Anticoagulation Management in Patients with Atrial Fibrillation and Cirrhosis

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Introduction

Anticoagulation to prevent thromboembolic complications associated with atrial fibrillation (AF) is widely accepted. (1, 2) While 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 cirrhosis patients. Individuals with cirrhosis may have underlying portal hypertension and associated gastroesophageal varices, and it is increasingly recognized that these patients have a complex and "re-balanced" coagulation system that can place them at risk for both bleeding and clotting. (5, 6) In addition, traditional tests of coagulation (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 are paramount for clinicians caring for these patients.

Challenges Regarding the Risks and Benefits of Treatment of Atrial Fibrillation 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 one-year follow up (Table 1). (7) The risk of major bleeding with anticoagulation for AF is often measured using the HAS-BLED score (Table 1). (8) While 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, as 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 over 10,000 patients with cirrhosis and AF, noting a reduced risk of ischemic stroke in those taking VKA and no benefit in the antiplatelet group compared to no treatment at all (HR 0.76, 95% CI 0.58-0.99). (12) There was no difference in risk of hemorrhagic stroke. A systemic review and meta-analysis of 7 cohort studies of nearly 20,000 patients with AF and cirrhosis found that the use of anticoagulation was associated with a reduced risk of stroke (pooled HR of 0.58, 95% CI 0.35-0.96) and was not significantly associated with an increased risk of bleeding (HR 1.45, 95% CI 0.96-2.17) compared to those who did not receive anticoagulation. (13)

Treatment Options

Vitamin-K Antagonists

Vitamin-K Antagonists (VKA) affect anticoagulation by interfering with the carboxylation of vitamin K dependent coagulation factors (II, VII, IX, X), which, in turn, decreases their pro-coagulant effect. (14) Warfarin undergoes hepatic metabolism and its metabolites are excreted in the urine, with a half-life of around 40 hours. (14) While 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.

Available evidence suggests that VKA is associated with a reduced risk of 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 of ischemic stroke compared to no therapy (1.8% vs 4.7% per year, $p = 0.01$), albeit with a higher risk of major bleeding (9.6% vs 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 higher risk of major bleeding, whereas those with more advanced cirrhosis (CTP B and C) had a significantly higher risk of major bleeding (14.5% vs 4.9% per year, $p < 0.001$). In a separate retrospective analysis of 465 cirrhotic patients with AF, the incidence of ischemic stroke was comparable between VKA users and nonusers (0.9% vs 1.2% per person-year), with a higher risk of bleeding events (5.9% vs 2.6%, $p < 0.05$). (16) A large database study of over 10,000 patients with cirrhosis (9,056 with CHA_2DS_2 scores >/2) found a significantly reduced risk of ischemic stroke in those receiving VKA compared to no treatment (HR 0.76, 95% CI = 0.58-0.99), and no benefit to antiplatelet therapy. (12) There were no differences in risk of intracranial bleeding between groups, although other forms of bleeding were not evaluated. Studies examining VKA in patients with AF and cirrhosis are generally restricted to retrospective database analysis which may introduce bias and limits generalizability. Furthermore, amalgamating of 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 (DOAC) 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), while rivaroxaban, edoaxaban, 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 predominantly cleared through renal system, while apixaban is cleared predominantly through the hepatobiliary system and intestine. Direct acting reversal agents exist of for both factor Xa inhibitors (andexanet alfa) and factor IIa inhibitors (idarucizumab). (18-20)

Several studies have emerged evaluating DOAC in patients with cirrhosis for a variety of indications, though 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 7 cohort studies involving nearly 20,000 individuals with cirrhosis and AF, anticoagulation was significantly associated with a reduced risk of stroke compared to no anticoagulation (pooled HR 0.58, 95%CI 0.35-0.96), while DOACs were associated with a lower risk of 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 to VKA, with lower risks of major bleeding. A recent retrospective analysis of a United States national database of patients with cirrhosis whom developed atrial fibrillation found that AC with VKA or DOAC were both associated with lower all-cause mortality than no AC at all. (24) In addition, this study found a lower incidence of bleeding on DOAC when compared with those patients on VKA on secondary analysis (HR: 0.49, 95% CI 0.26-0.94, P=.03). While these findings are encouraging, data remains limited in patients with cirrhosis as study design is generally limited to retrospective observational database analysis and granular level information pertaining to presence of cirrhosis, degree of hepatic dysfunction, 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, as these individuals are often excluded from randomized prospective trials. Anticoagulation has a clear benefit of reducing the risk of ischemic stroke in individuals with AF, and available observational data suggests 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, gastroesphageal varices) is recommended prior to initiating therapy. Patients with decompensated cirrhosis (CTP B and C) may be at higher risk to bleed 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 VKA 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.

Table 1

HAS-BLED	Score	**CHA2DS2-VASc**	Score

Hypertension (Systolic blood pressure > 160)	1	**C**ongestive heart failure	1
Abnormal renal and liver function**	1 or 2	**H**ypertension	1
Stroke	1	**A**ge ≥ 75	2
Bleeding tendency	1	**D**iabetes Mellitus	1
Labile INRs (VKA)	1	**S**troke/TIA/TE	2
Elderly (age > 65)	1	**V**ascular Disease (prior MI, PAD, Aortic Plaque)	1
Drugs or Alcohol	1 or 2	**A**ged 65 -74	1
		Sex Category (female)	1
Maximum Score	9	Maximum Score	9

Abnormal renal function is defined as 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 on concomitant anti-platelet or NSAID medicines, or presence of excess alcohol. Abbreviations: INR: International Normalized Ratio, TIA: Transient Ischemic Attack, TE: Thromboembolic, MI: Myocardial Infarction, PAD: Peripheral Arterial Disease adapted from Lip GY. Implications of the CHA(2)DS(2)-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation. Am J Med. 2011;124(2):111-114. doi:10.1016/j.amjmed.2010.05.007

Table 2: Choosing an Anticoagulant 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

a. **Above data based on package inserts for Warfarin (25), Dabigatran (26), Edoxaban (27), Apixaban (28), Rivaroxaban (29)**

Table 3

Key Considerations for Anticoagulation with VKA versus DOAC in Compensated Cirrhotics

Vitamin-K Antagonists (VKA)	**Direct Oral Anticoagulants (DOAC)**
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	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

- Multiple drug/dietary interactions	

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