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REVIEW ARTICLE

Exploring Anticoagulation Modalities in Heart Failure with Reduced Ejection Fraction: A Systematic Review Across Sinus Rhythm and Atrial Fibrillation Populations

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Abstract

Introduction: Heart failure with reduced ejection fraction (HFrEF) is a cause of morbidity, mortality, and healthcare use, and despite multidrug therapy, thromboembolic complications, ischemic stroke, and systemic embolism remain. Although HFrEF fulfills the elements of Virchow's triad and supports a rationale for anticoagulation without atrial fibrillation (AF), the benefit depends on whether reduced thromboembolism outweighs bleeding. **Objectives:** This study aimed to clarify the balance between thromboembolic prevention and bleeding, identify the evidence supporting current recommendations, and define the patient subgroups that warrant further prospective investigation. **Methods:** This Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020-adherent systematic review evaluated anticoagulation in HFrEF with sinus rhythm and concomitant AF by searching, applying Population-Intervention-Comparator-Outcome criteria, using duplicate screening and extraction, and assessing bias with Risk of Bias 2 and the Newcastle–Ottawa Scale; heterogeneity precluded meta-analysis. **Results:** From 122 PubMed records, five trials were included. In sinus rhythm, HELAS and WASH were underpowered with low event rates and no outcome differences; WATCH suggested that warfarin reduced ischemic stroke but not the primary composite endpoint. WARCEF (n = 2,305) found no difference in the primary composite (heart rate [HR]: 0.93, 95% confidence interval [CI]: 0.79–1.10), despite fewer ischemic strokes with warfarin (HR: 0.52, 95% CI: 0.33–0.82) and more major hemorrhage (1.78 vs 0.87 events/100 patient-years). COMMANDER heart failure (n = 5,022) showed that rivaroxaban did not reduce death, myocardial infarction, or stroke (HR: 0.94, 95% CI: 0.84–1.05), although *post hoc* analyses suggested modest stroke/ transient ischemic attack (TIA) reductions. For HFrEF with AF, subgroup and observational data support guideline-based anticoagulation with favorable DOAC safety versus warfarin. **Conclusion:** Overall, routine long-term anticoagulation is not supported for unselected HFrEF in sinus rhythm; priority is precision anticoagulation in risk-enriched subgroups while minimizing bleeding.

Key words: Anticoagulation, atrial fibrillation, direct oral anticoagulants, Heart failure with reduced ejection fraction, sinus rhythm, thromboembolic complications

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INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) remains a major cause of morbidity, premature mortality, and healthcare utilization worldwide. Contemporary HFrEF management has been transformed by multidrug guideline-directed therapy, yet thromboembolic complications remain clinically important, particularly ischemic stroke and systemic embolism.[1-3]

The biological rationale for anticoagulation in HFrEF is compelling. Ventricular dilatation and impaired contractility promote intracardiac stasis, while endothelial dysfunction, inflammation, platelet activation, and coagulation abnormalities contribute to a prothrombotic milieu. These mechanisms align with Virchow's triad and have historically supported the hypothesis that anticoagulation might reduce thromboembolic events even in the absence of atrial fibrillation (AF).[4] The key clinical question, however, is not whether anticoagulants reduce thrombosis, but whether the absolute reduction in thromboembolic events exceeds the accompanying risk of major bleeding.

Randomized trials have repeatedly tested this balance. Earlier studies, including HELAS and WASH, were underpowered for definitive clinical outcomes. WATCH subsequently compared warfarin with aspirin and clopidogrel in chronic HFrEF, while WARCEF provided the largest direct comparison of warfarin and aspirin in HFrEF with sinus rhythm. WARCEF demonstrated a clear reduction in ischemic stroke with warfarin, but that benefit was offset by more major hemorrhage and no significant improvement in the composite of death, ischemic stroke, or intracerebral hemorrhage.[5-8]

The emergence of direct oral anticoagulants (DOACs) renewed interest in antithrombotic strategies because these agents offer more predictable pharmacokinetics and lower intracranial bleeding risk than warfarin in many AF populations. Importantly, however, the efficacy of DOACs in AF cannot be directly extrapolated to HFrEF without AF. COMMANDER heart failure (HF) specifically addressed this gap in patients with worsening chronic HFrEF, coronary artery disease, and sinus rhythm: Rivaroxaban 2.5 mg twice daily did not significantly reduce the composite of all-cause death, myocardial infarction, or stroke compared with placebo.[9]

Current guideline positions therefore depend strongly on rhythm and indication. The 2021 European Society of Cardiology (ESC) HF guideline states that routine anticoagulation is not supported for HFrEF in sinus rhythm without another indication, whereas patients with HF and AF should receive oral anticoagulation according to thromboembolic risk, with DOACs preferred over vitamin K antagonists in eligible patients.[3] The 2022 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America guideline (HFSA) guideline similarly does not support anticoagulation in chronic HFrEF without a specific indication.[2] For AF, the 2024 ESC AF guideline reinforces a risk-based approach and generally prefers DOACs over Vitamin K antagonists except in specific settings such as mechanical valves or moderate-to-severe mitral stenosis.[10]

Against this background, this systematic review critically evaluates anticoagulation in HFrEF across two clinically distinct settings: HFrEF with sinus rhythm and HFrEF with concomitant AF. The principal aim is to clarify the balance between thromboembolic prevention and bleeding, identify the evidence supporting current recommendations, and define the patient subgroups that warrant further prospective investigation.

MATERIALS AND METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement and its explanation-and-elaboration document.[11,12]

The eligibility criteria used the Population-Intervention-Comparator-Outcome-Study framework. The population included adults aged 18 years and older with HFrEF, defined by a left ventricular ejection fraction (LVEF) of 40% or less, although studies using 35% were considered if other criteria were met. Eligible interventions were oral anticoagulation with warfarin or a DOAC. Comparators included placebo, no anticoagulation, aspirin, other antiplatelet strategies, and different oral anticoagulants. The outcomes were all-cause mortality, ischemic stroke, systemic embolism, major bleeding, intracranial hemorrhage, and HF hospitalization. Eligible primary study designs included randomized controlled trials and prospective or retrospective observational studies.

Studies were excluded if they addressed only HF with preserved or mildly reduced ejection fraction without separable HFrEF data; assessed anticoagulation only for procedural reasons, ventricular assist devices, or non-cardiac purposes; were case reports or very small case series; lacked clinical outcomes; or were available only as abstracts without sufficient methodological detail. Risk-of-bias assessments were not used as a *post hoc* eligibility filter; instead, methodological limitations informed the certainty and interpretation of the synthesis.

Searches covered PubMed/MEDLINE from January 01, 2006, to July 31, 2026 for English reports. PubMed search strategy included ("heart failure with reduced ejection fraction" OR HFrEF OR "systolic heart failure") AND (anticoagulation OR anticoagulant* OR warfarin OR "vitamin K antagonist*" OR rivaroxaban OR apixaban OR dabigatran OR edoxaban OR DOAC* OR NOAC*) AND (stroke OR thromboembol* OR

bleeding OR hemorrhage OR mortality OR hospitalization OR outcomes).

Two reviewers independently screened titles and abstracts, assessed texts, and resolved disagreements by consensus or a third reviewer. Data extraction used a standardized form capturing study design, setting, sample size, LVEF criteria, rhythm status, anticoagulant regimen, comparator, follow-up, primary outcomes, and estimates. Multiple publications from the same trial were linked to avoid double counting. Randomized trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) framework, and observational cohort and case-control studies were assessed using the Newcastle-Ottawa Scale. Risk-of-bias assessments were integrated into the interpretation of the evidence.

Given the contexts, comparators, anticoagulant regimens, outcome definitions, and follow-up durations, a narrative synthesis was conducted rather than pooling. Primary synthesis was categorized by rhythm status: (1) HFrEF in sinus rhythm, assessing anticoagulation without an AF indication and (2) HFrEF with concurrent AF, with anticoagulation following guidelines and focusing on selection and safety. Effect estimates are accompanied by confidence intervals as reported.

This is a systematic review of published and open data that did not involve human subjects. Approval from an ethics committee was not required. This study is based on Council for International Organizations of Medical Sciences guidelines such as justice based on fair distribution of the benefits and burdens of research, as well as scientific and ethical evaluation.

RESULTS

Through structured searches, the authors identified 122 studies from PubMed. The initial screening process involved application of predetermined eligibility criteria. After excluding 38 studies owing to unavailable full-text data, 84 were screened. Of these, 66 studies were excluded. The remaining 18 studies underwent an eligibility assessment, resulting in 13 studies being excluded due to inadequate data and conclusions. Ultimately, five papers satisfied the inclusion criteria and were included in this systematic review.[5-9] Figure 1 illustrates the selection process and Table 1 lists the five studies included.

The clinical heterogeneity of the evidence base requires interpretation by rhythm status. In patients with sinus rhythm, the randomized evidence comes from HELAS, WASH, WATCH, WARCEF, and COMMANDER HF, supported by mechanistic research and secondary analyses of stroke risk and anticoagulation quality. In AF, evidence mainly comes from subgroup analyses of AF trials and observational studies, where anticoagulation is indicated and comparisons center on effectiveness and safety.

HFrEF with sinus rhythm

Initial trials were limited by small samples and low event rates. HELAS included 197 patients with an EF of less than 35% and found few embolic events with no significant difference in outcomes. WASH randomized 279 patients to no antithrombotic therapy, aspirin, or warfarin and found no significant difference in death, non-fatal myocardial infarction, or non-fatal stroke.[5,6] These findings suggested that thromboembolic rates in unselected ambulatory HF were too low for routine anticoagulation to provide net benefit.

WATCH studied 1,587 patients with HFrEF and sinus rhythm, comparing warfarin with aspirin or clopidogrel. Although warfarin reduced ischemic stroke, it did not show superiority for the primary composite endpoint. Early termination for recruitment challenges limited precision and emphasized the need for a larger trial.[7]

WARCEF randomized 2,305 patients with LVEF ≤35% and sinus rhythm to warfarin or aspirin. The primary composite of ischemic stroke, intracerebral hemorrhage, or all-cause death did not differ between groups (7.47 vs. 7.93 events/100 patient-years; heart rate [HR]: 0.93, 95% confidence interval [CI]: 0.79-1.10; $P = 0.40$). Warfarin reduced ischemic stroke (0.72 vs. 1.36 events/100 patient-years; HR: 0.52, 95% CI: 0.33-0.82; $P = 0.005$) but increased major hemorrhage (1.78 vs. 0.87 events/100 patient-years; $P < 0.001$). Thus, anticoagulation prevented ischemic stroke, but in unselected sinus-rhythm patients, the absolute benefit was offset by bleeding risk.[8]

Warfarin control affected outcomes. A WARCEF analysis showed that higher time in therapeutic range was associated with better net outcomes, indicating that Vitamin K antagonism depends on anticoagulation quality.[13] However, this does not support warfarin as standard therapy for HFrEF in sinus rhythm; it informs management when warfarin is required for another indication.

DOACs tested a more convenient anticoagulant strategy. COMMANDER HF randomized 5,022 patients with chronic HF, LVEF ≤40%, coronary artery disease, elevated natriuretic peptides, and no AF after worsening HF. Rivaroxaban 2.5 mg twice daily did not significantly reduce death, myocardial infarction, or stroke versus placebo (HR: 0.94, 95% CI: 0.84–1.05; $P = 0.27$), and all-cause mortality was unchanged.[9] Therefore, the absence of net benefit in sinus-rhythm HFrEF cannot be attributed only to warfarin's limitations.

Risk enrichment and higher-risk subgroups

Neutral outcomes of anticoagulation strategies have shifted focus to risk enrichment. In a combined analysis of PARADIGM-HF, ATMOSPHERE, and DAPA-HF, Kondo *et al.* assessed 12,751 participants without AF at

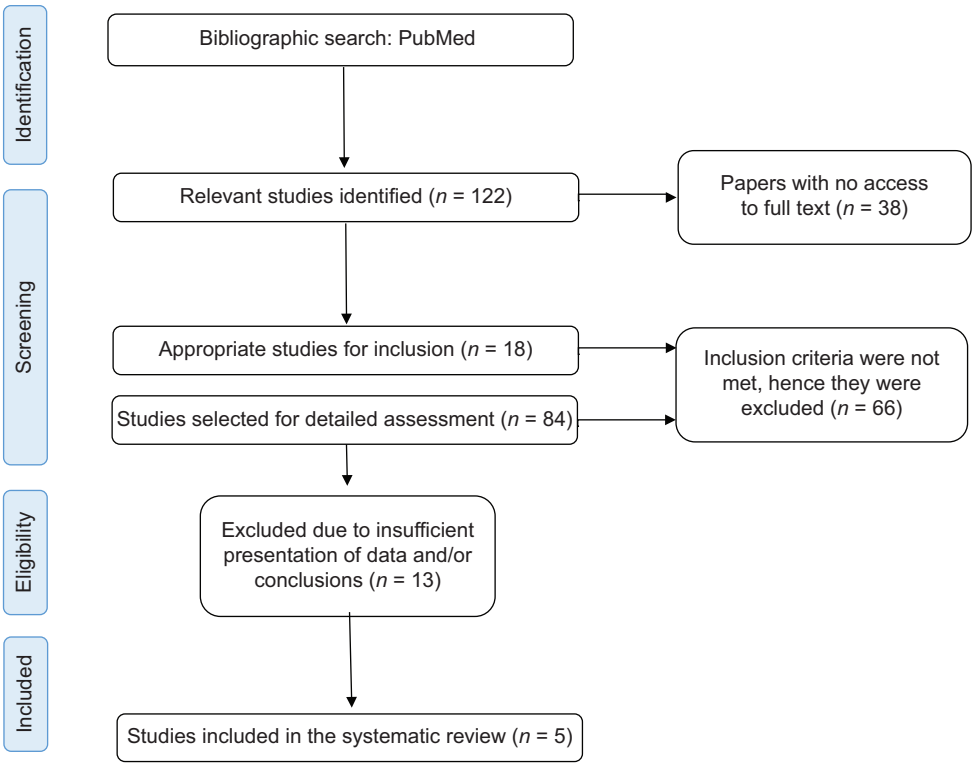


Figure 1: PRISMA flowchart depicting the literature search and study selection process for the systematic review

Table 1: Pivotal randomized evidence informing anticoagulation in HFrEF with sinus rhythm

Study	Population	No. of patients	Intervention	Comparator	Key efficacy findings	Key safety/ interpretation
Cokkinos *et al.,* 2006 (HELAS)[5]	Chronic HF, EF <35%, sinus rhythm	197	Warfarin	Aspirin or placebo	Low embolic event rate; no significant between-group advantage	Pilot-sized study; insufficient evidence for routine anticoagulation
Cleland *et al.,* 2004 (WASH)[6]	HF with LV systolic dysfunction	279	Warfarin	Aspirin or no antithrombotic therapy	No significant difference in death, MI, or stroke	Feasibility trial; hospitalization signal with aspirin
Massie *et al.,* 2009 (WATCH)[7]	Chronic HFrEF, sinus rhythm	1,587	Warfarin	Aspirin or clopidogrel	No significant difference in primary composite; fewer ischemic strokes with warfarin	Trial stopped early; stroke reduction did not establish overall net benefit
Homma *et al.,* 2012 (WARCEF)[8]	LVEF ≤35%, sinus rhythm	2,305	Warfarin (INR 2.0–3.5)	Aspirin 325 mg/day	Primary HR: 0.93 (95% CI: 0.79–1.10); ischemic stroke HR: 0.52 (95% CI: 0.33–0.82)	Major hemorrhage 1.78 versus 0.87 events/100 patient-years; stroke benefit offset by bleeding
Zannad *et al.,* 2018 COMMANDER HF)[9]	HFrEF (LVEF ≤40%), CAD, recent worsening HF, no AF	5,022	Rivaroxaban 2.5 mg twice daily	Placebo	Death/MI/stroke HR: 0.94 (95% CI: 0.84–1.05); no mortality benefit	Did not support routine low-dose rivaroxaban for broad HFrEF population in sinus rhythm

HF: Heart failure, EF: Ejection fraction, HFrEF: Heart failure with reduced ejection fraction, LVEF: Left ventricular ejection fraction, CI: Confidence interval, HR: Heart rate, CAD: Computer-aided design, MI: Myocardial infarction

baseline and recorded 346 strokes over a median follow-up of 2 years.[14] The risk of stroke increased with a history of stroke, insulin-dependent diabetes, and elevated N-terminal pro-B-type natriuretic peptide levels. The highest-risk quintile

had a stroke rate comparable to that of patients with AF who did not receive anticoagulant therapy. Anticoagulation might benefit selected HFrEF patients at high thromboembolic risk, but this remains unverified in randomized trials.

Other indications should not be conflated with the routine anticoagulant therapy for HFrEF. Patients with left ventricular thrombus, previous systemic embolism, mechanical prosthetic valves, venous thromboembolism, or AF may require anticoagulant therapy. Decisions should be based on indications and the specific evidence.

HFrEF with concomitant AF

When AF is present with HFrEF, management changes because AF indicates stroke prevention based on thromboembolic risk. Current AF guidelines advocate oral anticoagulation in eligible patients, preferring DOACs over vitamin K antagonists, except in those with mechanical heart valves or moderate-to-severe mitral stenosis.[10]

Subgroup analyses from AF trials support the use of DOACs in patients with HF. In the ROCKET AF trial, rivaroxaban was consistently effective and safe in patients with and without HF.[15] In ARISTOTLE, patients with left ventricular systolic dysfunction had a higher risk of stroke/systemic embolism or death than those without HF/LV systolic dysfunction, underscoring the importance of anticoagulation.[16] Observational studies have indicated similar or favorable bleeding profiles for DOACs versus warfarin in HF populations, although residual confounding remains a significant limitation.

In the RoB 2 assessment, concerns were raised regarding stroke-related outcomes across all five included trials. The HELAS and WASH trials lacked accessible reporting to verify several domain judgments. In the WATCH trial, the open-label comparison with warfarin required attention to deviations from the assigned treatment. Although WARCEF employed blinded treatment and independent endpoint adjudication, periods of non-adherence should be considered. Although the COMMANDER HF trial was double-blind, stroke events were not evaluated by an independent adjudication committee. These judgments should be finalized by reviewing the complete trial reports and protocols before submission.

DISCUSSION

This review underscores a theme over 30 years: HFrEF induces a prothrombotic condition; however, this rationale does not equate to clinical advantage from universal anticoagulation in patients in sinus rhythm. While warfarin decreases ischemic stroke risk, this advantage is counterbalanced by bleeding, and modern low-dose rivaroxaban failed to enhance the composite outcome in COMMANDER HF. The inquiry has evolved from "Should all HFrEF patients be anticoagulated?" to "Which patients possess a thromboembolic risk high enough to warrant anticoagulation despite the bleeding risk?"[4,8,14]

WARCEF remains central to illustrating the trade-off with warfarin. It demonstrated a 48% relative reduction in ischemic stroke; however, the absolute stroke incidence was low, and major bleeding increased. This distinction is crucial. A relative reduction in a rare event may still yield minimal net benefit if treatment causes more frequent or serious harm. This also clarifies why underpowered studies and COMMANDER HF did not endorse universality.[6-9]

A synthesis distinguishes sinus-rhythm HFrEF from HFrEF with AF. Merging them can obscure the issue. In AF, anticoagulation is not used because HFrEF is assumed to be thrombogenic; it is employed because AF presents an embolic risk that oral anticoagulation can mitigate. Heart failure aids risk stratification, but rhythm status alters the indication. Therefore, evidence from AF trials should guide agent selection and safety in HFrEF with AF, rather than serve as proof that DOACs are advantageous in HFrEF without AF.[10,15,16]

Risk-enrichment analyses provide a credible path forward. Kondo *et al.*'s model indicates that some HFrEF patients without AF can reach stroke rates similar to untreated AF populations. Factors including prior stroke, insulin-dependent diabetes, and elevated natriuretic peptides may identify a phenotype where the absolute benefit of anticoagulation is greater. However, prediction does not equal treatment effect modification. A high predicted stroke risk does not confirm that anticoagulation will enhance net outcomes, especially if these patients also face bleeding risk. Thus, prospective randomized validation is crucial.[14]

Secondary analyses clarify the discrepancy between the primary outcome of COMMANDER HF and its stroke-related findings. Mehra *et al.* reported a lower incidence of stroke or transient ischemic attack with rivaroxaban than with placebo, with an adjusted HR: 0.68, 95% CI: 0.49-0.94, despite event rates of 1.29 and 1.90/100 patient-years, respectively.[17] Greenberg *et al.* observed a decrease in a *post hoc* composite of thromboembolic events. These results suggest an antithrombotic effect; however, neither analysis altered the trial's conclusion that rivaroxaban did not significantly reduce the primary composite of death, myocardial infarction, or stroke.[18]

Further analyses assessed differential benefits among patients. In the COMMANDER HF trial, Ferreira *et al.* found reduced strokes primarily in participants with D-dimer levels exceeding 515 ng/mL.[19] A WARCEF subgroup analysis by Homma *et al.* indicated that age influenced warfarin versus aspirin, favoring warfarin in patients under 60 years. These

subgroup and *post hoc* findings remain hypotheses for future testing and not prescribing guidance in HFrEF.[20]

In practice, four principles apply. First, reduced LVEF alone should not prompt long-term anticoagulation in sinus rhythm. Second, clinicians must identify indications including AF, left ventricular thrombus, venous thromboembolism, mechanical valves, or prior systemic embolism. Third, when AF is present and anticoagulation is required, agents should follow guidelines, with DOACs preferred for eligible patients. Finally, decisions should consider bleeding risk, renal function, drug interactions, adherence, and, for warfarin, ability to maintain an adequate therapeutic range.

Strengths include distinguishing sinus-rhythm HFrEF from AF-associated HFrEF, integrating randomized evidence with risk-stratification studies, and interpreting findings within current HF/AF guidelines. It also emphasizes net clinical benefit over efficacy endpoints.

However, limitations exist. The search excluded Embase, narrowing retrieval, and limiting studies to English may have introduced language bias. Heterogeneity in populations, rhythm status, comparators, regimens, outcomes, and follow-up precluded pooling. Several reports were secondary analyses of the same parent trials and therefore non-independent evidence. Observational evidence remained vulnerable to residual confounding despite assessment. These issues underscore interpreting effect estimates within study design and clinical indication.

Future trials should move beyond broad, unselected HFrEF populations. Priority is a randomized, adequately powered anticoagulation study in risk-enriched HFrEF without AF, using validated stroke-risk enrichment and pre-specified bleeding-risk criteria. Modern anticoagulants should be compared with placebo or standard care, assessing disabling/fatal stroke, major bleeding, mortality, HF hospitalization, and patient-reported outcomes. Studies should also explore whether biomarkers, imaging-defined ventricular thrombus risk, or continuous rhythm monitoring can identify patients in whom occult AF or thrombogenicity alters treatment effect.

CONCLUSION

Long-term anticoagulation is not routinely recommended for patients with HFrEF in sinus rhythm and no other indications. While warfarin can lower ischemic stroke risk, it also increases major bleeding. In addition, low-dose rivaroxaban did not reduce the composite outcome of death, myocardial infarction, or stroke in the COMMANDER HF trial. For patients with concurrent AF, anticoagulation should follow AF guidelines, with DOACs favored over vitamin K antagonists when appropriate. The approach is precision anticoagulation: identifying HFrEF subgroups with high absolute thromboembolic risk to achieve a positive net clinical benefit and testing this hypothesis in studies.

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