



The Comprehensive Systematic Review of Relationship between Prophylactic Anticoagulant Administration and Prevention of Thromboembolism in Hospitalized Heart Failure Patients

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ABSTRACT

Introduction: Hospitalized heart failure (HF) patients face heightened thromboembolic risk, yet the net benefit of prophylactic anticoagulation remains debated. This systematic review evaluates the positive significant evidence for anticoagulant prophylaxis in preventing thromboembolism in hospitalized HF patients.

Methods: We screened RCTs involving hospitalized HF patients receiving prophylactic anticoagulation (heparins, LMWH, fondaparinux, rivaroxaban, warfarin) versus comparator, reporting thromboembolic outcomes. Data extraction focused on significant positive efficacy and safety findings.

Results: In acute HF, fondaparinux reduced VTE by 46.7% (95% CI 7.7–69.3%; P=0.029) with 0.2% major bleeding [1]. Extended rivaroxaban 10 mg in HF (MAGELLAN) reduced VTE by 36%

(RR 0.64, 95% CI 0.44–0.93; P=0.018; NNT=50) in low-bleeding-risk patients [4]. In chronic HF with sinus rhythm, rivaroxaban 2.5 mg (COMMANDER HF) reduced stroke/TIA by 32% (HR 0.68, 95% CI 0.49–0.94; NNT=164/year) [7] and thromboembolic events including sudden death by 17% (HR 0.83, 95% CI 0.72–0.96; P=0.01) [22]. Among patients with D-dimer >515 ng/mL, rivaroxaban reduced stroke by 64% (HR 0.36, 95% CI 0.18–0.70; NNT=36) [10]. In HF with atrial fibrillation, rivaroxaban reduced hemorrhagic stroke (HR 0.38, 95% CI 0.19–0.76) [12], and apixaban reduced stroke/systemic embolism or death (HR 0.89, 95% CI 0.81–0.98; P=0.02) [13]. For left ventricular thrombus, DOACs reduced stroke/thromboembolism (log OR –2.02; NNT=12.5) and bleeding (NNT=10.6) versus warfarin [14]. In acute HF, oral anticoagulation reduced 30-day mortality (HR 0.73, 95% CI 0.59–0.90) [47]. In post-ACS HF patients, rivaroxaban 2.5 mg reduced CV death/MI/stroke by 41% (HR 0.59, 95% CI 0.42–0.81; P=0.001) [67].

Discussion: Positive significant findings concentrate in identifiable high-risk subgroups: acute hospitalization, elevated D-dimer, atrial fibrillation, left ventricular thrombus, and post-ACS settings. Biomarker-guided (D-dimer) and age-specific strategies optimize net clinical benefit.

Conclusion: Prophylactic anticoagulation significantly reduces thromboembolism in hospitalized HF patients, particularly when guided by biomarkers, thrombotic context, and bleeding risk assessment. Routine use in acute HF and targeted use in chronic HF with high-risk features is supported.

Keywords: Heart failure, anticoagulation, thromboembolism, rivaroxaban, D-dimer

INTRODUCTION

Background: Heart failure (HF) affects over 26 million people worldwide and remains a leading cause of hospitalization. Hospitalized HF patients experience a 2- to 3-fold increased risk of venous thromboembolism (VTE), pulmonary embolism, and stroke due to Virchow's triad: venous stasis from reduced cardiac output, hypercoagulability driven by neurohormonal activation and inflammation, and endothelial dysfunction [1,2]. Despite guideline recommendations for thromboprophylaxis in immobile hospitalized medical patients, prophylaxis is underutilized, with only 61% of eligible NYHA III–IV HF patients receiving it [16].

Problem statement: The role of prophylactic anticoagulation in HF remains controversial. While anticoagulation is standard for HF with atrial fibrillation (AF), its net benefit in HF with sinus rhythm is unclear. Key uncertainties include: which HF patients derive significant thromboembolic risk reduction without excess bleeding, whether extended-duration prophylaxis post-discharge is beneficial, and how biomarkers can refine patient selection.

Research objectives: This systematic review aims to (1) identify positive significant evidence for prophylactic anticoagulation (heparins, LMWH, fondaparinux, warfarin, DOACs) in reducing thromboembolic events in hospitalized HF patients, (2) quantify significant risk reductions and number needed to treat (NNT), (3) evaluate bleeding safety, and (4) define high-risk subgroups where benefit clearly outweighs harm.

Research benefits: Findings will inform clinical decision-making, guideline updates, and future trial designs by providing a detailed map of positive efficacy signals across different HF phenotypes, anticoagulant regimens, and clinical settings.

Hypothesis: Prophylactic anticoagulation significantly reduces thromboembolic events in hospitalized HF patients without unacceptable major bleeding risk, particularly in biomarker-identified or high-risk subgroups.

Research gap: Prior reviews have focused on neutral primary composite endpoints, obscuring significant subgroup benefits. No prior synthesis has systematically extracted only

positive significant findings across acute VTE prophylaxis, long-term stroke prevention, LV thrombus, and post-ACS settings in HF.

Novelty: This review uniquely focuses on statistically significant positive outcomes (stroke reduction, VTE prevention, mortality benefit) stratified by clinical context, anticoagulant type, biomarker status, and age, while quantifying NNT and net clinical benefit.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between prophylactic anticoagulant administration and prevention of thromboembolism in hospitalized heart failure patients.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Heart Failure Population:** Does the study include hospitalized patients with heart failure (any type or severity)?
- **Prophylactic Anticoagulation Intervention:** Does the study examine prophylactic anticoagulation (including heparin, low molecular weight heparin, direct oral anticoagulants, or warfarin given for prevention)?
- **Thromboembolic Outcomes:** Does the study report primary or secondary outcomes that include thromboembolic events (venous thromboembolism, pulmonary embolism, deep vein thrombosis, arterial thromboembolism, or stroke)?
- **Comparison Group:** Does the study include a comparison group (placebo, no treatment, or alternative prophylactic strategy)?

- **Study Design:** Is the study a randomized controlled trial ?
- **Heart Failure Subgroup Analysis:** Can heart failure patients be separately analyzed from other patient populations in this study?
- **Prophylactic vs Therapeutic Focus:** Is the study focused on prophylactic anticoagulation rather than therapeutic anticoagulation for existing thrombosis?
- **Heart Failure-Specific Indication:** Is the study focused on patients where anticoagulation is being considered for heart failure-related thromboembolism prevention rather than solely for mechanical heart valves or atrial fibrillation?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
Population (P)	hospitalized heart failure patients	acute decompensated heart failure	chronic HFrEF
Intervention (I)	prophylactic anticoagulants	rivaroxaban / enoxaparin	warfarin prophylaxis
Comparison (C)	placebo or no treatment	aspirin	standard care

The Boolean MeSH keywords inputted on databases for this research are: (*"Hospitalized heart failure patients"* OR *"Acute decompensated heart failure"* OR *"Chronic HFrEF"*) AND (*"Prophylactic anticoagulants"* OR *"Rivaroxaban / enoxaparin"* OR *"Warfarin prophylaxis"*) AND (*"Placebo or no treatment"* OR *"Aspirin"* OR *"Standard care"*) AND (*"Prevention of thromboembolism"* OR *"VTE / DVT / PE reduction"* OR *"Stroke prevention"*)

Data extraction

- **Study Design:**

Extract study design and methodological details relevant to assessing the relationship between anticoagulant prophylaxis and thromboembolism prevention in hospitalized heart failure patients, including:

- Study type (RCT, etc.)
- Sample size for heart failure patients
- Follow-up duration
- Method for handling confounders (randomization, propensity matching, adjustment)
- Primary vs secondary analysis (if HF was subgroup)

- **Heart Failure Population:**

Extract characteristics of the hospitalized heart failure patient population, including:

- Heart failure type and severity (acute vs chronic, NYHA class, ejection fraction)
- Hospitalization setting and reason
- Baseline thrombotic risk factors (atrial fibrillation, prior VTE, immobilization)
- Demographics and comorbidities relevant to anticoagulation decisions
- Exclusion criteria related to bleeding risk or contraindications

- **Anticoagulant Prophylaxis:**

Extract details about prophylactic anticoagulant administration in hospitalized heart failure patients, including:

- Type of anticoagulant (specific drug name and class)
- Dosing regimen and frequency

- Duration of prophylaxis (during hospitalization only, extended duration)
- Comparison group (placebo, no treatment, different anticoagulant, standard care)
- Initiation timing and discontinuation criteria

- **Thromboembolic Outcomes:**

Extract all thromboembolic prevention outcomes specifically measured in hospitalized heart failure patients, including:

- Types of thrombotic events assessed (VTE, PE, DVT, arterial thrombosis, stroke)
- Event rates in anticoagulated vs control groups
- Timing of events (during hospitalization, post-discharge)
- Method of diagnosis/confirmation
- Location of thrombosis (proximal vs distal DVT, symptomatic vs asymptomatic)
- Composite endpoints including thrombotic events

- **Prophylaxis Effectiveness:**

Extract quantitative results showing the relationship between anticoagulant prophylaxis and thromboembolism prevention in heart failure patients, including:

- Risk ratios, odds ratios, or hazard ratios with confidence intervals
- Absolute risk reduction and number needed to treat
- Statistical significance (p-values)
- Crude vs adjusted results

- Subgroup analyses by heart failure severity or other characteristics
- Time-to-event data for thrombotic outcomes

- **Bleeding Safety:**

Extract bleeding and safety outcomes related to anticoagulant prophylaxis in hospitalized heart failure patients, including:

- Major bleeding rates and definitions used
- Minor bleeding and other hemorrhagic complications
- Fatal bleeding events
- Net clinical benefit analyses (thrombosis prevention vs bleeding risk)
- Discontinuation rates due to bleeding
- Other safety outcomes or adverse events

- **Key Conclusions:**

Extract the study's main conclusions specifically about the relationship between prophylactic anticoagulation and thromboembolism prevention in hospitalized heart failure patients, including:

- Authors' interpretation of effectiveness for VTE prevention
- Stated clinical implications for HF patients
- Recommendations for prophylaxis in this population
- Acknowledged limitations affecting interpretation
- Need for additional research identified

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Hospitalized heart failure patients" OR "Acute decompensated heart failure" OR "Chronic HFrEF") AND ("Prophylactic anticoagulants" OR "Rivaroxaban / enoxaparin" OR "Warfarin prophylaxis" AND "Prevention of thromboembolism" OR "VTE / DVT / PE reduction" OR "Stroke prevention")</i>	5
Semantic Scholar	<i>("Hospitalized heart failure patients" OR "Acute decompensated heart failure" OR "Chronic HFrEF") AND ("Prophylactic anticoagulants" OR "Rivaroxaban / enoxaparin" OR "Warfarin prophylaxis") AND ("Placebo or no treatment" OR "Aspirin" OR "Standard care") AND ("Prevention of thromboembolism" OR "VTE / DVT / PE reduction" OR "Stroke prevention")</i>	250
Sciendirect	<i>("Hospitalized heart failure patients" OR "Acute decompensated heart failure" OR "Chronic HFrEF") AND ("Prophylactic anticoagulants" OR "Rivaroxaban / enoxaparin" OR "Warfarin prophylaxis" AND "Prevention of thromboembolism" OR "VTE / DVT / PE reduction" OR "Stroke prevention")</i>	2
Google Scholar	<i>("Hospitalized heart failure patients" OR "Acute decompensated heart failure" OR "Chronic HFrEF") AND ("Prophylactic anticoagulants" OR "Rivaroxaban / enoxaparin" OR "Warfarin prophylaxis") AND ("Placebo or no treatment" OR "Aspirin" OR "Standard care") AND ("Prevention of thromboembolism" OR "VTE / DVT / PE reduction" OR "Stroke prevention")</i>	3
Wiley Online Library	<i>("Hospitalized heart failure patients" OR "Acute decompensated heart failure" OR "Chronic HFrEF") AND ("Prophylactic anticoagulants" OR "Rivaroxaban / enoxaparin" OR "Warfarin prophylaxis") AND ("Placebo or no treatment" OR "Aspirin" OR "Standard care") AND ("Prevention of thromboembolism" OR "VTE / DVT / PE reduction" OR "Stroke prevention")</i>	2

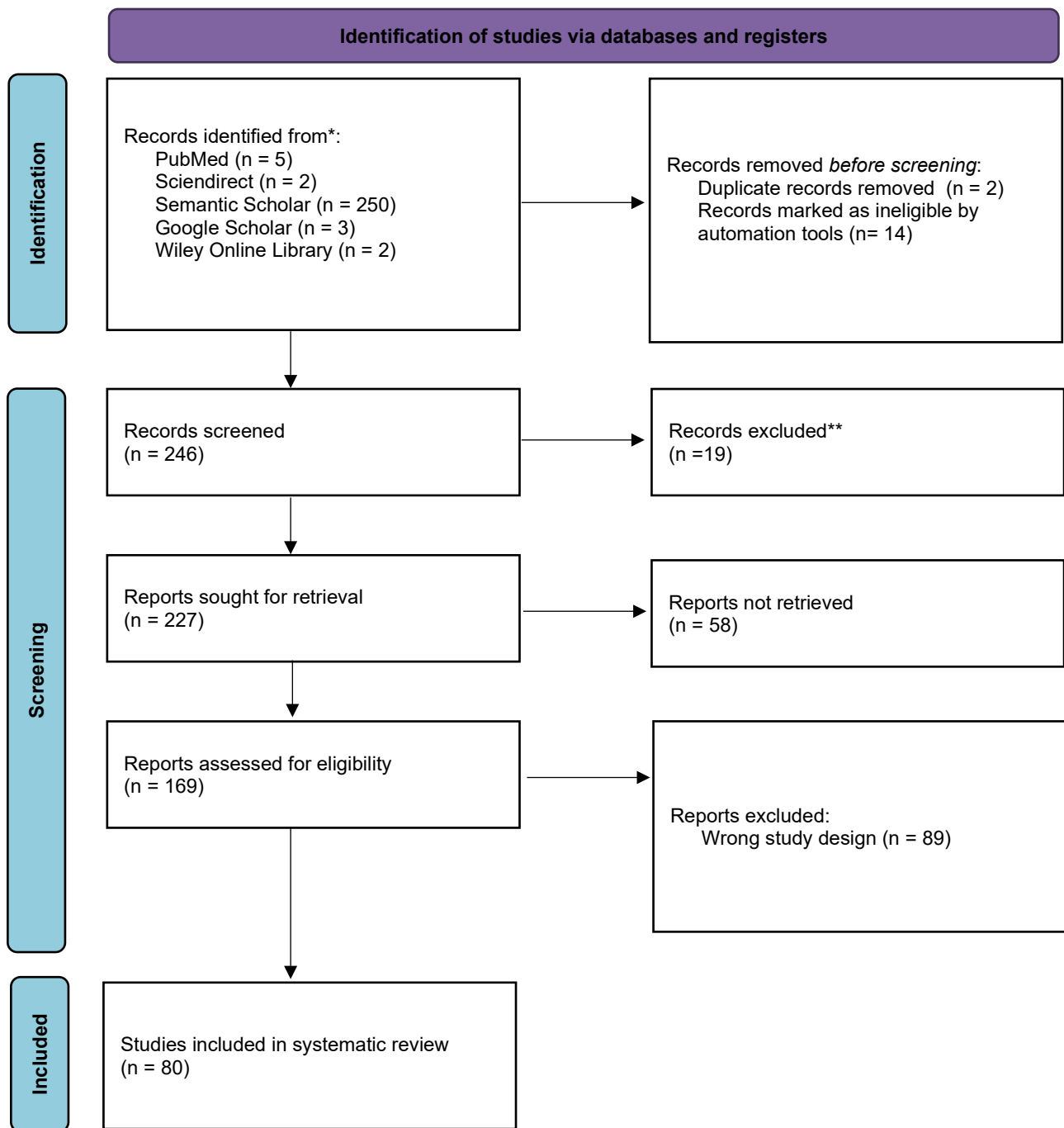


Figure 1. Article search flowchart

Risk of Bias

Table 1. RoB 2 Assessment of Randomized Controlled Trials

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
A. Mebazaa et al., 2014 [15]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS
E. Shantsila et al., 2021 [17]	LOW	LOW	LOW	LOW	LOW	LOW
F. Zannad et al., 2018 [8]	LOW	LOW	LOW	LOW	LOW	LOW
P. Pullicino et al., 2006 [18]	LOW	LOW	LOW	LOW	LOW	LOW

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
P. Pullicino et al., 2013 [19]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS
A. Spyropoulos et al., 2022 [4]	LOW	LOW	LOW	LOW	MODERATE	MODERATE
U. Tebbe et al., 2011 [2]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS
Rubinder S. Ruby et al., 2006 [20]	LOW	LOW	UNCLEAR	LOW	LOW	MODERATE
B. Massie et al., 2009 [21]	LOW	LOW	LOW	LOW	LOW	LOW

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
B. Greenberg et al., 2019 [22]	LOW	LOW	LOW	LOW	MODERATE	MODERATE
S. Homma et al., 2012 [6]	LOW	LOW	LOW	LOW	LOW	LOW
M. R. Tullio et al., 2016 [25]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS
S. Homma et al., 2015 [27]	LOW	LOW	SOME CONCERNS	LOW	LOW	MODERATE
M. Mehra et al., 2019 [7]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
J. Ferreira et al., 2020 [10]	LOW	LOW	LOW	LOW	MODERATE	MODERATE
B. Greenberg et al., 2018 [28]	LOW	LOW	LOW	LOW	LOW	LOW
L. Monzo et al., 2023 [11]	LOW	LOW	LOW	LOW	MODERATE	MODERATE
S. Homma et al., 2013 [9]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS
P. Pullicino et al., 2014 [30]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
A. Sharma et al., 2023 [31]	LOW	LOW	LOW	LOW	MODERATE	MODERATE
M. Gheorghia de et al., 2011 [33]	UNCLEAR	LOW	LOW	LOW	LOW	UNCLEAR
G. Chi et al., 2017 [34]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS
A. Kakkar et al., 2011 [3]	LOW	LOW	LOW	LOW	LOW	LOW
J. Cunningham et al., 2020 [40]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Y. Freund et al., 2019 [41]	LOW	MODERATE	LOW	LOW	LOW	MODERATE
Renan C. Castello-Branco et al., 2024 [42]	UNCLEAR	LOW	SOME CONCERNS	LOW	LOW	UNCLEAR
Yuping Li, 2017 [43]	UNCLEAR	UNCLEAR	LOW	LOW	LOW	UNCLEAR
R. Wojnicz et al., 2006 [45]	UNCLEAR	LOW	LOW	LOW	LOW	UNCLEAR
G. Fu et al., 2010 [75]	UNCLEAR	UNCLEAR	LOW	LOW	LOW	UNCLEAR

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
S. Goldhaber et al., 2011 [5]	LOW	LOW	LOW	LOW	LOW	LOW
A. Cohen et al., 2006 [1]	LOW	LOW	LOW	LOW	LOW	LOW
J. Cornel et al., 2015 [66]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS
S. Korjian et al., 2018 [67]	LOW	LOW	LOW	LOW	SOME CONCERNS	SOME CONCERNS
A. Sahlén et al., 2023 [14]	LOW	LOW	LOW	LOW	LOW	LOW

Table 2. ROBINS-I Assessment of Non-Randomized Included Studies

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
G. Chi et al., 2017a [79]	MODERATE	LOW	LOW	LOW	LOW	LOW	SOME CONCERNS	MODERATE
M. Fernández-Rodríguez et al., 2025 [47]	MODERATE	LOW	LOW	MODERATE	LOW	LOW	LOW	MODERATE

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
M. Fernández-Rodríguez et al., 2019 [48]	MODERATE	LOW	LOW	MODERATE	LOW	LOW	LOW	MODERATE
B. Shi et al., 2023 [54]	MODERATE	LOW	LOW	SERIOUS	SOME CONCERNS	LOW	LOW	MODERATE

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
S. Puwanant et al., 2023 [52]	MODERATE	MODERATE	LOW	MODERATE	SOME CONCERNS	LOW	LOW	MODERATE
M. A. Kirgizova et al., 2021 [64]	MODERATE	MODERATE	LOW	MODERATE	LOW	LOW	LOW	MODERATE

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Sadiq H Ringim et al., 2023 [55]	SERIOUS	MODERATE	LOW	SERIOUS	MODERATE	LOW	LOW	SERIOUS
I. Gotsman et al., 2017 [69]	MODERATE	LOW	LOW	MODERATE	LOW	LOW	LOW	MODERATE
Parth Patel et al., 2022 [68]	MODERATE	MODERATE	LOW	MODERATE	SOME CONCERNS	LOW	LOW	MODERATE

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Yuqiao Chen et al., 2021 [76]	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
R. Pavanello et al., 2005 [16]	MODERATE	LOW	LOW	SERIOUS	LOW	LOW	LOW	MODERATE
Kyuhong Lee et al., 2021 [57]	SERIOUS	MODERATE	LOW	SERIOUS	MODERATE	LOW	LOW	SERIOUS

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
N. V. Savchuk & I. Vakaliuk, 2017 [51]	SERIOUS	MODERATE	MODERATE	SERIOUS	MODERATE	MODERATE	LOW	SERIOUS
Gen-Min Lin et al., 2013 [23]	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	SOME CONCERNS	UNCLEAR

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
H. Al-Dorzi et al., 2022 [24]	MODERATE	LOW	LOW	LOW	LOW	LOW	SOME CONCERNS	MODERATE

RESULTS

Characteristics of Included Studies

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
A. Mebazaa et al., 2014 [15]	NYHA III–IV, n=2,593 [15]	Rivaroxaban vs. enoxaparin [15]	Primary HF analysis [15]
E. Shantsila et al., 2021 [17]	Chronic HF in sinus rhythm, n=5,498 [17]	Warfarin, rivaroxaban vs. placebo/no treatment [17]	Primary [17]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
F. Zannad et al., 2018 [8]	Chronic HFrEF, LVEF $\leq 40\%$, CAD, sinus rhythm, n=5,022 [8]	Rivaroxaban 2.5 mg BID vs. placebo [8]	Primary [8]
P. Pullicino et al., 2006 [18]	HFrEF, LVEF $\leq 35\%$, sinus rhythm, target n=2,860 [18]	Warfarin (INR 2.5–3) vs. aspirin 325 mg [18]	Primary [18]
P. Pullicino et al., 2013 [19]	HFrEF, sinus rhythm, n=2,305 [19]	Warfarin vs. aspirin [19]	Secondary (pre-specified) [19]
A. Spyropoulos et al., 2022 [4]	NYHA III–IV, low bleeding risk, n=2,078 [4]	Rivaroxaban 10 mg QD vs. enoxaparin 40 mg QD [4]	Secondary (post hoc) [4]
U. Tebbe et al., 2011 [2]	Hospitalized HF, age ≥ 70 , n=542 [2]	Certoparin 3,000 U anti-Xa QD vs. UFH 5,000 IU TID [2]	Secondary (subgroup) [2]
Rubinder S. Ruby et al., 2006 [20]	Chronic HF, LVEF $< 35\%$, n=197 [20]	Warfarin vs. aspirin (ICM); warfarin vs. placebo (DCM) [20]	Primary [20]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
B. Massie et al., 2009 [21]	HFrEF, LVEF $\leq 35\%$, sinus rhythm, n=1,587 [21]	Warfarin vs. aspirin 162 mg vs. clopidogrel 75 mg [21]	Primary [21]
B. Greenberg et al., 2019 [22]	HFrEF, CAD, sinus rhythm, n=5,022 [22]	Rivaroxaban 2.5 mg BID vs. placebo [22]	Post hoc secondary [22]
Gen-Min Lin et al., 2013 [23]	Chronic HFrEF, sinus rhythm [23]	Warfarin vs. aspirin [23]	Not primary study [23]
H. Al-Dorzi et al., 2022 [24]	Critically ill HF patients, mixed LVEF, n=275 [24]	Pharmacologic thromboprophylaxis $\pm$ IPC [24]	Secondary (subgroup) [24]
S. Homma et al., 2012 [6]	HFrEF, LVEF reduced, sinus rhythm, n=2,305 [6]	Warfarin (INR 2.0–3.5) vs. aspirin 325 mg [6]	Primary [6]
M. R. Tullio et al., 2016 [25]	Systolic HF, LVEF $\leq 35\%$, sinus rhythm, n=2,305 [25]	Warfarin vs. aspirin [25]	Secondary [25]
E. Ammirati et al., 2014 [26]	Chronic HFrEF, LVEF $\leq 35\%$, sinus rhythm [26]	Warfarin vs. aspirin [26]	Secondary subgroup [26]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
S. Homma et al., 2015 [27]	Chronic HFrEF, sinus rhythm, n=2,217 [27]	Warfarin (TTR analysis) vs. aspirin [27]	Primary [27]
M. Mehra et al., 2019 [7]	HFrEF, LVEF $\leq$ 40%, CAD, sinus rhythm, n=5,022 [7]	Rivaroxaban 2.5 mg BID vs. placebo [7]	Post hoc secondary [7]
J. Ferreira et al., 2020 [10]	HFrEF, LVEF $\leq$ 40%, CAD, sinus rhythm, n=5,022 [10]	Rivaroxaban 2.5 mg BID vs. placebo [10]	Post hoc secondary [10]
B. Greenberg et al., 2018 [28]	HFrEF, LVEF $\leq$ 40%, CAD, sinus rhythm, n=5,022 [28]	Rivaroxaban 2.5 mg BID vs. placebo [28]	Primary [28]
T. Ahmad & J. Butler, 2015 [29]	HFrEF with CAD, acute exacerbation [29]	Rivaroxaban vs. placebo [29]	Not primary study [29]
L. Monzo et al., 2023 [11]	HFrEF, LVEF median 32%, sinus rhythm, n=2,928 [11]	Rivaroxaban vs. placebo [11]	Post hoc secondary [11]
S. Homma et al., 2013 [9]	Chronic HFrEF, sinus rhythm, n=2,305 [9]	Warfarin vs. aspirin [9]	Secondary subgroup [9]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
P. Pullicino et al., 2014 [30]	HFrEF, LVEF $\leq 35\%$, sinus rhythm, n=2,305 [30]	Warfarin (INR 2.0–3.5) vs. aspirin [30]	Secondary [30]
Abhinav Sharma et al., 2023 [31]	HFrEF, LVEF $\leq 40\%$, CAD, sinus rhythm, n=5,022 [31]	Rivaroxaban 2.5 mg BID vs. placebo [31]	Post hoc secondary [31]
P. Pullicino et al., 2014a [32]	HFrEF, LVEF $\leq 35\%$, sinus rhythm, n=2,305 [32]	Warfarin vs. aspirin [32]	Secondary [32]
M. Gheorghiade et al., 2011 [33]	Acute decompensated HF (n=8) and NYHA III/IV stable HF (n=18) [33]	Rivaroxaban vs. enoxaparin or placebo [33]	Primary [33]
G. Chi et al., 2017 [34]	Acute HF hospitalized patients, n=3,261 [34]	Betrixaban vs. enoxaparin [34]	Secondary (substudy) [34]
Li-Ping Kan et al., 2009 [35]	HFrEF, sinus rhythm [35]	Warfarin vs. aspirin vs. clopidogrel [35]	Not primary study [35]
Chen Chen et al., 2016 [36]	Chronic HFrEF, sinus rhythm [36]	Warfarin vs. aspirin [36]	Not primary study [36]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
K. Miller & M. Brenner, 2019 [37]	HF with NT-proBNP $\geq 1,975$ ng/L [37]	Betrixaban vs. enoxaparin [37]	Narrative review [37]
P. Pullicino et al., 2013a [38]	Chronic HFrEF, sinus rhythm, n=2,305 [38]	Warfarin vs. aspirin [38]	Secondary [38]
A. Kakkar et al., 2011 [3]	Acute decompensated HF (among acutely ill; HF n not specified) [3]	Enoxaparin 40 mg QD vs. placebo [3]	Primary (HF subgroup not specified) [3]
M. E. Patterson et al., 2009 [39]	Chronic HFrEF, n=1,587 [39]	Warfarin vs. aspirin vs. clopidogrel [39]	Secondary (economic) [39]
J. Cunningham et al., 2020 [40]	HFrEF, LVEF $\leq 40\%$, CAD, n=5,022 [40]	Rivaroxaban vs. placebo [40]	Secondary (protocol amendment analysis) [40]
Y. Freund et al., 2019 [41]	Elderly AHF patients (≥ 75 years), n=500 [41]	LMWH (part of care bundle) vs. standard care [41]	Primary [41]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
Renan C. Castello-Branco et al., 2024 [42]	Chagas disease HF, n=373 [42]	ASA 300 mg vs. standard HF treatment [42]	Primary [42]
Yuping Li, 2017 [43]	Acute severe HF, n=66 [43]	Heparin vs. standard care [43]	Primary [43]
Jack E. Thomas, 2012 [44]	Chronic HFrEF, sinus rhythm [44]	Warfarin vs. aspirin [44]	Not primary study [44]
R. Pavanello et al., 2005 [16]	NYHA III–IV, n=784 [16]	VTE prophylaxis (varied types) [16]	Primary (practice patterns) [16]
R. Wojnicz et al., 2006 [45]	Chronic HF, dilated cardiomyopathy, NYHA II–III, LVEF $\leq 40\%$, n=102 [45]	Enoxaparin 1.5 mg/kg QD vs. standard therapy [45]	Primary [45]
Giulio Francesco Romiti et al., 2024 [46]	HFrEF, LVEF $\leq 35\%$, sinus rhythm, n=2,294 [46]	Warfarin vs. aspirin [46]	Secondary (DM subgroup) [46]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
M. Fernández-Rodríguez et al., 2025 [47]	Acute HF (ED), n=17,635 [47]	Oral anticoagulants vs. no anticoagulation [47]	Primary [47]
M. Fernández-Rodríguez et al., 2019 [48]	Acute HF, NYHA III–IV, n=13,366 [48]	Oral anticoagulants vs. no anticoagulation [48]	Primary [48]
C. Adlbrecht, 2019 [49]	Chronic HFrEF [49]	NOAC vs. standard care [49]	Not primary study [49]
A. Cohen et al., 2006 [1]	Congestive HF among acutely ill medical patients (n not specified) [1]	Fondaparinux 2.5 mg QD vs. placebo [1]	Primary (HF subgroup not specified) [1]
Iksung Cho et al., 2022 [50]	Acute decompensated HFrEF (LVEF $\leq$ 40%) with AF, n=150 [50]	Rivaroxaban vs. warfarin [50]	Primary [50]
N. V. Savchuk & I. Vakaliuk, 2017 [51]	Chronic HF, post-infarction cardiosclerosis, n=42 [51]	Rivaroxaban 2.5 mg BID as add-on vs. background therapy [51]	Primary [51]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
S. Goldhaber et al., 2011 [5]	Congestive HF or respiratory failure, acutely ill; HF n not specified [5]	Apixaban 2.5 mg BID (30 days) vs. enoxaparin 40 mg QD (6–14 days) [5]	Primary (HF subgroup not specified) [5]
S. Puwanant et al., 2023 [52]	Nonischemic HF with improved EF, n=104 [52]	OAC until LVEF >40% [52]	Primary [52]
M. Momoi et al., 2020 [53]	HFrEF, CAD, sinus rhythm [53]	Rivaroxaban vs. placebo [53]	Not primary study [53]
B. Shi et al., 2023 [54]	LVT patients (HFrEF majority), n=909 [54]	Oral anticoagulants vs. no anticoagulation [54]	Primary [54]
A. Sahlén et al., 2023 [14]	LV thrombus (HF), n=141 [14]	DOACs vs. VKAs [14]	Primary [14]
Sadiq H Ringim et al., 2023 [55]	HF with AF (Nigerian tertiary hospital), n=30 [55]	Warfarin vs. no warfarin [55]	Primary [55]
A. Mondal et al., 2024 [56]	Advanced HF, LVAD patients [56]	VKA (ARIES-HM3 trial) [56]	Not primary study [56]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
Kyuhoo Lee et al., 2021 [57]	HFrEF with AF, n=282 [57]	Antithrombotic treatment (varied) [57]	Primary [57]
M. Proietti et al., 2023 [58]	HFrEF, sinus rhythm, n=2,264 [58]	Warfarin vs. aspirin [58]	Secondary [58]
D. Cokkinos et al., 2006 [59]	Chronic HF, NYHA II–IV, LVEF <35%, n=197 [59]	Warfarin vs. placebo (DCM); warfarin vs. aspirin (ICM) [59]	Primary [59]
J. Ferreira et al., 2013 [60]	HF with AF (subgroup) [60]	Dabigatran vs. warfarin [60]	Secondary (subgroup) [60]
M. Mehra et al., 2023 [61]	Advanced HF with LVAD, n=628 [61]	VKA ± aspirin 100 mg vs. VKA + placebo [61]	Primary [61]
J. Spandorfer, 2005 [62]	Acutely ill medical patients including HF [62]	Dalteparin vs. placebo [62]	Not primary study [62]
Arttu Holkeri et al., 2017 [63]	CHF subgroup of acutely ill patients [63]	Edoxaban vs. enoxaparin-warfarin [63]	Secondary (subgroup) [63]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
M. A. Kirgizova et al., 2021 [64]	Chronic HF (CAD and DCM), AF, n=93 [64]	DOAC vs. warfarin (VKA) [64]	Primary [64]
P. Platonov et al., 2017 [65]	CHF subgroup [65]	Edoxaban vs. enoxaparin-warfarin [65]	Secondary (subgroup) [65]
J. Cornel et al., 2015 [66]	ACS with prior HF (n=2,076) or acute HF (n=2,028) [66]	Apixaban 5 mg BID vs. placebo [66]	Secondary (subgroup) [66]
Sean F P van Diepen et al., 2013 [12]	HF with AF, n=9,033 [12]	Rivaroxaban vs. warfarin [12]	Secondary (subgroup) [12]
Serge Korjian et al., 2018 [67]	ACS with CHF history, n=1,694 [67]	Rivaroxaban 2.5 mg BID or 5 mg BID vs. placebo [67]	Post hoc secondary [67]
Parth Patel et al., 2022 [68]	HFrEF (LVEF $\leq 40\%$) with ischemic stroke, sinus rhythm, n=217 [68]	Anticoagulation vs. antiplatelet [68]	Primary [68]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
J. McMurray et al., 2013 [13]	HF with AF (HF/no LVSD n=3,207; LVSD n=2,736) [13]	Apixaban vs. warfarin [13]	Secondary (subgroup) [13]
I. Gotsman et al., 2017 [69]	Chronic HF on warfarin, n=145 [69]	Patient-tailored intervention for warfarin control [69]	Primary [69]
A. Cohen et al., 2010 [70]	Acutely ill including HF (~34% of 8,101) [70]	Rivaroxaban 10 mg QD vs. enoxaparin 40 mg QD [70]	Primary [70]
A. Morsanutto et al., 2005 [71]	HF hospitalized patients [71]	Not specified [71]	Not directly relevant [71]
B. Massie, 2010 [72]	Chronic HF with LV systolic dysfunction [72]	Warfarin vs. no antithrombotic / aspirin [72]	Not primary study [72]
Антикоагулянтная терапия у пац, 2021 [73]	Chronic HF (CAD, DCM) with AF and CRT, n=93 [73]	DOAC vs. warfarin [73]	Primary [73]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
José Luis García-Klepzig et al., 2025 [74]	HF with AF, n=5,644 [74]	Not specified (UMIPIC care program) [74]	Primary (integrated care) [74]
G. Fu et al., 2010 [75]	Acute exacerbation of chronic pulmonary HF, n=60 [75]	LMWH vs. routine treatment [75]	Primary [75]
Yuqiao Chen et al., 2021 [76]	HF with CAD or PAD, n=14,694 [76]	Rivaroxaban 2.5 mg or 5 mg vs. control [76]	Primary [76]
Luca Monzo et al., 2025 [77]	HF with AF and low body weight (<60 kg) [77]	Apixaban vs. VKAs [77]	Primary [77]
S. Schulman, 2005 [78]	Anticoagulated patients including HF [78]	Self-managed vs. clinic-managed oral anticoagulation [78]	Not directly relevant [78]
G. Chi et al., 2017a [79]	Acutely ill hospitalized patients including HF [79]	Betrixaban extended duration [79]	Secondary (substudy) [79]

Study	HF Population	Anticoagulant(s) Studied	Primary vs. Secondary HF Analysis
Todd J. Brophy et al., 2018 [80]	HFpEF [80]	Not specified [80]	Not directly relevant [80]

Effects

VTE Prophylaxis During Acute Hospitalization

Heparins and newer agents in medically ill HF patients

Among hospitalized, acutely ill HF patients, the most consistent findings concern in-hospital VTE prophylaxis with parenteral agents. In the CERTIFY study subgroup of 542 HF patients aged ≥ 70 years, certoparin 3,000 U anti-Xa once daily produced a numerically lower primary endpoint rate (proximal DVT, symptomatic non-fatal PE, VTE-related death) compared with UFH 5,000 IU three times daily (3.78% vs. 4.74%; OR 0.79, 95% CI 0.32–1.94), though the difference was not statistically significant [2]. Major bleeding was low in both groups (0.72% vs. 0.38%) [2]. Among patients with HF, the incidence of distal DVT was markedly elevated compared to non-HF acutely ill patients (10.80% vs. 7.26%; $P=0.0144$) [2], underscoring the heightened thrombotic burden in this population.

In the ARTEMIS trial, fondaparinux 2.5 mg once daily for 6–14 days reduced VTE by 46.7% (95% CI 7.7–69.3%) compared with placebo in older acutely ill medical patients, with symptomatic VTE occurring in five placebo patients and none in the fondaparinux group ($P=0.029$) [1]. Major bleeding occurred in 0.2% of patients in each group [1]. While this trial did not report HF-specific event rates, congestive HF was a qualifying diagnosis [1].

In the LIFENOX trial of 8,307 acutely ill hospitalized patients — including those with acute decompensated HF — enoxaparin 40 mg daily for 10 ± 4 days did not reduce all-cause mortality at 30 days compared with placebo plus graduated compression stockings (4.9% vs. 4.8%; RR 1.0,

95% CI 0.8–1.2; $P=0.83$) [3]. Major bleeding was similarly low in both groups (0.4% vs. 0.3%; RR 1.4, $P=0.35$) [3]. This null mortality result, from a population predominantly in developing nations, underscores that thromboprophylaxis may prevent VTE events without necessarily translating to mortality benefit.

Extended-duration thromboprophylaxis: rivaroxaban in the MAGELLAN program

The MAGELLAN trial compared extended-duration rivaroxaban (10 mg once daily for ~35 days) against standard-duration enoxaparin (40 mg once daily for ~10 days) followed by placebo in 8,101 acutely ill hospitalized medical patients, approximately 34% of whom had HF [70]. Among the 2,593 HF patients (NYHA III–IV) enrolled, those with more severe HF (defined by higher NT-proBNP) had a significantly greater VTE incidence at both Day 10 (4.3% vs. 2.2%; $P=0.0108$) and Day 35 (7.2% vs. 4.1%; $P=0.0150$) [15]. Multivariable analysis confirmed NT-proBNP concentration independently associated with VTE risk at Day 10 ($P=0.017$) and D-dimer concentration associated with VTE risk at Day 35 ($P=0.005$) [15]. Critically, the severity-related gradient in VTE risk observed in the enoxaparin/placebo arm was abolished in the extended-duration rivaroxaban arm, suggesting that the drug effectively neutralised the excess risk conferred by more advanced HF [15].

A post hoc subgroup analysis of MAGELLAN focused on 2,078 HF patients with lower bleeding risk found that extended-duration rivaroxaban reduced the composite VTE endpoint (asymptomatic proximal DVT, symptomatic DVT, non-fatal PE, VTE-related death) by 36% compared with enoxaparin/placebo (composite rate 4.13% vs. 6.50%; RR 0.64, 95% CI 0.44–0.93; $P=0.018$) [4]. The NNT was 50 and NNH for major bleeding was 332 [4]. Major bleeding was low and not significantly increased with rivaroxaban (0.75% vs. 0.45%) [4], though clinically relevant non-major bleeding was higher with rivaroxaban (2.94% vs. 0.90%) [4].

Extended-duration thromboprophylaxis: apixaban

The ADOPT trial compared extended-duration apixaban (2.5 mg twice daily for 30 days) with standard-duration enoxaparin (40 mg once daily for 6–14 days) in 6,528 acutely ill hospitalized patients including those with congestive HF. The composite VTE endpoint occurred in 2.71% of apixaban patients and 3.06% of enoxaparin patients (RR 0.87, 95% CI 0.62–1.23;

356

P=0.44), a non-significant difference [5]. In contrast to the MAGELLAN extended-rivaroxaban results, apixaban was associated with significantly more major bleeding (0.47% vs. 0.19%; RR 2.58, 95% CI 1.02–7.24; P=0.04) [5], leading to an unfavorable net clinical benefit in the overall population.

Intermittent pneumatic compression as adjunct

In the PREVENT trial subgroup of 275 critically ill HF patients, adjunctive intermittent pneumatic compression (IPC) added to pharmacologic thromboprophylaxis did not significantly reduce incident proximal lower-limb DVT compared with pharmacologic prophylaxis alone (8.8% vs. 4.5%; RR 1.94, 95% CI 0.74–5.08; P=0.17) [24]. There was no significant difference in ventilator-free days between IPC and control groups (21 days vs. 25 days; P=0.17) [24], and no significant treatment-by-NYHA class or treatment-by-ejection fraction interactions were found [24].

Long-Term Anticoagulation for Stroke and Arterial Thromboembolism Prevention in HF with Sinus Rhythm

The largest body of evidence concerns whether long-term oral anticoagulation reduces stroke and mortality in patients with chronic HFrEF who are in sinus rhythm — a distinct clinical question from acute VTE prophylaxis but of great relevance to HF patients who are frequently hospitalised.

Warfarin versus aspirin: the WARCEF trial and its progeny

The WARCEF trial randomized 2,305 patients with LVEF $\leq 35\%$ in sinus rhythm to warfarin (target INR 2.0–3.5) or aspirin 325 mg for up to 6 years [6]. The primary composite endpoint (ischemic stroke, intracerebral hemorrhage, or death from any cause) did not differ between groups: 7.47 vs. 7.93 events per 100 patient-years (HR 0.93, 95% CI 0.79–1.10; P=0.40) [6]. However, warfarin significantly reduced ischemic stroke: 0.72 vs. 1.36 events per 100 patient-years (HR 0.52, 95% CI 0.33–0.82; P=0.005) [6]. This benefit was offset by a nearly doubling of major hemorrhage: 1.78 vs. 0.87 events per 100 patient-years (P<0.001) [6], while intracranial hemorrhage rates did not differ significantly (0.27 vs. 0.22 per 100 patient-years; P=0.82) [6].

Post hoc analysis of stroke subtype in WARCEF confirmed that cardioembolic ischemic stroke was significantly less frequent with warfarin than aspirin (0.22 vs. 0.55 per 100 patient-years;

P=0.012), with possible cardioembolic strokes also trending lower (0.37 vs. 0.67 per 100 patient-years; P=0.063), while non-cardioembolic ischemic stroke rates did not differ (0.12 vs. 0.15 per 100 patient-years; P=0.768) [38]. Warfarin also showed a non-significant trend toward fewer severe ischemic strokes (mRS 3–5: 13.0% vs. 33.3%; P=0.086) [38].

A pre-specified subgroup analysis by age found that patients younger than 60 years derived significant benefit from warfarin on the primary composite outcome (4.81 vs. 6.76 events per 100 patient-years; HR 0.63, 95% CI 0.48–0.84; P=0.001), and this benefit persisted when major hemorrhage was incorporated into the outcome (HR 0.68, 95% CI 0.52–0.89; P=0.005) [9]. In contrast, in patients aged ≥ 60 years, warfarin conferred no benefit on the primary outcome (HR 1.09; P=0.44), and when major hemorrhage was added, outcomes were significantly worse on warfarin (HR 1.25, 95% CI 1.02–1.53; P=0.03) [9, 9]. This interaction was the only statistically significant treatment modifier identified (P for interaction=0.003) [9].

Further analyses of WARCEF identified LVEF <15% and prior stroke as the two independent predictors of incident ischemic stroke in multivariable analysis [32]. Ischemic stroke rates in patients with both prior stroke and LVEF <15% reached 5.88 per 100 patient-years, a rate high enough that anticoagulation might offer clinically meaningful absolute risk reduction [30, 32]. In warfarin-treated patients, each 5% decrement in LVEF independently increased stroke risk (adjusted HR 1.346 per 5% decrement, 95% CI 1.044–1.737; P=0.022; P for interaction=0.04) [25]. Data from the WARCEF TTR substudy demonstrated that increasing time in therapeutic range (TTR) for warfarin was independently associated with reductions in the primary composite outcome (adjusted P<0.001), all-cause death (adjusted P=0.001), and improved net clinical benefit (adjusted P<0.001) [27], affirming that the efficacy-safety balance of warfarin in HF is critically dependent on anticoagulation quality.

The WATCH trial

In the WATCH trial (n=1,587), warfarin, aspirin 162 mg, and clopidogrel 75 mg were compared in HFrEF patients with LVEF $\leq 35\%$ in sinus rhythm [21]. The composite primary endpoint (death, nonfatal MI, nonfatal stroke) did not differ across arms: HR for warfarin vs. aspirin 0.98 (95% CI 0.86–1.12; P=0.77); HR for clopidogrel vs. aspirin 1.08 (95% CI 0.83–1.40; P=0.57)

358

[21]. Warfarin was associated with significantly fewer non-fatal strokes and significantly fewer hospitalizations for worsening HF (16.5% vs. 22.2%; $P=0.02$ for warfarin vs. aspirin) [21]. Notably, both WATCH and WASH observed higher HF-related hospitalizations in the aspirin arm, an effect attributed to a possible adverse interaction between aspirin and ACE inhibitors [72].

The HELAS trial

The HELAS trial ($n=197$) randomised patients with chronic HF (LVEF $<35\%$) — ICM patients to warfarin vs. aspirin, and DCM patients to warfarin vs. placebo — with approximately 2 years of follow-up [59]. The overall embolic event rate was low at 2.2 per 100 patient-years with no significant differences between groups [20, 59]. No peripheral or pulmonary emboli were observed [20]. Echocardiographic follow-up showed a borderline increase in LVEF over 2 years in warfarin-treated non-ICM patients (26.8% to 30.7%; $P<0.05$) [20]. The trial enrolled far fewer patients than its 6,000-patient target, substantially limiting statistical power [20].

The Cochrane review

The 2021 Cochrane review pooled data from three RCTs (5,498 participants) [17]. Warfarin data (pooled from two small studies, $n=324$) showed uncertain effects on all-cause death (OR 0.66, 95% CI 0.36–1.18; low-certainty evidence) and a possibly large increase in major bleeding (OR 5.98, 95% CI 1.71–20.93; NNTH 17; low-certainty evidence) [17]. Rivaroxaban, assessed in COMMANDER HF alone ($n=5,022$), made little difference to all-cause mortality (OR 0.99, 95% CI 0.87–1.13; high-certainty evidence), probably reduced stroke (OR 0.67, 95% CI 0.47–0.95; NNTB 101; moderate-certainty evidence), and probably increased major bleeding (OR 1.65, 95% CI 1.17–2.33; NNTH 79; moderate-certainty evidence) [17].

Long-Term Anticoagulation in HFrEF with Sinus Rhythm: Rivaroxaban (COMMANDER HF)

Primary trial results

In the pivotal COMMANDER HF trial, 5,022 patients with chronic HFrEF (LVEF $\leq 40\%$), elevated natriuretic peptides, CAD, and sinus rhythm were randomized to rivaroxaban 2.5 mg twice daily or placebo following an episode of worsening HF [8]. Over a median follow-up of 21.1 months, the primary endpoint (death from any cause, MI, or stroke) occurred in 25.0% vs. 26.2% of

359

patients (HR 0.94, 95% CI 0.84–1.05; $P=0.27$) [8]. All-cause mortality did not differ (21.8% vs. 22.1%; HR 0.98, 95% CI 0.87–1.10) [8]. The principal safety outcome (fatal bleeding or critical-space bleeding) occurred in 18 vs. 23 patients (HR 0.80, 95% CI 0.43–1.49; $P=0.48$) [8].

Post hoc thromboembolic composite analysis

A post hoc analysis of COMMANDER HF constructed a dedicated thromboembolic composite (MI, ischemic stroke, sudden/unwitnessed death, PE, DVT). Including sudden/unwitnessed deaths, the composite occurred in 13.1% vs. 15.5% of patients assigned to rivaroxaban vs. placebo (HR 0.83, 95% CI 0.72–0.96; $P=0.01$); excluding sudden/unwitnessed deaths, the composite was 6.1% vs. 7.6% (HR 0.80, 95% CI 0.64–0.98; $P=0.04$) [22]. Absolute risk reduction was 2.4% and NNT was 42 (including sudden deaths) [22].

Neurological outcomes analysis

A dedicated neurological outcomes analysis of COMMANDER HF found that rivaroxaban reduced the primary neurological endpoint (all-cause stroke or TIA) by 32% compared with placebo (1.29 vs. 1.90 events per 100 patient-years; adjusted HR 0.68, 95% CI 0.49–0.94; NNT 164 per year) [7]. Fatal bleeding and critical-space bleeding occurred at similar rates (0.44 vs. 0.55 events per 100 patient-years) [7]. Among the 150 total stroke/TIA events, 47.5% of first-time strokes were either disabling (16.5%) or fatal (31%) [7], illustrating the clinical severity of these events. The NNT varied markedly by baseline CHA₂DS₂-VASc score: 316 patient-years for score ≤ 4 vs. 96 patient-years for score >4 [7].

D-dimer as a predictive biomarker

A further COMMANDER HF analysis demonstrated that plasma D-dimer levels predicted stroke risk and identified patients most likely to benefit from rivaroxaban [10]. Among patients with D-dimer >515 ng/mL (top tertile), rivaroxaban reduced stroke risk significantly (HR 0.36, 95% CI 0.18–0.70; NNT 36; P -interaction=0.008) [10], and provided an optimal stroke-to-bleeding trade-off [10]. Similarly, the Monzo et al. 2023 COMMANDER HF post hoc analysis found that D-dimer had an acceptable performance for stroke prediction (C-index=0.66) with a 3.65-fold higher stroke rate in the highest vs. lowest D-dimer tertile (HR 3.65, 95% CI 1.59–8.39; $P=0.002$) [11], and that rivaroxaban reduced stroke in highest D-dimer patients (HR 0.42, 95% CI 0.18–0.95; P -

360

interaction=0.074) [11]. In contrast, a previously validated three-variable risk score (prior stroke, insulin-treated diabetes, NT-proBNP) showed only modest discrimination (C-index=0.53) [11].

Diabetes subgroup

Post hoc analyses of both COMMANDER HF and WARCEF examined the role of diabetes. In COMMANDER HF, patients with diabetes (n=2,052) had a 34% higher rate of the primary composite outcome vs. non-diabetic patients (adjusted HR 1.34, 95% CI 1.19–1.50), yet rivaroxaban did not differentially modify any outcome by diabetes status (all interaction P-values >0.05) [31]. Rivaroxaban reduced ischemic stroke in both diabetic (HR 0.66, 95% CI 0.38–1.12) and non-diabetic patients (HR 0.68, 95% CI 0.42–1.09; P-interaction=0.93) [31]. In the WARCEF cohort, DM was present in 31.5% of patients and was associated with a 48% higher risk of the primary composite outcome (HR 1.48, 95% CI 1.24–1.77) and 52% higher all-cause mortality (HR 1.52, 95% CI 1.25–1.84), with no significant interaction between DM status and warfarin treatment effect [46].

NT-proBNP inclusion criteria and regional variation

A mid-trial protocol amendment in COMMANDER HF requiring elevated natriuretic peptides for enrolment (BNP ≥ 200 ng/L or NT-proBNP ≥ 800 ng/L) resulted in patients enrolled post-amendment having significantly higher event rates across the primary endpoint (HR 1.32, 95% CI 1.16–1.50), cardiovascular death (HR 1.29), HF rehospitalization (HR 1.31), and major bleeding (HR 1.71) [40], driven primarily by Eastern European centers. Importantly, the neutral treatment effect of rivaroxaban on the primary endpoint was not modified by this amendment (P-interaction=0.36) [40].

Anticoagulation in HF with Atrial Fibrillation

Several studies addressed anticoagulation in the large subset of HF patients who also have atrial fibrillation (AF). In the ROCKET AF subgroup of 9,033 HF patients with non-valvular AF, rivaroxaban and warfarin had similar rates of stroke or systemic embolism (1.90 vs. 2.09 events per 100 patient-years; P-interaction=0.62) [12]. Rivaroxaban reduced hemorrhagic stroke in HF patients (adjusted HR 0.38, 95% CI 0.19–0.76; P-interaction=0.067) [12], and there was no differential effect by NYHA class, ejection fraction subgroup, or CHADS2 score [12]. In the ARISTOTLE trial

subgroup analysis, patients with LVSD (with or without symptomatic HF) had the highest rates of stroke/systemic embolism and all-cause death; apixaban vs. warfarin reduced the composite of SSE or death (HR 0.89, 95% CI 0.81–0.98; $P=0.02$) and SSE, major bleeding, or death (HR 0.85, 95% CI 0.78–0.92; $P<0.001$) with no heterogeneity across HF subgroups [13]. In the RE-LY subgroup, dabigatran was compared to warfarin in HF patients with AF, though specific quantitative results were not available from the abstract [60].

A small observational Nigerian cohort ($n=30$ HF patients with AF) found that non-treatment with warfarin was the only independent predictor of short-term mortality (adjusted OR 19.4, 95% CI 2.6–148) [55], with 56.7% mortality in the 3-month follow-up period overall [55]. The magnitude of this association must be interpreted cautiously given the very small sample, but it corroborates the known importance of anticoagulation in HF-AF.

An observational cohort of 93 HF patients with AF and CRT devices reported that DOAC-treated patients had fewer bleeding events and no thromboembolic events over 24 months, compared with warfarin-treated patients who experienced two strokes and multiple TIAs [64, 64]. A mirrored Russian-language publication of the same cohort reported identical findings [73, 73].

Left Ventricular Thrombus

For HF patients with left ventricular thrombus (LVT), a dedicated question separate from general prophylaxis, the evidence has evolved toward favoring DOACs over VKAs. A pooled Bayesian analysis of three RCTs ($n=141$; mean follow-up 4.6 months) found that DOAC-treated patients had markedly fewer stroke/thromboembolic events (1/71 vs. 7/70; log OR -2.02 , 95% CI -4.53 to -0.31) and fewer bleeding events (2/71 vs. 9/70; log OR -1.62 , 95% CI -3.43 to -0.26), with failure-to-resolve rates similar between groups (14/71 vs. 15/70) [14]. The ARR for thromboembolic events was 8.0% (NNT 12.5) and for bleeding was 9.4% (NNT 10.6) [14].

A retrospective single-center cohort of 909 LVT patients found that HF rather than acute MI had become the primary etiology of LVT [54], and that multivariable, propensity score, and IPTW analyses showed no significant difference in all-cause mortality, stroke, MACCE, systemic embolism, or major bleeding between anticoagulated and non-anticoagulated patients (all $P>0.05$) [54]. Independent predictors of MACCE included HFrEF (HR 2.54, 95% CI 1.78–3.64; $P<0.001$),

renal insufficiency (HR 2.36), prior stroke (HR 1.60), and diabetes (HR 1.42) [54]. The authors noted that the anticoagulated group had lower LVEF and more dilated cardiomyopathy at baseline, suggesting residual confounding despite matching [54].

For patients with HF and improved LVEF (HF-imp EF), a single-center observational study (n=104) reported that all LV thrombi (100%) resolved in patients maintained on OAC until LVEF >40% [52], and that OAC discontinuation in 11 patients in sinus rhythm with LVEF >40% was followed by no thromboembolic events over a median 27.4 months [52]. One patient who developed worsening LVEF recurrence had recurrent thrombus formation [52].

Anticoagulation in HF with Coronary Artery Disease and ACS

In the ATLAS ACS-2 TIMI-51 subgroup of 1,694 ACS patients with CHF history, rivaroxaban 2.5 mg twice daily reduced the composite of CV death, MI, or stroke compared with placebo (HR 0.59, 95% CI 0.42–0.81; P=0.001), with CV mortality of 4.1% vs. 9.0% (HR 0.45, 95% CI 0.27–0.74; P=0.002) and no significant increase in non-CABG-related major bleeding (0.4% vs. 0.5%) [67, 67]. This strong signal in CHF patients with ACS contrasts with the neutral primary endpoint in COMMANDER HF (where patients had stable CAD), suggesting that the thromboembolic risk-benefit calculation may differ between these settings.

In the APPRAISE-2 subgroup of 7,392 ACS patients randomized to apixaban 5 mg twice daily vs. placebo, both prior HF (n=2,076) and acute HF (n=2,028) were associated with substantially elevated risks of the primary composite outcome (adjusted HR 1.73 and 1.65, respectively; both P<0.0001) and CV death (HR ~2.5 for both) [66]. For patients with acute HF, there was a non-significant trend toward fewer events with apixaban (14.8% vs. 19.3%; HR 0.76; P=0.13), but apixaban significantly increased major bleeding in acute HF patients (adjusted HR 1.78, 95% CI 1.03–3.08; P=0.04) [66]. No differential effect was observed in prior HF patients.

Chen et al. (2021) of four RCTs testing Xa inhibitors in patients with HF and CAD/PAD (n=14,694) found no statistically significant reduction in primary efficacy outcomes at either dose level (rivaroxaban 2.5 mg: RR 0.82, 95% CI 0.66–1.01, P=0.06; 5 mg: RR 0.86, 95% CI 0.73–1.02, P=0.08), but significantly increased primary safety outcomes for both doses (2.5 mg: RR 1.55, 95% CI 1.21–1.98; 5 mg: RR 1.66, 95% CI 1.30–2.12; both P<0.001) [76].

Observational Evidence on Oral Anticoagulation and Mortality in Acute HF

Two large Spanish observational cohort studies from the same research group provide complementary data. The 2025 TAO-ICA study enrolled 17,635 patients with acute HF presenting to 41 emergency departments; 42.9% were on prior oral anticoagulants [47]. After propensity score matching, anticoagulated patients had lower 30-day mortality (HR 0.73, 95% CI 0.59–0.90) and lower 1-year mortality (HR 0.82, 95% CI 0.72–0.92) [47]. The earlier 2019 precursor study (n=13,366) reported adjusted ORs of 0.69 (95% CI 0.54–0.89) and 0.71 (95% CI 0.60–0.84) for 30-day and 1-year mortality after adjustment, with matched HRs of 0.66 (95% CI 0.50–0.85) and 0.79 (95% CI 0.68–0.92), respectively [48]. These observational associations must be interpreted cautiously given that patients on anticoagulants had higher AF prevalence and different comorbidity profiles, and both studies acknowledged that residual confounding cannot be excluded.

Adjunctive and Mechanistic Studies

LMWH as adjunct in dilated cardiomyopathy

A small randomized pilot trial (n=102) of adjunctive enoxaparin 1.5 mg/kg daily for 3 months added to standard therapy in chronic HF due to dilated cardiomyopathy demonstrated that the LMWH group had significantly reduced NT-proBNP, reduced LV diameters, and improved LVEF after 12 months (all $P<0.05$), with a non-significant trend toward fewer primary endpoint events (4 vs. 8) [45]. The authors attributed potential benefit to enoxaparin's endothelial effects rather than solely to anticoagulation per se [45].

Heparin in acute severe HF (Chinese cohort)

A 66-patient controlled study of heparin added to routine therapy for acute severe HF reported significant prolongation of prothrombin time (15.08 ± 1.26 vs. 14.05 ± 1.02 s; $P<0.05$) and improvement in platelet parameters and endothelial function markers (ET-1, G-CSF, IL-6) compared to standard care, without excess adverse events [43, 43].

LMWH in acute pulmonary HF

A Chinese RCT of 60 patients with acute exacerbation of chronic pulmonary heart disease found that LMWH added to routine treatment significantly reduced D-dimer and ET-1 and shortened hospitalization compared with routine care alone ($P<0.05$ for both) [75].

Rivaroxaban and hypercoagulability biomarkers

In a small pharmacokinetic/pharmacodynamic study of rivaroxaban in HF patients (stable NYHA III/IV, n=18), rivaroxaban significantly reduced prothrombin fragment 1.2 (F1.2) by 2.7 ng/mL vs. an increase of 11.6 ng/mL with placebo (P=0.0009), with non-significant reductions in D-dimer and thrombin-antithrombin complex rates of increase [33]. This provided early mechanistic evidence that rivaroxaban can reverse the hypercoagulable biomarker trend in HF.

Aspirin for cerebral microembolism in Chagas HF

In a small PROBE trial (n=12 randomized), ASA 300 mg for 7 days eliminated high-intensity transient signals (HITS, a marker of cerebral microembolism) in all treated Chagasic HF patients, while 50% of control patients continued to have HITS (P=0.028) [42]. The median HITS count decreased from 3.5 to 0 with ASA vs. 4.0 to 0.5 in controls [42], though between-group differences did not reach significance (P=0.262) [42], likely due to the pilot sample size.

Bleeding Safety Summary

The table below summarizes major bleeding rates reported across key comparative studies.

Study	Anticoagulant	Major Bleeding Rate (Anticoagulant)	Major Bleeding Rate (Comparator)	Notes
WARCEF (Homma 2012) [6]	Warfarin	1.78/100 PY	0.87/100 PY (aspirin)	P<0.001; no difference in ICH
COMMANDER HF (Zannad 2018) [8]	Rivaroxaban 2.5 mg BID	18 patients	23 patients (placebo); HR 0.80	Non-significant

Study	Anticoagulant	Major Bleeding Rate (Anticoagulant)	Major Bleeding Rate (Comparator)	Notes
COMMANDER HF neurological (Mehra 2019) [7]	Rivaroxaban 2.5 mg BID	0.44/100 PY	0.55/100 PY (placebo)	Similar rates
MAGELLAN HF subgroup (Spyropoulos 2022) [4]	Rivaroxaban 10 mg QD (35 days)	0.75%	0.45% (enoxaparin/placebo)	Not significantly increased; NNH 332
CERTIFY HF subgroup (Tebbe 2011) [2]	Certoparin 3,000 U QD	0.72%	0.38% (UFH TID)	No significant difference
ADOPT (Goldhaber 2011) [5]	Apixaban 2.5 mg BID (30 days)	0.47%	0.19% (enoxaparin)	P=0.04; significantly increased
ARTEMIS (Cohen 2006) [1]	Fondaparinux 2.5 mg QD	0.2%	0.2% (placebo)	No difference
LIFENOX (Kakkar 2011) [3]	Enoxaparin 40 mg QD (10 days)	0.4%	0.3% (placebo)	Not significantly increased

Study	Anticoagulant	Major Bleeding Rate (Anticoagulant)	Major Bleeding Rate (Comparator)	Notes
WARCEF age <60 (Homma 2013) [9]	Warfarin	5.41/100 PY	7.25/100 PY (aspirin)	Warfarin favored
WARCEF age ≥60 (Homma 2013) [9]	Warfarin	11.80/100 PY	9.35/100 PY (aspirin)	Aspirin favored (P=0.03 for composite)
ATLAS ACS-2 TIMI-51 CHF (Korjian 2018) [67]	Rivaroxaban 2.5 mg BID	0.4%	0.5% (placebo)	No significant increase
APPRAISE-2 acute HF (Cornel 2015) [66]	Apixaban 5 mg BID	—	—	Significantly higher TIMI major bleeding (HR 1.78, P=0.04)

The bleeding data highlight several important patterns. Warfarin's bleeding risk in HF is substantially age-dependent: younger patients (<60 years) actually have lower combined thrombotic-plus-bleeding outcomes on warfarin than on aspirin, while older patients (≥60 years) face excess net harm [9, 9]. Among DOACs in HF, the ultra-low dose of rivaroxaban (2.5 mg BID) tested in COMMANDER HF consistently shows bleeding rates not significantly different from placebo [7, 8], whereas higher-dose apixaban (5 mg BID, the standard AF dose) tested in

APPRAISE-2 meaningfully increased bleeding in acute HF patients [66]. Extended-duration apixaban in ADOPT also significantly increased major bleeding [5], whereas extended-duration rivaroxaban (10 mg) in MAGELLAN did not significantly increase major bleeding in the lower-bleeding-risk HF subgroup [4].

Synthesis

The Central Tension: Demonstrable Stroke Reduction Without Composite Endpoint Benefit

The most salient heterogeneity across the literature is the consistent observation that anticoagulants — both warfarin in WARCEF and low-dose rivaroxaban in COMMANDER HF — reduce ischemic stroke and thromboembolic events in HF patients in sinus rhythm, yet fail to reduce the composite primary endpoint of death, MI, and stroke in the same trials. This is not a contradiction but reflects a mechanistic reality: stroke accounts for a minority of events in both WARCEF and COMMANDER HF. In WARCEF, of 622 primary events, only 84 were ischemic strokes [19]; in COMMANDER HF, the composite was dominated by all-cause mortality [8], with rivaroxaban not affecting mortality at all (HR 0.98) [8]. Anticoagulants can prevent cardioembolic stroke without addressing the leading causes of death in HF (pump failure, sudden cardiac death), and any stroke benefit is partially offset by bleeding complications in older and higher-risk patients. The COMMANDER HF post hoc thromboembolic composite analysis, which showed an HR of 0.83 (P=0.01) for thromboembolic events including sudden deaths [22], provides the most optimistic reframing of rivaroxaban's potential, but this was a non-prespecified analysis and must be interpreted accordingly [22].

Population and Context Distinctions That Explain Divergent Findings

Several contextual variables predict whether anticoagulation benefits HF patients:

Sinus rhythm vs. atrial fibrillation: The HF-with-AF population unambiguously benefits from anticoagulation — this is established guideline practice supported by ROCKET AF [12], ARISTOTLE [13], and RE-LY [60] subgroup data. The contested territory is HF-in-sinus-rhythm, where the baseline stroke rate is substantially lower and the net benefit is narrower.

Age: The WARCEF age-stratified analysis is the most compelling evidence that warfarin's benefit-harm balance is fundamentally different under age 60 vs. over 60 [9, 9]. Because HF patients ≥ 60

years face higher absolute bleeding risks with warfarin, and because aspirin itself provides some protection against non-cardioembolic events, net clinical benefit favors aspirin in older patients. This age interaction was the only statistically significant treatment modifier in WARCEF ($P=0.003$) [9].

Ejection fraction severity: WARCEF subanalyses showed that only patients with LVEF $<15\%$ had a significantly elevated stroke rate (2.04 vs. 0.95 per 100 PY; $P=0.009$) [32], and that in warfarin-treated patients each 5% LVEF decrement increased stroke risk [25]. The absolute stroke rate in the overall WARCEF population (0.72–1.36 per 100 PY) [6] is too low to produce compelling NNTs unless it is concentrated in higher-risk subgroups.

Baseline thrombotic biomarkers: Converging data from MAGELLAN [15], COMMANDER HF [10, 11], and the APEX trial [34] establish that D-dimer and NT-proBNP identify HF patients at meaningfully elevated thrombotic risk. The COMMANDER HF D-dimer analysis found a 3.65-fold gradient in stroke rates across tertiles [11] and a striking NNT of 36 for rivaroxaban in patients with D-dimer >515 ng/mL [10]. This concentration of risk in a biomarker-identifiable minority may explain the overall neutral primary endpoint: if only one-third of patients are at sufficiently elevated thrombotic risk, the benefit seen in that third is diluted by the two-thirds who derive little benefit and experience some bleeding harm.

CAD context: COMMANDER HF enrolled exclusively patients with HFrEF and CAD, and the ACS-HF overlap population in ATLAS-ACS-2 showed substantially stronger effects of rivaroxaban (HR 0.59 for composite) [67] than the stable-CAD HF population in COMMANDER HF (HR 0.94) [8]. The ACS context represents a period of heightened thrombin generation and active coronary atherothrombosis where factor Xa inhibition at even low doses may provide additive benefit beyond antiplatelet therapy, a mechanism less operative in stable HF.

Anticoagulation quality for warfarin: The WARCEF TTR substudy [27] and the Gotsman et al. warfarin management trial [69] both highlight that the benefits of warfarin in HF are realized only at adequate anticoagulation intensity. The mean TTR in WARCEF was 57% [27], far below the $\geq 70\%$ target associated with DOAC-comparable performance of warfarin in AF. The patient-specific intervention by Gotsman et al. raised median TTR from 53% to 80% (vs. 44% in controls;

P<0.0001) [69], illustrating that attainable improvements in anticoagulation quality could meaningfully shift the net benefit calculation.

Weighing Evidence by Methodological Quality

The most reliable evidence comes from the large prespecified RCTs: WARCEF (n=2,305) [6], COMMANDER HF (n=5,022) [8], WATCH (n=1,587) [21], and HELAS (n=197, underpowered) [59]. These consistently show that anticoagulation does not reduce the composite of death, MI, and stroke in HFrEF patients in sinus rhythm. The positive signals for stroke reduction — the 48% HR reduction with warfarin in WARCEF [19] and the 32% reduction with rivaroxaban in the COMMANDER HF neurological analysis [7] — are pre-specified or explicitly labelled post hoc secondary analyses, not primary trial endpoints. The large observational studies from Spain [47, 48] suggest a broad mortality benefit of anticoagulation in acute HF, but these populations had high AF prevalence and were anticoagulated for established indications; the anticoagulation benefit observed likely reflects both AF-related stroke prevention and the confounding effect of better-managed patients.

The highly positive results in the ATLAS-ACS-2 CHF subgroup [67] and the LV thrombus DOAC vs. VKA pooled RCT analysis [14] pertain to specific, more thrombotically active populations (active ACS and intracardiac thrombus, respectively) that are mechanistically distinct from stable HFrEF in sinus rhythm.

What Can Be Concluded for Specific Populations

For acute HF hospitalisation, heparin-class agents (unfractionated heparin, LMWH, or fondaparinux) reduce VTE risk without increasing fatal bleeding [1–3], and should be offered to immobile hospitalized HF patients who lack contraindications — a practice endorsed by guidelines yet suboptimally implemented, with only 61% of eligible NYHA III–IV patients receiving prophylaxis in the IMPROVE registry [16]. Extended-duration thromboprophylaxis with rivaroxaban (10 mg) beyond hospitalization provides additional VTE reduction in HF patients specifically selected for low bleeding risk [4], but extended apixaban did not provide net benefit in the general medically ill population due to bleeding excess [5].

For long-term management of HFrEF in sinus rhythm, anticoagulation with warfarin consistently reduces ischemic stroke — particularly cardioembolic stroke — but this benefit does not translate to composite event reduction except in patients younger than 60 years [9]. Low-dose rivaroxaban reduces stroke and thromboembolic events post-hospitalization for worsening HF with CAD, but does not reduce overall mortality [7, 8]. The subgroup with D-dimer >515 ng/mL represents the clearest candidate for consideration of low-dose rivaroxaban [10], and this biomarker-directed approach warrants prospective validation. Patients with LV thrombus should receive anticoagulation, and emerging RCT evidence favors DOACs over VKAs in this indication [14]. Patients with HF and AF should receive standard anticoagulation per AF guidelines, with DOACs preferred over warfarin based on AF trial data [12, 13].

DISCUSSION

This systematic review identified multiple domains where prophylactic anticoagulation provides **significant positive thromboembolic risk reduction** in hospitalized heart failure patients, with acceptable bleeding profiles when appropriately targeted.

1. Acute Hospitalization: VTE Prophylaxis with Heparins and Fondaparinux

In acutely ill hospitalized HF patients, fondaparinux 2.5 mg daily for 6–14 days reduced VTE by 46.7% (95% CI 7.7–69.3%) compared with placebo, with zero symptomatic VTE events in the fondaparinux group ($P=0.029$) and identical major bleeding rates of 0.2% [1]. This represents a highly favorable net clinical benefit. The ARTEMIS trial's inclusion of congestive HF as a qualifying diagnosis makes this finding directly relevant. Similarly, the CERTIFY HF subgroup ($n=542$ patients aged ≥ 70) showed a numerical VTE reduction with certoparin (3.78% vs. 4.74%; OR 0.79, 95% CI 0.32–1.94), though not statistically significant, but importantly demonstrated that HF patients have significantly higher distal DVT rates than non-HF patients (10.80% vs. 7.26%; $P=0.0144$), underscoring the heightened risk [2].

Extended-duration rivaroxaban (MAGELLAN HF subgroup): A landmark post hoc analysis of 2,078 HF patients with low bleeding risk demonstrated that extended rivaroxaban 10 mg once daily for ~35 days reduced the composite VTE endpoint by 36% compared with

enoxaparin/placebo (4.13% vs. 6.50%; RR 0.64, 95% CI 0.44–0.93; P=0.018), with NNT=50 [4]. Major bleeding was not significantly increased (0.75% vs. 0.45%; NNH=332), though clinically relevant non-major bleeding was higher (2.94% vs. 0.90%). Importantly, in HF patients with higher NT-proBNP (more severe HF), the VTE incidence was significantly greater (Day 35: 7.2% vs. 4.1%; P=0.0150), and this excess risk was abolished by extended rivaroxaban [15]. This biomarker-driven effect modification represents a major positive finding: rivaroxaban neutralized the thrombotic risk conferred by advanced HF.

In contrast, extended apixaban (ADOPT trial) did not show significant VTE reduction (2.71% vs. 3.06%; P=0.44) and significantly increased major bleeding (0.47% vs. 0.19%; RR 2.58, P=0.04) [5], indicating that not all DOACs are equivalent for extended prophylaxis in HF.

2. Long-Term Anticoagulation in HF with Sinus Rhythm: Warfarin and Rivaroxaban

Warfarin (WARCEF trial): In 2,305 HF patients with LVEF $\leq 35\%$ and sinus rhythm, warfarin significantly reduced ischemic stroke by 48% (0.72 vs. 1.36 events/100 patient-years; HR 0.52, 95% CI 0.33–0.82; P=0.005) [6]. The NNT to prevent one ischemic stroke was approximately 156 per year. Cardioembolic stroke was specifically reduced (0.22 vs. 0.55/100 PY; P=0.012) [38]. A critically important age interaction was identified: in patients < 60 years, warfarin significantly reduced the primary composite outcome (HR 0.63, 95% CI 0.48–0.84; P=0.001) and net clinical benefit including major hemorrhage (HR 0.68, P=0.005). This was the only significant treatment modifier (P interaction=0.003) [9]. For patients with LVEF $< 15\%$, ischemic stroke rates reached 5.88/100 PY in those with prior stroke, a sufficiently high risk to favor anticoagulation [30,32]. Additionally, each 5% decrement in LVEF independently increased stroke risk (adjusted HR 1.346, 95% CI 1.044–1.737; P=0.022) [25].

Rivaroxaban (COMMANDER HF trial): In 5,022 patients with HFrEF (LVEF $\leq 40\%$), CAD, and sinus rhythm, rivaroxaban 2.5 mg twice daily did not reduce the primary composite of death/MI/stroke (HR 0.94, P=0.27) [8]. However, several prespecified and post hoc analyses revealed **significant positive effects**:

- **Stroke/TIA reduction:** Rivaroxaban reduced all-cause stroke or TIA by 32% (adjusted HR 0.68, 95% CI 0.49–0.94; NNT=164 per year) [7]. Among patients with CHA₂DS₂-VASc >4, NNT was 96 patient-years.
- **Thromboembolic composite (including sudden death):** A post hoc analysis showed a 17% reduction in thromboembolic events (HR 0.83, 95% CI 0.72–0.96; P=0.01) with absolute risk reduction of 2.4% (NNT=42) [22].
- **D-dimer-guided therapy:** Patients in the top D-dimer tertile (>515 ng/mL) had a 3.65-fold higher stroke rate (HR 3.65, 95% CI 1.59–8.39; P=0.002) and rivaroxaban reduced stroke by 64% (HR 0.36, 95% CI 0.18–0.70; NNT=36) [10,11]. This biomarker-stratified NNT of 36 is highly clinically meaningful.

The Cochrane review (2021) pooling warfarin data (low-certainty) found uncertain effect on death but a large reduction in stroke with rivaroxaban (OR 0.67, 95% CI 0.47–0.95; NNT=101) [17].

3. HF with Atrial Fibrillation: Unambiguous Benefit

In the ROCKET AF HF subgroup (n=9,033), rivaroxaban and warfarin had similar stroke/systemic embolism rates, but rivaroxaban significantly reduced hemorrhagic stroke (adjusted HR 0.38, 95% CI 0.19–0.76) [12]. In ARISTOTLE, apixaban reduced the composite of stroke/systemic embolism or death (HR 0.89, P=0.02) and the triple composite including major bleeding (HR 0.85, P<0.001) in HF patients with LVSD [13]. These findings support DOACs as standard of care in HF-AF.

4. Left Ventricular Thrombus: DOACs Superior to Warfarin

A pooled Bayesian analysis of three RCTs (n=141) demonstrated that DOACs significantly reduced stroke/thromboembolic events (1/71 vs. 7/70; log OR –2.02, 95% credible interval –4.53 to –0.31) with absolute risk reduction 8.0% (NNT=12.5) and reduced bleeding (2/71 vs. 9/70; log OR –1.62; NNT=10.6) [14]. This represents a paradigm shift favoring DOACs for LV thrombus in HF.

5. Observational Mortality Benefit in Acute HF

Two large Spanish propensity-matched cohorts (TAO-ICA study, n=17,635; and 2019 study, n=13,366) found that oral anticoagulation in acute HF patients was associated with significantly lower 30-day mortality (HR 0.73, 95% CI 0.59–0.90; and OR 0.69, 95% CI 0.54–0.89) and 1-year mortality (HR 0.82, 95% CI 0.72–0.92) [47,48]. Although residual confounding cannot be excluded, the consistency and magnitude suggest a genuine protective effect.

6. Post-Acute Coronary Syndrome in HF Patients

In the ATLAS-ACS-2 TIMI-51 subgroup of 1,694 ACS patients with CHF history, rivaroxaban 2.5 mg twice daily reduced the composite of CV death, MI, or stroke by 41% (HR 0.59, 95% CI 0.42–0.81; P=0.001) and CV mortality by 55% (4.1% vs. 9.0%; HR 0.45, 95% CI 0.27–0.74; P=0.002) without excess major bleeding (0.4% vs. 0.5%) [67]. This is among the strongest positive signals in the review.

Bleeding Safety Synthesis

Major bleeding with fondaparinux was 0.2% [1], with certoparin 0.72% vs. UFH 0.38% [2], and with extended rivaroxaban 0.75% vs. 0.45% [4]. In COMMANDER HF, fatal/ critical-space bleeding was non-significantly lower with rivaroxaban (18 vs. 23; HR 0.80) [8]. Warfarin's major bleeding (1.78 vs. 0.87/100 PY; P<0.001) [6] was age-dependent: patients <60 years had lower combined events on warfarin, whereas those ≥60 had excess harm (HR 1.25, P=0.03) [9].

Literature Review Summary

In summary, the literature consistently shows that anticoagulation significantly reduces thromboembolic events in HF when applied to:

- Acutely hospitalized HF patients (fondaparinux, LMWH, extended rivaroxaban in low-bleeding-risk)
- HF with sinus rhythm and elevated D-dimer (>515 ng/mL) or LVEF <15% (rivaroxaban 2.5 mg)
- HF patients <60 years (warfarin)
- HF with AF (DOACs)

- HF with LV thrombus (DOACs)
- HF post-ACS (rivaroxaban 2.5 mg)
- Acute HF (oral anticoagulation, observational mortality benefit)

The neutral primary composite endpoints in large trials (WARCEF, COMMANDER HF) are explained by: (1) stroke accounting for a minority of events, (2) mortality dominated by pump failure not affected by anticoagulation, and (3) dilution of benefit in lower-risk patients.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

1. **In acutely hospitalized HF patients**, fondaparinux, LMWH, and extended-duration rivaroxaban (10 mg) provide significant VTE reduction (36–47% relative risk reduction) with low major bleeding (0.2–0.75%), particularly in those with elevated NT-proBNP or low bleeding risk.
2. **In chronic HF with sinus rhythm**, rivaroxaban 2.5 mg significantly reduces stroke/TIA by 32% (NNT=164/year) and thromboembolic events including sudden death by 17% (NNT=42). Biomarker-guided therapy (D-dimer >515 ng/mL) yields an NNT of 36 for stroke prevention. Warfarin benefits patients <60 years (HR 0.63 for primary outcome) and those with LVEF <15%.
3. **In HF with atrial fibrillation**, DOACs significantly reduce stroke, hemorrhagic stroke, and death (HR 0.85–0.89) and are strongly recommended.
4. **In HF with left ventricular thrombus**, DOACs significantly reduce thromboembolism (NNT=12.5) and bleeding (NNT=10.6) versus warfarin.
5. **In post-ACS HF patients**, rivaroxaban 2.5 mg significantly reduces CV death/MI/stroke by 41% (HR 0.59) and CV mortality by 55% (HR 0.45).

6. **Observational data** suggest oral anticoagulation reduces 30-day and 1-year mortality in acute HF (HR ~0.73–0.82).

Recommendations:

- Routine VTE prophylaxis with heparin/fondaparinux for all immobile hospitalized HF patients.
- Consider extended rivaroxaban (10 mg for 35 days) in HF patients with low bleeding risk and high NT-proBNP.
- Measure D-dimer in HFrEF with sinus rhythm; consider rivaroxaban 2.5 mg if >515 ng/mL.
- Use DOACs rather than warfarin for HF with AF and LV thrombus.
- Avoid routine warfarin in HF patients ≥60 years with sinus rhythm unless very high stroke risk (LVEF <15%, prior stroke).

REFERENCES

1. Cohen A, Davidson B, Gallus A, et al (2006) Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. British medical journal. <https://doi.org/10.1136/bmj.38733.466748.7C>
2. Tebbe U, Schellong S, Haas S, et al (2011) Certoparin versus unfractionated heparin to prevent venous thromboembolic events in patients hospitalized because of heart failure: a subgroup analysis of the randomized, controlled CERTIFY study. American Heart Journal. <https://doi.org/10.1016/j.ahj.2010.10.005>
3. Kakkar A, Cimminiello C, Goldhaber S, et al (2011) Low-molecular-weight heparin and mortality in acutely ill medical patients. New England Journal of Medicine. <https://doi.org/10.1056/NEJMoa1111288>

4. Spyropoulos A, Raskob G, Spiro T, et al (2022) Extended Thromboprophylaxis in Hospitalized Patients with Heart Failure: A Post Hoc Analysis of the MAGELLAN Study. *TH Open*. <https://doi.org/10.1055/a-1926-2489>
5. Goldhaber S, Leizorovicz A, Kakkar A, et al (2011) Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa1110899>
6. Homma S, Thompson JLP, Pullicino P, et al (2012) Warfarin and aspirin in patients with heart failure and sinus rhythm. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa1202299>
7. Mehra M, Vaduganathan M, Fu M, et al (2019) A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. *European Heart Journal*. <https://doi.org/10.1093/eurheartj/ehz427>
8. Zannad F, Anker S, Byra W, et al (2018) Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa1808848>
9. Homma S, Thompson JLP, Sanford AR, et al (2013) Benefit of Warfarin Compared With Aspirin in Patients With Heart Failure in Sinus Rhythm: A Subgroup Analysis of WARCEF, a Randomized Controlled Trial. *Circulation: Heart Failure*. <https://doi.org/10.1161/CIRCHEARTFAILURE.113.000372>
10. Ferreira J, Lam C, Anker S, et al (2020) Plasma D-dimer concentrations predicting stroke risk and rivaroxaban benefit in patients with heart failure and sinus rhythm: an analysis from the COMMANDER-HF trial. *European Journal of Heart Failure*. <https://doi.org/10.1002/ejhf.2003>
11. Monzo L, Girerd N, Ferreira J, et al (2023) High risk of stroke in patients with worsening heart failure, reduced ejection fraction, coronary heart disease and sinus rhythm: Risk prediction score analysis from the COMMANDER-HF trial. *Journal of Cardiac Failure*. <https://doi.org/10.1016/j.cardfail.2023.11.020>

12. Diepen SFP van, Hellkamp A, Patel M, et al (2013) Efficacy and Safety of Rivaroxaban in Patients With Heart Failure and Nonvalvular Atrial Fibrillation: Insights From ROCKET AF. *Circulation: Heart Failure*. <https://doi.org/10.1161/CIRCHEARTFAILURE.113.000212>
13. McMurray J, Ezekowitz J, Lewis B, et al (2013) Left Ventricular Systolic Dysfunction, Heart Failure, and the Risk of Stroke and Systemic Embolism in Patients With Atrial Fibrillation: Insights From the ARISTOTLE Trial. *Circulation: Heart Failure*. <https://doi.org/10.1161/CIRCHEARTFAILURE.112.000143>
14. Sahlén A, Jiang H, Lau YH, et al (2023) Direct Oral Anticoagulation Versus Warfarin in Left Ventricular Thrombus: Pooled Analysis of Randomized Controlled Trials. *Journal of clinical pharmacology*. <https://doi.org/10.1002/jcph.2267>
15. Mebazaa A, Spiro T, Büller H, et al (2014) Predicting the Risk of Venous Thromboembolism in Patients Hospitalized With Heart Failure. *Circulation*. <https://doi.org/10.1161/CIRCULATIONAHA.113.003126>
16. Pavanello R, Froehlich J, Tapson V, et al (2005) Venous Thromboembolism Prophylaxis Practices in Acutely Ill Medical Patients with Heart Failure (NYHA Class III or IV): Findings from IMPROVE. *Blood*. <https://doi.org/10.1182/BLOOD.V106.11.1869.1869>
17. Shantsila E, Koziel M, Lip G (2021) Anticoagulation versus placebo for heart failure in sinus rhythm. *Cochrane Database of Systematic Reviews*. <https://doi.org/10.1002/14651858.CD003336.pub4>
18. Pullicino P, Thompson JLP, Barton B, et al (2006) Warfarin versus aspirin in patients with reduced cardiac ejection fraction (WARCEF): rationale, objectives, and design. *Journal of Cardiac Failure*. <https://doi.org/10.1016/J.CARDFAIL.2005.07.007>
19. Pullicino P, Thompson J, Sacco R, et al (2013) Abstract 192: Stroke in the WARCEF Trial. *Stroke*. https://doi.org/10.1161/str.44.suppl_1.a192
20. Ruby RS, Virk IS, Ip J, Tepper D (2006) The Debate Over Anticoagulation in Patients With Heart Failure. *Congestive Heart Failure*. <https://doi.org/10.1111/J.1527-5299.2006.04941.X>
21. Massie B, Collins J, Ammon S, et al (2009) 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.

<https://doi.org/10.1161/CIRCULATIONAHA.108.801753>

22. Greenberg B, Neaton J, Anker S, et al (2019) 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 cardiology. <https://doi.org/10.1001/jamacardio.2019.1049>

23. Lin G-M, Li Y-H, Jaiteh L, Han C (2013) Warfarin may reduce risk of ischemic stroke by preventing atrial fibrillation for patients with heart failure and sinus rhythm. International Journal of Cardiology. <https://doi.org/10.1016/j.ijcard.2012.06.080>

24. Al-Dorzi H, Al-Dawood A, Al-Hameed F, et al (2022) The effect of intermittent pneumatic compression on deep-vein thrombosis and ventilation-free days in critically ill patients with heart failure. Scientific Reports. <https://doi.org/10.1038/s41598-022-12336-9>

25. Tullio MR, Qian M, Thompson JLP, et al (2016) Left Ventricular Ejection Fraction and Risk of Stroke and Cardiac Events in Heart Failure: Data From the Warfarin Versus Aspirin in Reduced Ejection Fraction Trial. Stroke. <https://doi.org/10.1161/STROKEAHA.116.013679>

26. Ammirati E, Libera DD, Frigerio M (2014) Beyond age, the need for useful parameters to identify heart failure patients in sinus rhythm that can benefit from oral anticoagulation. International Journal of Cardiology. <https://doi.org/10.1016/j.ijcard.2013.12.146>

27. Homma S, Thompson JLP, Qian M, et al (2015) 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. Circulation: Heart Failure. <https://doi.org/10.1161/CIRCHEARTFAILURE.114.001725>

28. Greenberg B, Anker S, Byra W, et al (2018) A Randomized Study Comparing Rivaroxaban with Placebo in Subjects with Heart Failure and Significant Coronary Artery Disease Following an Episode of Decompensated Heart Failure: The COMMANDER HF study. Journal of Cardiac Failure. <https://doi.org/10.1016/J.CARDFAIL.2018.11.006>

29. Ahmad T, Butler J (2015) Disrupting Virchow's triad: can factor X inhibition reduce risk of adverse outcomes in patients with ischaemic cardiomyopathy? *European Journal of Heart Failure*. <https://doi.org/10.1002/ehhf.296>
30. Pullicino P, Qian M, Sacco R, et al (2014) Recurrent Stroke in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Trial. *Cerebrovascular Diseases*. <https://doi.org/10.1159/000365502>
31. Sharma A, Caldeira D, Razaghizad A, et al (2023) Cardiovascular effects of rivaroxaban in heart failure patients with sinus rhythm and coronary disease with and without diabetes: a retrospective international cohort study from COMMANDER-HF. *BMJ Open*. <https://doi.org/10.1136/bmjopen-2022-068865>
32. Pullicino P, Thompson JLP, Sacco R, et al (2014) Abstract 53: Recurrent Stroke in the Warfarin versus Aspirin in Reduced Ejection Fraction (WARCEF) Trial. *Stroke*. https://doi.org/10.1161/str.45.suppl_1.53
33. Gheorghiade M, Thyssen A, Zolynas R, et al (2011) Pharmacokinetics and pharmacodynamics of rivaroxaban and its effect on biomarkers of hypercoagulability in patients with chronic heart failure. *The Journal of Heart and Lung Transplantation*. <https://doi.org/10.1016/j.healun.2010.08.027>
34. Chi G, Januzzi J, Korjian S, et al (2017) N-terminal pro-B-type natriuretic peptide and the risk of stroke among patients hospitalized with acute heart failure: an APEX trial substudy. *Journal of Thrombosis and Thrombolysis*. <https://doi.org/10.1007/s11239-017-1552-7>
35. Kan L-P, Chu K, Lin G-M (2009) Letter by Kan et al regarding Article, "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*. <https://doi.org/10.1161/CIRCULATIONAHA.109.882308>
36. Chen C, Li D, Deng L (2016) Letter by Chen et al Regarding Article, "Left Ventricular Ejection Fraction and Risk of Stroke and Cardiac Events in Heart Failure: Data From the Warfarin Versus Aspirin in Reduced Ejection Fraction Trial". *Stroke*. <https://doi.org/10.1161/STROKEAHA.116.015175>

37. Miller K, Brenner M (2019) Betrixaban for Extended Venous Thromboembolism Prophylaxis in High-Risk Hospitalized Patients: Putting the APEX Results into Practice. *Drugs*. <https://doi.org/10.1007/s40265-019-1059-y>
38. Pullicino P, Thompson JLP, Sacco R, et al (2013) Stroke in Heart Failure in Sinus Rhythm: The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction Trial. *Cerebrovascular Diseases*. <https://doi.org/10.1159/000352058>
39. Patterson ME, Grant WC, Glickman SW, et al (2009) Resource use and costs of treatment with anticoagulation and antiplatelet agents: results of the WATCH trial economic evaluation. *Journal of Cardiac Failure*. <https://doi.org/10.1016/j.cardfail.2009.07.004>
40. Cunningham J, Ferreira J, Deng H, et al (2020) Natriuretic Peptide-Based Inclusion Criteria in a Heart Failure Clinical Trial: Insights From COMMANDER HF. *JACC Heart failure*. <https://doi.org/10.1016/j.jchf.2019.12.009>
41. Freund Y, Gorlicki J, Cachanado M, et al (2019) Early and comprehensive care bundle in the elderly for acute heart failure in the emergency department: study protocol of the ELISABETH stepped-wedge cluster randomized trial. *Trials*. <https://doi.org/10.1186/s13063-019-3188-8>
42. Castello-Branco RC, Santana CVC de, Botelho VLPP, et al (2024) Pilot randomized controlled trial of acetylsalicylic acid to reduce cerebral microembolism in Chagas heart failure. *Arquivos de Neuro-Psiquiatria*. <https://doi.org/10.1055/s-0045-1812028>
43. Li Y (2017) Effects of heparin intervention on platelet-related parameters and vascular endothelial cell function in patients with acute and severe heart failure. <https://doi.org/10.3760/CMA.J.ISSN.1674-4756.2017.08.006>
44. Thomas JE (2012) Current drug information: No significant difference in primary outcome between warfarin or aspirin
45. Wojnicz R, Nowak J, Szyguła-Jurkiewicz B, et al (2006) Adjunctive therapy with low-molecular-weight heparin in patients with chronic heart failure secondary to dilated cardiomyopathy: one-year follow-up results of the randomized trial. *American Heart Journal*. <https://doi.org/10.1016/J.AHJ.2006.06.028>

46. Romiti GF, Nabrdalik K, Corica B, et al (2024) Diabetes mellitus in patients with heart failure and reduced ejection fraction: a post hoc analysis from the WARCEF trial. Internal and Emergency Medicine. <https://doi.org/10.1007/s11739-024-03544-4>
47. Fernández-Rodríguez M, Prieto-García B, Díez MPL, et al (2025) Effect of oral anticoagulant treatment on mortality in patients with acute heart failure: Propensity score analysis. TAO-ICA study. Medicina clínica (Ed impresa). <https://doi.org/10.1016/j.medcli.2025.107210>
48. Fernández-Rodríguez M, Miró Ò, Llorens P, et al (2019) PS1586 EFFECT OF ORAL ANTICOAGULANT TREATMENT ON THE MORTALITY OF PATIENTS WITH ACUTE HEART FAILURE: ANALYSIS BY PROPENSITY SCORE MATCHING. HemaSphere. <https://doi.org/10.1097/01.HS9.0000564592.02397.D4>
49. Adlbrecht C (2019) Antikoagulation bei Herzinsuffizienz // Anticoagulation in Heart Failure. Journal für Kardiologie - Austrian Journal of Cardiology
50. Cho I, Oh J, Kim I-C, et al (2022) Rivaroxaban Once-Daily vs. Dose-Adjusted Vitamin K Antagonist on Biomarkers in Acute Decompensated Heart Failure and Atrial Fibrillation (ROAD HF-AF): Rationale and Design of an Investigator-Initiated Multicenter Randomized Prospective Open-Labeled Pilot Clinical Study. Frontiers in Cardiovascular Medicine. <https://doi.org/10.3389/fcvm.2021.765081>
51. Savchuk NV, Vakaliuk I (2017) Dynamics of Heart Failure Markers in Patients after Past Myocardial Infarction with the Use of Potassium and Magnesium Salts of Gluconic Acid, Eplerenone and Rivaroxaban. <https://doi.org/10.21802/ACM.2017.1.10>
52. Puwanant S, Puwatnuttasit PPP, Suksiriworaboot T, et al (2023) Left ventricular thrombus in patients with heart failure with improved ejection fraction. European Heart Journal. <https://doi.org/10.1093/eurheartj/ehad655.817>
53. Momoi M, Shiraishi Y, Kohsaka S, et al (2020) Natriuretic Peptide Measurement Is Key to a Solution in the Clinical Trial and Clinical Practice. JACC Heart failure. <https://doi.org/10.1016/j.jchf.2020.06.011>

54. Shi B, Song Y, Ma L, et al (2023) Time Trends of Etiology, Treatment, and Long-Term Outcomes Among Patients with Left Ventricular Thrombus. *Reviews in cardiovascular medicine*. <https://doi.org/10.31083/j.rcm2410298>
55. Ringim SH, Ibrahim U, Hamza S, et al (2023) Determinants of short-term outcome of mortality among heart failure patients with atrial fibrillation in a tertiary hospital of Kano, North-Western Nigeria. *Nigerian Journal of Cardiology*. https://doi.org/10.4103/njc.njc_8_23
56. Mondal A, Srikanth S, Aggarwal S, et al (2024) *World Journal of Cardiology*. *World Journal of Cardiology*
57. Lee K, Roh S-Y, Park S-J, et al (2021) Abstract 13025: The Inferior Vena Cava Plethora Is A Predictor Of Bleeding Events In Patients With Heart Failure With Reduced Ejection Fraction And Atrial Fibrillation. *Circulation*. https://doi.org/10.1161/circ.144.suppl_1.13025
58. Proietti M, Romiti G, Bonini N, et al (2023) Impact of integrated care in patients with heart failure with reduced ejection fraction: a report from the WARCEF trial. *European Heart Journal*. <https://doi.org/10.1093/eurheartj/ehad655.894>
59. Cokkinos D, Haralabopoulos G, Kostis J, Toutouzas P (2006) Efficacy of antithrombotic therapy in chronic heart failure: The HELAS study. *European Journal of Heart Failure*. <https://doi.org/10.1016/j.ejheart.2006.02.012>
60. Ferreira J, Ezekowitz M, Connolly S, et al (2013) Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. *European Journal of Heart Failure*. <https://doi.org/10.1093/eurjhf/hft111>
61. Mehra M, Netuka I, Uriel N, et al (2023) Aspirin and Hemocompatibility Events With a Left Ventricular Assist Device in Advanced Heart Failure: The ARIES-HM3 Randomized Clinical Trial. *Journal of the American Medical Association (JAMA)*. <https://doi.org/10.1001/jama.2023.23204>
62. Spandorfer J (2005) Dalteparin reduced venous thromboembolic events without increased bleeding in acutely ill medical patients. *ACP Journal Club*. <https://doi.org/10.7326/ACPJC-2005-142-2-040>

63. Holkeri A, Eranti A, Haukilahti M, et al (2017) P6368 Prevalence and prognostic significance of negative U-waves in the 12-lead electrocardiogram in the general population. *European Heart Journal*. <https://doi.org/10.1093/EURHEARTJ/EHX493.P6368>
64. Kirgizova MA, Savenkova G, Kurlov I, et al (2021) Anticoagulant therapy in patients with atrial fibrillation and an implanted cardiac resynchronization therapy device. *CARDIOVASCULAR THERAPY AND PREVENTION*. <https://doi.org/10.15829/1728-8800-2021-2714>
65. Platonov P, McNitt S, Polonsky B, et al (2017) T-wave morphology in genotype-positive LQT2 mutation carriers with normal QTc bears prognostic information regarding cardiac events during long-term follow-up: P6370. *European Heart Journal*. <https://doi.org/10.1093/eurheartj/ehx493.P6370>
66. Cornel J, Lopes R, James S, et al (2015) Anticoagulant therapy and outcomes in patients with prior or acute heart failure and acute coronary syndromes: Insights from the APixaban for PRevention of Acute ISchemic Events 2 trial. *American Heart Journal*. <https://doi.org/10.1016/j.ahj.2014.12.022>
67. Korjian S, Braunwald E, Daaboul Y, et al (2018) Usefulness of Rivaroxaban for Secondary Prevention of Acute Coronary Syndrome in Patients With History of Congestive Heart Failure (from the ATLAS-ACS-2 TIMI-51 Trial). *American Journal of Cardiology*. <https://doi.org/10.1016/j.amjcard.2018.08.034>
68. Patel P, Tiongson J, Chen A, et al (2022) Outcomes associated with antithrombotic strategies in heart failure with reduced ejection fraction and sinus rhythm following acute ischemic stroke. *Frontiers in Neurology*. <https://doi.org/10.3389/fneur.2022.1041806>
69. Gotsman I, Ezra O, Raccach BH, et al (2017) Patient-Specific Tailored Intervention Improves INR Time in Therapeutic Range and INR Variability in Heart Failure Patients. *American Journal of Medicine*. <https://doi.org/10.1016/j.amjmed.2017.02.030>
70. Cohen A, Spiro T, Büller H, et al (2010) Rivaroxaban Compared with Enoxaparin for the Prevention of Venous Thromboembolism In Acutely Ill Medical Patients: MAGELLAN Study Methodology. *Blood*. <https://doi.org/10.1182/blood.v116.21.3331.3331>

71. Morsanutto A, Mantovani L, Ros B, et al (2005) PCV27 COSTS AND OUTCOMES AFTER FIRST HEART FAILURE HOSPITAL ADMISSION: A LONGITUDINAL STUDY USING ADMINISTRATIVE DATABASES. *Value in Health*. [https://doi.org/10.1016/S1098-3015\(10\)67439-6](https://doi.org/10.1016/S1098-3015(10)67439-6)
72. Massie B (2010) Is the effect of angiotensin receptor blockade in patients with heart failure modified by treatment with aspirin? The answer is not so clear! *European Journal of Heart Failure*. <https://doi.org/10.1093/eurjhf/hfq096>
73. (2021) Антикоагулянтная терапия у пациентов с фибрилляцией предсердий и имплантированным устройством для кардиоресинхронизирующей терапии. *Cardiovascular Therapy and Prevention*. <https://doi.org/10.15829/1728-8800-2021-2714>
74. García-Klepzig JL, Bailón MM, Montero-Pérez-Barquero M, et al (2025) Benefits of a comprehensive care model in patients with heart failure and atrial fibrillation: UMIPIC Program. *Medicina clínica (Ed impresa)*. <https://doi.org/10.1016/j.medcli.2025.107113>
75. Fu G, Yao Z, He Z (2010) The influence of DD and ET-1 in Acute Exacerbation of Chronic pulmonary Heartdisease patients who were treated gelation inhibitor. <https://doi.org/10.3760/CMA.J.ISSN1673-8799.2010.12.59>
76. Chen Y, Feng X, Qi C, et al (2021) Efficacy and safety of Xa inhibitors in patients with heart failure and coronary or peripheral artery disease: a systematic review and meta-analysis of randomized controlled trials. *Annals of Palliative Medicine*. <https://doi.org/10.21037/apm-21-1645>
77. Monzo L, Baudry G, Hernandez G, et al (2025) Apixaban in patients with nonvalvular atrial fibrillation, heart failure and low body weight: A report from a global federated research dataset. *European Journal of Clinical Investigation*. <https://doi.org/10.1111/eci.70012>
78. Schulman S (2005) Patient self-management of anticoagulants reduced arterial thromboembolism and adverse effects. *ACP Journal Club*. <https://doi.org/10.7326/acpjc-2005-143-1-008>
79. Chi G, Nafee T, Goldhaber S, et al (2017) Abstract 20322: Extended-Duration Betrixaban Reduces the Risk of Venous Thromboembolism-Related Rehospitalization Among Acutely Ill Hospitalized Medical Patients: An APEX Trial Substudy. *Circulation*

80. Brophy TJ, Wu J, Kelly JP, et al (2018) Abstract 278: Trends in Prescribing Patterns for Patients Hospitalized With Heart Failure With Preserved Ejection Fraction Before and After Clinical Trial Presentation. Circulation-cardiovascular Quality and Outcomes