Anticoagulation in Patients with Heart Failure and Sinus Rhythm

Xiao Li, MD, Jingmin Yang, MD and Danyan Xu, MD

Summary

The risk of thromboembolic events is significantly increased among patients with heart failure, even in those without atrial fibrillation. However, it is still unclear whether patients with heart failure and sinus rhythm can benefit from prophylactic anticoagulant therapy.

This was a retrospective review of the pathophysiological mechanisms, epidemiological studies, and clinical trials on anticoagulation in patients with heart failure and sinus rhythm.

Some subgroup analyses of clinical trials found that prophylactic anticoagulant therapy could reduce the incidence of stroke in patients with heart failure and sinus rhythm, and the risk of bleeding was significantly increased. Regarding the incidence of primary endpoint outcomes, all results from clinical trials were negative.

Prophylactic anticoagulation did not improve the clinical outcome in patients with heart failure and sinus rhythm.

Key words: Rivaroxaban, Warfarin, Dabigatran

The 5-year survival rate of heart failure, which represents the end stage of various types of cardiovascular diseases, is similar to that of malignant tumors. The prognosis of heart failure has improved in recent years due to the advancement of medical and non-medical therapy. However, the morbidity of thromboembolism in patients with heart failure has increased substantially, even in patients without atrial fibrillation (AF). According to the existing guidelines, anticoagulation in patients with heart failure and sinus rhythm is not currently generally recommended. This paper reviewed the pathophysiological mechanisms, epidemiology, and current clinical trials involving anticoagulation in patients with heart failure and sinus rhythm.

Although Virchow’s triad (stasis, hypercoagulability, and endothelial injury) is involved in the process of thromboembolism in patients with heart failure (Figure), the precise mechanism underlying thrombosis in heart failure with sinus rhythm remains to be determined.

Systolic dysfunction, cardiomegaly, low cardiac output, and poor contractility in heart failure can lead to flow stasis in cardiac chambers, predisposing patients to intracardiac thrombus formation, subsequent to pulmonary or systemic thromboembolism. In addition, increased venous pressure, edema of the lower limbs, and being bedridden over long periods of time in combination with heart failure result in flow stasis. Furthermore, neurohumoral activation of heart failure in association with an elevated level of norepinephrine, angiotensin II, endothelin, and von Willebrand factor generates platelet activation and high blood viscosity, which are related to hypercoagulability, thereby promoting thromboembolism. In addition, organ tissue hypoperfusion and ischemia followed by oxidative stress can also promote the activation of platelets, leukocytes, and endothelial cells, contributing to the production of pro-inflammatory cytokines in patients with heart failure. Inflammatory cytokines are elevated in patients with heart failure, and certain inflammatory cytokines have been found to be associated with activation of the coagulation system, including tumor necrosis factor and interleukin-6. Moreover, the activation of inflammatory cytokines contributes to decreased levels of activated protein C and endothelial protein C receptor (EPCR), which lead to hypercoagulability.

Circulating microparticles are small membrane vesicles derived from activated or apoptotic cells, which are involved in thrombosis and can express tissue factor activity as well as provide procoagulant surfaces by exposing anionic phospholipids that are required for the assembly of the components of the coagulation cascade.

Heart failure is the most important risk factor for cardioembolic stroke beyond AF. The Survival and Ventricular Enlargement trial revealed an 18% increase in stroke risk for every 5% reduction in left ventricular ejection fraction (LVEF). An analysis of the Controlled Rosuvastatin in Multinational Trial in Heart Failure study and Gruppo Italiano per lo Studio della Sopravvivenza nell’Insuff scienza Cardiac-Heart Failure study demonstrated that among patients without AF, the stroke rate was 11.1/1000 patient-years compared with 16.8/1000 patient-years among patients with HF. The Sudden Cardiac Death in Heart Failure trial showed that among patients without AF...
or atrial flutter, 3.35% of patients reportedly suffered from stroke, peripheral embolism, or pulmonary embolism by 45.5 months of follow-up.\textsuperscript{17) Most of the patients with heart failure in the aforementioned trials had heart failure with reduced ejection fraction (HFrEF) or were patients with heart failure from some small-sample clinical trials. In addition, the heart failure with preserved ejection fraction (HFpEF) revealed that the morbidity of stroke in patients with HFpEF resembled that in patients with HFrEF. In a subgroup analysis of CHARM-Preserved and I-Preserved trials, the authors found there was no difference in performance of the stroke model derived from the HFpEF cohort and the published HFrEF model (c-index 0.71, 95% confidence interval: 0.57-0.84 versus c-index 0.73, 0.59-0.85, respectively) as the predictive variables overlapped.\textsuperscript{18) Similarly, in another study data from ACTIVE A and W trial, Sandhu, \textit{et al}. found that patients with HFpEF exhibited similar risk of embolic events as those with HFrEF (4.3% versus 4.4% per 100 person-years; hazard ration 1.01; 95% confidence interval, 0.78-1.31).\textsuperscript{19) However, additional evidence should be confirmed by large-sample clinical trials.

Venous thromboembolism (VTE) in patients with HF has been less well studied than systemic thromboembolism. A recently published meta-analysis of 71 clinical studies of HF reported that the incidence of VTE over the past 60 years showed that the overall median symptomatic VTE rate was 2.48%. The incidence rate of symptomatic VTE was 3.73% for patients who did not receive thromboprophylaxis and 1.47% for those who did receive thromboprophylaxis. Moreover, the incidence of VTE in patients hospitalized for HF was twofold higher than that in outpatients, and the severity of HF appeared to be an independent risk factor for VTE.\textsuperscript{20-22) A multicenter, randomized, parallel group efficacy and safety study for the prevention of VTE in hospitalized medically ill patients comparing rivaroxaban with enoxaparin reported a VTE rate of 6.2% during a 35-day follow-up of patients with HF. In addition, N-terminal pro-brain natriuretic peptide concentration and D-dimer concentration as predictive factors of VTE were associated with VTE risk. However, considering that VTE screening may be too costly and that numerous VTE patients present with nonsymptomatic VTE, the incidence of VTE in the real world may be higher than reported.

**Methods**

**Literature search:** A computer search of the literature was performed using Medline and EMBASE from inception of these databases to March 2020. We used the disease-related key words anticoagulation, heart failure, sinus rhythm, without AF, warfarin, Non-vitamin K oral anticoagulants, dabigatran, rivaroxaban, edoxaban, and apixaban, together with the additional key words incidence, prevalence, mortality, case fatality, morbidity, surveillance, and epidemiology, to search the titles and abstracts of articles in these databases. We excluded articles published in languages other than English.

**Results**

Anticoagulation has been the standard of care in patients with HF and AF since research on the CHA2DS2-VASc score was published. Nevertheless, the argument for anticoagulation therapy in patients with HF and sinus rhythm has persisted for decades. Several random control clinical trials have attempted to determine the effectiveness and safety of anticoagulation therapy for patients with HF and sinus rhythm during the past 20 years (Ta-
| Trial      | Year | Inclusion criteria | Patients | Follow-up | Treatment | Primary endpoints                                                                 | Results                                                                 |
|------------|------|--------------------|----------|-----------|----------|------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| WASH       | 2004 | HF LVEF ≤ 35%      | 279      | 27 ± 1 months | No ATT versus aspirin (300 mg daily) versus warfarin (INR 2.0-3.0) | Death, nonfatal myocardial infarction, or nonfatal stroke               | Primary endpoints: no ATT 26% versus aspirin 32% versus warfarin 26%, P = NS for all comparisons |
|            |      |                    |          |           |          | HF hospitalizations: no ATT 48% versus aspirin 64% versus warfarin 47%, P = 0.044  for aspirin versus warfarin |
|            |      |                    |          |           |          | Major bleedings: no ATT n = 0 versus aspirin n = 1 versus warfarin n = 4, P = 0.028 for warfarin versus no ATT |
| HELAS      | 2006 | HF NYHA class II-IV LVEF < 35% | 197      | 19-22 months | IHD: aspirin (325 mg daily) versus warfarin (INR 2.0-3.0) DCM: warfarin (INR 2.0-3.0) versus placebo | Nonfatal stroke, peripheral or PE, MI, re-hospitalization, exacerbation of HF, or death from any cause | Primary endpoints: IHD/A 14.9% versus IHD/W 15.7% versus DCM/W 8.9% versus DCM/P 14.8%, P = NS for all comparisons |
|            |      |                    |          |           |          | HF hospitalizations: IHD/A 3.2% versus IHD/W 2.4% versus DCM/W 4.4% versus DCM/P 5.9%, P = NS for all comparisons |
|            |      |                    |          |           |          | Major bleedings: IHD/A 0% versus IHD/W 4.8% versus DCM/W 4.4% versus DCM/P 0%, P = NS for all comparisons |
| WATCH      | 2009 | HF LVEF ≤ 35% Sinus rhythm | 1587     | 21 months | Warfarin (INR 2.5-3.0) versus aspirin (162 mg daily) versus clopidogrel (75 mg daily) | Death, nonfatal MI, or nonfatal stroke                                  | Primary endpoints: Warfarin versus aspirin: HR = 0.98, 95% CI, 0.86-1.12, P = 0.77 |
|            |      |                    |          |           |          | Clopidogrel versus aspirin: HR = 1.08, 95% CI, 0.83-1.40, P = 0.57                  | Warfarin versus clopidogrel: HR = 0.89, 95% CI, 0.68-1.16, P = 0.39 |
|            |      |                    |          |           |          | Major bleedings: Warfarin versus aspirin: 5.2% versus 3.6%, P = 0.21                | Warfarin versus clopidogrel: 2.1% versus 3.6%, P = 0.13 |
|            |      |                    |          |           |          | Warfarin versus aspirin: HR = 0.93, 95% CI, 0.79-1.10, P = 0.40                    | Warfarin versus clopidogrel: HR = 0.52, 95% CI, 0.33-0.82, P = 0.005 |
|            |      |                    |          |           |          | Ischemic stroke: Warfarin versus aspirin: HR = 1.77, 95% CI, 0.32-9.98, P = 0.51   | Intracerebral hemorrhage: Warfarin versus aspirin: HR = 0.94, 95% CI, 0.84-1.15, P = 0.27 |
|            |      |                    |          |           |          | Death from any cause, MI, or stroke                                               | All-cause mortality: Warfarin versus placebo: HR = 0.98, 95% CI, 0.87-1.10, P = NS |
| WARCEF     | 2012 | HF LVEF ≤ 35% Sinus rhythm | 2305     | 3.5 ± 1.8 years | Warfarin (INR 2.0-3.5) versus aspirin (325 mg daily) | Ischemic stroke, intracerebral hemorrhage, or death from any cause.   | Primary endpoints: Warfarin versus aspirin: HR = 0.52, 95% CI, 0.33-0.82, P = 0.005 |
| COMMAND- | 2018 | HF LVEF ≤ 40% Sinus rhythm CAD | 5022     | 21.1 months | Rivaroxaban (2.5 mg twice daily) versus placebo | Death from any cause, MI, or stroke                                      | Primary endpoints: Rivaroxaban versus placebo: HR = 0.94, 95% CI, 0.84-1.15, P = 0.27 |

HF indicates heart failure; LVEF, left ventricular ejection fraction; ATT, antithrombotic therapy; INR, international normalized ratio; NS, no significance; NYHA, New York Heart Association; IHD, ischemic heart disease; DCM, dilated cardiomyopathy; PE, pulmonary embolism; MI, myocardial infarction; IHDA, patients with ischemic heart disease on aspirin; IHD/W, patients with ischemic heart disease on warfarin; DCM/W, patients with dilated cardiomyopathy on warfarin; DCM/P, patients with dilated cardiomyopathy on placebo; HR, hazard ratio; CI, confidence interval; and CAD, coronary artery disease.
ble). However, there has been a lack of evidence to verify this hypothesis to date.

**The Warfarin/Aspirin Study in Heart Failure (WASH) study:** The WASH study published in 2004 was an open-label, randomized, controlled trial that included 279 patients with HF and left ventricular systolic dysfunction. Patients randomly received warfarin (target international normalized ratio of 2.5), aspirin (300 mg once daily), or placebo. The primary outcome was the composite outcome of death, nonfatal myocardial infarction, and nonfatal stroke. During a mean follow-up time of 27 months, there was no significant difference among the three treatments in terms of the primary outcome; however, a significant difference in all-cause hospitalization was observed in the three groups, and the aspirin group showed the greatest risk of events ($P < 0.05$). Regarding safety outcomes, treatment with warfarin and aspirin promoted a high risk of hemorrhage compared with placebo treatment (13%, 17%, and 5%, respectively; $P = 0.033$). Therefore, negative results were found in this study, as they did not find any benefit from anticoagulation therapy in patients with HF and sinus rhythm. Furthermore, the prophylactic use of aspirin could increase the risk of HF deterioration in patients with HF with no indication for antiplatelet therapy. The mechanism by which aspirin exacerbates heart failure is uncertain. One possible mechanism is that aspirin may interfere with the increase in prostaglandin levels that occurs in heart failure that is further enhanced by angiotensin-converting enzyme inhibitors (ACEIs).

Prostaglandins such as prostacyclin and prostaglandin E1 have vasodilator, natriuretic, and antiaggregatory activities, which appear to play compensatory roles in patients with heart failure. It should be noted that despite most of the population in the WASH study being in sinus rhythm, 18 AF patients remained in this study.

**The Heart failure Long-term Antithrombotic Study (HELAS):** HELAS was a multicenter, randomized, double-blind, placebo-controlled trial published in 2006 that enrolled 197 patients with HF and an LVEF < 35%, divided into an ischemic heart disease group and a dilated cardiomyopathy group according to the pathology. Patients in the ischemic heart disease group were randomized to receive either aspirin (325 mg once daily) or warfarin (with a target international normalized ratio of 2.0-3.0), and the dilated cardiomyopathy group was randomized to receive either warfarin or placebo. The primary endpoints were any of nonfatal stroke, peripheral or pulmonary embolism, myocardial infarction, rehospitalization, exacerbation of HF, or death from any cause. During the 2-year follow-up, AF occurred in three patients, all of whom had withdrawn from the study. In the remaining patients, the incidence of the primary endpoints did not differ between the two groups. However, in the subgroup analysis, the rate of LVEF recovery in the warfarin subgroup was significantly higher than that in the placebo subgroup in the dilated cardiomyopathy group. The baseline LVEF values in the warfarin and placebo subgroups were 26.8% ± 2.3% and 27.5% ± 5.5%, respectively, which increased to 32.2% ± 9.4% and 28.7% ± 6.3%, respectively, during a 1-year follow-up ($P < 0.05$). Because this study was performed over 15 years ago and because the standard medicinal therapy in HF was incomplete, the usage rate of ACEIs, angiotensin II receptor blockers (ARBs), and β blockers differed between each group. A total of 62% of patients received ACEIs/ARBs for ischemic heart disease in the aspirin-treated group compared with 51.2% in the warfarin-treated group. The β blockers were administered in 17.4% of patients in the ischemic heart disease group treated with aspirin compared with only 5.5% of patients in the dilated cardiomyopathy treated with placebo group. In addition, an aldosterone receptor antagonist was not mentioned in any of the four groups. Whether the differences in these therapies that have been confirmed could improve prognosis and impact the results of the study remains unknown.

**The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) study:** The WATCH study was a prospective, randomized, open-label clinical trial published in 2009 that represented the first large-sample clinical trial of anticoagulation therapy in patients with HF and sinus rhythm. This study enrolled a total of 1587 patients in sinus rhythm with LVEF of ≤ 35%, randomized to receive either warfarin (with a target international normalized ratio of 2.5 to 3.0) or aspirin (162 mg once daily) or clopidogrel (75 mg once daily). The primary endpoints included the composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke. The mean follow-up duration was 1.9 years, and the incidence of primary endpoints was not significantly different for warfarin compared with aspirin (hazard ratio: 0.98; 95% confidence interval: 0.86-1.12; $P = 0.77$), for clopidogrel compared with aspirin (hazard ratio: 1.08; 95% confidence interval: 0.83-1.40; $P = 0.57$), and for warfarin compared with clopidogrel (hazard ratio: 0.89; 95% confidence interval: 0.68-1.16; $P = 0.39$). Warfarin was associated with fewer nonfatal strokes than aspirin ($P = 0.009$) or clopidogrel ($P = 0.003$). Compared with aspirin, warfarin significantly reduced hospitalizations for worsened HF (22.2% versus 16.5%; $P = 0.019$). Nevertheless, for the safety outcomes, major bleeding events were more frequent in warfarin-treated patients than those in the clopidogrel-treated patients ($P = 0.007$) but not in aspirin-treated patients ($P = 0.22$). There were also more patients with minor bleeding events in the warfarin-treated group than those in the clopidogrel-treated group ($P = 0.025$), and a similar trend was observed in the aspirin-treated group ($P = 0.054$). This study opposed the original hypothesis that warfarin and clopidogrel were superior to aspirin for improving the prognosis of patients with HF and sinus rhythm. Although warfarin was found to reduce the incidence of stroke, it was accompanied by an increase in the incidence of bleeding events, and the net clinical benefit was not significantly improved.

**Warfarin versus Aspirin treatment in the Reduced Cardiac Ejection Fraction (WARCEF) study:** The WARCEF study, which was published in 2012, was the largest study to date to investigate the efficacy and safety of anticoagulant therapy for patients with HF and sinus rhythm. This study included 2305 patients who had a normal sinus rhythm, no contraindication to warfarin therapy, and an LVEF of ≤ 35%. Patients were randomized to receive either warfarin (with a target international normal-
ized ratio of 2.0 to 3.5) or aspirin (325 mg once daily). The primary outcomes consisted of the composite of ischemic stroke, intracerebral hemorrhage, or death from any cause. During a 3.5 ± 1.8-year follow-up, the incidence of the primary outcomes did not significantly differ between the patients treated with aspirin and those treated with warfarin (hazard ratio with warfarin: 0.93; 95% confidence interval: 0.79-1.10; P = 0.40). A time-varying analysis showed a small benefit for warfarin compared with aspirin over time. The hazard ratio decreased by a factor of 0.89 per year (95% confidence interval: 0.80-0.99; P = 0.046) and became borderline significant by year 4 (hazard ratio with warfarin: 0.76; P = 0.04). Warfarin was associated with a significantly reduced incidence of ischemic stroke (hazard ratio with aspirin: 0.52; 95% confidence interval: 0.33-0.82; P = 0.005) and was accompanied by a significantly increased incidence of major hemorrhage events (hazard ratio with aspirin: 1.65; 95% confidence interval: 1.34-2.05; P < 0.001); however, there were no significant differences in the incidence of intracerebral hemorrhage (hazard ratio with aspirin: 2.48; 95% confidence interval: 0.51-17.6; P = 0.45) or intracranial hemorrhage (hazard ratio with aspirin: 0.86; 95% confidence interval: 0.29-2.85; P = 1.00) between the two groups.

Age is not only a risk factor for thrombosis but also a risk factor for bleeding. Hommas, et al. analyzed a subgroup from the WARCEF study, and patients were randomized to a younger group and an older group, where age was dichotomized as < 60 versus ≥ 60 years. The primary outcomes remained the same as those in the WARCEF study, and it was found that younger patients benefited from treatment with warfarin over aspirin regarding the primary outcome (hazard ratio with aspirin: 0.63; 95% confidence interval: 0.48-0.84; P = 0.001); however, in the older patients, the therapies did not differ (hazard ratio with aspirin: 1.09; 95% confidence interval: 0.88-1.35; P = 0.44). The subgroup analysis showed that young patients with HF and sinus rhythm could benefit from anticoagulation treatment, but due to the increased risk of bleeding, older patients with HF and sinus rhythm could not get clinical benefits from anticoagulation therapy.

The time in therapy range (TTR) for warfarin therapy was closely related to the quality of anticoagulation. The mean TTR in the warfarin group from the WARCEF study was 57%. To investigate the relationship between the TTR and clinical outcomes in the WARCEF study population, Hommas, et al. divided the patients into a low TTR subgroup and a high-TTR subgroup from the warfarin group in the WARCEF study, which dichotomized TTR as < 60% versus ≥ 60%. The primary outcomes were the same as those in the WARCEF study, and the median follow-up duration was 3.6 years. It was found that increasing the TTR could significantly reduce the incidence of primary endpoints and mortality and significantly improve the net clinical benefit. Every 10% increase in the TTR could reduce the incidence of primary endpoints by 8% (hazard ratio with a low TTR: 0.92; 95% confidence interval: 0.89-0.96; P < 0.001) and mortality by 7% (hazard ratio with a low TTR: 0.93; 95% confidence interval: 0.89-0.97; P = 0.001). This subgroup analysis suggested that the quality of anticoagulation was closely related to the prognosis in the application of anticoagulants. In addition, the severity of HF could affect the TTR. Lee, et al. further explored the WARCEF study and found that the New York Heart Association and Minnesota Living with HF scores were closely related to the TTR, and an increased severity of HF was associated with a lower TTR.

A Study Assessing the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER-HF) trial: The COMMANDER-HF trial was a double-blind, randomized trial published in 2018, and it was the first clinical trial to investigate the effect of non-vitamin K oral anticoagulants (NOACs) on the anticoagulation of patients with HF and sinus rhythm. The study was based on the findings of the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) and Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) studies that demonstrated the efficacy and safety of low dose rivaroxaban therapy in patients with acute coronary syndrome and stable coronary heart disease. Therefore, it was reasonable to speculate that treatment with a low dose of rivaroxaban could improve the prognosis of patients with HF and coronary heart disease, even in patients without AF. The study included 5022 patients who had chronic HF, an LVEF of ≤ 40%, coronary artery disease, and sinus rhythm, randomized to receive either rivaroxaban (2.5 mg twice daily) or a placebo in addition to standard care following treatment for an episode of worsening heart failure. The primary efficacy outcome was the composite of death from any cause, myocardial infarction, or stroke. The principal safety outcome was the composite of fatal bleeding or bleeding into an acritical space with the potential to cause permanent disability. The median follow-up duration was 21.1 months and neither the primary efficacy outcome (hazard ratio: 0.94; 95% confidence interval: 0.84-1.05; P = 0.27) nor principle safety outcome (hazard ratio: 0.80; 95% confidence interval: 0.43-1.49; P = 0.48) significantly differed between treatment with rivaroxaban or placebo.

Greenberg, et al. performed further research in the form of a post hoc analysis of the COMMANDER-HF trial, with a focus on thromboembolic endpoints, which were defined as myocardial infarction, ischemic stroke, sudden death/unwitnessed death, symptomatic pulmonary embolism, symptomatic deep venous thrombosis, or all of the previous components, except sudden/unwitnessed deaths because not all of these are caused by thromboembolic events. Over a median follow-up of 19.6 months, fewer patients who received rivaroxaban than those who received placebo experienced thromboembolic endpoints, including sudden death/unwitnessed death (hazard ratio: 0.83; 95% confidence interval: 0.72-0.96; P = 0.01). When sudden death/unwitnessed death was excluded, there were no significant differences in the incidence of thromboembolic endpoints between treatment with rivar-
oxaban and placebo (hazard ratio: 0.80; 95% confidence interval: 0.64-0.98; \( P = 0.04 \)). This study concluded that although thromboembolic events are common in patients with HF and sinus rhythm, they may not represent a major cause of death in patients with HF.

**Meta-analysis:** Lee, et al.\textsuperscript{36} reviewed the WASH, HELAS, WATCH, and WARCEF studies and found that although warfarin was associated with a lower risk of any stroke (risk ratio: 0.56; 95% confidence interval: 0.38-0.82; \( P = 0.003 \)) and ischemic stroke (risk ratio: 0.45; 95% confidence interval: 0.24-0.86; \( P = 0.02 \)) compared with aspirin, it had a neutral effect on death (risk ratio: 1.01; 95% confidence interval: 0.89-1.14; \( P = 0.89 \)) and a high risk of major bleeding (risk ratio: 1.95; 95% confidence interval: 1.37-2.76; \( P = 0.0002 \)).

Beggs, et al.\textsuperscript{35} reviewed all five previous clinical trials and found that anticoagulant therapy did not reduce all-cause mortality (risk ratio: 0.99; 95% confidence interval: 0.90-1.08; \( P = 0.74 \)), rehospitalization for HF (risk ratio: 0.97; 95% confidence interval: 0.82-1.13; \( P = 0.68 \)), or nonfatal myocardial infarction (risk ratio: 0.92; 95% confidence interval: 0.75-1.13; \( P = 0.44 \)). Moreover, anticoagulation treatment reduced the rate of nonfatal stroke (risk ratio: 0.63; 95% confidence interval: 0.49-0.81; \( P = 0.001 \)), but this result was offset by an increase in the incidence of major bleeding (risk ratio: 1.88; 95% confidence interval: 1.49-2.38; \( P = 0.001 \)). The researchers believe that thromboembolic events did not play a major role in HFrEF.

**Discussion**

Although the hypothesis regarding the efficacy of anticoagulation in patients with HF and sinus rhythm has been well established, there is no strong evidence to support this hypothesis. However, a review of several previous clinical trials revealed certain characteristics.

First, coronary artery disease represented the majority of heart failure pathology in the included population from all five clinical trials. In addition, the COMMANDER-HF trial investigated the effect of patients with HF and coronary artery disease, and the proportion of patients with myocardial infarction and ischemic cardiomyopathy in the WARCEF study was 48.24% and 42.99%, respectively, whereas the proportion of patients with ischemic heart disease in the WATCH study was 73%. Antiplatelet therapy must be involved in patients with ischemic heart disease, especially in those with acute coronary syndrome, for whom dual antiplatelet therapy is required. Although most previous trials compared warfarin with aspirin, it is unclear whether the combination of antiplatelet and anticoagulant therapy has any effect on outcomes; however, there continues to be a lack of clinical research on large samples of diseases that do not require routine application of antiplatelet drugs (e.g., dilated cardiomyopathy and hypertensive heart disease), which is also a direction of future exploration.

Second, the definition of endpoints impacted the results of the trials. Almost all previous clinical trials defined endpoints as a composite of myocardial infarction, stroke, or death from any cause. However, according to epidemiological and pathophysiological mechanisms, VTE appears to be more common in heart failure, especially in patients with heart failure who are prone to repeated hospitalizations, which increases the risk of VTE. The Padua score is the VTE risk score for medical inpatients.\textsuperscript{37} Heart failure, immobilization, infection, and an age > 70 years old are all included as the VTE risk factors in this score. The incidence of VTE in patients with a Padua score \( \geq 4 \) without preventive anticoagulation measures is 11%. In addition, the post hoc analysis of the COMMANDER-HF trial found that when including VTE in the primary endpoints, anticoagulant therapy could significantly reduce the incidence of endpoint events. Although no epidemiological data on intracardiac thrombosis exist for heart failure, intracardiac thrombosis is relatively common in clinical practice and is frequently reported in case reports, especially in patients with significantly decreased LVEF.\textsuperscript{38-40} Intracardiac thrombus may exist in the left cardiac system, right cardiac system, or both. Although a thrombus located in the left cardiac system is prone to causing systemic embolism, a thrombus located in the right cardiac system is prone to inducing pulmonary embolism. Therefore, based on the perspective of the pathophysiological mechanism and epidemiology, it appears reasonable to include VTE or intracardial thrombosis in the endpoint events. Indeed, some researchers believe that although HF can increase the risk of VTE, it does not affect the patient survival rate.\textsuperscript{41} Thus, additional evidence is required to explain these problems.

HF comprises a group of clinical syndromes, rather than a single disease, etiology, clinical manifestation, treatment method, or prognosis, that differs among patients with HF. Similar to the CHA\textsubscript{2}-VASc score for nonvalvular AF,\textsuperscript{42} the risk stratification of thromboembolic events in patients with HF is also required, rather than investigating all patients with heart failure in general. In addition, NOACs have been available for years and have previously been shown to be effective in patients with HF and AF;\textsuperscript{43} however, in patients with sinus heart failure, only rivaroxaban has been completed in the research performed to date (COMMANDER-HF trial). The evidence of low dose (2.5 mg twice daily) rivaroxaban applied in the therapy group is based on the data from the ATLAS ACS 2-TIMI 51 and COMPASS studies. Nevertheless, whether treatment with a low dose of rivaroxaban exerts an anticoagulant effect is unknown, and additional studies regarding different doses of various types of NOACs are required in the future. In summary, there is currently no evidence based on clinical trials to confirm the efficacy of anticoagulation in patients with HF and sinus rhythm; however, it is necessary to evaluate the risk of VTE in hospitalized patients, and short-term in-hospital anticoagulation therapy could be performed in patients with a high risk of VTE.

**Conclusion**

In patients with heart failure and sinus rhythm, prophylactic anticoagulation did not improve clinical outcomes.
Disclosures

Conflicts of interest: None.

Authors' contributions: Danyan Xu conceived of the scope of the review and helped revise the manuscript. Xiao Li was involved in the accumulation of the relevant references and drafted the manuscript. Jingmin Yang helped revise the manuscript. All authors read and approved the final manuscript.

References

1. Maggioni AP, Dahitroum U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013; 15: 808-17.

2. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995; 273: 1450-6.

3. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000; 283: 1295-302.

4. Pitt B, Zannad F, Remme WI, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341: 709-17.

5. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371: 993-1004.

6. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. JAMA 2015; 314: 1030-8.

7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)/Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-208.

8. Sharouzi E, Bradshaw A, Andreotti F, Tuddenham E, Oakley CM, Cleland JG. Relationship between hemostatic abnormalities and neuroendocrine activity in heart failure. Am Heart J 1994; 127: 607-12.

9. Aukrust P, Solheim OH, Konstam MA. Antiplatelet agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial. J Am Coll Cardiol 1998; 31: 419-25.

10. Chin BS, Conway DS, Chung NA, Blann AD, Gibbs CR, Lip GY. Interleukin-6, tissue factor and von Willebrand factor in acute decompensated heart failure: Relationship to treatment and prognosis. Blood Coagul Fibrinolysis 2003; 14: 515-21.

11. Mosnier LO, Zlokovic BV, Griffin JJ. The cytoprotective protein C pathway. Blood 2007; 109: 3161-72.

12. Loubele ST, Spek CA, Leenders P, et al. Activated protein C protects against myocardial ischemia-reperfusion injury via inhibition of apoptosis and inflammation. Arterioscler Thromb Vasc Biol 2009; 29: 1087-92.

13. Nozaki T, Sugiyama S, Sugamura K, et al. Prognostic value of endothelial microparticles in patients with heart failure. Eur J Heart Fail 2010; 12: 1223-8.

14. Sinning JM, Losch J, Valenta K, Böhm M, Nickenig G, Werner N. Circulating CD31+/annexin V+ microparticles correlate with cardiovascular outcomes. Eur Heart J 2011; 32: 2034-41.

15. Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. N Engl J Med 1997; 336: 251-7.

16. Abdul-Rahim AH, Perez AC, Fulton RL, et al. Risk of Stroke in Chronic Heart Failure Patients without atrial fibrillation: analysis of the Controlled rosuvastatin in Multinational Trial Heart Failure (Corona) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials. Circulation 2015; 131: 1486-94; discussion 94.

17. Freudenberger RS, Hellkamp AS, Halperin JL, et al. Risk of thromboembolism in heart failure: an analysis from the sudden cardiac death in Heart Failure Trial (SCD-HeFT). Circulation 2007; 115: 2637-41.

18. Abdul-Rahim AH, Perez AC, MacIsaac RL, et al. Risk of stroke in chronic heart failure patients with preserved ejection fraction, but without atrial fibrillation: analysis of the CHARM-Preserved and I-Preserve trials. Eur Heart J 2017; 38: 742-50.

19. Sandhu RK, Hohnloser SH, Pfeffer MA, et al. Relationship between degree of left ventricular dysfunction, symptom status, and risk of embolic events in patients with atrial fibrillation and heart failure. Stroke 2015; 46: 667-72.

20. Tang L, Wu YY, Lip GY, Yin P, Hu Y. Heart failure and risk of venous thromboembolism: a systematic review and meta-analysis. Lancet Haematol 2016; 3: e30-44.

21. Megabaa A, Spiro TE, Bührer HR, et al. Predicting the risk of venous thromboembolism in patients hospitalized with heart failure. Circulation 2014; 130: 410-8.

22. Melgaard L, Nielsen PB, Overvad TF, Skjøth F, Lip GYH, Larsen TB. Sex differences in risk of incident venous thromboembolism in heart failure patients. Clin Res Cardiol 2019; 108: 1-9.

23. Cleland JG, Findlay I, Jafari S, et al. The warfarin/aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J 2004; 148: 157-64.

24. Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Antiplatelet agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial. J Am Coll Cardiol 1998; 31: 419-25.

25. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK, HELAS investigators. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. Eur J Heart Fail 2006; 8: 428-32.

26. Massie BM, Collins JF, Ammon SE, et al. 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: 1616-24.

27. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012; 366: 1859-69.

28. Homma S, Thompson JL, Sanford AR, et al. Benefit of warfarin compared with aspirin in patients with heart failure in sinus rhythm: a subgroup analysis of WARCEF, a randomized controlled trial. Circ Heart Fail 2013; 6: 988-97.

29. Homma S, Thompson JL, Qian M, et al. Quality of anticoagulation control in preventing adverse events in patients with heart failure in sinus rhythm: warfarin versus aspirin in Reduced Cardiac Ejection Fraction trial substudy. Circ Heart Fail 2015; 8: 504-9.

30. Lee TC, Qian M, Lip GYH, et al. Heart failure severity and quality of warfarin anticoagulation control (from the WARCEF Trial). Am J Cardiol 2018; 122: 821-7.

31. Zannad F, Anker SD, Byta WM, et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N Engl J Med 2018; 379: 1332-42.

32. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012; 366: 9-19.

33. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with
or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377: 1319-30.
34. Greenberg B, Neaton JD, Anker SD, et al. Association of rivaroxaban with thromboembolic events in patients with heart failure, coronary disease, and sinus rhythm: A post hoc analysis of the COMMANDER HF Trial. JAMA Cardiol 2019; 4: 515-23.
35. 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: 287-92.
36. Beggs SAS, Rørth R, Gardner RS, McMurray JJV. Anticoagulation therapy in heart failure and sinus rhythm: a systematic review and meta-analysis. Heart 2019; 105: 1325-34.
37. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: The Padua Prediction Score. J Thromb Haemost 2010; 8: 2450-7.
38. Ballo P, Fibbi V, Granelli M, et al. Giant isolated intracardiac thrombus presenting as acute heart failure secondary to right ventricular outflow tract obstruction in a patient with renal carcinoma. Oxf Med Case Rep 2018; 2018: omy019.
39. Akutsu Y, Kawamura M, Tanisawa H, et al. Intracardiac thrombosis and heart failure in a patient with hepatocellular carcinoma and cardiac amyloidosis and an implanted cardiac resynchronization therapy device. Am J Case Rep 2019; 20: 933-6.
40. Bhat AG, Golchin A, Pasupula DK, Hernandez-Montfort JA. Right sided intracardiac thrombosis during veno-arterial extracorporeal membrane oxygenation: A case report and literature review. Case Rep Crit Care 2019; 2019: 8594681.
41. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016; 18: 1609-78.
42. Ferreira J, Ezekowitz MD, Connolly SJ, et al. 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: 1053-61.
43. van Diepen S, Hellkamp AS, Patel MR, et al. Efficacy and safety of Rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. Circ Heart Fail 2013; 6: 740-7.
44. McMurray JJ, Ezekowitz JA, Lewis BS, et al. 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: 451-60.
45. Magnani G, Giugliano RP, Ruff CT, et al. 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: 1153-61.