. Converse MP, Sobhanian M, Taber DJ, Houston BA, Meadows HB, Uber WE. Effect of angiotensin II inhibitors on gastrointestinal bleeding in patients with left ventricular assist devices. *J Am Coll Cardiol* 2019; **73**: 1769–1778.
30. Phillips W, Piller LB, Williamson JD, Whittle J, Jafri SZ, Ford CE, Einhorn PT, Oparil S, Furberg CD, Grimm RH Jr, Alderman MH, Davis BR, Probstfield JL, Group ACR. Risk of hospitalized gastrointestinal bleeding in persons randomized to diuretic, ACE-inhibitor, or calcium-channel blocker in ALLHAT. *J Clin Hypertens (Greenwich)* 2013; **15**: 825–832.