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Evaluating Anticoagulation Strategies in Atrial Fibrillation with Liver Disease: A Meta-Analytical Comparison of Direct Oral Anticoagulants and Warfarin

Mohamed S. Imam[1*], Fahad Saeed Algahtani[2], Asim Abdullah Saleh Alqahtani[3], Nawaf Mohammed Ali Naser[4], Abdulaziz Ali Mohammed Asiri[5], Shaimaa Mulfi Hussein Alqahtani[6], Naif Ayidh Alshabab[7], Bayan Sami Altalhi[8], Shmookh Abdulrazak Abdrabuh Altalhi[9], Norah S. Alotaibi[10], Amjad Homoud Masoud Alotaibi[11], Saleh Abdulrahman Saleh Hunjur[12], Rahaf Haif Ajlan Alshehri[13], Yara Abdulaziz Alharthi[14] and Ouns Naif Mosa Muderba[15]

[1]Department of Pharmacy, Alnahda College, Riyadh, Kingdom of Saudi Arabia
[2]Department of Restorative Dental Science, Faculty of Dentistry, Taif University, P.O. Box 11099, 21944 Taif, Saudi Arabia
[3-6]College of Pharmacy, King Khalid University, 62529 Abha, Saudi Arabia
[7]Al-Dawaa Medical Services Company, Riyadh, Saudi Arabia
[8-14]College of Pharmacy, Taif University, 21944 Taif, Saudi Arabia
[15]College of Pharmacy, Jazan University, 82912 Jazan, Saudi Arabia

Author Designation: [1-2]Faculty Member, [3-5,7,8,9-13]Pharmacist, [6,15]PharmD Student

*Corresponding author: Mohamed S. Imam (e-mail: imammohamed311@gmail.com).

Abstract **Background:** Anticoagulation is crucial for preventing stroke and Atrial Fibrillation (AF) is a significant risk factor for thromboembolism. However, because of changed medication metabolism and coagulation profiles, treating anticoagulation in patients with concurrent Liver Disease (LD) is difficult. The safety and effectiveness of direct oral anticoagulants (DOACs) and warfarin in patients with AF and LD are compared in this meta-analysis. **Methods:** A comprehensive literature search was implemented through January 2025. The study included ten observational studies that involved 417,754 patients with AF and LD. The outcomes that were evaluated included all-cause mortality, intracranial hemorrhage, stroke or systemic embolism, major bleeding and gastrointestinal bleeding. Random-effects models were employed to calculate pooled Odds Ratios (ORs) with 95% Confidence Intervals (CIs). The I^2 statistic was employed to evaluate heterogeneity. **Results:** DOACs were associated with substantially reduced risks of all-cause mortality (OR = 0.76, 95% CI: 0.58-0.99; p = 0.04), intracranial hemorrhage (OR = 0.48, 95% CI: 0.24-0.94; p = 0.03) and major bleeding (OR = 0.65, 95% CI: 0.49-0.87; p = 0.003) compared to warfarin. There were no significant differences observed in the incidence of stroke or systemic embolism (OR = 0.76, 95% CI: 0.56-1.02; p = 0.07) or gastrointestinal hemorrhage (OR = 0.97, 95% CI: 0.79-1.20; p = 0.81). Substantial heterogeneity was observed among outcomes (I^2>90% in multiple analyses). **Conclusion:** It appears that DOACs provide comparable efficacy and enhanced safety in patients with AF and LD when compared to warfarin. Nevertheless, the observational design of the included studies and the substantial heterogeneity of the data necessitate caution in the interpretation of these results. Additional randomized controlled trials are required to verify these findings and inform clinical decision-making.

Key Words Atrial Fibrillation, Warfarin, Major Adverse Events, Liver Disease, Direct Oral Anticoagulants, Meta-Analysis, Bleeding Risk

INTRODUCTION

Atrial Fibrillation (AF) is the most prevalent persistent arrhythmia, characterized by an irregular, uncoordinated ventricular rhythm and erratic atrial electrical signals [1-3]. This rhythm disturbance results in impaired atrial contraction and stasis of blood within the atria, predisposing patients to thromboembolic events, particularly ischemic stroke [4,5]. The incidence of AF is still rising globally, fueled by aging populations, increasing prevalence of cardiovascular comorbidities and improvements in diagnostic capabilities [6,7]. Worldwide, AF is linked to significant mortality and healthcare consumption, highlighting the need for effective treatment approaches targeted at preventing strokes, managing symptoms and minimizing negative effects [8,9].

The mainstay of stroke prevention for AF patients is oral anticoagulation, particularly for those who are moderately to highly at risk as determined by instruments like the

CHA_2DS_2-VASc score [10,11]. Warfarin, a vitamin K antagonist (VKA), has long been the cornerstone of anticoagulant treatment [12]. However, a restricted therapeutic window, frequent dosage modifications and monitoring, a large number of food and medication interactions and unpredictable pharmacokinetics limit its usage [13,14]. Direct oral anticoagulants (DOACs), including dabigatran, apixaban, edoxaban and rivaroxaban have become increasingly popular as viable alternatives in the past decade [15]. These medications provide predictable pharmacokinetics, minimal regular monitoring and fewer dietary restrictions, all of which have improved patient satisfaction and adherence [16]. DOACs have been shown to be at least as effective as warfarin in reducing the risk of stroke and systemic embolism in patients with non-valvular AF in large-scale Randomized Controlled Trials (RCTs). In some cases, they have demonstrated superior efficacy. Additionally, DOACs are known to have a more favorable safety profile, with a lower incidence of intracranial hemorrhage [17].

The utility of DOACs in patients with concomitant Liver Disease (LD) remains incompletely understood, despite their widespread efficacy in the general AF population [18]. Liver disease, ranging from mild hepatic dysfunction to advanced cirrhosis, complicates anticoagulation management due to the liver's critical role in synthesizing coagulation factors, regulating hemostasis and metabolizing medications [19,20]. Patients with both AF and LD present a paradoxical challenge: they are simultaneously at increased risk of thrombotic events due to endothelial dysfunction, inflammation and stasis and at heightened risk of bleeding because of thrombocytopenia, impaired synthesis of clotting factors and altered platelet function [21]. As a consequence, the net therapeutic benefit of anticoagulation in this group is not readily foreseeable, requiring complex risk classification.

Importantly, individuals with moderate to severe hepatic impairment have been systematically excluded from most pivotal DOAC RCTs, resulting in limited high-quality evidence to inform practice [22,23]. Furthermore, current guidelines from major cardiology and hepatology societies offer little clarity on optimal anticoagulation strategies for patients with both AF and LD, often defaulting to cautious or individualized approaches. The International Normalized Ratio (INR), which is sometimes employed to monitor warfarin, may not be precise in cases of advanced liver disease due to baseline coagulopathy, which complicates the determination of whether therapeutic anticoagulation is being produced [24]. Moreover, warfarin's metabolism via hepatic cytochrome P450 enzymes may be impaired in LD, leading to unpredictable effects [19].

In contrast, DOACs differ in their metabolic profiles and reliance on hepatic clearance. Dabigatran, for example, is primarily renally excreted, whereas apixaban, edoxaban and rivaroxaban undergo varying degrees of hepatic metabolism [25,26]. Rivaroxaban is expressly prohibited for patients with moderate or severe hepatic impairment; however, individuals with less severe liver dysfunction should exercise caution when using apixaban and edoxaban [26]. These pharmacologic variations indicate that the safety and efficacy of different DOACs in LD patients may vary. Therefore, without stratified investigation, it may be unfeasible to make generalizations about this medication class.

Thus far, an expanding yet still relatively modest collection of observational research and real-world evidence has explored how DOACs compare to warfarin in terms of clinical outcomes among individuals with AF and LD [27,28]. Findings from these studies suggest that, within this high-risk population, DOACs use may be associated with reduced rates of major bleeding, intracranial hemorrhage and overall mortality. However, the interpretation and generalizability of results are complicated by variations in research design, patient groups, liver disease classifications and outcome measures. Furthermore, many of these studies are retrospective and subject to selection bias, unmeasured confounding and incomplete data reporting.

A thorough review of the available data is necessary in light of these uncertainties and the therapeutic significance of optimizing anticoagulation in individuals with AF and LD. Meta-analysis serves as a powerful tool to aggregate data across studies, enhance statistical power and identify patterns or trends not discernible in individual reports. This analysis is particularly relevant in populations where prospective randomized data are sparse or infeasible due to ethical, logistical or financial constraints.

Consequently, this meta-analysis was performed to undertake a thorough assessment of the comparative safety and efficacy of DOACs versus warfarin in individuals who have been diagnosed with both AF and LD. To be more precise, the objective of this review was to establish quantitative differences in critical clinical outcomes, such as all-cause mortality, intracranial hemorrhage, gastrointestinal bleeding, systemic or stroke embolism and major bleeding. By synthesizing data from available studies, we sought to address the current evidence gap and provide clearer guidance on anticoagulant selection in this complex and vulnerable patient population. Moreover, this analysis explores whether DOACs use in patients with AF and LD is associated with clinically meaningful advantages over warfarin and whether such benefits extend across various bleeding and thromboembolic endpoints. The results of our study may be beneficial in guiding clinical judgment, the development of guidelines and the planning of additional research to ascertain the optimal anticoagulant regimen for patients who are managing the combined risks of hepatic dysfunction and AF.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were followed in conducting this meta-analysis [29]. The implementation of a

methodologically sound and structured approach was implemented to guarantee comprehensiveness, reproducibility and transparency. The experiment aimed to assess the comparative safety and effectiveness of DOACs and warfarin in people with AF and concurrent LD. The procedures for searching literature, choosing studies, extracting data, evaluating quality and doing statistical analysis are described in this section.

The methodology for this study was pre-specified and based on recommendations from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and PRISMA statements. A formal review protocol was developed prior to conducting the literature search and analysis, including predefined eligibility criteria, outcome definitions and analytical strategies.

Literature Search Strategy

The electronic databases enumerated in Table 1 were employed to conduct a thorough literature search that encompassed the period from inception to January 2025. The search strategy was developed using the PICOS (Population, Intervention, Comparison, Outcomes and Study design) framework to ensure thorough identification of relevant studies [30].

A comprehensive search strategy was developed using key terminology and their various combinations to ensure broad retrieval of relevant studies. The principal search terms included: "novel oral anticoagulants," "DOACs," "direct oral anticoagulants," and "non-vitamin K antagonist oral anticoagulants"; in addition to "warfarin," "atrial fibrillation," and hepatic-related descriptors such as "liver disease," "hepatic impairment," and "cirrhosis."

To expand the scope, Medical Subject Headings (MeSH) and Boolean operators (AND, OR) were used when appropriate. Table 1 lists all of the search tactics for every database. EndNote reference management software was used to import all detected citations in order to remove duplicates and enable methodical filtering.

Study Selection

If a study satisfies all of the following requirements, it was included:

- **Population:** Adults diagnosed with AF and underlying liver disease of any severity
- **Intervention:** Treatment with any DOAC (e.g., apixaban, rivaroxaban, edoxaban, dabigatran)
- **Comparison:** Treatment with warfarin
- **Outcomes:** Reported one or more of the following outcomes: all-cause mortality, gastrointestinal bleeding, major bleeding, systemic or stroke embolism or intracranial hemorrhage
- **Study design:** Observational studies (prospective or retrospective cohort), RCTs or case-control studies

Exclusion Criteria

- Non-human or preclinical studies
- Case reports, reviews, editorials or commentaries
- Studies without a direct comparison between DOACs and warfarin
- Studies that did not report outcome-specific effect measures

The abstracts and titles were individually evaluated by two researchers. The full texts of potentially eligible studies were retrieved and assessed for inclusion. Disputes regarding the eligibility of the research were resolved through consultation with or discussion with a third reviewer.

Data Extraction

To guarantee consistency between investigations, a consistent data extraction form was created. Data extraction was meticulously carried out for all studies that fulfilled the eligibility criteria. The collected variables encompassed the name of the first author, publication year and the geographical location of the investigation, including both country and region. In addition, methodological details such as study design and study period were documented. Demographic and baseline population data were also retrieved, including participants' age, sex distribution and the total number of patients diagnosed with both liver disease and atrial fibrillation. Furthermore, information regarding the anticoagulant regimen was recorded, specifically the type of direct oral anticoagulant administered and the comparator treatment, namely warfarin. Clinical endpoint data were comprehensively extracted, covering all-cause mortality, gastrointestinal bleeding events, ischemic or hemorrhagic stroke, systemic embolism, major bleeding and intracranial hemorrhage. Measures of association reported by the included studies, such as odds ratios, relative risks or hazard ratios together with their corresponding 95% confidence intervals, were also collected. Moreover, details of the adjusted confounding variables applied in the statistical analyses, as well as the duration of patient follow-up, were systematically obtained.

The most completely adjusted values were employed in studies that reported multiple effect estimates. Two researchers conducted data extraction independently. Re-evaluation and consensus were implemented to resolve discrepancies.

Risk of Bias and Quality Assessment

The QUIPS tool was employed to assess the quality of the observational studies included in this analysis, which focuses on six critical areas [31]: Participant selection, loss to follow-up, accuracy of prognostic factor measurement, outcome assessment, control of confounding variables and the robustness of statistical analysis and reporting. Each methodological domain was carefully evaluated to determine the likelihood of bias and studies were accordingly classified as having a low, moderate or high risk of bias. Whenever randomized controlled trials were identified among the eligible studies, assessment was planned using the Cochrane Risk of Bias Tool. Differences in judgment between the independent reviewers were resolved through detailed discussion until a mutual consensus was achieved.

Statistical Analysis

All quantitative analyses were conducted using Review Manager (RevMan) software, version 5.3, produced by the Nordic Cochrane Centre. For every investigated clinical endpoint, combined odds ratios together with their 95% confidence intervals were estimated. The choice of statistical model was based on the degree of interstudy heterogeneity: a random-effects approach was adopted when substantial between-study variation was present, whereas a fixed-effects approach was utilized when heterogeneity was minimal or not statistically significant.

The I^2 statistic was employed to quantify the extent of heterogeneity [32]. The magnitude of heterogeneity was interpreted according to conventional cutoff values, where an I^2 ranging from 0-25% was considered indicative of low inconsistency, values from 26-50% represented moderate heterogeneity and estimates above 50% denoted marked heterogeneity among the included studies. Furthermore, subgroup analyses were planned in advance based on the specific clinical endpoint being examined. To verify the robustness and consistency of the meta-analytic results, sensitivity analyses were also undertaken through sequential exclusion of studies judged to carry a high risk of bias, in addition to applying different statistical models to determine whether the overall pooled estimates remained stable.

Publication Bias

Publication bias was assessed using a dual approach. First, funnel plots were visually examined to determine the degree of symmetry between the reported effect estimates and their corresponding standard errors. Second, Egger's regression analysis was applied, with a probability value below 0.05 considered suggestive of potential small-study effects. Nevertheless, because some outcome-specific analyses incorporated only a limited number of eligible studies, the findings related to publication bias were interpreted with caution, acknowledging that the ability to reliably identify funnel plot asymmetry or detect small-study influences is diminished when statistical power is low.

RESULTS

Study Selection and Characteristics

Through extensive database searching throughout the electronic databases specified in Table 1, 1,076 records in total were initially identified. No other studies could be found elsewhere. 434 distinct records were left for preliminary screening after duplicates were eliminated. One hundred articles remained for full-text review after 334 articles were eliminated for not meeting the fundamental

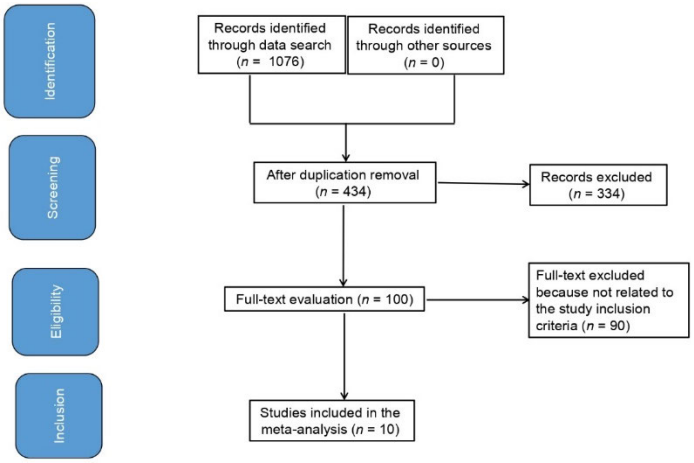

Figure 1: Schematic Representation of the Study Protocol

Table 2: Summary of Included Studies and Their Key Characteristics for the Meta-Analysis

Study		Total	DOACs	Warfarin
Goriacko and Veltri [37]	USA	233	75	158
Pastori *et al.* [38]	Italy	2330	1033	1297
Wang *et al.* [39]	Taiwan	6451	4390	3332
Lee *et al.* [40]	Taiwan	2624	1438	990
Lee *et al.* [41]	Korean	37353	24575	12778
Qamar *et al.* [42]	Global	1083	718	365
Lee *et al.* [36]	Taiwan	107802	55768	52034
Halvorsen *et al.* [35]	Denmark, Norway and Sweden	229216	114608	114608
Tsai *et al.* [34]	Taiwan	15361	10916	4445
Li *et al.* [33]	Taiwan	15301	6566	8735
Total		417754	220087	198742

Table 3: Summary of Key Findings of Our Study

Outcome	Pooled OR (95% CI)	p-value	Interpretation
All-Cause Mortality	0.76 (0.58-0.99)	0.04	↓ Mortality with DOACs
Major Bleeding	0.65 (0.49-0.87)	0.003	↓ Risk with DOACs
Intracranial Hemorrhage	0.48 (0.24-0.94)	0.03	↓ Risk with DOACs
Stroke/Systemic Embolism	0.76 (0.56-1.02)	0.07	No significant difference
GI Bleeding	0.97 (0.79-1.20)	0.81	No significant difference

relevance requirements based on the assessment of titles and abstracts. Ninety of these studies were disqualified for failing to satisfy the predetermined inclusion criteria, which included failing to report germane clinical outcomes, failing to include patients with both AF and LD or failing to provide comparison data between DOACs and warfarin, following a diligent review. Ultimately, ten publications met all of the eligibility criteria and were incorporated into the final meta-analysis [33-42]. Figure 1 depicts this selection procedure.

The main features of the 10 trials that made up this meta-analysis, which together comprised 417,754 individuals with AF with underlying LD, are listed in Table 2. Of them, 198,742 patients were treated with warfarin, while 220,087 patients were treated with DOACs. The studies span multiple geographic regions, including the United States, Italy, Korea, Taiwan, Scandinavia (Denmark, Norway and Sweden) and global cohorts, reflecting a diverse international representation. Sample sizes varied widely, from smaller cohorts such as the study by Goriacko and Veltri [37] in the USA with 233 patients, to large-scale population-based cohorts such as Halvorsen *et al.* [35], which included 229,216 patients equally divided between DOACs and warfarin. Taiwan contributed the most data, with five studies originating from there and representing a significant portion of the total population analyzed. The DOAC-to-warfarin ratio varied across studies, with some, like Lee *et al.* [36], showing relatively balanced groups (55,768 vs. 52,034), while others, such as Tsai *et al.* [34], had a greater skew toward DOAC use (10,916 vs. 4,445). The broad spectrum of geographical representation together with the variation in study sample sizes strengthens the external validity of the pooled evidence, thereby providing a more reliable and comprehensive basis for comparing the therapeutic effectiveness and safety profiles of DOACs versus warfarin among patients suffering from both AF and LD. The summary of key findings of our study is depicted in Table 3.

All-Cause Mortality

The results of five trials comparing warfarin and DOACs in terms of all-cause mortality among patients with AF and LD are summarized in a forest plot in Figure 2. The magnitude

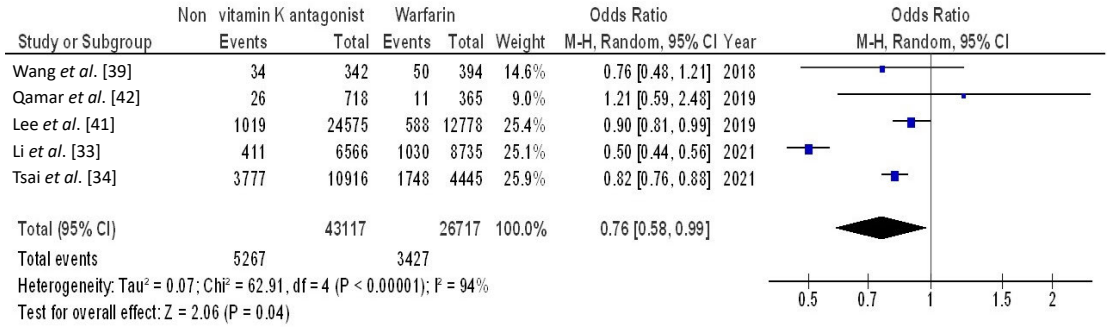

Figure 2: Forest Plot Comparing the Intake of DOACs to Warfarin Concerning All-Cause Mortality in Individuals with AF and LD

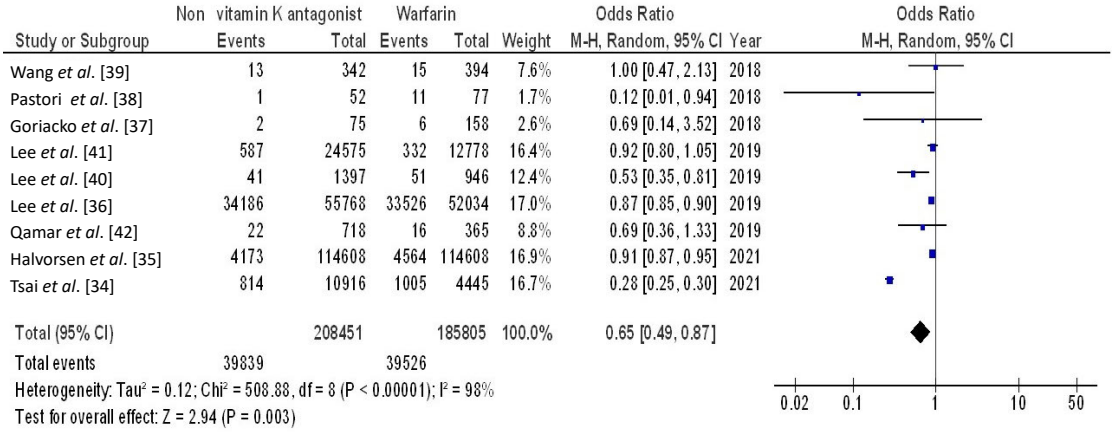

Figure 3: Forest Plot Comparing the Intake of DOACs to Warfarin About Severe Bleeding in Individuals with AF and LD

of the impact varied among the various studies. For instance, Wang *et al.* [39] reported an OR of 0.76 [95% CI: 0.48-1.21], which implies a non-significant decrease in mortality associated with DOACs. In contrast, Qamar *et al.* [42] yielded an OR of 1.21 [0.59-2.48], indicating an insignificant trend toward higher mortality with DOACs. However, larger and more statistically precise studies such as those by Li *et al.* [33], Tsai *et al.* [34] and Lee *et al.* [41] demonstrated statistically significant reductions in all-cause mortality in the DOACs group, with ORs of 0.90 [0.81-0.99], 0.50 [0.44-0.56] and 0.82 [0.76-0.88], respectively. These studies contributed the highest weights to the pooled analysis, ranging from 25.1-25.9%.

A random-effects model yielded a pooled effect estimate of 0.76 [0.58-0.99], which showed a statistically significant 24% decrease in the risks of all-cause death while taking DOACs as compared to warfarin ($p = 0.04$). Nevertheless, the studies exhibited a high degree of heterogeneity ($I^2 = 94\%$, $Chi^2 = 62.91$, $p<0.00001$), which indicates a significant degree of variability in the outcomes of the studies. Although variability was observed across the included studies, the predominance of a uniform effect trend, particularly among investigations enrolling larger patient cohorts, suggests that DOACs may confer a favorable survival advantage compared with warfarin in individuals with concomitant AF and LD. While differences in patient-level factors and methodological diversity among the included studies warrant cautious interpretation, the present findings indicate that direct oral anticoagulants may represent a comparatively safer therapeutic alternative to warfarin in patients with atrial fibrillation accompanied by concomitant liver disease.

Major Bleeding Events

Figure 3 presents the forest plot evaluating the incidence of major bleeding among patients with atrial fibrillation and liver disease receiving direct oral anticoagulants compared with those treated with warfarin. This pooled analysis incorporated nine eligible studies, involving 208,451 individuals in the DOAC-treated arm and 185,805 individuals in the warfarin-treated arm. The integrated results demonstrated that treatment with direct oral anticoagulants was associated with a statistically significant reduction in major bleeding events, yielding an overall odds ratio of 0.65 (95% CI: 0.49-0.87), thus favoring DOAC therapy over warfarin ($p = 0.003$). Most notably, the studies by Tsai *et al.* [34], Lee *et al.* [36] and Lee *et al.* [40] contributed the greatest weight to the analysis (16.7%, 12.4% and 17.0%, respectively) and showed consistent risk reductions, with Tsai *et al.* [34] reporting a remarkably low OR of 0.28 [0.25-0.30].

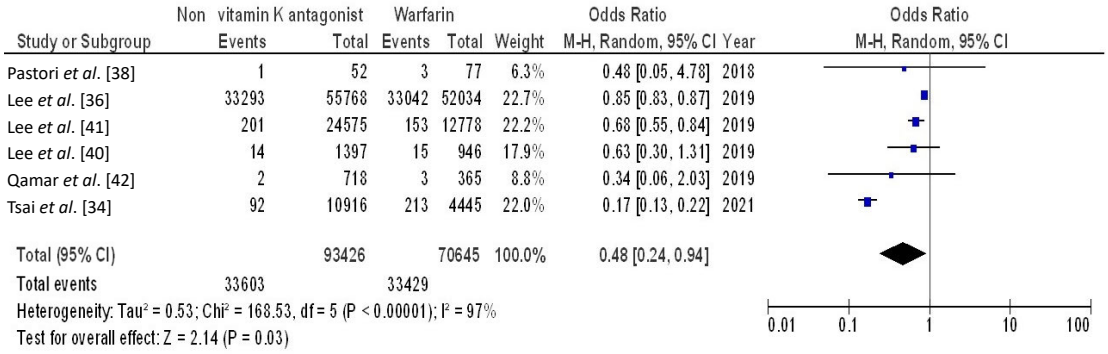

Figure 4: Forest Plot Comparing the Intake of DOACs to Warfarin Concerning Intracranial Hemorrhage in Individuals with AF and LD

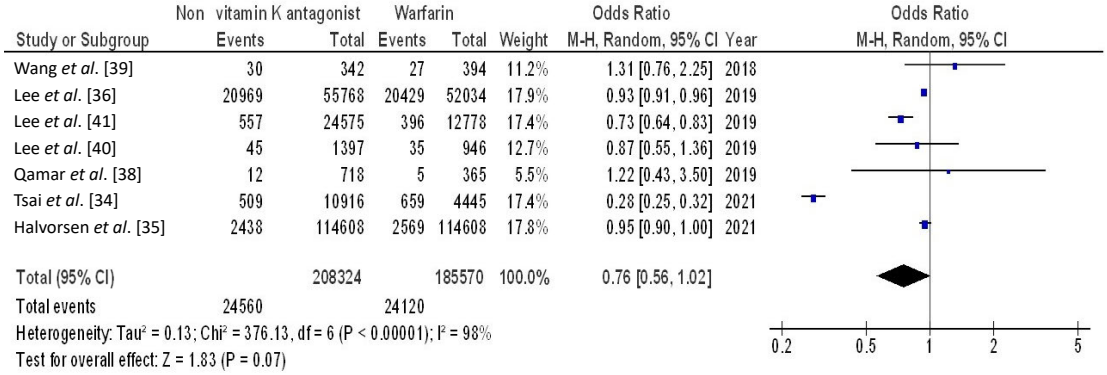

Figure 5: Forest Plot Comparing the Intake of DOACs to Warfarin Concerning Stroke and Systemic Embolism in Individuals with AF and LD

Despite the positive overall impact, the meta-analysis demonstrated substantial heterogeneity among the included studies (I^2 = 98%, Chi^2 = 508.88, p<0.00001), indicating substantial diversity in study results. This variability may stem from differences in baseline patient characteristics, liver disease severity, definitions of severe bleeding or follow-up durations. However, the directionality of effect was consistent across most studies, with the majority indicating a lower bleeding risk associated with DOACs. Even smaller studies, such as Pastori *et al.* [38] and Lee *et al.* [40], supported this trend with ORs well below 1. In patients with AF with underlying liver dysfunction, our results imply that, on the whole, DOACs may provide a safer bleeding profile than warfarin; nonetheless, physicians should still customize anticoagulant treatment according to patient-specific risk factors.

Intracranial Hemorrhage

Figure 4 illustrates a forest plot that contrasts the risk of cerebral hemorrhage in individuals with AF and LD who are administered DOACs with those who are administered warfarin. Throughout the six trials that were included, the DOAC group consisted of 93,426 individuals, while the warfarin group consisted of 70,645. As demonstrated by the pooled OR of 0.48 [95% CI: 0.24-0.94] (p = 0.03), patients who received DOACs had a statistically significant 52% reduced risk of cerebral hemorrhage. Notably, the study by Tsai *et al.* [34] contributed the most compelling evidence with an OR of 0.17 [0.13-0.22], reinforcing the protective effect of DOACs against this life-threatening complication.

Although the overall outcome was favorable, the included studies exhibited significant heterogeneity (I^2 = 97%, Chi^2 = 168.53, p<0.00001), which was indicative of variations in study populations, methodologies and hemorrhage definitions. While most studies supported the trend toward reduced intracranial bleeding with DOACs, such as Lee *et al.* [36] and Lee *et al.* [41], which reported ORs of 0.85 and 0.68, respectively, some studies, like Lee *et al.* [40] and Qamar *et al.* [42], had wide confidence intervals crossing unity, indicating non-significant findings. The survey by Pastori *et al.* [38], although small, reported a favorable OR of 0.48 but with broad uncertainty [0.05-4.78]. These results collectively support the safety advantage of DOACs over warfarin in this high-risk population, particularly in minimizing intracranial hemorrhage but also highlight need for individualized therapy and high-quality studies.

Stroke and Systemic Embolism

Figure 5 illustrates a forest plot comparing the occurrence of stroke and systemic embolism among patients with atrial fibrillation and liver disease treated with direct oral

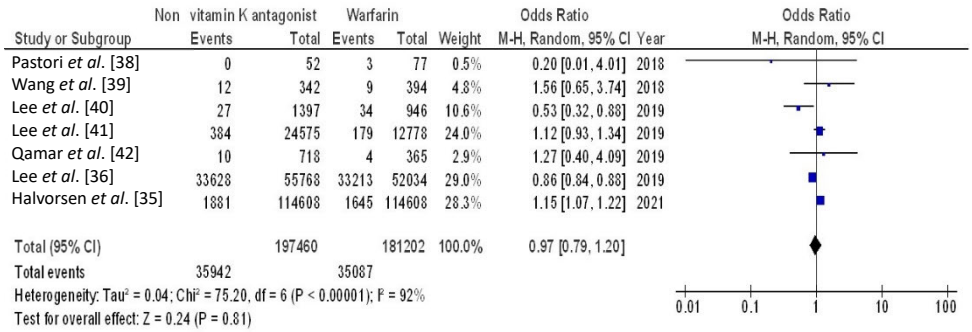

Figure 6: Forest Plot Illustrating the Comparison Between DOAC Use and Warfarin in Relation to Gastrointestinal Bleeding Among Patients with AF and LD

anticoagulants (classified as non-vitamin K antagonist oral anticoagulants) versus those receiving warfarin. The meta-analysis incorporated data from seven trials conducted between 2018 and 2021. The total sample included 208,324 patients in the DOAC group and 185,570 patients in the warfarin group. The ORs for individual studies range widely: While Tsai *et al.* [34] reported a notably reduced risk in DOAC group (OR = 0.28 [0.25-0.32]), Wang *et al.* [39] and Qamar *et al.* [42] reported insignificant increase in risk with DOAC use (OR = 1.31 [0.76-2.25] and OR = 1.22 [0.43-3.50], respectively). Overall, five of the seven studies reported a point estimate favoring DOACs, indicating a trend toward reduced stroke/systemic embolism risk compared to warfarin.

When comparing direct oral anticoagulants with warfarin, the pooled odds ratio across all included studies was 0.76 (0.56-1.02), suggesting a 24% relative reduction in the risk of stroke or systemic embolism with DOAC therapy. However, this overall effect did not reach statistical significance ($Z = 1.83$, $p = 0.07$) and the confidence interval crossed the null value of 1.00. Marked heterogeneity was observed among the studies ($I^2 = 98\%$, $p<0.00001$), reflecting considerable inconsistency in the findings, which may be attributed to variations in patient populations, differing definitions of liver disease and differences in anticoagulation treatment protocols across the included trials. These results point to a possible advantage of DOACs over warfarin in this high-risk group but the variability and marginal significance highlight the need for careful interpretation and more research using meta-analyses or randomized trials.

Gastrointestinal Bleeding

Figure 6 illustrates a forest plot that contrasts the risk of gastrointestinal (GI) hemorrhage in patients with AF and LD who are administered DOACs versus warfarin. The meta-analysis includes seven studies comprising 197,460 patients on DOACs and 181,202 on warfarin. The individual study results are mixed, with some suggesting a protective effect of DOACs and others indicating a higher risk compared to warfarin. In contrast to Halvorsen *et al.* [35], who observed a considerably greater risk (OR = 1.15, 1.07-1.22), Lee *et al.* [41] identified a significantly decreased GI bleeding risk with DOACs (OR = 0.53, 0.32-0.83). Non-significant findings with large confidence ranges were found in several studies, including Wang *et al.* [39] and Qamar *et al.* [42], indicating uncertainty and variability in results.

The pooled analysis indicates that the risk of gastrointestinal hemorrhage is not significantly different between warfarin and DOACs in this patient cohort. This is indicated by an overall odds ratio of 0.97 (95% confidence interval: 0.79-1.20). The aggregate effect test ($Z = 0.24$, $p = 0.81$) further supports the absence of a significant difference. However, notable heterogeneity is present across the included studies ($I^2 = 92\%$, $p<0.00001$), reflecting substantial variability in study design, population characteristics, liver disease severity and anticoagulant dosing. While the overall result does not suggest a clear advantage for either treatment, the direction and strength of effects in individual studies highlight the complexity of anticoagulant management in patients with both AF and LD. This heterogeneity further emphasizes the necessity of individualized therapeutic decisions and the necessity of additional subgroup analyses or patient-level data to elucidate the safety of DOACs in this high-risk cohort.

Subgroup and Sensitivity Analyses

Subgroup analyses were conducted by outcome category; however, stratified analyses on patient-level covariates were not feasible due to the scarcity of studies that reported subgroup-specific data (e.g., by age, gender or ethnicity). The robustness of the primary findings was suggested by the fact that the aggregate estimates remained directionally consistent, despite the fact that sensitivity analyses were conducted by removing studies one at a time.

Assessment of Publication Bias

The publication bias was evaluated using both Egger's regression test (data not presented) and visual examination of funnel plots. There was no statistically significant evidence of publication bias or small study effects. Nevertheless, the capacity to precisely identify bias may have been compromised by the limited number of studies included per outcome.

DISCUSSION

This comprehensive meta-analysis evaluated both the effectiveness and safety profiles DOACs versus warfarin by integrating evidence from ten studies involving roughly 417,000 patients with AF and coexisting LD. The findings indicate that, relative to warfarin, DOAC therapy is associated with significantly reduced risks of major bleeding, intracranial hemorrhage and overall mortality. Various previous studies demonstrated that DOACs are significantly associated with reduced risks of major bleeding [43,44], intracranial hemorrhage [43,45] and all-cause mortality [43,46], compared to warfarin. These outcomes are particularly noteworthy considering the complex hemostatic alterations seen in hepatic dysfunction patients, where both thrombotic and bleeding risks are amplified due to disrupted coagulation factor synthesis, thrombocytopenia and altered drug metabolism.

The observed 24% reduction in all-cause mortality with DOAC use underscores a potentially meaningful survival benefit. This advantage could be attributed to the more predictable DOACs pharmacokinetics, reduced need for frequent INR monitoring, fewer drug-food interactions and potentially lower variability in anticoagulation control, especially relevant in liver-impaired patients where warfarin metabolism via hepatic cytochrome P450 enzymes can be erratic. Additionally, the safety profile of DOACs is further substantiated by the lower rates of major bleeding and intracranial hemorrhage. DOACs, including dabigatran, are more dependent on renal clearance, whereas apixaban and edoxaban have varied elimination pathways. In contrast, warfarin's metabolism is predominantly hepatic, increasing the risk of overdose or subtherapeutic effects in cirrhotic patients with compromised liver function.

Despite these advantages, the research did not find a statistically significant difference between DOACs and warfarin in terms of the incidence of GI bleeding (pooled OR = 0.97, p = 0.81) or stroke or systemic embolism (pooled OR = 0.76, p = 0.07). This observation is supported by findings from multiple research studies [47,48]. The lack of significance in stroke prevention may be due to insufficient statistical power or inherent heterogeneity among studies, including differences in liver disease severity, co-medications and follow-up durations. The variation in GI bleeding outcomes likely stems from the pharmacodynamic differences among DOACs; for example, rivaroxaban has been associated with increased GI bleeding in previous literature. The insignificance of GI bleeding is supported by findings from multiple research studies [49-51]. The wide heterogeneity (I^2>90%) in both outcomes further suggests diverse study populations and definitions.

Importantly, the findings must be interpreted in the context of limited randomized data. Most included studies were retrospective observational cohorts, subject to residual confounding despite multivariable adjustments. Geographical and ethnic differences were common; many investigations were carried out in East Asian populations, which would have limited the generalizability. Furthermore, more complex comparisons were hampered by inconsistent reporting on the degree of liver disease, duration in the warfarin therapeutic range and stratification by particular DOACs.

The current international guidelines from the ESC and ACC/AHA offer general recommendations for anticoagulation in AF. However, they are non-specific in relation to patients with LD, as they are excluded from pivotal trials. Our results suggest that DOACs, particularly those with lower hepatic metabolism, may be preferable in AF patients with liver impairment (mild to moderate). However, clinicians must remain cautious, especially in patients with advanced hepatic dysfunction, where DOAC pharmacokinetics and bleeding risk may be unpredictable.

Our meta-analysis builds upon and significantly advances the findings of prior systematic reviews by Su *et al.* [27] and Fu *et al.* [28], offering several key improvements in scope, methodology and clinical relevance. First, our study includes a substantially larger and more diverse patient population (417,754 patients from 10 studies), compared to ~50,000 patients in each of the previous meta-analyses. This enhanced sample size improves statistical power and generalizability, particularly as our analysis incorporates data from multiple geographic regions (U.S., Europe and Asia), whereas prior works predominantly relied on East Asian cohorts. Methodologically, our study adheres rigorously to PRISMA and MOOSE guidelines, employs random-effects models (for heterogeneity) and conducts sensitivity analyses to test robustness, features not uniformly emphasized in earlier reviews. Furthermore, we systematically assess publication bias, addressing a limitation acknowledged by Fu *et al.* [28] due to their smaller number of included studies. Our stratified outcome analyses also provide deeper insights, particularly for major bleeding (OR 0.65, *p* = 0.003) and intracranial hemorrhage (OR 0.48, *p* = 0.03), where we demonstrate stronger evidence of DOAC safety than Su *et al.* [27] (OR 0.73, *p* = 0.06 for major bleeding). Notably, while all three meta-analyses agree on the mortality benefit of DOACs, our study offers more precise estimates (OR 0.76 vs. 0.90 in Su *et al.* [27]). It explicitly explores heterogeneity sources (e.g., liver disease severity, study design), which were less thoroughly examined previously. Clinically, our findings strengthen the argument for DOACs as first-line therapy in AF patients with liver disease, particularly given their consistent safety advantages. However, we highlight critical gaps, such as variability in GI bleeding risk and the need for individualized therapy, that were not fully addressed in earlier works. By integrating broader evidence and more rigorous methodology, our study provides a definitive, actionable synthesis for clinicians while underscoring the necessity of prospective trials to validate these observations.

Lawal *et al.* [18] analyzed a U.S.-based cohort of 10,209 patients, focusing primarily on a single geographic region. In contrast, our meta-analysis synthesizes data from

10 observational studies encompassing 417,754 patients across multiple regions, including the U.S., Europe and Asia. This larger and more diverse sample enhances the generalizability of our findings, capturing a wider spectrum of patient demographics, liver disease severities and clinical practices. While in contrast to Lawal *et al.* [18], who investigated ischemic stroke/systemic embolism and major bleeding as primary outcomes, our meta-analysis assesses five critical endpoints: all-cause mortality, major bleeding, gastrointestinal bleeding, intracranial hemorrhage and stroke/systemic embolism. Our results indicate that DOACs result in statistically significant reductions in all-cause mortality (OR: 0.76), severe bleeding (OR: 0.65) and intracranial hemorrhage (OR: 0.48) when compared to warfarin. This information allows for a more detailed evaluation of the safety and efficacy of the treatment. Lawal *et al.* [18] reported similar trends but did not explicitly quantify the risk reduction for intracranial hemorrhage, a life-threatening complication particularly relevant in liver disease patients. Our study explicitly addresses the substantial heterogeneity (I^2>90%) observed across included studies, conducting sensitivity analyses to ensure robustness. Lawal *et al.* [18] acknowledged heterogeneity but did not perform stratified analyses based on liver disease severity or individual DOAC types. Our meta-analysis, while also limited by variability in liver disease definitions, provides a more transparent discussion of heterogeneity and its implications for clinical interpretation.

The findings of this meta-analysis collectively advocate for the use of DOACs over warfarin in the reduction of significant bleeding, cerebral hemorrhage and all-cause mortality in patients with AF and liver disease. They are also equally effective in avoiding stroke and systemic embolism. However, further prospective research, particularly RCTs, is required to validate these findings and direct tailored anticoagulation treatments in this susceptible group because of the significant variability and observational nature of the data.

CONCLUSIONS

This meta-analysis indicates that, in patients with atrial fibrillation and concurrent liver disease, direct oral anticoagulants (DOACs) are linked to reduced rates of overall mortality, major bleeding events and intracranial hemorrhage when compared with warfarin, while offering similar effectiveness in the prevention of stroke and systemic embolism. These results favor the use of DOACs in this group, especially among individuals with mild to moderate hepatic dysfunction. Nevertheless, due to the marked variability across studies and the predominance of observational data, treatment decisions should remain patient-specific, taking into account hepatic status, bleeding risk and other clinical considerations. Additional high-quality randomized controlled trials are needed to validate these observations and to inform optimal anticoagulation approaches.

Limitations

Despite the fact that this meta-analysis offers valuable insights into the relative safety and efficacy of DOACs in patients with AF and LD compared to warfarin, a number of limitations must be acknowledged. At first, the selection bias and residual confounding risks were inherent to the majority of the included studies, which were observational in character. Although multivariable adjustments and propensity score matching were employed in some studies, unmeasured confounders, such as severity of liver dysfunction, concurrent medications, nutritional status and adherence to anticoagulation, may have influenced the outcomes. Second, substantial heterogeneity was observed across studies, particularly in outcomes such as gastrointestinal bleeding and stroke/systemic embolism. This heterogeneity is likely due to variations in the design of the study, the patient populations, the classification of liver disease (e.g., the varying definitions and severity of hepatic impairment), the administration of anticoagulants and the duration of follow-up. Not all studies reported detailed baseline liver function metrics, limiting our ability to perform stratified analyses based on hepatic function.

Third, time in therapeutic range, a critical measure for evaluating warfarin effectiveness, was not consistently reported across the studies. Without this data, direct comparisons of anticoagulation control and efficacy between warfarin and DOACs remain limited. Fourth, demographic variables such as age, sex and ethnicity were not uniformly reported or adjusted for, precluding detailed subgroup analyses. The generalizability of the findings to more diverse global populations may be restricted by the fact that numerous studies included predominantly Asian populations. Lastly, the absence of RCTs in this meta-analysis limits the strength of causal inference. Well-designed prospective RCTs are necessary to validate these findings and inform clinical guidelines, particularly in underrepresented populations such as those with AF and LD, where real-world data are essential.

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