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Challenges of anticoagulant treatment in atrial fibrillation with liver disease

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ABSTRACT

Managing anticoagulation therapy in individuals with atrial fibrillation who also have liver disease is highly challenging due to altered blood clotting processes and the risk of bleeding due to liver dysfunction. The literature highlights the complex nature of anticoagulant therapy in these patients, emphasizing the need for personalized treatment methods that take into account both thrombosis and bleeding risks. Research has shown a higher occurrence of atrial fibrillation in people with cirrhosis, highlighting the need to find the best anticoagulation methods based on the severity of liver disease and patient-specific factors. The debate over the safety and effectiveness of direct oral anticoagulants compared to traditional drugs like warfarin in cirrhotic patients with atrial fibrillation is still ongoing. Collaborative initiatives between experts in hepatology and cardiology are needed to address the complicated interplay between liver disease and atrial fibrillation, promoting interdisciplinary care models that enhance patient safety and treatment effectiveness. By prioritizing a patient-centered approach guided by extensive research, future directions in the hemostatic management of cirrhotic patients with atrial fibrillation may improve clinical decision-making and therapeutic outcomes.

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Introduction

The heart and liver maintain a close anatomical and functional connection, with liver disease exerting a considerable impact on the hemostatic mechanisms, thereby complicating atrial fibrillation (AF) treatment strategies. Although the benefits of anticoagulation in stroke prevention among AF patients are widely acknowledged, liver disease's unique pathophysiological traits bring about significant uncertainties concerning the safety and efficacy of conventional antithrombotic medications [1]. Research has indicated a heightened incidence of thrombotic incidents in cirrhotic patients with AF, necessitating a carefully balanced approach to anticoagulation. Moreover, the altered coagulation parameters in liver cirrhosis create a scenario where therapeutic interventions must be meticulously tailored to mitigate embolic events while addressing potential hemorrhagic complications, thereby complicating anticoagulant therapeutic approaches [2]. Historically, cirrhosis was thought to be an acquired bleeding disorder, but now it is widely accepted that the hemostatic system of patients with cirrhosis remains in balance due to acquired defects in both pro- and antihemostatic pathways [3-5]. Deficiencies in certain coagulation factors, notably factors II, V, VII, and X, could increase the risk of bleeding during

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anticoagulant treatment. On the other hand, liver dysfunction might unexpectedly elevate thrombotic risks by diminishing the production of natural anticoagulants such as protein C and antithrombin. Current studies indicate an elevated frequency of AF in those with liver cirrhosis, raising significant concerns about effectively managing thrombotic threats in this patient subgroup [3]. The absence of distinct guidelines specifically for cirrhotic patients with AF highlights the urgent need for more research to determine the most effective and safe anticoagulant protocols. Additionally, burgeoning evidence suggests that direct oral anticoagulants (DOACs) could serve as a promising alternative to the traditional warfarin therapy in cirrhotic patients with AF, potentially signaling a paradigm shift in managing thrombotic risks. Through exploring the interconnections between liver disease, AF, and anticoagulant therapy, clinicians may better maneuver through therapeutic complexities to enhance patient outcomes while reducing the risks associated with coagulation irregularities in liver dysfunction [2]. Advances in the understanding of DOACs and their prospective advantages over traditional agents like warfarin present a forward-looking perspective on anticoagulant therapy for individuals with liver dysfunction [3].

In addition, thrombocytopenia resulting from hypersplenism, reduced levels of thrombopoietin, platelet dysfunction, impaired drug metabolism, low plasma levels of coagulation proteins and the existence of gastroesophageal varices all contribute to the complexity of this fragile hemostatic state [6,7]. The American Association for the Study of Liver Disease (AASLD) has defined 3 potential causes of bleeding in patients with cirrhosis, such as portal hypertension, provoked bleeding and bleeding related to hemostatic failure. It has been demonstrated that variceal bleeding is not worsened by using anticoagulant drugs, while hemostatic drugs have little effect in stopping it. This suggest that hemostatic failure isn't the primary driver of induction or propagation of a variceal bleed, but portal pressure is. Also, provoked bleeds caused by mechanical injury to vessels are not caused by hemostatic failure, which proves that prophylactic procoagulant therapy is unlikely to prevent them.

These irregularities highlight the importance of customizing anticoagulant treatment plans that adapt to the shifting hemostatic state caused by liver disease. Changes in coagulation factor activity due to liver conditions affect both the safety and efficacy of anticoagulant therapy, thus presenting substantial challenges for healthcare providers.

Research focusing on liver disease's specific impacts on coagulation factors within the framework of anticoagulant therapy will improve precision in treatment and enhance patient health outcomes. Our research aim is to compare the efficacy and safety of anticoagulants in patients with liver cirrhosis, searching articles published from 2015, in PubMed and MEDLINE databases, using keywords "liver cirrhosis", "atrial fibrillation", "DOACs", "vitamin K antagonists". Our search is limited to publications in English language and human studies.

Given the fact that severe liver disease is an exclusion criterion in most randomized clinical trials (RCTs) studying DOACs, there is limited data in regards to the efficacy and safety of DOACs in AF patients with liver disease or cirrhosis.

Discussions

Atrial Fibrillation and Liver Disease

Atrial fibrillation (AF) is the most frequent arrhythmia in the general adult population, with an estimated prevalence of 2-4% [8]. AF's prevalence rates have been rising steadily, presenting big challenges in its management because of related risks such as stroke, heart failure, and death. Prevalence of AF together with liver disease causes difficulties due to changed hemostasis and bleeding possibilities. Researches show how complex is to administer anticoagulation therapy here, indicating necessity for specialized methods. The issue is about balancing stroke prevention and bleeding probability, most difficult in cirrhotic patients where usual risk-scoring methods may lack adequacy [9]. AASLD guidelines considering vascular liver condition and related procedures in liver disease [10], presenting problematics in anticoagulation management in cirrhosis cases.

A longitudinal study on the incidence of AF that included 3596 patients with liver cirrhosis selected from the Korean National Health Insurance Service National Sample Cohort with randomly sampled (5:1 ratio) age- and sex-matched non-LC controls demonstrated a higher incidence of AF in LC patients than in controls (incidence: 3.48 and 2.16 per 1,000 person-years, respectively, hazard ratio (HR), 1.46; 95% confidence interval (CI), 1.18-1.80). While LC patients showed increased overall mortality (HR, 4.80; 95% CI, 4.47-5.15), there was no correlation found between the development of AF (Atrial Fibrillation) in patients with LC (Liver Cirrhosis) and increased mortality [11].

When taking to account patients with severe disease, the prevalence seems to be even higher. In a retrospective study involving 1727 patients with end stage liver disease evaluated for liver transplantation between 2006 and 2015 there was observed an AF prevalence of 11.2% and an incidence 8.5% at median follow-up time of 1.04 years (including pre-existing AF at the time of the evaluation). It should be noted that the liver disease severity, as measured by Model for End Stage Liver Disease, was strongly correlated with new-onset AF [12].

In a cohort of 696937 patients with HC, 45745 with concomitant AF from The National Inpatient Sample (NIS) database showed AF is associated with higher risks of stroke, acute kidney injury, prolonged hospitalization and increased mortality in hospitalized LC patients.

Anticoagulants In Liver Disease

As liver disease rates keep climbing globally, grasping the intricacies of anticoagulation in such patients is essential for better patient management. Management of anticoagulant therapy for liver disease patients, especially those with atrial fibrillation (AF), is full of unique complexities. The challenge lies in the balancing act between minimizing thrombotic events and managing an increased risk of bleeding due to liver dysfunction. Conditions like liver cirrhosis, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH) change the pharmacokinetics and pharmacodynamics of anticoagulant drugs, potentially affecting their safety and effectiveness [2]. For example, hindered hepatic clearance might lead to increased drug concentration, heightening the likelihood of bleeding complications in patients enduring liver disease [13]. Furthermore, changes in hepatic function may influence the production of clotting factors and disrupt the overall hemostatic equilibrium, thereby affecting the reaction to anticoagulant therapy [14]. Contemporary guidelines underscore the necessity for personalized treatment paradigms, considering factors such as liver function, portal vein thrombosis (PVT), and other vascular liver conditions. Research indicates that direct oral anticoagulants (DOACs) can have certain advantages over traditional agents like warfarin in select scenarios, pointing to the importance of patient-specific treatment approaches [9]. The deployment of DOACs, such as apixaban, may present safer alternatives compared to warfarin, especially in decompensated liver disease scenarios [15]. However, discerning when to opt for anticoagulation versus interventions like left atrial appendage occlusion (LAAO) remains a clinical quandary, particularly for patients simultaneously at risk for stroke and bleeding [16]. Incorporating practices grounded in evidence, including platelet monitoring and the use of thrombopoietin receptor agonists, can improve outcomes for cirrhosis patients needing anticoagulation due to AF [17]. Evaluating the efficacy of DOACs in preventing portal vein thrombosis and enhancing survival among cirrhotic patients highlights the dynamic nature of anticoagulant therapy in liver disease contexts [18]. While traditional anticoagulants like warfarin still hold relevance, emerging DOACs offer promising prospects for managing thrombotic risks and mitigating bleeding complications in this patient cohort [19].

Diverse studies underline the necessity of rigorous monitoring of DOAC concentrations, particularly in patients with cirrhosis, to ensure therapeutic efficacy while preventing adverse effects [20]. Incorporating precise assessments and customized monitoring schemes is essential in enhancing outcomes of anticoagulant therapy for individuals with liver disease and atrial fibrillation [21]. Within the milieu of anticoagulation therapy in liver disease, the deployment of dependable risk assessment methodologies such as the CHA2DS2-VASc score becomes critical for informing treatment choices and tracking patient progress [22].

Health practitioners, hepatologists, and pharmacists must collaborate to customize anticoagulant treatments based on the patient's hepatic function status, ensuring the finest results while reducing risks [13]. More scholarly work examining the specific mechanisms by which hepatic function affects anticoagulant metabolism is necessary to direct clinical decisions and enhance the safety profile of anticoagulant treatment in this difficult patient category [20].

Types of anticoagulants commonly used

Anticoagulation therapy holds a critical position in managing atrial fibrillation (AF) amidst patients with liver disease, presenting specific challenges stemming from altered hemostasis. Conventional anticoagulants encompass vitamin K antagonists like warfarin and direct oral anticoagulants (DOACs) such as dabigatran, apixaban, rivaroxaban, and edoxaban. Vitamin K antagonists, like Warfarin, hinder the production of clotting factors II, VII, IX, and X in the hepatic tissue, thereby obstructing the coagulation sequence. It has long been the standard for AF but necessitates stringent monitoring due to its narrow therapeutic index and numerous medication interactions. DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban posse a selective inhibition characteristic against certain factors, notably thrombin or factor Xa, to attain anticoagulant outcomes [13]. DOACs provide benefits including swift onset of action, more predictable pharmacokinetics, and reduced food and drug interactions. Research indicates that DOACs might offer enhanced safety and efficacy over warfarin for stroke prevention in AF patients with liver cirrhosis [18]. The decision regarding anticoagulants must factor in liver function, potential drug interactions, and bleeding risks to achieve optimal outcomes in this multifaceted patient group. Nonetheless, selecting between DOACs and warfarin in cirrhotic individuals with AF entails balancing stroke prevention with bleeding risks, requiring personalized treatment strategies [20]. Emerging evidence proposes that DOACs might notably decrease stroke and major bleeding episodes in cirrhosis patients, suggesting a possible trend towards greater use in this demographic [14]. Grasping the pharmacological attributes and clinical consequences of diverse anticoagulants is vital for optimizing AF treatment in the context of liver disease. The advent of DOACs has transformed anticoagulation therapy by presenting a convenient oral substitute to traditional drugs in managing AF and preventing thrombotic events in liver cirrhosis patients [21]. DOACs emerge as a promising choice with comparable or potentially superior efficacy in stroke prevention and diminished bleeding risks relative to warfarin in this intricate clinical scenario [23] However, challenges like drug interactions and complexities of liver metabolism remain, with ongoing research striving to clarify the best role of DOACs in managing AF with liver

disease. Future research concentrating on the prolonged safety and effectiveness of DOACs in cirrhotic patients with AF is crucial to steer evidence-based anticoagulation strategies and improve patient outcomes [24].

Tables 1-8 present a summary of eight studies examining the use of anticoagulant therapies in patients with both atrial fibrillation and liver disease, including cirrhosis. The studies investigate various anticoagulation strategies, such as antiplatelet agents, vitamin-K antagonists, and non-vitamin K oral anticoagulants, focusing on their safety and effectiveness in this high-risk population. Each study evaluates a different aspect of therapy, such as the incidence of stroke, bleeding complications, and overall mortality, offering critical insights into the management of AF in patients with liver dysfunction.

Table 1.		**Study:** Lai et al. (2016) [25]
PICO framework	**Population**	AF patients with and without liver disease
	Intervention	Antiplatelet agents (aspirin, ticlopidine, dipyridamole) or vitamin-K antagonists (VKA, i.e., warfarin)
	Comparison	Liver vs. Non-Liver Cohort
	Outcome	The rate of cerebrovascular accidents requiring hospitalization.
Short description		Investigated the cerebrovascular outcome in patients using antithrombotic.
Main conclusions		Conventional antithrombotic, such as antiplatelet agents and VKA, do not reduce the increased thromboembolic risk in AF patients with or without liver disease, regardless of the CHA2DS2-VASc score.
Participants		3293
Male		53.1**%**
Age (mean ± SD)		70.1 ± 14.2
Therapy comparison		Antiplatelet agents / VKA
Bleeding rate %		Not provided
Stroke risk reduction		Not provided
Other characteristics		In the Liver Cohort, the percentage of patients with hypertension was significantly lower. Compared to the non-liver cohort, The Liver Cohort was older and comorbidities (COPD and renal failure) were more prevalent.

Table 2.		**Study:** Kuo et al. (2017) [26]
PICO framework	**Population**	AF Patients with Liver Cirrhosis with CHA2DS2-VASc Score ≥2
	Intervention	No therapy vs. antiplatelet therapy vs. warfarin
	Comparison	Treatment vs. non-treatment
	Outcome	The risk of ICH and ischemic stroke in AF patients with liver cirrhosis compared to those without LC.
Short description		The risk of ICH and benefit of reducing ischemic stroke risk were analyzed between untreated patients vs. those with antiplatelet agents or warfarin use.
Main conclusions		Warfarin use was associated with a lower risk of ischemic stroke and positive NCB when compared with being untreated or only receiving antiplatelet therapy.
Participants		9056
Male		60.8
Age (mean ± SD)		73.1 ± 11.2
Therapy comparison		No therapy vs. antiplatelet therapy vs. warfarin
Bleeding rate %		Increased with cirrhosis
Stroke risk reduction		Warfarin reduces stroke risk by 24%
Other characteristics		The CHA2DS2-VASc score was calculated for each patient.

Table 3.		**Study:** Choi et al. (2017) [27]
PICO framework	**Population**	Cirrhotic patients diagnosed with non-valvular AF
	Intervention	Warfarin
	Comparison	Anticoagulation. no anticoagulation
	Outcome	The incidence of major ischemic events (stroke or TIA).
Short description		Analyzed the risk vs benefits of using anticoagulation (Warfarin) in patients diagnosed with AH and LC.
Main conclusions		Anticoagulation with warfarin in cirrhotic AF patients doesn't significantly reduce the risk of ischemic stroke. It does however increase the prevalence of hemorrhagic complications.
Participants		465
Male		74.6
Age (mean ± SD)		63.5 ± 10.0

Therapy comparison	Warfarin vs. no anticoagulation
Bleeding rate %	3.9% (VKA)
Stroke risk reduction	Significant stroke prevention with warfarin
Other characteristics	The following scores were determined for all patients: CHA2DS2-VASc, Child-Pugh and HAS-BLED scores.

Table 4.		**Study:** Lee et al. (2015) [28]
PICO framework	**Population**	AF patients with early (Child-Pugh A) vs advanced (Child-Pugh B/C) LC
	Intervention	Warfarin vs. no anticoagulation
	Comparison	AF patients with early or advanced LC using Warfarin vs no VKA.
	Outcome	To determine the risk and benefits of using VKA in AF patients with LC Child-Pugh A or B/C.
Short description		Investigated the effects of using VKA (Warfarin) in AF patients with different stages of LC.
Main conclusions		The VKA treatment might be beneficial to reduce bleedings in early LC but not in the advanced LC group.
Participants		321
Male		68.6
Age (mean ± SD)		62.1 ± 10.3 (VKA); 62.5 ± 11.3 (no VKA)
Therapy comparison		Warfarin vs. no anticoagulation
Bleeding rate %		Not provided
Stroke risk reduction		Not provided
Other characteristics		Criteria used to define LC were clinical diagnosis, biochemistry, Doppler ultrasound, CT scan, and when possible, biopsy. Criteria used to diagnose AF was 12-lead EKG or 24-hour Holter recording.

Table 5.		**Study:** Pastori et al. (2018) [29]
PICO framework	**Population**	Patients with AF and advanced liver fibrosis
	Intervention	VKAs (warfarin or acenocumarol) or NOACs
	Comparison	Patients treated with VKAs vs NOACs
	Outcome	The occurrence of any major or minor bleeding events.
Short description		Analyzed the risks of major bleeding in AF patients in treatment with VKAs or NOACs.
Main conclusions		Patients with AF and LF treated with VKA were associated with a higher risk of major bleeding which was not evident in patients on NOACs.
Participants		2330
Male		54.1
Age (mean ± SD)		74.4 ± 9.3 (no LF); 78.9 ± 7.5 (LF)
Therapy comparison		VKAs vs. NOACs
Bleeding rate %		2.2% (NOAC) vs. 4.3% (VKA)
Stroke risk reduction		Reduced with NOACs compared to VKAs
Other characteristics		Patients treated with NOACs were older, thus more likely to have hypertension, heart failure and previous cerebrovascular events.

Table 6.		**Study:** Goriacko et al. (2018) [30]
PICO framework	**Population**	Patients with CLD and AF
	Intervention	DOAC (apixaban, dabigatran, rivaroxaban) vs. warfarin
	Comparison	Rates of bleeding between warfarin and DOAC.
	Outcome	Bleeding rates are similar between both groups.
Short description		To assess the safety of using DOACs versus warfarin in CLD patients with AF.
Main conclusions		There were no significant differences in bleeding rates in patients treated with DOAC or treated with warfarin.
Participants		233
Male		58.8
Age (mean ± SD)		66.00 (DOAC) 65.00 (Warfarin)
Therapy comparison		DOAC vs. Warfarin
Bleeding rate %		8.4% (DOAC) / 8.8% (Warfarin)
Stroke risk reduction		Not provided
Other characteristics		It was found that a higher MELD-XI score and previous episodes of bleeding were associated with increased bleeding.

Table 7.		Study: Lee et al. (2019) [31]
PICO framework	**Population**	NVAF Patients with Liver Cirrhosis
	Intervention	NOACs (Apixaban, Dabigatran, and Rivaroxaban) and warfarin
	Comparison	The benefits of using NOACs vs warfarin
	Outcome	To determine the safety of taking NOACs or warfarin.
Short description		To investigate the effectiveness of NOACs versus warfarin in cirrhotic AF patients during a long follow up period.
Main conclusions		NOACs appear to be a safer and more effective alternative to warfarin among the Asian patients with AF and LC, especially when it comes to those with early stage and non-alcoholic liver cirrhosis.
Participants		2428
Male		63.6
Age (mean ± SD)		74.3 ± 10.5 (NOACs); 69.9 ± 12.4 (warfarin)
Therapy comparison		NOACs vs. Warfarin
Bleeding rate %		3.3% (NOAC) / 3.9% (VKA)
Stroke risk reduction		Similar stroke prevention with NOACs
Other characteristics		The population studied was Asian.

Table 8.		Study: Lee SR et al. (2019) [32]
PICO framework	**Population**	AF patients with liver disease on newly prescribed warfarin or DOACs.
	Intervention	Warfarin or DOACs (rivaroxaban, dabigatran, apixaban, and edoxaban)
	Comparison	DOACs vs. warfarin in patients with NVAF and LC.
	Outcome	To determine the effects of DOACs vs warfarin.
Short description		DOACs were associated with lower risks for ischemic stroke, bleeding events and all-cause death when compared with warfarin.
Main conclusions		In this Asian AF population with liver disease, DOACs were associated with better effectiveness and safety than warfarin.
Participants		37,353
Male		59.6
Age (mean ± SD)		66.4 ± 11.0 (warfarin); 70.3 ± 8.9 (NOACs)
Therapy comparison		DOACs vs. Warfarin
Bleeding rate %		Not provided
Stroke risk reduction		DOACs
Other characteristics		Patients with NVAF who recently started DOAC therapy during the study period and with active liver disease diagnosed within 3 years before starting DOAC.

AF-atrial fibrillation; CLD-chronic liver disease; COPD-chronic obstructive pulmonary disease; DOACs-direct oral anticoagulants; ICH-intracranial haemorrhage; LC-liver cirrhosis; LF-liver fibrosis; NCB-net clinical benefit; NOACs-non–vitamin K antagonist oral anticoagulants; NVAF-non-valvular atrial fibrillation; TIA-transient ischemic attack; VKA-vitamin-K antagonists.

The studies involve diverse populations, with sample sizes ranging from 233 to 37,353 participants. They mostly consist of elderly populations (mean ages ranging from 62 to 78 years), a demographic that is at higher risk for both thrombotic and hemorrhagic events. The majority of participants are male, which may affect the generalizability of these findings to female populations. The studies primarily compare the outcomes of traditional anticoagulants like warfarin with newer treatments such as NOACs and direct oral anticoagulants, assessing their effectiveness in preventing ischemic events and their associated bleeding risks.

The studies highlight important clinical considerations for anticoagulation therapy in patients with both AF and liver disease. The findings suggest that NOACs and DOACs might provide a safer alternative to VKAs, especially in reducing the risk of bleeding. However, the efficacy of these treatments in preventing stroke and other thromboembolic events remains a key focus, as patients with liver disease present a particularly challenging clinical scenario due to their altered coagulation profiles. The studies offer valuable insights into the management of anticoagulation in AF patients with liver disease. It is evident that traditional anticoagulants like warfarin present significant bleeding risks, particularly in patients with advanced liver disease. In contrast, NOACs and DOACs are increasingly favored due to their lower incidence of major bleeding events while maintaining efficacy in

reducing ischemic stroke risk. For example, the findings of Pastori et al. (2018) [29] and Lee SR et al. (2019) [32] highlight the safety and effectiveness of NOACs, making them a preferred option in AF patients with cirrhosis.

Despite the benefits of NOACs, certain studies, such as Choi et al. (2017) [27] and Goriacko et al. (2018) [30], show the importance of careful patient selection and risk stratification. These studies suggest that in patients with more advanced liver disease, the bleeding risks associated with all anticoagulants, including NOACs, may still be significant. Therefore, the decision to initiate anticoagulation therapy should be individualized, based on factors like liver disease severity, the risk of thromboembolism, and the patient's overall clinical status. The risk-benefit ratio must be carefully considered, particularly in those with more severe liver dysfunction.

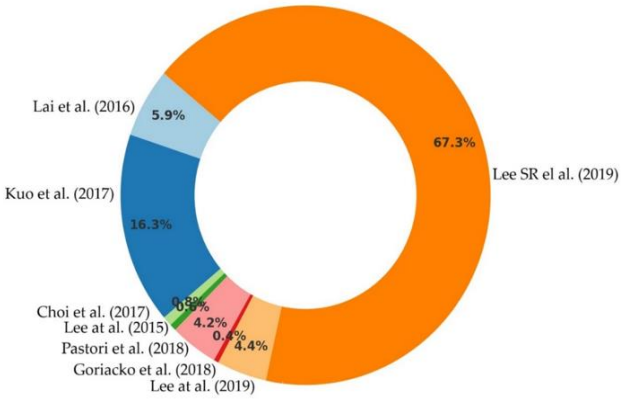

Figure 1. Distribution of participants across the studies

The pie chart in Figure 1 illustrates the distribution of participants across the different studies selected for this review. The largest proportion of participants, 67.3%, is from the study by Lee SR et al. (2019) [32], indicating this study had a much larger sample size compared to the others, which suggests it might have higher statistical power and more generalizable results. Kuo et al. (2017) [26] follows with 16.3% of participants, making it the second-largest study in terms of sample size.

Smaller studies like Choi et al. (2017) [27], Lee et al. (2015) [28], Pastori et al. (2018) [29], and Goriacko et al. (2018) [30] contributed only small proportions, ranging from 0.4% to 4.4%, showing that while these studies provide valuable insights, their conclusions might be less generalizable due to the limited number of participants. This imbalance in sample size is important to consider when interpreting the outcomes, as larger studies typically provide more robust and reliable results.

Tables 1-8 also provide a comparison of studies that investigate the use of anticoagulation treatments (mainly VKAs, NOACs, and DOACs) in patients with AF, with a focus on bleeding rates and stroke prevention outcomes. As previously mentioned, the sample sizes in the studies range from 233 to 37,353 participants, with the majority of patients being male (ranging from 53.1% to 74.6% male). The average age across the studies varies from 62 to 74 years, highlighting the elderly population that typically suffers from AF and liver disease.

The findings demonstrate a consistent trend where warfarin provides significant stroke prevention, as seen in studies such as Kuo et al. (2017) [26] and Choi et al. (2017) [27], where warfarin reduced stroke risk by approximately 24% compared to no treatment. However, bleeding risks, particularly in cirrhotic patients, are more concerning with warfarin. Choi et al. (2017) [27] reported a bleeding rate of 3.9% with warfarin, and Goriacko et al. (2018) [30] reported a slightly higher rate of 8.8%.

NOACs and DOACs appear to offer similar, if not better, stroke prevention with lower bleeding risks. For instance, in Pastori et al. (2018) [29], NOACs demonstrated a lower bleeding rate (2.2%) compared to warfarin (4.3%). Lee et al. (2019) [31] also reported favorable outcomes for NOACs with a 3.3% bleeding rate compared to 3.9% for warfarin. This trend supports the growing preference for DOACs in clinical practice, particularly when reducing the risk of major bleeding is a priority, as seen in Lee SR et al. (2019) [32], where DOACs showed a lower stroke risk compared to warfarin.

Thus, while warfarin remains effective for stroke prevention, newer anticoagulants like NOACs and DOACs show similar efficacy with a more favorable safety profile, particularly in terms of reduced bleeding risks, making them a better option for many patients.

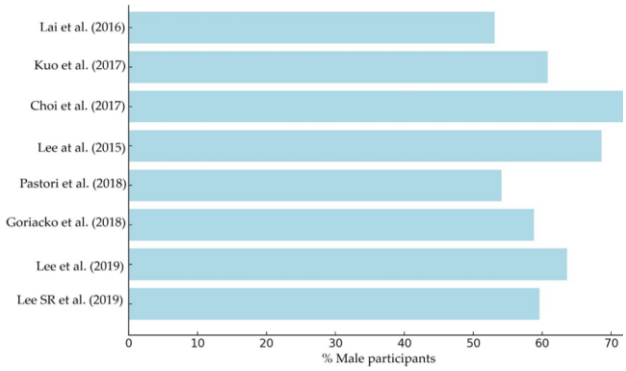

Figure 2. Percentage of male participants in the selected studies.

The bar chart in Figure 2 displays the percentage of male participants in the selected studies. It can be seen a relatively high representation of male participants, ranging from around 53% to 75%.

The study by Choi et al. (2017) [27] had the highest male representation at 74.6%, while Lai et al. (2016) [25] had the lowest male percentage at 53.1%. This variation in gender distribution may impact the generalizability of the study results, especially regarding how these treatments affect female patients. Gender differences can play a role in the response to anticoagulation therapies, with varying risks of bleeding or stroke across men and women.

Table 9. Summary statistics for participants and bleeding rate across the studies

Variable	Mean	Min	Max
Participants	6934.87	233	37353
Bleeding rate (DOAC)	4.26	2.2	8.4
Bleeding rate (Warfarin)	5.12	3.9	8.8

Table 9 presents summary statistics for participants and bleeding rates. Thus, it can be seen that DOACs show a lower average bleeding rate of 4.26%, ranging from 2.2% to 8.4%, whereas Warfarin has a slightly higher average bleeding rate of 5.12%, with a range from 3.9% to 8.8%. This suggests that, on average, DOACs are associated with a lower bleeding risk compared to Warfarin, which aligns with the findings of many clinical studies advocating for the use of DOACs due to their more favorable safety profile.

The higher variability in the bleeding rates for both DOACs and Warfarin highlights the importance of patient-specific factors and treatment settings, suggesting that while DOACs generally perform better, individual risks may vary based on underlying health conditions and specific treatment circumstances.

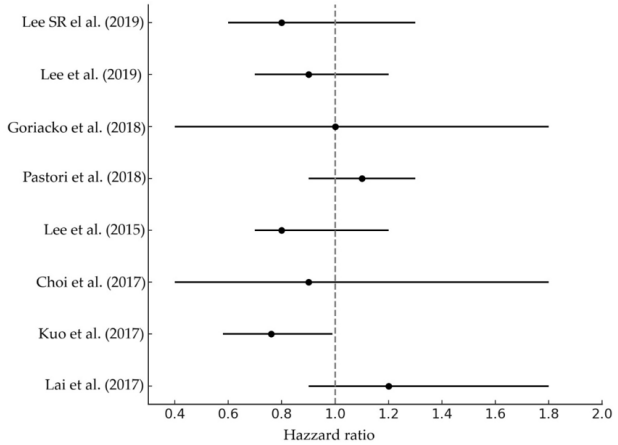

Figure 3. Forest plot comparing the hazard ratios for bleeding and stroke risk across the selected studies

The forest plot illustrates the hazard ratios (HR) for the studies included in this analysis. The vertical dashed line at HR = 1 represents the point of no effect, where values to the left suggest a reduced risk and values to the right suggest an increased risk compared to the baseline (typically Warfarin or no treatment).

Studies such as Kuo et al. (2017) [26] and Pastori et al. (2018) [29] show hazard ratios significantly below 1, indicating a reduced risk of adverse events for patients receiving treatments like DOACs compared to warfarin. Lee et al. (2015) [28] and Choi et al. (2017) [27] also show hazard ratios close to 1, indicating similar outcomes between the treatments studied, with minimal increased or decreased risk. The wider confidence intervals for studies like Goriacko et al. (2018) [30] and Kuo et al. (2017) [26] suggest more uncertainty in these studies' estimates, potentially due to smaller sample sizes or higher variability in outcomes.

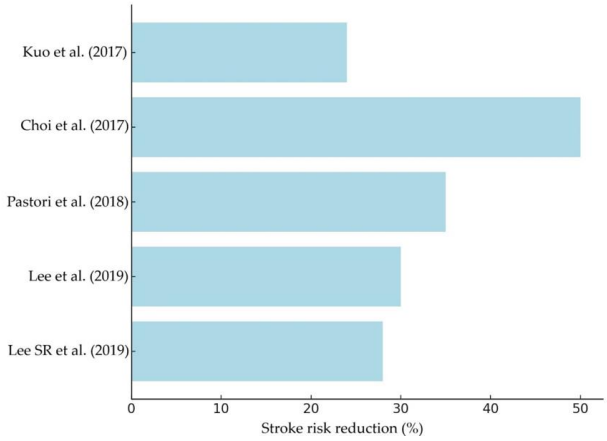

Figure 4. Stroke risk reduction across selected studies

Figure 4 shows the stroke risk reduction, with varying percentages of risk reduction achieved by different treatments. Choi et al. (2017) [27] demonstrates the most significant stroke risk reduction at approximately 50%, indicating a strong protective effect of the intervention studied. Other studies, such as Pastori et al. (2018) [29], Lee et al. (2019) [31], and Lee SR et al. (2019) [32], show moderate reductions in stroke risk, ranging between 25% and 35%. Kuo et al. (2017) [26] reports the lowest stroke risk reduction, at around 24%.

Table 10. Bleeding rates for DOACs and Warfarin across four studies

Study	Bleeding rate (DOACs)	Bleeding rate (Warfarin)
Choi et al. (2017) [27]	Not available	3.9
Pastori et al. (2018) [29]	2.2	4.3
Goriacko et al. (2018) [30]	8.4	8.8
Lee et al. (2019) [31]	3.3	3.9

Table 10 shows that DOACs generally have lower bleeding rates compared to Warfarin. For example, in Pastori et al. (2018) [29], the bleeding rate for DOACs is 2.2%, which is nearly half the rate of Warfarin at 4.3%. Similarly, Lee et al. (2019) [31] reports a bleeding rate of 3.3% for DOACs versus 3.9% for Warfarin, again favoring DOACs for reduced bleeding risks.

Goriacko et al. (2018) [30] reports the highest bleeding rates for both treatments, with DOACs at 8.4% and Warfarin at 8.8%, but even in this case, DOACs maintain a slightly lower bleeding risk. This study suggests that in higher-risk populations or specific circumstances, bleeding rates are elevated for both therapies, yet DOACs remain marginally safer.

In Choi et al. (2017) [27], only Warfarin's bleeding rate is available (3.9%), leaving a gap in the data for DOACs.

This comparison recommends that DOACs are associated with consistently lower bleeding risks than Warfarin across the studies where data are available, reinforcing the preference for DOACs in clinical practice for patients at risk of bleeding.

Data from the National Health Insurance Research Database in Taiwan [26] in regards to the risk of ischemic stroke in liver cirrhosis patients and atrial fibrillation showed that the risk of ischemic stroke was comparable between those taking antiplatelet therapy and those not taking any antithrombotic therapy (hazard ratio=1.02, 95%CI=0.88-1.18). However, warfarin users had a significantly reduced risk of ischemic stroke (hazard ratio=0.76, 95%CI=0.58-0.99), thus showing a net benefit of warfarin over antiplatelet drugs, with no significant differences in regards to intracranial hemorrhage [26].

A meta-analysis of six studies involving 41,859 patients with liver disease and atrial fibrillation [33] studying the impact of either warfarin or DOACs on ischemic stroke risk showed that DOACs significantly decreased the risk of ischemic stroke compared with warfarin in AF patients with liver disease (pooled HR, 0.68; 95% CI, 0.54–0.86; P = 0.001), with no statistically significant differences between the regular-DOAC dose regimen subgroup and reduced-DOAC dose regimen subgroup. In regards to safety DOACs significantly decreased major bleeding risk (pooled HR, 0.66; 95% CI, 0.58–0.75; P < 0.001). especially in the reduced-DOAC dose regimen group (pooled HR, 0.64; 95% CI, 0.56–0.74; P < 0.001). However, there was no reduction in the risk of GI bleeding in AF patients with liver disease compared with warfarin [33].

A reduced mortality of anticoagulated patients with AF and liver disease was also remarked in a cohort of 2,694 LC and newly diagnosed AF patients (1,694 veterans for the warfarin cohort-614 on warfarin and 1,080 matched controls and 704 for the DOAC cohort - 201 on DOACs and 503 matched controls [34]. Among patients matched with warfarin, those who did not receive anticoagulant therapy had an incidence rate of 27.2 per 100 person-years for all-cause mortality compared to 17.0 for those who received warfarin (P<.001). In the DOAC-matched cohort, mortality incidence rates were similar (16.1 with DOACs, 23.1 with no AC; P<.01). Other domains were explored as well: The incidence rate of hepatic decompensation was significantly lower in the warfarin versus non anticoagulated cohort (5.3 per 100 person-years with warfarin versus 7.1 with no AC; P=0.02), however, this was not significant for the DOAC group (6.3 per 100 person-years with no AC versus 4.6 with DOACs; P=0.14). In the no AC group, the incidence rate of splanchnic thrombosis was 0.5 per 100-person years compared to 0.3 with warfarin (P=.05) whilst in the DOAC-matched cohort, there was no significant difference observed in the incidence of splanchnic thrombosis between anticoagulation statuses in the DOAC cohort. Furthermore, no significant differences were observed in the incidence of ischemic stroke, MACE (Major Adverse Cardiovascular Events), or bleeding in both the warfarin and DOAC cohorts [33].

Data from the Korean National Health Insurance Service database [35], suggests a better effectiveness and safety of DOAC than warfarin: A total of 37,353 patients with AF and liver disease were included in the study, with 12,778 patients newly prescribed warfarin and 24,575 patients prescribed DOACs. Among those on DOACs, 42.5% of patients (n=10,440) received rivaroxaban, 27.4% (n=6,724) received dabigatran, 22.6% (n=5,561) received apixaban, and 7.5% (n=1,850) received edoxaban. Reduced doses of DOACs were prescribed to 52.5% of patients. Compared to warfarin, DOACs showed reduced risks of various health outcomes including ischemic stroke (HR: 0.548; 95% CI: 0.485 to 0.618), intracranial hemorrhage (HR: 0.479; 95% CI 0.394 to 0.581), gastrointestinal bleeding (HR: 0.819; 95% CI: 0.619 to 0.949), major bleeding (HR: 0.650; 95% CI: 0.575 to 0.736), all-cause death (HR: 0.698; 95% CI: 0.636 to 0.765), and the composite outcome (HR: 0.610; 95% CI: 0.567 to 0.656). The study found that the clinical benefit of DOACs was consistent across all types and dose regimens, as well as across various subgroups of patients with liver disease and AF. Notably, the risk of hospitalization for gastrointestinal bleeding was similar between rivaroxaban and warfarin in this patient population, while other DOACs demonstrated a lower risk [35].

An investigation by Qi et al. [24] accentuates the critical function of DOACs in stroke prevention for patients with nonvalvular atrial fibrillation. This research underlines the potential advantages of DOACs in mitigating the risk of thromboembolic incidents in individuals with atrial fibrillation paired with liver disease, stressing the necessity of weighing efficacy against safety considerations in this susceptible demographic. Furthermore, authors illuminate the comparative efficiency of DOACs versus conventional anticoagulants in managing hemorrhagic risk in liver disease patients, presenting invaluable perspectives on treatment modalities for this intricate group. Scrutinizing the subtleties of employing DOACs in liver disease patients with atrial fibrillation uncovers the requirement for tailored treatment methodologies. Evidence has shown that DOACs may represent a safer option than warfarin, particularly in cirrhotic patients, displaying effectiveness in lowering stroke risk without considerably augmenting bleeding rates. Additionally, the meta-analysis by Chokesuwattanaskul et al. [36] lends further credence to the effectiveness of DOACs in stroke prophylaxis and stresses the significance of individualized care to optimize results for this patient cohort. Incorporating DOACs into the framework of anticoagulant therapy for individuals with liver disease and atrial fibrillation presents both hurdles and

prospects. Maintaining a fine equilibrium between averting thrombotic events and minimizing hemorrhagic risks remains critical [24]. As continuous research advances our comprehension of the efficacy and safety profile of DOACs in this context, the adoption of customized strategies grounded in evidence-based practices and patient-specific factors will be crucial in enhancing clinical outcomes in this medically complex scenario [37-39].

Conclusions

Summarizing challenges of anticoagulant treatment in patients with atrial fibrillation and liver disease requires comprehensive consideration of available evidence. Intricate balance between preventing thrombotic events and minimizing bleeding risks underscores need for tailored therapeutic approaches in this complex patient population. Existing research, such as meta-analyses and observational studies, highlights efficacy of direct oral anticoagulants (DOACs) compared to traditional agents like warfarin, showing potential benefits in stroke prevention and reduced bleeding rates. However, gaps in knowledge persist, necessitating further investigation into optimal dosing regimens, safety profiles, and outcomes in severe cirrhosis cases. Furthermore, when navigating nuances of anticoagulation therapy in liver disease patients with atrial fibrillation, individualized nature of treatment decisions emerges as critical consideration. Clinicians must assess factors like liver function, comorbidities, and bleeding risks to determine most suitable anticoagulant regimen for each patient. While DOACs show promise in addressing unique challenges of this population, ongoing research is essential to elucidate their long-term safety and efficacy, especially in severe liver cirrhosis. Formulating comprehensive guidelines that incorporate liver-specific parameters, such as the Child-Pugh score and Model for End-Stage Liver Disease (MELD) score, into anticoagulant decision-making is necessary to improve patient outcomes and reduce risks Nevertheless, optimal dosing, monitoring tactics, and the reversibility of DOACs within this patient segment are areas demanding further inquiry. Despite progress within anticoagulation therapy, the lack of specific guidelines for AF management in cirrhotic patients highlights the current evidence gaps. Meta-analyses presented by indicate that DOACs might offer safety and efficacy levels comparable to warfarin in cirrhotic AF patients, stressing the necessity for more randomized controlled trials to substantiate these observations.

Future research efforts should focus on elucidating the underlying mechanisms of the altered hemostatic state in cirrhotic patients with AF to inform tailored management strategies. Prospective studies that assess the long-term benefits and risks of anticoagulation therapy in cirrhotic patients with AF are crucial for developing evidence-based clinical protocols that balance thrombotic prevention and bleeding risk. Collaborative initiatives between hepatology and cardiology experts are required to address the intricate interplay between liver disease and AF, fostering interdisciplinary care models that enhance patient safety and treatment effectiveness. By prioritizing a patient-centered approach guided by robust research, future directions in hemostatic management for cirrhotic patients with AF can improve clinical decision-making and therapeutic results.

In conclusion, evolving landscape of anticoagulant treatment for patients with atrial fibrillation and liver disease necessitates nuanced and multidisciplinary approach.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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