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Anticoagulation in patients with atrial fibrillation and liver cirrhosis

Eleni Karapedi[a], Nikolaos Papadopoulos[a], Eleni-Myrto Trifylli[a], Evangelos Koustas[a], Melanie Deutsch[b], Georgios Aloizos[a]

417 Army Share Fund Hospital; Medical School of National and Kapodistrian University of Athens, Hippokration General Hospital, Athens, Greece

Abstract

Atrial fibrillation (AF) is an increasingly recognized comorbidity in patients with liver cirrhosis, mainly associated with nonalcoholic fatty liver disease and alcohol-associated liver disease, affecting the quality of life and prognosis. On the other hand, cirrhosis is associated with an elevated risk of both thrombosis and bleeding, making the decision about anticoagulation therapy very challenging. Direct-acting oral anticoagulants (DOACs) are approved for patients with non-valvular AF. However, there is limited clinical experience and scientific evidence about their efficacy and safety in liver cirrhosis. This review article investigates the published literature concerning the administration of DOACs and traditional antithrombotic agents, such as vitamin K antagonists and heparins, in patients with liver cirrhosis and AF.

Keywords Atrial fibrillation, nonalcoholic fatty liver disease, direct-acting oral anticoagulants, vitamin K antagonists

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Introduction

Atrial fibrillation (AF) is the most frequent sustained heart arrhythmia in adults worldwide, with an estimated prevalence of 2-4% and steadily increasing rates annually [1]. It is associated with greater morbidity and mortality compared to healthy individuals, resulting in a significant burden on healthcare systems [1].

[a]1st Department of Internal Medicine, 417 Army Share Fund Hospital (Eleni Karapedi, Nikolaos Papadopoulos, Eleni-Myrto Trifylli, Evangelos Koustas, Georgios Aloizos); [b]2nd Academic Department of Internal Medicine, Medical School of National and Kapodistrian University of Athens, Hippokration General Hospital (Melanie Deutsch), Athens, Greece

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Correspondence to: Nikolaos Papadopoulos, MD, PhD, Monis Petraki 10-12, 11521, Athens, Greece, e-mail: nipapmed@gmail.com

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AF and liver cirrhosis

A higher prevalence of AF seems to be documented in patients with liver cirrhosis, independently of the cause [2]. Data from a retrospective analysis of 1727 patients with liver disease evaluated for liver transplantation, presented by Huang *et al*, revealed an 11.2% prevalence of new-diagnosis AF in patients with cirrhosis (P<0.001) and a risk that increased with the severity of liver disease, estimated by model for end-stage liver disease (MELD) score [3]. A retrospective cohort study based on a nationwide patient database indicated that patients with liver cirrhosis were at higher risk for AF development compared to controls (hazard ratio [HR] 1.46, 95% confidence interval [CI] 1.18-1.80) after multivariate adjustment [2]. Concurrently, AF is reported as a predictor of morbidity and mortality in liver cirrhosis [4,5]. Abnormal autonomic neurotransmission, with increased parasympathetic and sympathetic activation, is associated with AF in patients with liver cirrhosis. Moreover, upregulated levels of neuropeptides, such as vasoactive intestinal peptides, inflammatory cytokines, such as interleukin-6, interleukin-8, and tumor necrosis factor-α, oxidative radicals, and factors implicated in fibrosis, such as Galectin-3, are mediated by the autonomic dysfunction that occurs in liver cirrhosis and portal hypertension [2,3,6].

Moreover, liver disease is an independent risk factor for new-onset AF, mainly associated with nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and alcohol-

associated liver disease (ALD) [7-9]. As NAFLD/NASH is the emerging leading cause of chronic liver disease, cardiovascular complications, including AF, are expected to be significant comorbidities in these patients [10]. Concurrently, excessive alcohol intake also represents a well-established risk factor for AF development, a correlation mainly attributed to alcoholic cardiomyopathy, the subsequent increased sympathetic response, and the enlargement of the left atrium [6,11,12].

Anticoagulation and liver cirrhosis

Vitamin K antagonists (VKAs) have been the main antithrombotic therapy in AF, and the international normalized ratio (INR) is used to monitor their therapeutic range. During the past few years, direct-acting oral anticoagulants (DOACs) have emerged as the optimal evidence-based treatment for non-valvular AF. However, patients with liver cirrhosis were characteristically excluded from the pivotal trials of these drugs because of the assumed impaired hemostasis in this population.

Anticoagulation in patients with AF and liver cirrhosis constitutes a significant challenge. Liver cirrhosis is characterized by several fundamental changes in pro- and anti-hemostatic pathways—some favor bleeding and others favor clotting, leading to a re-balanced hemostatic equilibrium [13]. Moreover, thrombocytopenia due to splenic sequestration, decreased thrombopoietin levels, platelet dysfunction, impaired drug metabolism, defective protein synthesis for protein-bound drugs, and the presence of gastroesophageal varices further complicate this fragile hemostatic state [14]. Although routine diagnostic tests of hemostasis, such as INR prolongation, suggest a hypocoagulable state, patients with liver disease also tend to develop thrombotic events [15-17]. In a large retrospective cohort study based on Taiwan's nationwide health insurance database**,** Lai *et al* demonstrated that chronic liver diseases, including hepatoma, cirrhosis and viral hepatitis, are not only associated with a greater bleeding risk, as previously thought, but are also predictors for ischemic cerebrovascular events, stroke and stroke equivalents. Thus, AF and liver disease patients have an increased risk of ischemic cerebrovascular events [18].

Data concerning the initiation of antithrombotic treatment in this population are limited, and there is still no evidence-based management. Therefore, this review article aims to examine evidence for the safety and efficacy of antithrombotic drugs in patients with AF and liver cirrhosis and to propose potential therapeutic strategies.

Methodology

We searched the PubMed, NCBI and MEDLINE databases for articles published from 2006 until 10/2021 using keywords "AF", "DOACS", "anticoagulation", "vitamin K antagonists", "warfarin" AND "liver cirrhosis", looking for studies comparing the efficacy and safety of anticoagulants in patients with liver cirrhosis. We limited our search to human studies and publications in the English language. We also searched the reference lists of the included studies for additional articles of interest. Meeting abstracts were also included. We focused on major bleeding events and/or intracranial hemorrhage (ICH) as primary safety endpoints, while stroke and all-cause death were the primary efficacy endpoints (Fig. 1).

DOACs

A recent retrospective analysis of a US national database included patients with mostly Child-Pugh (CP) A cirrhosis

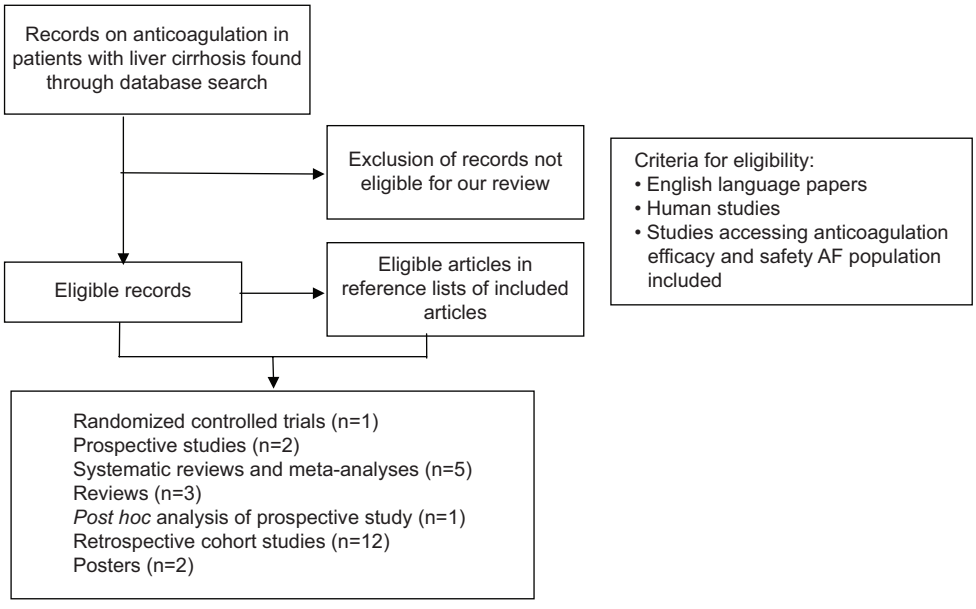

Figure 1 Flow chart study collection
AF, atrial fibrillation

who experienced the development of AF [19]. The authors concluded that DOACs were associated with lower all-cause mortality than no anticoagulants (Table 1).

Dabigatran

Dabigatran, a direct thrombin inhibitor, is metabolized via conjugation with activated glucuronic acid, resulting in pharmacodynamically active glucuronides, and is mainly renally excreted as an unchanged drug. Therefore, the hepatic elimination of dabigatran is only 20% [20]. Nevertheless, dabigatran administration in patients with cirrhosis resulted in a more pronounced reduction in thrombin generation time compared to controls, reflecting a higher anticoagulation effect [21]. However, its pharmacokinetic and pharmacodynamic properties appear intact in mild and moderate disease, according to *in vivo* and *vitro* studies [21,22]. Thus, it is proposed that dabigatran can be used with caution in standard doses in CP A and B cirrhosis [20].

Apixaban

Similar suggestions are made for apixaban, an Xa inhibitor that primarily affects antithrombin and its effects on the coagulation cascade, rather than thrombin itself. It is predominantly cleared through the hepatobiliary system and partially metabolized via CYP450 [20,23].

Table 1. DOACs vs. no anticoagulation: characteristics of included studies

Reference	Serper *et al* [19]		
Study design	Retrospective		
	DOACs	NA	P-value
N	201	503	
Males, n (%)	200 (99.5)	497 (98.8)	
Age, years±SD	647.7	64.3±8.4	
AF patients, n (%)	201 (100)	503 (100)	
Cirrhosis, n (%) CP A, n (%) CP B, n (%) CP C, n (%)	201 (100) 184 (91.5) 17 (8.5) 0 (0)	503 (100) 455 (90.5) 48 (9.5) 0 (0)	
DOAC, n (%) Apixaban Rivaroxaban Dabigatran Edoxaban	201 (100)		
All-cause mortality	16.1*	23.1*	<0.01
Ischemic stroke	1.3*	2*	0.18
Bleeding	3.6*	4.8*	0.21

*Incidence rate per 100 person-years

DOACs, direct-acting oral anticoagulation; SD, standard deviation; AF, atrial fibrillation; CP score, Child-Pugh score; NA, no anticoagulation

Rivaroxaban

Regarding rivaroxaban, another Xa inhibitor, one-third of the total dose is renally cleared and approximately 60% is metabolized to both active and inactive metabolites. Rivaroxaban is metabolized by several CYP450 enzymes, while plasma protein (mainly albumin) binding for rivaroxaban is high (92-95%). Studies support the use in CP A but not in CP B and C. Interestingly, researchers observed an attenuated antithrombotic effect in CP C compared to CP A or B [20,21,24]. The anticoagulant effect among patients with liver cirrhosis differs among different DOACs. According to a recent study, the anticoagulant potency of rivaroxaban in patients with CPT B and C cirrhosis is reduced, while that of dabigatran is increased [25].

Edoxaban

Edoxaban's renal clearance accounts for approximately 50% of total clearance, while metabolism and biliary secretion account for the remaining 50%. A small 4-group cohort study that investigated pharmacokinetic and pharmacodynamic characteristics in patients with mild or moderate hepatic impairment compared to healthy groups after administration of 10 mg edoxaban, another direct Xa inhibitor, suggests that edoxaban exposure does not significantly increase in patients with mild or moderate hepatic impairment [26].

Safety

Direct-acting reversal agents exist for both factor Xa inhibitors (andexanet alfa) and factor IIa inhibitors (idarucizumab) for life-threatening bleeding [27]. Although DOAC-induced hepatotoxicity is unusual, recent data raised some concerns about the risk of rivaroxaban-induced liver injury [28]. These findings further led the Food and Drug Administration (FDA) to review a post-market report, which demonstrated a disproportionate risk for drug-induced liver injury in DOAC patients receiving rivaroxaban, compared to dabigatran and apixaban [29]. Although data from large prospective studies are lacking, in a recent meta-analysis including patients with AF and liver cirrhosis, DOACs reduced the risks of major bleeding (relative risk [RR] 0.53, 95%CI 0.37-0.76), gastrointestinal bleeding (RR 0.57, 95%CI 0.38-0.84), and intracranial hemorrhage (RR 0.55, 95%CI 0.31-0.97) compared to warfarin [30]. Moreover, preliminary data from 80 patients with liver cirrhosis (52% had esophageal varices) receiving DOACs revealed that 12% of these patients experienced a major bleeding event, but no variceal bleeding occurred. In addition, those with major bleeding had an average MELD score of 22, compared to an average of 14 in patients without major bleeding [31].

Summary

Although data remain limited to retrospective observational database analysis, DOACs seem a promising approach in these

patients, at least in compensated cirrhosis, as they indicate lower all-cause mortality than no anticoagulants, without significant major bleeding risk.

VKAs

Choi *et al* analyzed data from 465 patients diagnosed with liver cirrhosis and non-valvular AF, where 24.5% of them received warfarin, and 75.5% did not receive any anticoagulation. HAS-BLED scores were similar among groups. Viral hepatitis and ALD were the most frequent causes of cirrhosis (50.4% and 30.5%, respectively). Risk factors like the CP score and the frequency of gastroesophageal varices events were significantly lower in the warfarin group, whereas CHA_2DS_2-VASc scores were inversely correlated with the anticoagulation group. The investigators reported no significant difference in rates of ischemic events between the warfarin and no-warfarin groups (annual risk: 0.9% vs. 1.2%), but found higher rates of bleeding events, none of them fatal, among the warfarin group, despite low time in therapeutic range values and subtherapeutic INR values. CP score and age were introduced as valuable predictors of bleeding and ischemic events, respectively (P=0.016 and P=0.040, respectively) [32].

In a relatively small cohort, Girleanu *et al* compared the decompensation rate of liver cirrhosis, mostly alcohol-related, in 118 patients comorbid with AF taking acenocoumarol for stroke prevention, and in 1151 individuals with no AF diagnosis. The study concluded that there was a statistically significant cumulative risk reduction for decompensation, defined as hepatic encephalopathy, variceal bleeding or ascites, in patients with AF treated with acenocoumarol [33].

In another retrospective study of 1763 patients with chronic liver disease receiving warfarin, most of them with a non-valvular AF indication, the authors concluded that these patients experienced more major bleeding events (hazard ratio [HR] 2.02, 95%CI 1.69-2.42; P<0.001). The same authors designed a 4-point risk stratification score, which includes albumin and creatinine levels and helps clinicians identify patients with increased risk of bleeding after the initiation of warfarin. This consisted of a 4-point score system: patients received 1 point each for albumin (2.5-3.49 g/dL) or creatinine (1.01-1.99 mg/dL), and 2 points each for albumin (<2.5 g/dL) or creatinine (≥2 mg/dL). This score predicted both anticoagulation control and bleeding [34].

A retrospective cohort study of 9056 patients with liver cirrhosis comorbid with AF and a CHA_2DS_2-VASc score ≥2 compared the efficacy of antiplatelet medication (30.6%), warfarin (8.3%) and no anticoagulation therapy (61.1%). The group of patients with AF and cirrhosis, who did not receive antithrombotic treatment, had a significantly higher stroke incidence than those without liver cirrhosis. Moreover, individuals in the warfarin group had statistically significantly lower rates of ischemic stroke, whereas those in the antiplatelet or no-anticoagulation group demonstrated similar rates. Regarding ICH, no difference was observed among study groups. The researchers underlined that the use of warfarin has shown clinical benefits. However, the small sample size of this group and the fewer comorbidities associated with the CHA_2DS_2-VASc score should be considered when interpreting the results [35].

In a retrospective analysis of patients with cirrhosis and AF, VKAs reduced the risk for ischemic stroke compared with no therapy (1.8% vs. 4.7% per year, P=0.01) [36]. However, patients with more advanced cirrhosis (CP B and C) had a significantly greater risk for major bleeding (14.5% vs. 4.9% per year, P<0.001). Moreover, all-cause mortality was lower with warfarin versus no anticoagulants in a recent retrospective analysis of a United States national database that included patients with cirrhosis who experienced the development of AF [19] (Table 2).

Safety

The therapeutic effect of VKAs is traditionally monitored using the INR. The proposed target INR values for AF and well-compensated cirrhosis patients are 2.0-3.0. However, a narrower therapeutic range is recommended in patients with abnormal baseline INR values and esophageal varices or other signs of portal hypertension (1.8-2.20) [37]. On the other hand, it should be underlined that INR is not considered a reliable parameter for monitoring coagulation balance in patients with cirrhosis [17,32]. In contrast, platelet count, fibrinogen, and activated partial thromboplastin time are considered to have better predictive value for bleeding risk in cirrhotic patients [38]. In addition to warfarin discontinuation and complex concentrate administration, vitamin K infusion is appropriate for warfarin-treated patients with life-threatening bleeding [39].

Summary

VKAs seem a reasonable choice in patients with compensated liver cirrhosis. Data concerning CP C patients are minimal. However, considerations should be made for patients with elevated baseline INR and the need for frequent monitoring, since a narrower therapeutic range (1.8-2.20) of INR is recommended.

DOACs vs. VKAs

In a large retrospective study that included 2428 patients with liver cirrhosis and AF, 1438 patients received a DOAC regimen (apixaban, rivaroxaban, dabigatran), while 990 patients received warfarin. It was notable that the majority of the DOAC group received low-dose anticoagulation. Regarding efficacy outcomes, similar ischemic stroke/systematic embolism rates were reported among 3 different DOAC and warfarin groups. However, the time in therapeutic range for warfarin is unknown. In contrast, all major and

Table 2 VKAs vs. no anticoagulation: characteristics of included studies

Reference	Serper *et al* [19]			Choi *et al* [32]			Kuo *et al* [35]			Lee *et al* [36]		
Study design	Retrospective			Retrospective			Retrospective			Retrospective		
	VKAs	NA	P-value	VKAs	NA	P-value	VKAs	NA	P-value	VKAs	NA	P-value
N	614	1080		113	352		754	5532		173	148	
Males, n (%)	603 (98.2)	1064 (98.5)		85 (75.2)	262 (74.4)		471 (62.5)	3264 (59)		120 (69)	100 (68)	
Age, years±SD	64.6±7.5	64.2±8.4		64.3±10	63.3±10		68.9±11.4	73.5±11.7		62.1±10.3	62.5±11.3	
AF patients, n (%)	614 (100)	1080 (100)		113 (100)	352 (100)		754 (100)	5532 (100)		173 (100)	148 (100)	
Cirrhosis, n (%)	614 (100)	1080 (100)		113 (100)	352 (100)		754 (100)	5532 (100)				
CP A, n (%)	429 (69.9)	788 (73)										
CP B, n (%)	181 (29.5)	280 (25.9)										
CP C, n (%)	4 (0.65)	12 (1.1)										
All-cause mortality	17*	27.2*	<0.01	-	-	-	-	-	-	-	-	-
Ischemic stroke	2.3*	1.7*	0.11	0.9%/year	1.2%/year	NS	2.79 (2.12-3.46)**	4.09 (3.72-4.46)**	0.04	1.82	4.74	0.01
Major bleeding	5.9*	5.4*	0.29	5.9%/year	2.6%/year	0.006	1.11 (0.69-1.53)***	0.92 (0.75-1.09)***	0.284	9.61+	6.18+	0.04

*Incidence rate per 100 person-years, **Incidence (95% confidence interval), *** Intracranial hemorrhage, +Event rates for 100 person-years
VKAs, vitamin K antagonists; SD, standard deviation; AF, atrial fibrillation; CP score, Child-Pugh score; NA, no anticoagulation; NS, non-significant

gastrointestinal bleeding events were significantly lower in the DOAC group, especially in NAFLD-related cirrhosis, whereas in alcoholic cirrhosis, rates were similar [40]. In addition, the annual incidence of ICH episodes was comparable between the DOAC and warfarin groups (1% vs. 1.6%, P=0.1021). In a subgroup analysis, dabigatran and rivaroxaban exhibited a significantly lower risk of all major bleeding than warfarin (HR: 0.54, 95% CI, 0.33–0.89, p=0.0145 and HR: 0.38, 95% CI, 0.20–0.72, p=0.0028, respectively.A retrospective review of safety and efficacy outcomes of DOACs compared to VKAs evaluated 79 patients with AF and liver cirrhosis. Forty-nine of them received 1 of 3 different DOACs (69.1% apixaban, 21.4% rivaroxaban, 9.5% dabigatran), while 37 patients received warfarin. The researchers found no significant statistical differences in the primary and secondary endpoints of all-cause bleeding, major bleeding, and failed efficacy [41].

Another retrospective study involving 45 patients with liver cirrhosis and an indication for anticoagulation therapy gave 27 of them a DOAC in standard doses, while the remaining 18 received VKA or low-molecular-weight heparin (LMWH). Most of the patients had a CP B score and an average MELD score of 10. The results suggest that DOACs are equally efficient and safer in terms of all bleeding (P=0.03) and ICH events than traditional antithrombotic therapy with VKAs/LMWH. Researchers note that the therapeutic range VKAs was difficult to monitor with INR, and this group of patients spent more time with supratherapeutic levels of VKAs [42] (Table 3).

The ENGAGE-TIMI 48 trial was a double-blind, randomized clinical trial that compared the DOAC edoxaban with warfarin in patients with AF, followed for 2.8 years. A subgroup analysis of patients with a history of liver disease (5.1%) found no statistically significant differences in rates of ischemic stroke, systematic embolism or hemorrhagic stroke between patients receiving edoxaban with or without liver disease. However, all-bleeding and major bleeding rates were significantly higher in patients with liver disease [43]. Nevertheless, it should be noted that the ENGAGE-TIMI 48 trial referred only to patients with a history of liver disease, as defined by prior liver disease or elevated liver enzymes (alanine/aspartate aminotransferase ≥2 times the upper limit of normal) at randomization. Therefore, these promising results refer primarily to individuals with mild liver dysfunction and cannot be extrapolated to patients with liver cirrhosis.

Another retrospective cohort included 37,353 patients with AF and active liver disease on newly prescribed warfarin (n=12,778) or DOACs (n=24,575) [44]. In a separate analysis for patients with cirrhosis, who only made up 2% (n=768) of the study population, DOACs and warfarin groups had comparable risk for ischemic stroke, major bleeding and all-cause death.

Systemic reviews and meta-analyses

A systematic review and meta-analysis of 6 cohort studies of 41,954 patients with AF and liver disease (27,184 patients with DOACs and 14,770 patients with warfarin) found that the use

Table 3 DOACs vs. VKAs: characteristics of included studies

Reference	Lee *et al* [40]			Jones *et al* [41]			Hum *et al* [42]			Intagliata *et al* [48]		
Study design	Retrospective			Retrospective			Retrospective			Retrospective		
	DOACs*	VKAs	P-value	DOACs	VKAs	P-value	DOACs	VKAs***	P-value	DOACs+	VKAs++	P-value
N	1438	990		42	37		27	18		20	19	
Males, n (%)	(62.38%)	(66.56)		41 (97.6)	37 (100)		18 (67)	14 (78)		10 (50)	12 (63)	
Age, years±SD	74.35±10.5	69.93±12.42		71.9±6.2	70.3±7.5		61	58		57	60	
AF patients, n (%)	1438 (100)	990 (100)		33 (78.6)	29 (78.4)		-	-		4 (20)	1 (5)	
Cirrhosis, n (%)	1438 (100)	990 (100)		42 (100)	37 (100)		27 (100)	18 (100)		20 (100)	19 (100)	
CP A, n (%)				34 (81)	16 (43.2)		11 (41)	7 (39)		9 (45)	9 (47)	
CP B, n (%)				8 (19.1)	19 (51.4)		12 (44)	9 (50)		11 (55)	10 (53)	
CP C, n (%)				0 (0)	2 (5.4)		4 (15)	2 (11)		0 (0)	0 (0)	
DOAC, n (%)												
Apixaban	171 (12)			29 (69)			10 (37)			11 (55)		
Rivaroxaban	732 (51)			9 (21.5)			17 (63)			9 (45)		
Dabigatran	535 (37)			4 (9.5)			0 (0)			0 (0)		
Edoxaban	0 (0)			0 (0)			0 (0)			0 (0)		
All-cause mortality	-	-		0	3 (8.1)	0.1	-	-				
Ischemic stroke	3.2**	3.7**	0.4296	0	0	0.99	-	-				
Major bleeding	2.9**	5.4**	0.0003	1 (2.4)	2 (5.4)	0.6	1 (4)	5 (28)	0.03	1 (5)	2 (11)	NS

Reference	Goriacko P, *et al* [50]		
Study design	Retrospective		
	DOACs	VKAs	P-value
N	75	158	
Males, n (%)	43 (57.3)	94 (59.5)	
Age, years±SD	66	65	
AF patients, n (%)	75 (100)	158 (100)	
Cirrhosis, n (%)	75 (100)	158 (100)	
CP A, n (%)	48 (64.0)	56 (35.4)	
CP B, n (%)	26 (34.7)	93 (58.9)	
CP C, n (%)	1 (1.3)	9 (5.7)	

(*Contd...*)

Table 3 (*Continued*)

Reference	Lee *et al* [40]			Jones *et al* [41]			Hum *et al* [42]			Intagliata *et al* [48]		
Study design	Retrospective			Retrospective			Retrospective			Retrospective		
	DOACs*	VKAs	P-value	DOACs	VKAs	P-value	DOACs	VKAs***	P-value	DOACs+	VKAs++	P-value
DOAC, n (%)												
Apixaban	11 (15)											
Rivaroxaban	29 (39)											
Dabigatran	35 (47)											
Edoxaban	0 (0)											
All-cause mortality	8.3%/year	8.1%/year	NS									
Ischemic stroke	-	-	-									
Major bleeding	3.3%/year	3.9%/year	NS									

*90% of the patients were taking a low-dose DOAC, **Incidence rate per 100 person-years, ***Three patients treated with low molecular weight heparins (LMWHs), +25% of the patients were taking a low-dose DOAC, ++Six patients treated with LMWHs

DOACs, direct-acting oral anticoagulation; VKAs, vitamin K antagonists; SD, standard deviation; AF, atrial fibrillation; CP score, Child-Pugh score; NA, no anticoagulation; NS, non-significant

of anticoagulation was associated with lower risks of all-cause death (RR 0.78, 95%CI 0.66-0.93) and major bleeding (RR 0.68, 95%CI 0.53-0.88), but had comparable risks of stroke or system embolism (RR 0.80, 95%CI 0.57-1.12) and gastrointestinal bleeding (RR 0.90, 95%CI 0.61-1.34). Moreover, in the subgroup of AF patients with cirrhosis (3111 patients), DOACs showed significantly lower risks of major bleeding (RR 0.53, 95%CI 0.37-0.76), gastrointestinal bleeding (RR 0.57, 95%CI 0.38-0.84), and ICH (RR 0.55, 95%CI 0.31-0.97) compared with warfarin [30].

Another meta-analysis of 7 studies that included 19,798 patients with AF and cirrhosis found that, compared with no anticoagulation, anticoagulation was not significantly associated with a higher risk of bleeding, with a pooled HR of 1.45 (95%CI 0.96-2.17, I^2=72%). Furthermore, compared to warfarin, the use of DOACs was associated with a lower risk of bleeding among AF patients with cirrhosis, with a pooled odds ratio of 1.93 (95%CI 1.001-3.70, I^2=63%) [45].

In another recently published meta-analysis of 3 retrospective studies that included 4011 patients with AF and liver cirrhosis, the use of DOACs was associated with a significant reduction in ischemic stroke (HR 0.62, 95%CI 0.42-0.90; P=0.01), major bleeding events (HR 0.64, 95%CI 0.57-0.72; P<0.001), and intracranial hemorrhage (HR 0.49, 95%CI 0.40-0.59; P<0.001) [46]. The authors concluded that DOACs compared with warfarin appear to be associated with better efficacy and safety outcomes in patients with AF and liver cirrhosis.

A beneficial effect of DOACs vs. warfarin in AF patients with liver disease has been documented in another meta-analysis of 6 studies involving 41,859 patients (27,200 patients who received DOACs and 14,659 who received warfarin) [47]. DOACs demonstrated a significantly lower risk of ischemic stroke (pooled HR 0.68, 95%CI 0.54-0.86; P=0.001) compared with warfarin in AF patients with liver disease. This meta-analysis included a subgroup evaluation of patients with active liver disease and cirrhosis. The results showed that DOACs achieved a more significant reduction in major bleeding (pooled HR 0.51, 95%CI 0.35-0.73; P<0.001), and a moderately lower risk of ICH (pooled HR 0.55, 95%CI 0.32-0.95; P=0.032) and gastrointestinal bleeding (pooled HR 0.56, 95%CI 0.38-0.82; P=0.003) compared with warfarin. Moreover, this study provides additional data concerning the safety of reduced doses of different individual DOACs versus warfarin. Thus, a significantly lower risk of major bleeding was observed for reduced dabigatran, apixaban and edoxaban dose regimens, but not for a reduced rivaroxaban dose regimen (Table 4).

Safety

The safety of DOACs compared to traditional anticoagulation was evaluated in a small retrospective study with 39 CP A or B cirrhotic patients [48]. The DOACs group consisted of 20 patients (apixaban 55% and rivaroxaban 45%), and the traditional group consisted of 19 patients (VKA 68% and LMWH 32%). Major bleeding was similar in both groups.

Table 4 Efficacy and safety of DOACs compared to VKAs or no anticoagulation for AF in patients with liver disease: summary of meta-analyses and systematic reviews

Reference	Number of included studies	Number of involving patients	Objective	Risk of all-cause death	Risk of major bleeding	Risk of stroke	Conclusion
Fu *et al* [30]	6	41,954	Efficacy and safety of DOACs compared to VKAs in AF and liver disease	RR 0.78, 95%CI 0.66-0.93; P=0.005	RR 0.68, 95%CI 0.53-0.88; P=0.003 in liver disease RR 0.53, 95%CI 0.37-0.76 in liver cirrhosis	RR 0.80, 95%CI 0.57-1.12; P=0.008	DOACs at least non-inferior to VKAs
Chokesuwattanaskul *et al* [45]	7	19,798	Efficacy and safety of anticoagulation vs. no anticoagulation in AF and liver cirrhosis Risk of bleeding estimation of DOACs vs. VKAs in AF and liver cirrhosis	-	RR 1.45, 95%CI 0.96-2.17; P=0.076 coagulation was not significantly associated with a higher risk of bleeding vs. no coagulation RR 1.93, 95%CI 1.001-3.70; P=0.05 favors DOACs vs VKAs	RR 0.58, 95%CI 0.35-0.96; P=0.035 favors coagulation vs. no coagulation	Anticoagulation is associated with a lower risk of stroke without increasing the risk of bleeding vs. no anticoagulation DOACs are associated with a lower risk of bleeding vs. VKAs
Lee *et al* [44]	3	4,011	Efficacy and safety of DOACs compared to VKAs in AF and liver cirrhosis	RR 0.82, 95%CI 0.56-1.22; P=0.33	RR 0.64, 95%CI 0.57-0.72; P<0.001	RR 0.62, 95%CI 0.42-0.90; P=0.01	DOACs are associated with better efficacy and safety outcomes compared to VKAs
Huang *et al* [47]	6	41,859	Efficacy and safety of DOACs compared to VKAs in AF and liver disease	-	RR 0.66, 95%CI 0.58-0.75; P<0.001 in liver disease RR 0.51, 95%CI 0.35-0.73; P<0.001 in liver cirrhosis	RR 0.68, 95%CI 0.54-0.86; P=0.001 in liver disease	DOACs are associated with better efficacy and safety outcomes compared to VKAs

DOACs, direct-acting oral anticoagulation; VKAs, vitamin K antagonists; AF, atrial fibrillation; RR, relative risk; CI, confidence interval

The safety of DOACs compared to VKAs was also assessed in a *post hoc* analysis by Pastori *et al* in patients with advanced chronic liver disease. They found that a high FIB-4 score was associated with major bleeding in patients receiving VKAs (P=0.001) but not in the DOAC group [49]. However, the study involved only 129/2330 (5.5%) patients with FIB-4 score >3.25. The VKA group included 77 patients (5.9%) and the DOAC group 52 (5%). Moreover, there was no detailed analysis of the treatment's efficacy and safety in these patients.

In another study, there was no statistically significant difference between DOACs and warfarin in all-cause bleeding in different CP score groups [50]. However, the higher the MELD or CP score, the greater the bleeding hazard ratios. The all-cause mortality rate was 8.1% per year in the warfarin and 8.3% per year in the DOAC group of patients.

The safety of DOACs in patients with advanced liver disease has been indicated in a recently published multicenter retrospective study that included 47 patients—41/47 (87.2%) with liver cirrhosis and 30/47 (63.8%) with liver decompensation—who presented with Budd-Chiari syndrome [51]. The rate of major spontaneous bleedings in the DOAC treatment group (n=22) were comparable to the rates in the LMWH and VKA groups: DOAC vs. LMWH or VKA, incidence rate ratio 0.6, 95%CI 0.07-5.5; P=0.658.

Summary

In cirrhotic patients with AF, anticoagulation treatment with DOACs rather than VKAs may benefit all-cause death and major bleeding events. However, these results refer primarily to individuals with preserved liver function (CP A). Rivaroxaban and edoxaban have been used in CP B cirrhotic patients in some studies without significant adverse events, despite their contraindication in these patients, according to the FDA. There is no clear evidence yet as regards choosing the best DOAC agent, since available data are limited. However, dabigatran seems a reasonable choice because of its renal clearance.

Nevertheless, consideration should be given to each individual patient, keeping in mind possible drug interactions, renal clearance and liver function. In addition, we must remember that most of the available data are based on retrospective analyses, and most studies included a small number of patients with decompensated cirrhosis. Current data suggest that reduced-dose DOACs may be safe and efficacious in patients with liver disease. However, the appropriate dose reduction of DOACs in cirrhotic patients with AF remains to be determined.

LMWHs

Traditionally LMWHs, and less commonly warfarin, have been the anticoagulants of choice in cirrhotic patients with portal vein thrombosis (PVT). Although robust data on the optimal management of PVT in these patients are lacking, several studies have shown that LMWHs are well tolerated and effective [52]. Moreover, meta-regression analysis suggests that LMWHs could be more effective than warfarin [53]. However, there are no adequate data concerning their use in liver cirrhosis and AF patients. A small retrospective study revealed that DOACs are equally efficient and safer (P=0.03) in terms of all bleeding events, compared to therapy with VKAs/LMWHs [42].

Discussion

Liver cirrhosis has been increasingly recognized as a significant risk factor for new-onset non-valvular AF that affects morbidity and mortality. Coagulation homeostasis in patients with liver function impairment is fragile. Apart from a hemorrhagic predisposition, as traditionally thought, multiple pathophysiological factors lead to a prothrombotic status that increases the risk of ischemic and embolic events.

A variety of cohort studies, including systemic reviews and meta-analyses, suggest that anticoagulation offers a benefit in patients with cirrhosis and AF, in terms of a lower risk for stroke and lower all-cause mortality, without any greater risk for bleeding, compared with those who did not receive anticoagulation [30,45-47]. Moreover, DOACs have been associated with a beneficial effect in preventing ischemic stroke and systematic embolism in cirrhotic patients with non-valvular AF [54]. Regarding safety, the use of DOACs led to fewer major bleeding events compared to VKAs. On the other hand, VKAs protect against embolic phenomena compared to no anticoagulation, although frequent INR monitoring is recommended.

All DOAC regimens should be used with caution in patients with cirrhosis. However, recent data have raised some concerns about the risk of rivaroxaban-induced liver injury. Moreover, rivaroxaban and edoxaban, according to the FDA, are contraindicated in CP B cirrhotic patients. However, there are some limitations to these results. Scientific data on this topic are limited to retrospective observational studies, as patients with liver cirrhosis were excluded from large, randomized trials evaluating the efficacy and safety of oral anticoagulants. The diagnosis of AF was variable among several studies, while the number of patients with liver cirrhosis included in some studies appears to be a subgroup of the patients with liver disease. Moreover, data concerning advanced liver disease (CP B or C) are very limited, even in these retrospective studies, while the anticoagulant agents in each individual study ranged from VKAs to different kinds of DOACs. In addition, there is some heterogeneity in the definitions of outcomes concerning the risk of stroke, while the studies evaluated did not provide a universal definition of major and minor bleeding. Finally, some studies prescribed lower doses of DOACs, leading to a bias concerning safety.

Recognition of the critical connection between liver and heart diseases highlights the need for large, randomized trials with predetermined doses of anticoagulant regimens and a detailed cirrhosis status to examine the safety and efficacy of these regimens in such patients. Future considerations must also include modern approaches to AF management, such

as ablation, and emerging techniques for limiting thrombus burden, such as interventional left atrial appendage occlusion.

Concluding remarks

According to the existing scientific literature, the efficacy and safety outcomes of DOACs are comparable to those of traditional anticoagulants in cirrhotic patients with preserved liver disease (CP A/B) and non-valvular AF who present indications of thromboprophylaxis. Since the available data are limited to small, mainly retrospective analyses, continuous monitoring concerning safety is advised.

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