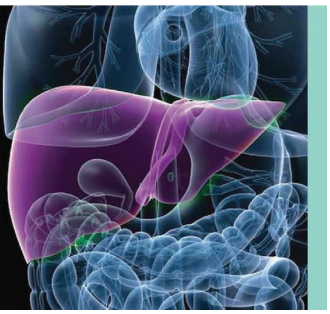

Anticoagulation Management in Patients With Atrial Fibrillation and Cirrhosis

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Anticoagulation to prevent thromboembolic complications associated with atrial fibrillation (AF) is widely accepted.[1,2] Although AF is the most common cardiac arrhythmia in the general population, it may be more prevalent in individuals with cirrhosis.[3] A variety of common risk factors between AF and cirrhosis may account for much of this increased prevalence, ranging from alcohol use to metabolic risk factors to increasing age. Although limited by retrospective study design and a lack of a control group, one study reported an association with worsening severity of underlying liver disease and new-onset AF.[4]

A variety of considerations can prove challenging when deciding on anticoagulation in this population. In this review, we aim to describe the challenges regarding the risks and benefits of anticoagulation for AF and different treatment options described in the literature in patients with cirrhosis. Individuals with cirrhosis may have underlying portal hypertension and associated gastroesophageal varices, and it is increasingly recognized that these patients have a complex and "rebalanced" coagulation system that can place them at risk for both bleeding and clotting.[5,6] In addition, traditional tests of coagulation (international normalized ratio [INR]) are often abnormal in cirrhosis, making it especially difficult to monitor the efficacy of treatment. Lastly, drug metabolism and clearance must be considered in the setting of potential underlying liver and kidney dysfunction. In this setting, understanding the potential risks and benefits of therapies is paramount for clinicians caring for these patients.

Abbreviations: AC, anticoagulant; AF, atrial fibrillation; CI, confidence interval; CTP, Child-Turcotte-Pugh Score; DOAC, direct oral anticoagulant; HR, hazard ratio; INR, international normalized ratio; PAD, peripheral arterial disease; TIA, transient ischemic attack; VKA, vitamin K antagonist.

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CHALLENGES REGARDING THE RISKS AND BENEFITS OF TREATMENT OF AF IN CIRRHOSIS

When individuals are diagnosed with AF, practitioners must consider strategies for rate control, as well as prevention of embolic complications. Determining who could benefit from antithrombotic therapy is often accomplished using the CHA_2DS_2-VASc score, a validated means to determine stroke and thromboembolism rates at 1-year follow-up (Table 1).[7] The risk for major bleeding with anticoagulation for AF is often measured using the HAS-BLED score (Table 1).[8] Although these scoring systems have not been prospectively validated in chronic liver disease, they continue to be widely used.

Determining the net clinical benefit of anticoagulation in those with cirrhosis and AF remains challenging because these individuals have been excluded from randomized control trials for stroke prevention with AF.[9-11] A variety of cohort studies, however, do suggest benefit. A large observational study using the National Health Insurance Research Database in Taiwan analyzed more than 10,000 patients with cirrhosis and AF, noting a reduced risk for ischemic stroke in those taking vitamin K antagonists (VKAs) and no benefit in the antiplatelet group compared with no treatment at all (hazard ratio [HR] 0.76, 95% confidence interval [CI]: 0.58-0.99).[12] There was no difference in risk for hemorrhagic stroke. A systematic review and meta-analysis of seven cohort studies of nearly 20,000 patients with AF and cirrhosis found that the use of anticoagulation was associated with a reduced risk for stroke (pooled HR, 0.58; 95% CI: 0.35-0.96) and was not significantly associated with an increased risk for bleeding (HR, 1.45; 95% CI: 0.96-2.17) compared with those who did not receive anticoagulation.[13]

TABLE 1. MAJOR BLEEDING vs. STROKE RISK SCORES IN ATRIAL FIBRILLATION

HAS-BLED	Score	CHA_2DS_2-VASc	Score
Hypertension (systolic blood pressure > 160 mm Hg)	1	Congestive heart failure	1
Abnormal renal and liver function	1 or 2	Hypertension	1
Stroke	1	Age ≥ 75 years	2
Bleeding tendency	1	Diabetes mellitus	1
Labile INRs (VKA)	1	Stroke/TIA/thromboembolic	2
Elderly (age > 65 years)	1	Vascular disease (prior myocardial infarction, PAD, aortic plaque)	1
Drugs or alcohol	1 or 2	Aged 65-74 years	1
		Sex category (female)	1
Maximum score	9	Maximum score	9

Abnormal renal function is defined as the presence of renal transplantation, serum creatinine ≥ 200 mmol/L, or chronic dialysis. Abnormal liver function is defined as chronic hepatic disease, such as cirrhosis, or hepatic injury with biochemical evidence, such as bilirubin 2-3 times the upper limit of normal, anemia with or without history of bleeding, INR that has not been in therapeutic range for >60%, patients taking concomitant antiplatelet or nonsteroidal antiinflammatory medicines, or presence of excess alcohol.

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TREATMENT OPTIONS

VKAs

VKAs affect anticoagulation by interfering with the carboxylation of vitamin K-dependent coagulation factors (II, VII, IX, X), which, in turn, decreases their procoagulant effect.[14] Warfarin undergoes hepatic metabolism, and its metabolites are excreted in the urine, with a half-life of around 40 hours.[14] Although this class of medication has been in use for decades, it can be challenging to use with advanced cirrhosis given its narrow therapeutic index and baseline abnormalities in INR levels (Tables 2).

Available evidence suggests that VKA is associated with a reduced risk for ischemic stroke, offset in part by potential bleeding risks. In a retrospective analysis of a cohort of individuals with cirrhosis and AF, VKA reduced the risk for ischemic stroke compared with no therapy (1.8% versus 4.7% per year; $P = 0.01$), albeit with a greater risk for major bleeding (9.6% versus 6.2% per year; $P = 0.04$).[15] On subgroup analysis, those with early cirrhosis (Child-Turcotte-Pugh Score [CTP] A) appeared to benefit most, given that they had a reduction in stroke risk without significantly greater risk for major bleeding, whereas those with more advanced cirrhosis (CTP B and C) had a significantly greater risk for major bleeding (14.5% versus 4.9% per year; $P < 0.001$). In a separate retrospective analysis of 465 patients with cirrhosis with AF, the incidence of ischemic stroke was comparable between VKA users and nonusers (0.9% versus 1.2% per person-year), with a greater risk for bleeding events (5.9% versus 2.6%; $P < 0.05$).[16] A large database study of more than 10,000 patients with cirrhosis (9,056 with CHA_2DS_2 scores ≥ 2) found a significantly reduced risk for ischemic stroke in those receiving VKA compared with no treatment (HR, 0.76; 95% CI: 0.58-0.99), and no benefit to antiplatelet therapy.[12] There were no differences in risk for intracranial bleeding between groups, although other forms of bleeding were not

TABLE 2. CHOOSING AN AC IN CIRRHOSIS

	Bioavailability	Renal Clearance	Hepatic Clearance	Half-Life	Reversal Agent	Mechanism of Action	Use in Cirrhosis
Warfarin	>95%	0%	100%	20-60 hours	Vitamin K	VKA	CTP-A: use with caution CTP-B, CTP-C: avoid use, not recommended
Dabigatran	~7%	80%	20%	~12-14 hours	Idarucizumab[18]	Direct thrombin inhibitor	CTP-A: no dose reduction CTP-B: large intersubject variability, limited evidence CTP-C: limited evidence
Edoxaban	~62% (60 mg dose)	50%	50%	~10-14 hours	No approved antidotes	Direct inhibitor factor Xa	CTP-A: no dose reduction CTP-B, CTP- C: not recommended
Apixaban	50%	25%	75%	~12 hours	Andexanet alfa[20]		CTP-A: no dose reduction CTP-B: limited evidence CTP-C: not recommended
Rivaroxaban	>80% (10 mg dose), 66% for 20 mg dose	35%	65%	~6-13 hours		Competitive inhibitor free and clot-based factor Xa	CTP-A: no dose reduction CTP-B, CTP-C: avoid use, not recommended

The data are based on package inserts for warfarin,[25] dabigatran,[26] edoxaban,[27] apixaban,[28] and rivaroxaban.[29]

evaluated. Studies examining VKA in patients with AF and cirrhosis are generally restricted to retrospective database analysis, which may introduce bias and limit generalizability. Furthermore, amalgamating patients with chronic liver disease into analysis with cirrhosis is a limitation, and data regarding safety and efficacy should not be extrapolated to patients with cirrhosis per se.

Given its longstanding use and the potential benefit of reduced stroke risk, VKA can be considered in individuals with cirrhosis, although considerations should be made for therapeutic goal with elevated baseline INR, potential for a variety of drug and dietary interactions, and the need for frequent monitoring.

Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs) are an increasingly preferred anticoagulation option for a variety of indications, with potential benefits including fixed dosing and the lack of need for monitoring. Dabigatran directly inhibits thrombin (factor IIa), whereas rivaroxaban, edoxaban, and apixaban act by inhibiting factor Xa.[17] Considerations when choosing the best agent for any individual patient include evaluating drug interactions, variable half-lives, as well as the degree of renal excretion and liver metabolism. Dabigatran and rivaroxaban are cleared predominantly through the renal system, whereas apixaban is cleared predominantly through the hepatobiliary system and intestine. Direct-acting reversal agents exist for both factor Xa inhibitors (andexanet alfa) and factor IIa inhibitors (idarucizumab).[18-20]

Several studies have emerged evaluating DOACs in patients with cirrhosis for a variety of indications, although a majority of these studies have excluded patients with CTP C cirrhosis.[21-23] These agents appear to have potential advantages over VKA in the treatment of AF. In a meta-analysis of seven cohort studies involving nearly 20,000 individuals with cirrhosis and AF, anticoagulation was significantly associated with a reduced risk for stroke compared with no anticoagulation (pooled HR, 0.58; 95% CI: 0.35-0.96), whereas DOACs were associated with a lower risk for bleeding than VKA.[13] Recently, several large cohort studies of individuals with AF and cirrhosis or advanced liver disease have also suggested similar or even better reductions of ischemic risk stroke with DOACs compared with VKAs, with lower risks for major bleeding (Table 3). A recent retrospective analysis of a US national database of patients with cirrhosis who experienced development of AF found that anticoagulants (ACs) with VKAs and ACs with DOACs were both associated with lower all-cause mortality than no ACs at all.[24] In addition, this study found a lower incidence of bleeding with DOACs when compared with those patients

TABLE 3. KEY CONSIDERATIONS FOR ANTICOAGULATION WITH VKAS VERSUS DOACS IN PATIENTS WITH COMPENSATED CIRRHOSIS

VKAs	DOACs
Advantages: • Oral administration • Established and familiar reversal strategies • Cost • Well-established efficacy Disadvantages: • Dosing based on INR • Gradual onset of action • Narrow therapeutic window • Frequent INR monitoring • Underlying abnormalities synthetic dysfunction (INR) in cirrhosis • Multiple drug/dietary interactions	Advantages: • Oral administration • Laboratory monitoring unnecessary • Fewer drug/dietary interactions • Emerging data suggesting decreased bleeding risk Disadvantages: • More expensive reversal agents • High cost • Pharmacodynamics in cirrhosis not established • Long-term safety not established

taking VKAs on secondary analysis (HR: 0.49; 95% CI: 0.26-0.94; $P = 0.03$). Although these findings are encouraging, data remain limited in patients with cirrhosis because study design is generally limited to retrospective observational database analysis and granular-level information pertaining to presence of cirrhosis, degree of hepatic dysfunction, and bleeding, and other outcomes are often lacking.

CONCLUSION

Determining the potential risks and benefits of anticoagulation in individuals with cirrhosis for any indication is challenging, because these individuals are often excluded from randomized prospective trials. Anticoagulation has a clear benefit of reducing the risk for ischemic stroke in individuals with AF, and available observational data suggest that this benefit is also seen in the cirrhosis population. We recommend careful collaboration with a multidisciplinary team when deciding on the use of anticoagulation for patients with cirrhosis and AF. Assessing for bleeding risk clinically and with upper endoscopy to screen for high-risk lesions (e.g., portal hypertensive gastropathy, gastric antral vascular ectasia, gastroesophageal varices) is recommended prior to initiating therapy. Patients with decompensated cirrhosis (CTP B and C) may be at higher risk for bleeding, and data on risks and benefits of anticoagulation are very sparse. Individual assessment on a case-by-case basis is essential in this setting with multidisciplinary collaboration. When anticoagulation is initiated, both VKAs and DOACs represent options for reducing stroke risk. This decision should be individualized, with considerations including the degree of underlying liver and renal dysfunction, the associated bleeding risk, the drug pharmacokinetics, and patient and provider preference. Prospective studies are now needed to better understand the safety and efficacy of these drugs in patients with compensated and decompensated cirrhosis.

CORRESPONDENCE

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