Stroke and Thromboembolism in Patients with Heart Failure and Sinus Rhythm: A Matter of Risk Stratification?

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Abstract

Patients with heart failure (HF) in sinus rhythm (SR) experience an increased incidence of thromboembolic events including stroke. Among patients with HF, high-quality evidence supports the use of oral anticoagulation when atrial fibrillation is present, but the benefit of anticoagulation in SR in the absence of other known indications for anticoagulation is unclear. In four randomized controlled trials (RCTs), warfarin did not improve a composite of clinical outcomes compared with aspirin or placebo in patients with HF with reduced ejection fraction (HFrEF) and SR. A recent RCT assessed the efficacy of the direct oral anticoagulant rivaroxaban versus placebo in patients with HFrEF (including mildly reduced ejection fraction), SR, and coronary artery disease. While rivaroxaban had a neutral effect on the primary composite outcome of myocardial infarction, stroke, or all-cause mortality, exploratory analyses revealed a significant reduction in strokes. It is thus possible that a subgroup of patients with HFrEF who are at high risk of stroke may benefit from anticoagulation. The challenge is to adequately identify this subgroup and to balance the potential benefit of anti-coagulation with the risk of major bleeding. There is also an unmet need for evidence around anticoagulation in HF with preserved ejection fraction and SR. This review explores the current evidence around anticoagulation in patients with HF and SR, identifies challenges regarding outcome definitions and patient selection, and offers suggestions for future research.

Keywords
► anticoagulants
► heart failure
► ischemic stroke
► sinus rhythm
► thromboembolism

Introduction

Patients with heart failure (HF) are at an increased risk of morbidity and mortality. Advances in medical management including guideline-directed medical therapy and implantable cardioverter-defibrillators have improved prognosis. Nevertheless, stroke continues to be a devastating complication in patients with HF.[1,2] Among patients with HF, it is hypothesized that the combination of endothelial dysfunction, comorbid conditions increasing the hypercoagulability of blood, and stasis of flow from atrial and ventricular dysfunction produces a prothrombotic state and subsequently increases the risk of intracardiac thrombi and stroke[1,3] (►Fig. 1). The estimated incidence of stroke among patients with HF in sinus rhythm (SR) is 1.1 to 1.6 per 100 patient-years.[4,5] Ischemic stroke is the presenting event in 82% of patients, with the majority of these first stroke events being fatal or causing significant disability.[5] This represents a 1.5- to 2.1-fold risk of ischemic stroke relative to patients in SR without HF.[6] However, current guidelines recommend anticoagulation in HF only in those patients with atrial fibrillation (AF) or another indication for anticoagulation, such as a prior history of thromboembolism or a prosthetic valve, with no specific recommendations based on ejection fraction. The purpose of this review is to summarize the literature around recommendations for anticoagulation in patients with HF and SR, and to identify challenges and opportunities regarding outcome definitions and patient selection in light of emerging evidence.

Clinical Trial Evidence: Anticoagulation in Heart Failure and Sinus Rhythm

The benefit of anticoagulation in reducing the risk of stroke has been well established in patients with HF and concomitant AF, but evidence to support the use of anticoagulation in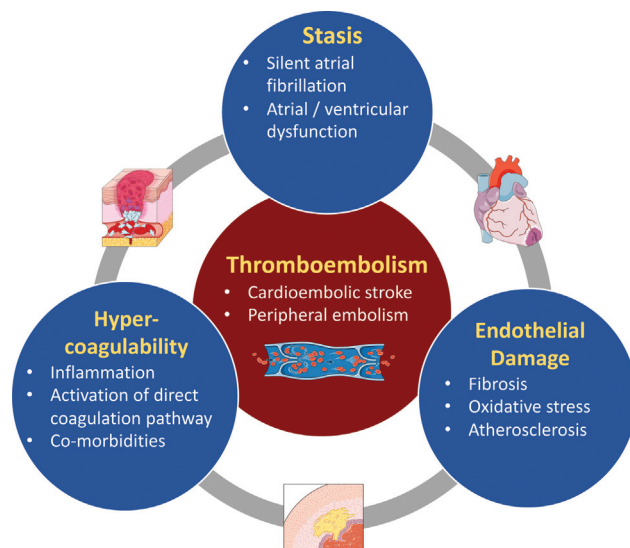 patients with HF and SR is lacking. AF is a well-defined independent risk factor for ischemic stroke. Earlier cohort studies with 30 years of follow-up in the general population revealed that 12% of strokes were associated with AF.[7] More recent evidence has suggested that AF is present in 51% of patients with HF and stroke,[7] and that patients with both comorbidities have a stroke incidence rate of 1.6% per year.[4] These findings suggest that AF may be a strong predictor of future stroke risk in patients with HF. AF is common in HF, estimated at 50% and even more common in patients with HF with preserved ejection fraction (HFpEF) who make up approximately half of the population of patients diagnosed with HF.[8] Both conditions are associated with similar risk factors including older age, diastolic dysfunction, and age-related comorbidities including hypertension, obesity, and sleep apnea.[9] Relative to HF with reduced ejection fraction (HFrEF), HFpEF may be associated with greater inflammation and oxidative stress and a higher risk of (AF-related) ischemic stroke.[10] Indeed, in an age- and sex- matched registry study of Korean patients with AF, the annual incidence of stroke and systemic embolism in patients with HFpEF and HFrEF was 2.8 and 1.1%, respectively.[11] Notably, the severity of HF symptoms may be associated with AF prevalence, with one study reporting less than 5% AF in patients with mild HF (NHYA [New York Heart Association] class I) and 50% in patients with severe HF (NHYA class IV).[8]

There have been five randomized controlled trials in over 9,000 patients with HFrEF and SR to assess the efficacy and safety of anticoagulant therapies (warfarin vs. placebo or antiplatelet agents; rivaroxaban vs. placebo)[12–14] (►Fig. 2 and ►Table 1). Methodological limitations in and knowledge gaps unaddressed by these trials preclude definitive conclusions.

The Warfarin/Aspirin Study in Heart Failure (WASH) open-label trial randomized 279 patients with HF, SR, and left ventricular ejection fraction (LVEF) ≤35% to warfarin, aspirin, or no antithrombotic therapy. After a mean follow-up of 27 months, neither warfarin nor aspirin improved the primary composite outcome of death, nonfatal myocardial infarction (MI), or nonfatal stroke relative to no antithrombotic therapy[12–14] (►Table 1). The Heart Failure Long-Term Antithrombotic Study (HELAS) enrolled 197 patients with HF, LVEF <35%, and either ischemic heart disease (history of MI) or dilated cardiomyopathy. The trial assessed the efficacy of warfarin versus aspirin in the ischemic heart disease cohort, and warfarin versus placebo in the dilated cardiomyopathy cohort. There were no significant differences between groups in the primary composite outcome of nonfatal stroke, peripheral or pulmonary embolism, recurrent MI, rehospitalization, exacerbation of HF, or all-cause death[12–14] (►Table 1). Importantly, both trials were small and had inadequate statistical power to detect between-group differences. Hence, inferences from these trials cannot be reliably made.

The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) double-blinded trial enrolled 1,587 patients with HF (NYHA class II–IV, LVEF ≤35%) and SR who had been treated with a diuretic and angiotensin-converting enzyme inhibitor for 60 days. The trial found no

Fig. 1 Thrombosis formation and specific heart failure-related components that pertain to Virchow's triad.

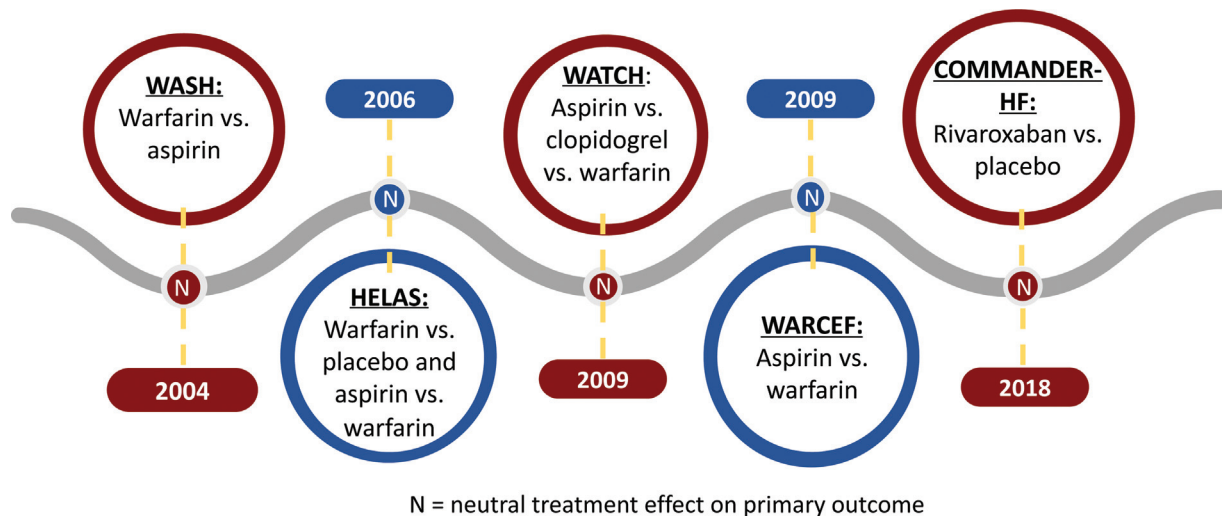N = neutral treatment effect on primary outcome

Fig. 2 Timeline of landmark randomized clinical trials assessing anticoagulation in patients with heart failure in sinus rhythm.

significant treatment benefit of warfarin versus aspirin and warfarin versus clopidogrel on the primary composite outcome of time to first death, nonfatal MI, or nonfatal stroke after a median follow-up of 21 months.[12–14] However, warfarin was associated with fewer nonfatal strokes compared with aspirin or clopidogrel (►**Table 1**). This finding was consistent with the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial that randomized 2,305 patients with chronic HF (NHYA class I–IV, LVEF ≤35%) and SR to warfarin versus aspirin. After a mean follow-up of 42 months, warfarin did not improve the primary composite outcome of time to first ischemic stroke, intracerebral hemorrhage, or death from any cause[12–14] (►**Table 1**). While warfarin reduced the rate of ischemic stroke relative to aspirin, this clinical benefit was associated with a twofold increased risk of major bleeding.

With the arrival of the direct oral anticoagulants, COMMANDER-HF sought to re-evaluate the possible benefits of anticoagulation therapy in HF. This event-driven trial randomized 5,022 patients with HF, LVEF ≤45%, and coronary artery disease to low-dose rivaroxaban versus placebo. After a median follow-up of 21 months, rivaroxaban did not significantly reduce the primary composite outcome of all-cause mortality, MI, or stroke[15] (►**Table 1**). However, in exploratory analyses, rivaroxaban was associated with a reduction in thromboembolism, when sudden/unwitnessed deaths were excluded from the thromboembolic composite outcome (MI, ischemic stroke, symptomatic pulmonary embolism, or systematic pulmonary embolism).[16] Further exploratory analysis of COMMANDER-HF suggested that low-dose rivaroxaban may reduce time to first event of any stroke or transient ischemic attack by 32%.[5] There was no statistically significant difference in fatal bleeding or bleeding into a critical space with the possibility for permanent disability.[5]

Whereas some of the trials are not adequately designed to reliably make inferences, the breadth of evidence suggests that anticoagulation may prevent thromboembolic events among patients with HFrEF and SR, but this benefit may be offset by bleeding. Two recent meta-analyses of WASH,

HELAS, WATCH, WARCEF, and COMMANDER-HF showed that anticoagulation consistently reduced stroke risk.[12,13] However, there was a significant increase in bleeding, a consistent finding across three of the largest trials regardless of the type of oral anticoagulant. Furthermore, the inclusion of all-cause death in the primary composite outcomes may attenuate the estimated benefit because stroke or bleeding events in this population represent a small proportion of deaths (2.5 and 0.4%, respectively) relative to other causes—such as pump failure or arrhythmias—that are not responsive to anticoagulation.[15] Future trials will need to consider the inclusion of cardiovascular death and all-cause death as secondary outcomes. Finally, the effect of anticoagulation in HFpEF and SR remains to be investigated.

Can Risk Stratification Identify Patients Who May Benefit from Anticoagulation?

Stroke and Bleeding: Clinical Risk Prediction

Risk stratification may identify a subset of patients with HF and SR that could benefit from anticoagulation. The challenge is to ensure that the thromboembolic risk outweighs the bleeding risk to warrant benefit from antithrombotic therapy (►**Fig. 3**). Risk factors associated with an increased risk of thromboembolism in patients with HF and SR include: older age, a history of stroke, diabetes, a higher body mass index, worsening NHYA class (III/IV), N-terminal pro B-type natriuretic peptide (NT-proBNP), and cardiomegaly.[4,17] In patients with HF in SR (NHYA class II–IV, LVEF ≤40%), a previous history of stroke, in particular, is a strong predictor for recurrent stroke (hazard ratio: 1.81, 95% confidence interval: 1.19–3.74, $p < 0.01$).[4] Following an ischemic stroke, older age (≥75 years), HF and high levels of NT-proBNP (>400 pg/mL), atrial tachyarrhythmias, and left atrial enlargement are associated with subsequent detection of AF.[18] Type of stroke (arterio-arterial embolism, cryptogenic or embolic stroke of undetermined source, and cardiac sources of stroke) is also associated with subsequent AF detection.[18] Together, these predictors may be helpful for determining

Table 1 Clinical trials evaluating outcomes of anticoagulation in patients with HF in SR

RCT (N of patients)	Study design	Population	Mean follow-up (mo)	Comparison group	Primary composite endpoint	Efficacy (results)	Safety outcome: major bleeding	Sex-based differences
WASH (2004) (n = 279)	Open label, multicenter Recruitment: 1994–1998	Clinical diagnosis of HF requiring diuretics and LVEF ≤35% Median age of 62 years and 74% male	27	ASA 300 mg versus warfarin (target INR: 2.0–3.0) versus no ATT	Death, nonfatal MI, nonfatal stroke	Aspirin versus no ATT: HR: 1.16 (95% CI: 0.74–1.85) Warfarin versus no ATT: HR: 0.88 (95% CI: 0.54–1.43) Aspirin versus warfarin: HR: 1.21 (95% CI: 0.70–2.09) No significant difference in primary composite outcome.	Warfarin 4%, aspirin 1% No ATT 0%	No analyses done
HELAS (2006) (n = 197)	Placebo-controlled, double-blinded, multicenter Recruitment: 1998–1999	Symptomatic HF and EF <35% IHD (59%); previous MI or coronary arteriography, median age of 61, and 89% male DCM (41%): median age of 55 and 77% male	IHD: 19 DCM: 20	DCM: warfarin (target INR 2.0–3.0) versus placebo IHD: ASA 325 mg versus warfarin (target INR: 2.0–3.0)	Nonfatal stroke, pulmonary embolism, MI re-infarction, HF hospitalization/exacerbation, or death from any cause	Endpoint event occurrence per 100 patient-years: IHD–ASA 14.9% versus IHD-warfarin 15.7% DCM–warfarin 8.9% versus DCM–placebo 14.8% No significant difference in primary composite outcome.	IDH: warfarin 4.8% and ASA 0% DCM: warfarin 4.4% and placebo 0%	No analyses done
WATCH (2009) (n = 1,587)	Open-label (warfarin) double-dummy (ASA and clopidogrel), double blinded, multicenter Recruitment: 1999–2002	Symptomatic HF, LVEF ≤35%, treated with diuretic and ACE for 60 days Median age of 63 and 85% male	21	Warfarin (target INR of 2.5–3.0) versus ASA 162 mg or clopidogrel 75 mg	All cause-mortality, nonfatal MI, and nonfatal stroke	Warfarin versus clopidogrel: HR: 0.89 (95% CI: 0.83–1.4) Warfarin versus aspirin: HR: 0.98 (95% CI: 0.86–1.12) Clopidogrel versus aspirin: HR: 0.89 (95% CI: 0.69–1.16) No significant difference in the primary composite outcome.	Warfarin 5.2% ASA 3.6% Clopidogrel 2.1%	Similar results between sex groups, with two nonfatal strokes (0.9%) in the female cohort
WARCEF (2012) (n = 2,305)	Double-blind, double-dummy, multicenter Recruitment: 2002–2010	HF with LVEF ≤35% Median age of 61 and 80% male	42	Warfarin (target INR of 2.5–3.0) versus ASA 325 mg	Ischemic stroke, intracerebral hemorrhage, or death from any cause	Warfarin vs. ASA: HR: 0.93 (95% CI: 0.79–1.10) No significant difference in the primary composite outcome. Reduction in ischemic strokes seen with warfarin versus aspirin (HR: 0.52; 95% CI: 0.33–0.82)	Warfarin 1.78%/patient-year ASA 0.87%/patient-year	No analyses done
COMMANDER-HF (2018) (n = 5,022)	Double-blinded, placebo-controlled, multicenter Recruitment: 2013–2017	LVEF ≤ 40%, CAD, and recent decompensated HF Median age of 66 and 77% male	Event-driven	Rivaroxaban 2.5 mg versus placebo	Death from any cause, MI, or stroke	Rivaroxaban versus placebo: HR: 0.94 (95% CI: 0.84–1.05) No significant difference in primary composite outcome. Neurological Endpoint of Rivaroxaban versus placebo: HR: 0.68 (95% CI: 0.49–0.94, p = 0.002) Posthoc analysis examined primary neurological endpoint of all-cause stroke or TIA, 32% decrease with rivaroxaban.	Rivaroxaban versus placebo; HR: 0.80 (95% CI: 0.43–1.49, p = 0.48)	Males: rivaroxaban versus placebo, HR: 0.92 (95% CI: 0.81–1.04) Females: rivaroxaban versus placebo, HR: 1.05 (95% CI: 0.83–1.33)

Abbreviations: ASA, aspirin; CAD, coronary artery disease; CI, confidence interval; DCM, dilated cardiomyopathy; HELAS, Heart Failure Long-Term Antithrombotic Study; HR, hazard ratio; HF, heart failure; IHD, ischemic heart disease; INR, international normalized ratio; LVEF, left ventricular ejection fracture; MI, myocardial infarction; SR, sinus rhythm; TIA, transient ischemic attack; WASH, The Warfarin/Aspirin Study in Heart Failure; WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart Failure; WARCEF, Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction.
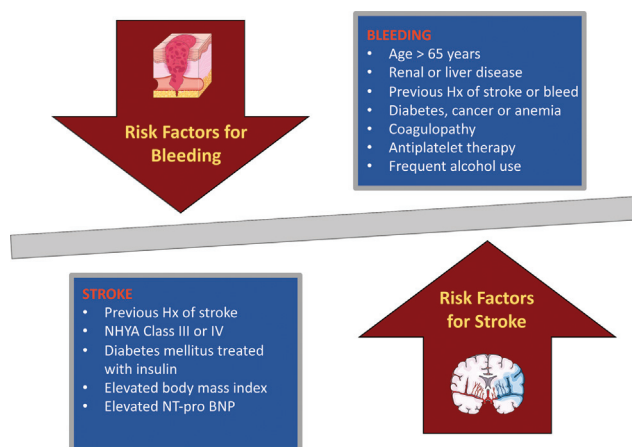
Fig. 3 Framework for balancing the risk factors for bleeding and for stroke in patients with heart failure in sinus rhythm.

which patients are at high risk for developing AF. A sub-analysis of the COMMANDER-HF trial also suggested that including venous thromboembolism in the thromboembolic endpoints could better identify the subset of patients with HF and SR who may benefit from antithrombotic therapy.[16]

The CHA$_2$DS$_2$-VASc score (congestive HF, hypertension, age ≥75 years, diabetes mellitus, prior stroke or thromboembolism, vascular disease, age 65 to 75 years, and female sex)—used to stratify the risk of stroke in patients with AF[19,20]—can predict thromboembolic events (ischemic stroke, transient ischemic attack, and peripheral arterial embolism) similarly well in patients in SR,[21–23] as it reflects the abovementioned risk factors for thromboembolism in patients with HF and SR. Patients with AF and with two or more CHA$_2$DS$_2$-VASc risk factors have an almost threefold increased risk of stroke compared with those without any risk factors.[24] A prospective cohort study which examined the predictive value of the CHA$_2$DS$_2$-VASc score in patients with HF in SR found a correlation between increasing scores and risk of ischemic stroke irrespective whether AF was present or not.[20] Higher CHA$_2$DS$_2$-VASc scores (≥4) in patients with HF were associated with a greater absolute risk of thromboembolism, irrespective of whether AF was present or not. The score demonstrated moderate discrimination for ischemic stroke but had a high negative predictive value for ischemic stroke and thromboembolism (92%) at 1-year follow-up for patients with HF and without AF.[20] The WARCEF trial also examined the accuracy of the CHA$_2$DS$_2$-VASc in patients with HF in SR and found that it predicted adverse outcomes with moderate accuracy.[25] Despite modest predictive accuracy, these findings suggest that the CHA$_2$DS$_2$-VASc score could have clinical utility in detecting a subgroup of patients with HF who are at low risk as well as those at high risk of AF.

When determining which patients with AF would benefit from anticoagulation, an important consideration to balance continues to be the bleeding risk. A validated score used to identify patients at high bleeding risk is the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, age >65 years, and concomitant use of drugs/alcohol), which in conjunction with the CHA$_2$DS$_2$-VASc score can be helpful for clinical decision making when deciding whether to start anticoagulation therapy.[26] However, there is evidence to suggest that increasing CHA$_2$DS$_2$-VASc scores correlate with an increased risk of bleeding, which is more than likely related to the overlap of shared risk factors for bleeding and stroke which are included in both risk scores.[27] Predictors such as older age and previous stroke are associated with both an increased risk of bleeding and ischemic stroke. A recent study that looked at a cohort of over 4,000 patients with AF compared the predictive accuracy of the HAS-BLED score relative to the CHA$_2$DS$_2$-VASc score and revealed that in patients naïve to anticoagulation, the two scores had similar predictive values for major bleeding.[27] In higher risk patients, the HAS-BLED score was found to have a slightly higher *c-statistic* compared with the CHA$_2$DS$_2$-VASc, but was still able to identify patients at high risk of bleeding. In patients with HF and SR, the CHA$_2$DS$_2$-VASc score may therefore be useful in not only stratifying stroke risk but also bleeding risk.[27] However, more evidence is needed to estimate the predictive accuracy and clinical utility of the CHA$_2$DS$_2$-VASc in a cohort that is specific to patients with HF in SR.

Biomarkers may also have a role in identifying patients who may benefit from antithrombotic therapy; for example, D-dimer levels which may have a high predictive value for stroke risk. In the COMMANDER-HF trial, higher rates of stroke of any cause and ischemic stroke were associated with higher plasma D-dimer concentrations at baseline.[22,28] More research regarding the mechanisms behind elevated D-dimer levels in patients with HF, their relevance, and whether screening for D-dimer levels can predict patients at risk of increased stroke is required.

Future studies could also explore the prognostic value of echocardiographic indicators including left ventricular (LV) wall hypertrophy, restrictive LV filling, and reduced global longitudinal strain (a measure of tissue deformation), which have all been associated with higher incidence of thromboembolic stroke in patients with HF.[21,22] These may be indicators of stroke risk but may also be on the causal pathway (►Table 2). The elevation in LV filling pressure is associated with left atrial remodeling and myopathy, which may be a risk factor for atrial dysrhythmias and thrombosis.[29]

Stroke: Rhythm and Risk Prediction

Remote monitoring with intracardiac and wearable devices can detect atrial tachyarrhythmias and AF, both risk factors for stroke.[23] The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) assessed the burden of subclinical AF (incidence of stroke or thromboembolic events) in patients with intracardiac devices. While only 14% of patients in ASSERT had HF, the trial demonstrated that more than one-third of patients with implantable devices had subclinical atrial tachyarrhythmias (atrial rate >190 bpm for longer than 6 minutes), associated with a

Table 2 Summary of knowledge gaps and areas for future research

Important knowledge gaps	Areas of potential advancement
Detecting a subgroup of patients with HF and SR who may benefit from anticoagulation	A time-dependent anticoagulation approach where patients with HF and transient AF are randomized to anticoagulation versus placebo following the arrhythmia.
Determining clinical benefit of anticoagulation in patients with HF in SR	Selecting endpoints in clinical trials that are sensitive to antithrombotic therapy such as thromboembolic events.
Identifying risk of stroke in patients with HF in SR	Integrating clinical variables, biomarkers, and echocardiographic indicators.

Abbreviations: AF, atrial fibrillation; HF, heart failure; SR, sinus rhythm.

5.6-fold increased risk of AF and a 2.5-fold adjusted risk of stroke or systemic embolism.[30] During the 3 months following device implantation, episodes of AF longer than 6 minutes in duration were associated with a 2.5-fold increase in subsequent stroke. While these findings are not specific to HF, they add insight into factors that may be useful to risk stratify patients with HF.

A recent case-crossover study of 891 patients with ischemic stroke and intracardiac devices explored the temporal association between incidence of AF and risk of ischemic stroke. Heart rhythms 30 days prestroke (cases) were compared with those 91 to 120 days prestroke (controls)[31]; 52 patients experienced AF episodes of 5.5 hours or more in the case period of 30 days in comparison to 14 patients in the control period—reflecting a 3.71-fold increased risk of stroke in weeks following multi-hour AF episodes.[31] The risk of stroke was highest within the first 5 days after an AF episode.[31] While this cohort was not specific to patients with HF and most patients did not meet the threshold of AF burden, these results suggest that remote monitoring for these variables could assist in risk stratification of patients (►**Fig. 4**).

Among patients with HF, remote monitoring has been shown to identify patients at high risk for stroke.[32,33] Exploratory analysis of the remote management of HF using implantable electronic devices (REM-HF) trial of 1,650 patients with chronic HF revealed that 4.6% of patients had subclinical AF.

The incidence of ischemic stroke was highest in this subgroup, and AF was associated with increased cardiovascular hospitalization.[32] Mobile health and wearable technologies can expand remote monitoring to patients with HF who do not have intracardiac devices and have the potential to replace remote monitoring, although they will first require validation.[34] The detection of subclinical atrial tachyarrhythmias and AF could identify a population of patients with HF at high risk of stroke who could be recruited into clinical trials of anticoagulation. Machine learning algorithms can also use electrocardiogram (ECG) patterns to identify patients at high risk for AF as well as stroke when standard ECG or Holter monitoring do not capture AF. Through identifying variables in both patients with and without AF as well as assessing ECG findings such as p-wave duration and cardiac biomarkers, models can be constructed to determine which variables can predict AF (►**Fig. 4**).[35,36]

Given the association between atrial tachyarrhythmias, including transient AF, and stroke as well as the proximity of stroke to AF episodes, a temporary time-dependent anticoagulation approach may be tested wherein patients with HF and these rhythms—as identified by wearable or intracardiac devices—are randomized to (temporary) anticoagulation versus placebo subsequent to the arrhythmia for a certain duration of time (►**Table 2**). Such an approach may be the optimal way to decrease stroke burden while minimizing bleeding risk and merits a clinical trial.
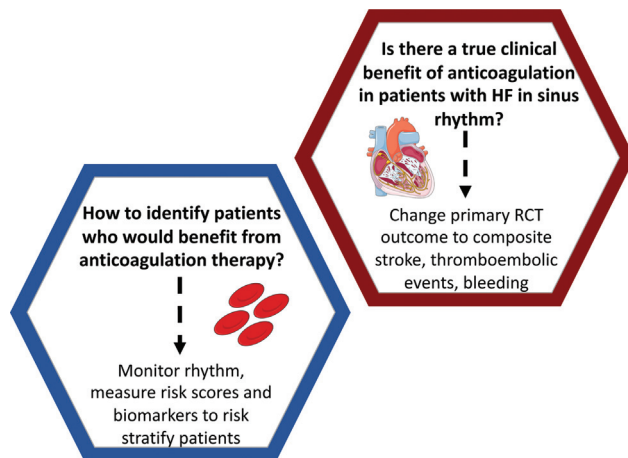
Conclusion

Despite the high risk of stroke in patients with HF, there is no clear evidence to support the use of antithrombotic therapy in those with SR and no other indications for anticoagulation. However, at least two of the five trials to date were inadequately powered and patients with HFpEF have not been included in any of the published trials. On balance, while anticoagulation decreased the risk of stroke, it did not decrease composite endpoints that include all-cause mortality, and its benefit is offset by an increased risk of major bleeding. However, most of the causes of death in patients with HF and SR are not amenable to risk reduction with anticoagulation. Thus, selection of endpoints that are sensitive to antithrombotic therapy may be an important consideration in future trials on the benefit of antithrombotic therapy.

Fig. 4 Considerations in anticoagulation in patients with heart failure in sinus rhythm and future avenues to explore.

In addition to adequately powered trials with appropriate endpoints, determining which subgroups of patients are at particularly high risk of stroke through remote monitoring and clinical risk prediction models could guide selection of patients likely to derive benefit from antithrombotic therapy (►**Fig. 4**). Patients with HF and atrial tachyarrhythmias, including transient AF, may represent a high-risk group that could be recruited into trials that test the efficacy of anticoagulation—possibly temporary and time-dependent—given the proximity of stroke incidents to AF episodes. Wearable devices certainly afford the opportunity for a time-dependent anticoagulation approach, which may be the optimal way to decrease stroke burden while minimizing bleeding risk. Combining better patient selection and endpoint definitions in future trials will help to determine whether there is indeed a benefit of antithrombotic therapy in patients with HF and SR.

Essentials

- Patients with heart failure (HF) in sinus rhythm (SR) may have a high risk of thromboembolic events including stroke.
- Oral anticoagulation is well established in patients with HF and atrial fibrillation, but the benefit in SR remains uncertain as clinical trial results have been neutral and any reduction in stroke rates appears to be countered by bleeding events.
- Identifying patients who may benefit from anticoagulation within this group may require adequately powered trials that risk stratify patients with HF and SR prior to recruitment, and focus primarily on efficacy and safety outcomes that are sensitive to the intervention.

Conflict of Interest
None declared.

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