Managing thrombotic complications in heart failure: role of warfarin and other anticoagulants

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Abstract.
This article summarizes the findings of research aimed at comparing the effectiveness of anticoagulants in patients with atrial fibrillation and concomitant conditions, including heart failure. The studies evaluated the impact of warfarin, aspirin, dabigatran, edoxaban, and rivaroxaban on the risk of stroke, systemic embolisms, and bleeding events. The results indicate significant differences in the efficacy and safety of these medications: warfarin reduces the risk of stroke but increases the likelihood of bleeding; edoxaban and rivaroxaban showed a decrease in bleeding risk while maintaining efficacy in stroke prevention. The research also identified the stability of drug effects based on the severity of heart failure, emphasizing the need for an individualized approach to treatment selection in this patient group.

Keywords:
warfarin
heart failure
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thrombotic complications
ischemic stroke
**Introduction:**

Heart failure (HF), a condition in which the heart is unable to efficiently supply the body with blood, is a serious condition associated with a high risk of thromboembolic complications. Anticoagulants, particularly warfarin, are widely used to prevent thrombotic events in patients with HF. However, the effectiveness and safety of warfarin in this context require detailed analysis and comparison with other anticoagulants.

The aim of this study is to comprehensively analyze warfarin as an anticoagulant in patients with heart failure to identify its effectiveness in preventing thrombotic complications and assess its safety relative to other anticoagulants. Patient characteristics, HF features, and risk factors are taken into account.

This study represents a significant contribution to understanding the role of warfarin in managing thromboembolic risks in patients with heart failure and allows for a comparative analysis with other anticoagulants. The methodology includes an extensive literature review, analysis of clinical trial results, and statistical data processing.

It is expected that the results of this study will pave the way for optimizing anticoagulation therapy strategies for patients with HF, providing physicians with more precise and individualized recommendations. A detailed investigation of warfarin's effects and its comparison with alternative anticoagulants considering the specifics of heart failure implies important practical and clinical implications for treating this patient population.

**Mechanism of Action:**

Warfarin is an oral anticoagulant that exerts its effects on the blood coagulation system by inhibiting the synthesis of clotting factors in the liver. The primary mechanism involves the inhibition of vitamin K epoxide reductase, leading to a reduction in the active form of vitamin K necessary for the synthesis of clotting factors II, VII, IX, and X. This process slows the formation of thrombin and fibrinogen, thereby reducing blood clotting and the risk of thrombus formation.

**Pharmacokinetics:**
Warfarin exhibits variable pharmacokinetics. Following oral administration, it is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentration approximately 90 minutes post-dose. It binds to plasma proteins by 99%. Metabolism occurs primarily in the liver via the cytochrome P450 system and is mainly deactivated through renal excretion. However, in elderly individuals and patients with impaired kidney or liver function, the pharmacokinetics of warfarin may be substantially altered.

Indications and Contraindications:
Warfarin is used for the prevention and treatment of thromboembolic complications such as venous thrombosis, pulmonary embolism, strokes in patients with atrial fibrillation, and after heart valve replacement. However, its use may be contraindicated in patients at high risk of bleeding, those hypersensitive to the drug, individuals with gastric ulcers, severe liver disease, vitamin K deficiency, or other conditions requiring meticulous attention to blood coagulation.

Side Effects:
Possible side effects of warfarin use include bleeding of various locations: gastrointestinal tract bleeding, skin bleeding, hematomas, among others. Hypersensitivity reactions, skin rashes, elevated liver enzymes are also possible, warranting careful monitoring during drug administration.

Results:
The WARCEF study, involving 1,067 patients on warfarin therapy, revealed that the mean Time in Therapeutic Range (TTR) was 62.6%. Participants with higher TTR (≥70%) were older, had a history of heart attacks, poorer kidney function, but better MLWHF scores, a longer distance walked in 6 minutes, and fewer hospitalizations due to heart failure. They were less prone to hypertension, stroke, or use of other antiplatelet agents [1].

A relationship between the severity of heart failure and TTR was identified: the more frequent hospitalizations due to heart failure, the lower the TTR. Patients with more severe symptoms also showed lower TTR [1-5].

The analysis showed that the number of hospitalizations...
due to heart failure, NYHA class III/IV, and poor quality of life were independently associated with a low TTR. Other factors influencing a high TTR were also identified, such as age, race, weight, smoking, and antiplatelet agents [1-3].

This study underscores the connection between the severity of heart failure and the quality of anticoagulation therapy, necessitating a reconsideration of approaches to anticoagulation in this population.

The presented study highlights the complexities associated with thrombus formation in non-valvular atrial fibrillation (NVAF) patients, especially in the context of anticoagulant therapy. The uniqueness of this study lies in the analysis of a wide spectrum of clinical and echocardiographic parameters to accurately predict the risk of thrombus formation with warfarin use [1].

Risk factors for thrombus formation were identified in patients not receiving anticoagulant therapy, such as duration of atrial fibrillation, presence of heart failure, diabetes, previous strokes or TIAs. For patients receiving warfarin, the significance of NYHA classes and CHADS2 scores in predicting thrombus formation was established.

Echocardiographic analysis identified key parameters associated with thrombus formation, including left atrial flow velocity, left ventricular ejection fraction, right ventricular pressure, and left ventricular mass index. These findings provide important information on which echocardiography parameters to consider when monitoring patients on anticoagulant therapy.

It is also noteworthy that even with therapeutic doses of warfarin, some patients experienced thrombus formation, indicating the need for more effective methods of preventing this complication.

Based on the study findings, there's a clear need for new approaches to predict and prevent thrombosis in patients with non-valvular atrial fibrillation (NVAF). Developing innovative medications considering a wide range of clinical and echocardiographic risk factors holds the potential to significantly enhance the prevention of thromboembolic complications in this patient group.

A clinical investigation aimed to compare the efficacy of
treating patients with reduced left ventricular ejection fraction (LVEF) and sinus rhythm using warfarin (target INR 2.0 to 3.5) versus aspirin (at a dosage of 325 mg/day). Over a study duration of up to 6 years involving 2305 patients, the primary outcome (a combination of ischemic stroke, intracranial hemorrhage, or all-cause mortality) did not show significant differences between warfarin and aspirin initially. However, a temporal analysis hinted at a slight benefit from warfarin, becoming marginally significant by the fourth year [1-2].

Warfarin exhibited a significant reduction in the risk of ischemic stroke compared to aspirin throughout the study. Nevertheless, this advantage was counterbalanced by an increased risk of major bleeding, particularly gastrointestinal bleeding, associated more prominently with warfarin use.

The uniqueness of this study lies in its duration – observing patients for six years, allowing the observation of treatment effects over time. It holds crucial importance for patients with reduced LVEF in sinus rhythm, indicating that although warfarin might reduce the risk of ischemic stroke, it elevates the risk of major bleeding compared to aspirin. This study underscores the necessity for an individualized treatment selection based on balancing stroke prevention and bleeding risk for each specific patient [1].

The study comparing Warfarin to other medications was based on data from the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction study, focusing on a secondary analysis of ischemic stroke subtypes in patients with low ejection fraction and sinus rhythm. While the primary outcome did not reveal differences between warfarin and aspirin regarding the incidence of ischemic strokes, the secondary analysis showed a 48% risk reduction in ischemic strokes with warfarin use, especially in cases of cardioembolic strokes [6].

Researchers classified incidents of ischemic strokes into specific, probable, and non-cardioembolic types using specific stroke subtype methods. Results demonstrated significantly lower rates of ischemic strokes among patients receiving warfarin compared to aspirin, particularly in cases
of specific and probable cardioembolic strokes. There were no differences observed in non-cardioembolic strokes. Additionally, the analysis indicated a trend toward reducing the number of severe ischemic strokes and probable cardioembolic strokes in the group of patients receiving warfarin.

The uniqueness of this study lies in its thorough examination of stroke subtypes, particularly in the significant reduction of cardioembolic strokes with warfarin use. This suggests that among patients with low ejection fraction and sinus rhythm, warfarin might offer substantial advantages in preventing certain types of ischemic strokes, especially those linked to cardioembolic causes, compared to aspirin.

In the RE-LY study [7], the effects of dabigatran compared to warfarin were assessed in a subgroup of patients with prior symptomatic heart failure (HF). Within the study involving 18,113 patients with atrial fibrillation and a high stroke risk, two fixed and blinded doses of dabigatran (110 and 150 mg twice daily) were compared to open-label warfarin. Among 4904 patients with HF, the annual rates of stroke or systemic embolism (SE) were 1.92% for patients on warfarin compared to 1.90% for dabigatran 110 mg [hazard ratio (HR) 0.99, 95% confidence interval (CI) 0.69–1.42] and 1.44% for dabigatran 150 mg (HR 0.75, 95% CI 0.51–1.10). Annual rates of major bleeding were 3.90% for the warfarin group compared to 3.26% for dabigatran 110 mg (HR 0.83, 95% CI 0.64–1.09) and 3.10% for dabigatran 150 mg (HR 0.79, 95% CI 0.60–1.03). Rates of intracranial hemorrhage were significantly lower for both doses of dabigatran compared to warfarin in patients with HF (dabigatran 110 mg vs. warfarin, HR 0.34, 95% CI 0.14–0.80; dabigatran 150 mg vs. warfarin, HR 0.39, 95% CI 0.17–0.89). The relative effects of dabigatran compared to warfarin on the occurrence of stroke or SE and major bleeding were consistent among patients with and without HF, as well as in patients with preserved or reduced left ventricular ejection fraction (LVEF).

The study underscores the similar overall benefits of dabigatran in preventing stroke/systemic embolism (SE) and reducing major and intracranial bleeding compared to warfarin.
Among patients with and without prior symptomatic heart failure. Additionally, it notes that patients with heart failure more frequently experienced higher rates of intracranial bleeding when on warfarin rather than dabigatran, a significant aspect for drug therapy selection in these patient groups.

The ENGAGE AF-TIMI 48 study [7] compared the effects of edoxaban with warfarin in patients with atrial fibrillation. It was found that edoxaban was non-inferior to warfarin in preventing stroke or SE and was associated with fewer bleeding events. The study also assessed the efficacy and safety of edoxaban based on the severity of heart failure (HF). Participants were divided into groups: without HF, with mild (NYHA class I-II), and severe (NYHA class III-IV) HF.

The results showed that edoxaban demonstrated comparable effectiveness in preventing stroke among patients with and without HF. Compared to warfarin, edoxaban was associated with a lower bleeding risk in all three patient groups, irrespective of HF severity. Cardiovascular mortality, hospitalization, and all-cause mortality rates also increased with worsening HF severity. These findings indicate the consistent effectiveness and safety of edoxaban regardless of HF severity. The study also revealed similar efficacy and safety outcomes in patients with preserved or reduced left ventricular ejection fraction (LVEF) and those at high cardiovascular risk.

Another study [8] evaluated the effectiveness and safety of rivaroxaban compared to warfarin in patients with atrial fibrillation (AF) and concomitant heart failure (HF). Using data from medical insurance databases in the USA from 2011 to 2016, researchers retrospectively observed patients who had not previously taken oral anticoagulants with AF and HF. Patients taking rivaroxaban (20 or 15 mg once daily) were compared to those taking warfarin, analyzing the frequency of stroke, SE, and bleeding events.

Rivaroxaban did not show a statistically significant difference in the frequency of stroke, SE, or bleeding events compared to warfarin in patients with AF and HF. There was also a lower incidence of intracranial hemorrhage among patients taking rivaroxaban. The study's results support the
effectiveness and safety of rivaroxaban in real clinical practice among patients with AF and concomitant heart failure, consistent with phase III clinical trial data.

It's crucial to note that the study was conducted on a large patient sample, and the results confirm the stability of rivaroxaban's effectiveness and safety in this population. These conclusions could be valuable for physicians considering the choice of anticoagulant for treating patients with AF and HF [8-11].

Conclusion:

The final conclusions of this study stem from a comprehensive analysis of the efficacy and safety of warfarin use in patients with heart failure (HF) concerning the prevention of thromboembolic complications. Warfarin, an oral anticoagulant, has long been the standard treatment for preventing thrombotic events in patients with various cardiovascular diseases. However, its use among patients with HF raises questions related to balancing effectiveness and bleeding risk.

The results of this study indicate the complexity of selecting anticoagulants for this patient category. Warfarin demonstrated its effectiveness in preventing thromboembolic complications, including ischemic strokes. However, this positive effect was accompanied by an increased risk of bleeding, including severe gastrointestinal bleeding.

Interesting findings emerged from the comparative analysis of warfarin with other anticoagulants like dabigatran and rivaroxaban. These alternative medications showed similar or even more favorable outcomes in preventing thrombotic events and reducing bleeding risk, especially intracranial bleeding, compared to warfarin.

It's essential to highlight that the effectiveness and safety of warfarin use in patients with HF are individualized and depend on various factors, including HF severity, age, presence of comorbidities, and other clinical parameters. This underscores the need for an individualized approach to choosing an anticoagulant for each HF patient, considering the balance between the benefits of preventing thromboembolic complications and bleeding risk.

In conclusion, this study emphasizes the importance of
further clinical research to refine the role of warfarin and other anticoagulants in managing thromboembolic risks in patients with heart failure. Given the complexities in choosing the optimal anticoagulant and the individual nature of this issue, further research will help shape more precise recommendations for physicians and improve treatment outcomes in this patient category.

References:


[8] Effectiveness and safety of rivaroxaban vs. warfarin in patients with
non-valvular atrial fibrillation and heart failure - PMC (nih.gov)

