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JACC REVIEW TOPIC OF THE WEEK

Oral Anticoagulation in Patients With Liver Disease

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CME/MOC Objective for This Article: Upon completion of this activity, the learner should be able to: 1) explain mechanistic underpinnings regulating bleeding and thrombosis in liver disease; 2) compare the pharmacologic properties of warfarin and NOACs in liver disease; and 3) develop a practical approach to prescribing oral anticoagulation in liver disease.

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Oral Anticoagulation in Patients With Liver Disease

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ABSTRACT

Patients with liver disease are at increased risks of both thrombotic and bleeding complications. Many have atrial fibrillation (AF) or venous thromboembolism (VTE) necessitating oral anticoagulant agents (OACs). Recent evidence has contradicted the assumption that patients with liver disease are "auto-anticoagulated" and thus protected from thrombotic events. Warfarin and non-vitamin K-antagonist OACs have been shown to reduce thrombotic events safely in patients with either AF or VTE. However, patients with liver disease have largely been excluded from trials of OACs. Because all currently approved OACs undergo metabolism in the liver, hepatic dysfunction may cause increased bleeding. Thus, the optimal anticoagulation strategy for patients with AF or VTE who have liver disease remains unclear. This review discusses pharmacokinetic and clinical studies evaluating the efficacy and safety of OACs in patients with liver disease and provides a practical, clinically oriented approach to the management of OAC therapy in this population.
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Liver disease represents a major global health burden contributing to >1 million deaths every year (1). Among the causes of liver disease, nonalcoholic fatty liver disease (NAFLD) is the major cause of liver disease worldwide (2). Approximately 60 million people have this disease in the United States alone (3), and its prevalence is expected to increase further. The high prevalence of NAFLD is attributed to an epidemic and clustering of cardiometabolic risk factors such as obesity, diabetes mellitus, metabolic syndrome, and dyslipidemia in the general population. NAFLD is not only associated with an increased risk of cirrhosis and hepatocellular carcinoma, but also with a heightened risk of cardiovascular events (4,5). Because atrial fibrillation (AF) and liver disease, particularly NAFLD, share common risk factors, AF is frequently present in these patients (6–9). Furthermore, given persistent systemic inflammation, advanced age, prolonged immobility, elevated estrogen levels, and decreased synthesis of endogenous anticoagulants in liver disease, patients with liver disease are also at an increased risk of venous thromboembolism (VTE) (10,11).

The presence of AF (with additional risk factors for stroke) and VTE in patients with liver disease necessitates the use oral anticoagulant agents (OACs) for the prevention of thrombotic events (12). However, the use of OACs in liver disease is complicated by the imbalance of endogenous procoagulant and anticoagulant factors. Understanding of coagulopathy in liver disease has evolved dramatically over the last 2 decades. Initially, patients with advanced liver disease, particularly with a baseline elevation in the international normalized ratio (INR), were considered to have an increased risk of bleeding and a low risk of thrombosis. However, recent data have contradicted the old dogma of cirrhotic "auto-anticoagulation" and have recognized an increased prevalence of thrombotic complications in these patients (13).

Warfarin and non-vitamin K-antagonist oral anticoagulant agents (NOACs) have been shown to reduce stroke and thromboembolism safely in the general groups of patients with AF and VTE. However, patients with liver disease have been mostly excluded from randomized clinical trials of OACs for the prevention of stroke and VTE. Furthermore, because all the currently approved NOACs undergo significant metabolism in the liver, impairment in hepatic function may lead to increased drug levels, decreased coagulation factors, and attendant bleeding risks. In addition, some NOACs depend on cytochrome P450 enzymes for metabolism (14), and the activity of these enzymes may be altered in liver disease. Thus, the optimal anticoagulation strategy for patients with AF and VTE who have concomitant liver disease is complex and not well defined. Indeed, management of antithrombotic therapies in this high-risk group is subject to significant practice variation (15). In this review, we discuss the risk-to-benefit profile and the pharmacokinetic, observational, and trial data on oral anticoagulation therapy in patients with liver disease, with an emphasis on prevention and treatment of thrombotic events in patients with AF and VTE. We offer a practical approach to patient selection, choice of OAC, and bleeding reduction strategies in patients with liver disease who require OACs.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

EMA = European Medicines Agency

FDA = Food and Drug Administration

INR = international normalized ratio

NAFLD = nonalcoholic fatty liver disease

NOAC = non-vitamin K-antagonist oral anticoagulant agent

OAC = oral anticoagulant agent

PCC = prothrombin complex concentrate

PT = prothrombin time

PVT = portal vein thrombosis

VTE = venous thromboembolism

BURDEN OF THROMBOTIC COMPLICATIONS IN PATIENTS WITH LIVER DISEASE

Several observational studies in the general population have reported that patients with liver disease face increased risks of ischemic stroke and VTE compared with patients without liver disease (16-18). In a retrospective analysis of 289,559 patients with AF from the National Health Insurance Research Database in Taiwan, the presence of liver cirrhosis was independently associated with a higher risk of ischemic stroke compared with patients without liver cirrhosis (17). Similarly, a meta-analysis of 9 observational studies found a 2.5-fold higher risk of ischemic stroke in patients with liver disease compared with patients without liver disease (18). Ischemic stroke in patients with liver disease is a marker of poor prognosis and is independently associated with higher rates of in-hospital death (19).

Several studies have reported an increased risk of VTE in patients with impaired hepatic function (10,11,20). For instance, in a Danish study of ~100,000 patients with VTE, the presence of liver disease was independently associated with a nearly 2-fold higher risk of VTE compared with patients without liver disease (10). Importantly, development of VTE in patients with liver cirrhosis is associated with 2-fold higher 30-day mortality rate relative to patients without liver cirrhosis (21). In addition to the risk of deep vein thrombosis and pulmonary embolism, patients with liver disease have a higher risk of portal vein thrombosis (PVT) secondary to slow flow in the splanchnic vessels, intra-abdominal infections, inflammation, and compression from splenomegaly and ascites. Studies have reported an 8% to 18% incidence of PVT in patients with cirrhosis, thus making PVT the most common thrombotic manifestation in patients with liver disease (22). The development of PVT is a marker of poor prognosis in patients with liver disease. In a prospective observational study of 1,243 patients with cirrhosis, PVT occurred in 11% of patients at 5 years and was independently associated with the presence of severe manifestations of liver disease, such as esophageal varices and hepatic coagulopathy (23). Taken together, patients with liver disease face heightened risks of thrombotic events, and prevention of these complications should be an important treatment goal.

MECHANISMS DRIVING BLEEDING AND THROMBOSIS IN LIVER DISEASE

Normal liver function is pivotal in maintaining the balance between hemostasis and prevention of thrombosis. However, the relationship between liver disease and the coagulation pathways is complex because of its diverse effects on platelets, coagulation factors, natural inhibitors (antithrombin, protein C, and protein S), and fibrinolysis (24) (**Figure 1**). Liver disease is associated with an increased risk of thrombosis resulting from decreased endogenous anticoagulants and high levels of circulating procoagulants. The decreased production of protein C and antithrombin appears to be the driving factor for thrombotic risk in patients with liver disease. In addition, patients with liver disease are also predisposed to thrombosis secondary to increased platelet aggregation related to high activity of von Willebrand factor and low levels of ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13), a modifier of von Willebrand factor activity (25,26). Low levels of plasminogen cause hypofibrinolysis that further predisposes patients to thrombosis. Prolongation of prothrombin time (PT) is a common finding in advanced liver disease. Elevated INR >2.0 was previously thought to be protective from VTE; however, more recent observations have refuted this claim and have shown high risks of VTE even in patients with an increased INR (27,28).

Furthermore, it is well known that liver disease is associated with increased risk of bleeding because all the coagulation factors (except for factor VIII and von Willebrand factor) are synthesized in the liver; thus, their levels are decreased in liver disease. Reduced levels of fibrinogen and of factors II, V, VII, and X are manifested by prolongation in PT, whereas decreased activity of fibrinogen and of clotting factors II, V, IX, X, XI, and XII results in prolongation of the activated partial thromboplastin time. The risk of bleeding is further increased by thrombocytopenia related to decreased production of thrombopoietin. Furthermore, liver disease has also been associated with increased fibrinolysis secondary to elevated levels of tissue plasminogen activator and reduced levels of plasmin inhibitor and thrombin-activatable fibrinolysis inhibitor (29).

WARFARIN IN LIVER DISEASE

Warfarin has traditionally been the OAC of choice for the treatment and prevention of thrombotic complications in liver disease. Warfarin inhibits the vitamin

FIGURE 1 **Mechanisms Driving Increased Thrombosis and Bleeding in Liver Disease**

⬆ Thrombosis	⬆ Bleeding
Increased Platelet-Vessel Wall Interaction	**Reduced Platelet-Vessel Wall Interaction**
• ↑ von Willebrand factor	• ↓ Platelet count
• ↑ ADAMTS 13	• ↓ Platelet function
High Thrombin Generation	**Low Thrombin Generation**
• ↑ Factor VIII	• ↓ Fibrinogen
• ↓ Protein C, Protein S	• ↓ Factor II, V, VII, IX, X, XI
• ↓ Antithrombin	
• ↓ TFPI	
Low Fibrinolysis	**High Fibrinolysis**
• ↓ Plasminogen	• ↑ Tissue-plasminogen activator
• ↑ PAI	• ↓ Plasmin inhibitor
	• ↓ TAFI

ADAMTS 13 = a disintegrin and metalloprotease with thrombospondin type 1 motif 13; PAI = plasminogen activator inhibitor; TAFI = thrombin-activatable fibrinolysis inhibitor; TFPI = tissue factor pathway inhibitor.

K-dependent synthesis of clotting factors II, VII, IX, and X in the liver. It also decreases the production of anticoagulant proteins, proteins C and S. It achieves nearly complete oral bioavailability and reaches a peak plasma concentration in 2 to 6 h. It has a small volume of distribution (0.14 l/kg) with significant plasma protein binding (~99%). The half-life of warfarin is 20 to 60 h. It is predominantly eliminated by the liver, where it is converted to an inactive metabolite through a cytochrome P450-dependent metabolism and does not rely on the kidney for its clearance (30).

Use of warfarin in routine clinical practice is challenging because of its narrow therapeutic index, particularly in patients with liver disease. Unfortunately, warfarin is prone to significant drug-drug interactions because of its metabolism through the cytochrome P450 system, thereby resulting in supratherapeutic or subtherapeutic INR levels. This feature can be detrimental in patients with liver disease who have heightened risks of both bleeding and thrombosis. According to AF and VTE guidelines for the general population, an INR between 2.0 and 3.0 is considered optimal for the prevention of thrombotic events. However, there are no specific guidelines for warfarin use in patients with impaired liver function. Patients with liver disease may

TABLE 1 Pharmacological Characteristics of Oral Anticoagulant Agents Approved for Use in Select Patients With Liver Disease

	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Target	VKORC1	Factor Xa	Factor IIa	Factor Xa	Factor Xa
Half-life, h	20–60	~12	12–17	10–14	7–13
Prodrug	No	No	Yes	No	No
Oral bioavailability, %	100	50	3–7	60	66
Renal clearance, %	None	25	80	50	35
Hepatic clearance, %	100	75	20	50	65
Requires CYP450	Yes	Yes	No	Minimal	Yes
Plasma protein binding, %	99	87	35	55	95
Substrate for P-gp	No	Yes	Yes	Yes	Yes
Coagulation monitoring required	Yes, INR	No	No	No	No
Coagulation assay	INR	Anti-Xa activity*	TT, ECT	Anti-Xa activity*	Anti-Xa activity*
Reversal agent	4F-PCC + vit K	4F-PCC	Idarucizumab	4F-PCC	4F-PCC

*Anti- factor Xa activity assay calibrated to specific anticoagulant agent.

CYP = cytochrome P; ECT = ecarin clotting time; INR = international normalized ratio; P-gp = P-glycoprotein; PPB = plasma protein binding; TT = thrombin time; vit = vitamin; VKORC1 = vitamin K epoxide reductase complex subunit 1; 4F-PCC = 4 factor prothrombin complex concentrate.

already have an elevated INR at baseline. Thus, the dose of warfarin and the target INR are not well defined in this population. Suboptimal dosing in response to an elevated INR at baseline may result in an increased risk of thrombotic events, and titrating to a supratherapeutic INR could result in bleeding complications (31). Patients with liver disease have a lower mean time in therapeutic range, which has been associated with a 2-fold increase in the incidence of bleeding when compared with patients without liver disease (32). This risk that may be significantly influenced by other factors such as serum albumin and renal function in patients with liver disease (32).

To date, no prospective clinical trial has examined the safety and efficacy of warfarin in reducing thrombotic events in patients with liver disease, and most data on warfarin use have been obtained from retrospective observational studies. Most of these observational studies have suggested a reduced risk of thromboembolism with warfarin compared with no anticoagulant therapy. In a propensity score-matched analysis of 10,336 patients with cirrhosis and a CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category [female]) score ≥2 in Taiwan, warfarin was associated with a 24% lower risk of ischemic stroke as compared with no antithrombotic therapy (17). In addition, warfarin may be effective in the treatment of PVT in patients with liver disease. In a retrospective cohort study that included 28 patients with PVT, anticoagulant therapy with warfarin that maintained an INR of 2.0 to 3.0 resulted in higher rates of recanalization of the portal vein and a lower incidence of recurrent thrombosis relative to no anticoagulation (33). Similarly, in a case series of 55 patients with cirrhosis and PVT, early initiation of warfarin was significantly associated with recanalization of the portal vein (34). However, anticoagulation with warfarin was associated with gastrointestinal bleeding in 5 patients (9%) that was attributed to high-grade esophageal varices.

As with any observational study, these analyses have several limitations related to residual confounding and the potential for bias; thus, the posited associations may not be causal. Although warfarin may lower risks of thromboembolism in patients with impaired liver function, it has several limitations in clinical practice, including the need for frequent INR monitoring, interaction with diet and medications, interindividual variability in response, and higher rates of intracranial bleeding and death compared with NOACs, as demonstrated in randomized trials of patients with AF and VTE.

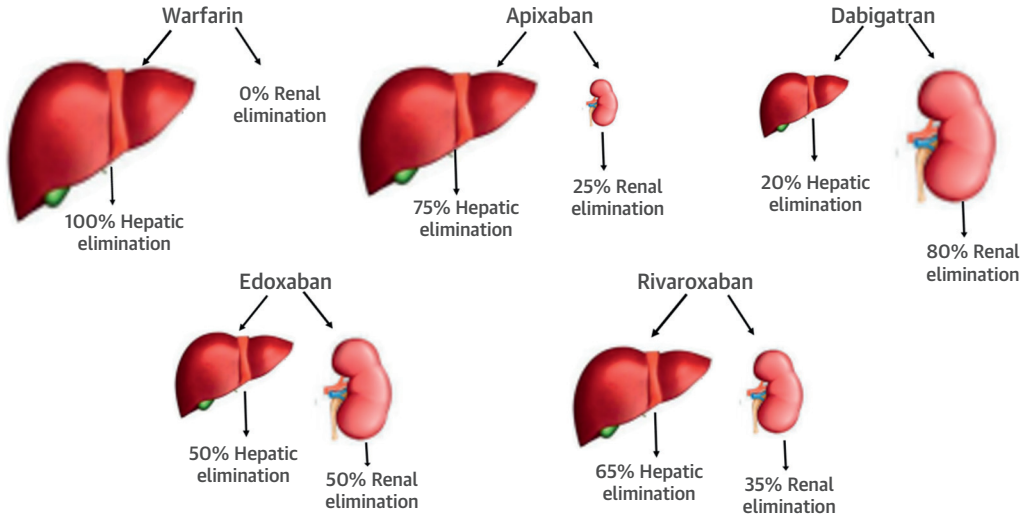
THE USE OF NOACs IN LIVER DISEASE

In the last decade, NOACs have emerged as a promising alternative to warfarin for the prevention and treatment of VTE and for the prevention of stroke in patients with AF (**Table 1**). Several randomized trials of apixaban, dabigatran, edoxaban, and rivaroxaban have demonstrated comparable or superior efficacy and safety profiles of NOACs compared with warfarin in patients with AF or VTE. Thus, NOACs are currently recommended as first-line treatment (35,36) or alternatives to warfarin (12,37) in the management of AF and VTE in guidelines from North America and Europe.

Although the safety of NOACs in patients with mild to moderate renal dysfunction has gained attention, the efficacy and safety of these drugs in the setting of liver disease have not been well studied (38–43). Unlike renal dysfunction, which can be easily detected and monitored with the measurement of creatinine clearance to guide dosing, liver disease may go undetected until it progresses to advanced stages to cause an elevation in INR or other abnormalities in laboratory test results. Unlike guidelines for the use of NOACs in renal disease, none of the clinical practice guidelines offer direction regarding the use of these drugs in patients with liver disease.

All NOACs undergo some degree of hepatic metabolism; therefore, any decrease in liver function could influence the effect of these drugs (**Figure 2**). In addition, the presence of hepatic coagulopathy would

FIGURE 2 Pharmacokinetic Characteristics and Primary Routes of Clearance of Oral Anticoagulant Agents



In the figure, the size of the liver or kidney denotes the extent of the organ's contribution to the clearance of the anticoagulant agent.

amplify the risk of bleeding in patients treated with NOACs. Randomized trials of NOACs in patients with AF and VTE have routinely excluded patients with liver disease. Hence, the basis for the evidence regarding the safety and efficacy of NOACs in patients with impaired liver function predominantly consists of pharmacokinetic studies, case reports, and small observational studies (44).

HEPATIC PHARMACOKINETICS AND PHARMACODYNAMICS OF NOACs

Liver disease could influence several aspects of NOAC pharmacokinetics, including their pre-systemic elimination after oral absorption, plasma protein binding, cytochrome P450-mediated metabolism, biliary excretion, and effect on renal function. Among the NOACs, apixaban undergoes the greatest hepatic elimination (~75%), followed by rivaroxaban (65%) and edoxaban (50%). Among the NOACs, only dabigatran etexilate is a prodrug; the biotransformation of dabigatran etexilate to active drug occurs by ubiquitous esterases; thus, metabolism is not limited to the liver. Because the synthesis of albumin is decreased in liver disease, the fraction of free drug levels may increase for patients with high plasma protein binding. The plasma protein binding for rivaroxaban, apixaban, edoxaban, and dabigatran is approximately 95%, 85%, 55%, and 35%, respectively. Moreover, the activity of cytochrome P450 enzymes and biliary excretion is reduced in liver disease, thereby resulting in decreased clearance of drugs dependent on these pathways. None of the NOACs depend entirely on the cytochrome P450 enzymes for metabolism; however, apixaban and rivaroxaban are predominantly metabolized by cytochrome P450, whereas edoxaban and dabigatran have minimal to no cytochrome P450 metabolism. Liver disease, when associated with hepatorenal syndrome or other forms of comorbid renal disease, may also affect the pharmacokinetic profile of NOACs that undergo significant renal clearance (e.g., dabigatran).

The U.S. Food and Drug Administration (FDA) recommends a pharmacokinetic study during drug development in patients with impaired liver function if hepatic metabolism or elimination accounts for >20% of the absorbed drug (as is the case with apixaban and rivaroxaban) or if published reports suggest a narrow therapeutic index of the drug irrespective of the extent of hepatic elimination (45). The European Medicines Agency (EMA) recommends a pharmacokinetic study in subjects with impaired hepatic function if the drug is likely to be used in patients with liver disease and if hepatic impairment could affect the metabolism and biliary excretion of the drug (46). The regulatory guidance recommends using the Child-Pugh classification to classify the degree of impairment in liver function to guide dosing in patients with liver disease (45,46). The Child-Pugh score uses the presence of clinical (encephalopathy and ascites) and biochemical (serum albumin, serum bilirubin, and PT or INR) abnormalities to assess the severity (A, B, and C

TABLE 2 Summary of the U.S. FDA and EMA Recommendations for Use of Warfarin and NOACs in Patients With AF or VTE on the Basis of the Severity of Underlying Liver Disease

Oral Anticoagulant Agent	Child-Pugh Class	FDA Recommendations	EMA Recommendations
Warfarin	A	Therapeutic INR	Therapeutic INR
	B		
	C		
Apixaban	A	No dose adjustment	Use with caution No dose adjustment
	B	Use with caution No dose adjustment	
	C	Not recommended	Not recommended
Dabigatran	A	No dose adjustment	Not recommended if AST/ALT>2× ULN or Liver disease expected to affect survival
	B	Use with caution No dose adjustment	
	C	Not recommended	
Edoxaban	A	No dose adjustment	No dose adjustment Use with caution, particularly if AST/ALT>2× ULN or total bilirubin>1.5× ULN
	B	Not recommended	
	C		Not recommended
Rivaroxaban	A	No dose adjustment	No dose adjustment
	B	Not recommended	Not recommended
	C		

AF = atrial fibrillation; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EMA = European Medicines Agency; FDA = Food and Drug Administration; INR = international normalized ratio; NOACs = non-vitamin K-antagonist oral anticoagulant agents; ULN = upper limit of normal; VTE = venous thromboembolism.

representing mild, moderate, and severe, respectively) and prognosis of liver disease. Hepatic impairment pharmacokinetic studies have been performed for all the currently approved NOACs.

Apixaban is a direct oral factor Xa inhibitor. Its bioavailability is ~50%, and it reaches its peak plasma concentration in 3 to 4 h after administration. The half-life of apixaban is ~12 h. In the liver, it is predominantly metabolized through a cytochrome P450-dependent mechanism and is also a substrate for the transporter P-glycoprotein system. Among the NOACs, apixaban undergoes the least amount of renal elimination (25%) (**Table 1**). On the basis of pharmacokinetic studies (47), the current FDA label recommends no dose adjustment of apixaban in patients with mild hepatic impairment (Child-Pugh A) (**Table 2**) (48). Because of limited data and concerns for bleeding in patients with moderate hepatic impairment (Child-Pugh B), caution is recommended with the use of apixaban, and no dosing recommendations are provided. Apixaban is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). The EMA does not recommend the use of apixaban in patients with liver disease associated with coagulopathy and a clinically relevant bleeding risk (49) (**Table 2**). The EMA also recommends liver function testing before starting apixaban.

Dabigatran is a direct oral thrombin inhibitor. Its bioavailability is 3% to 7%, and it reaches its peak plasma concentration within 1 to 2 h of oral administration. The half-life of dabigatran is 12 to 17 h. A small fraction of absorbed dabigatran is metabolized to glucuronides in the liver; however, this conjugation does not change the activity of dabigatran. Therefore, a decrease in liver function is not expected to affect the activity of dabigatran significantly. Furthermore, dabigatran undergoes elimination predominantly (80%) through the kidney (**Table 1**). On the basis of pharmacokinetic and pharmacodynamic assessment of dabigatran, the FDA recommends no dose adjustment for dabigatran in patients with mild or moderate hepatic impairment (**Table 2**) (50,51). However, the EMA does not recommend dabigatran in patients with elevated liver enzyme levels greater than twice the upper limit of normal and in patients with liver disease that is expected to have any impact on survival (52) (**Table 2**).

Edoxaban is a direct oral factor Xa inhibitor. Its bioavailability is approximately 60%, and it reaches peak concentration in 1 to 2 h. The half-life of edoxaban is 10 to 14 h. Metabolism and elimination of edoxaban are performed equally by the liver (50%) and kidney (50%). In the liver, edoxaban undergoes minimal (<10%) metabolism by hydrolysis, conjugation, and oxidation by the cytochrome P450 enzyme CYP3A4 (**Table 1**). On the basis of early-phase data (53), the FDA does not recommend dose adjustment of edoxaban in patients with mild hepatic impairment (Child-Pugh A) (**Table 2**) (54). Edoxaban is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (54). The EMA does not recommend dose adjustment of edoxaban in patients with mild or moderate hepatic impairment (Child-Pugh A or B) and does not recommend the use of this drug in patients with severe hepatic impairment (Child-Pugh C) (**Table 2**). In addition, the EMA label recommends against use of edoxaban in patients with hepatic disease associated with coagulopathy and a clinically relevant bleeding risk (55).

Rivaroxaban is a direct oral factor Xa inhibitor. Its bioavailability is dose dependent: for the 10-mg dose, it is ~80% to 100% and does not change with food; for the 20-mg dose, bioavailability is ~66% and increases with food. Rivaroxaban achieves peak levels in 2 to 4 h, and its elimination half-life is 7 to 13 h. One-third of rivaroxaban is cleared by the kidney, and two-thirds undergoes hepatobiliary metabolism (**Table 1**). On the basis of pharmacokinetic and

pharmacodynamic data (56), the FDA and EMA do not recommend the use of rivaroxaban in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or in patients with any liver disease associated with coagulopathy (**Table 2**) (57,58).

Although NOACs are being widely used in general groups of patients with AF or VTE, very limited data exist regarding the clinical use, safety, and efficacy of these drugs in patients with liver disease. Thus far, clinicians have reported their experience of using NOACs in patients with liver disease in the form of case reports, case series, and small observational studies. In a single-center retrospective analysis of 39 patients with liver disease, Intagliata et al. (59) compared patients receiving NOACs with patients receiving standard anticoagulation therapy and found no significant difference in the risk of major bleeding between the 2 groups at 1 year. There was 1 death in the warfarin group caused by intracranial bleeding.

In a case series of 94 patients with mild or moderate hepatic impairment (Child-Pugh A or B) who were prescribed NOACs (83% rivaroxaban, 11% dabigatran, and 6% apixaban) for treatment of VTE (75% PVT and 5% DVT) or AF (14%), bleeding requiring discontinuation of anticoagulation occurred in 5% of patients at a median follow-up of 21 months (60). No fatal or intracranial bleeding or NOAC-induced liver injury was observed. A recent retrospective cohort study of 45 patients with cirrhosis who were taking OACs (rivaroxaban, n = 17; apixaban, n = 10; warfarin, n = 15; enoxaparin, n = 3) for VTE or prevention of stroke in AF found lower rates of major bleeding in patients taking NOACs as compared with patients taking warfarin or enoxaparin over 3 years (4% vs. 28%) (61). There was no difference in the risk of thrombotic events between the 2 groups. In an observational study of 50 patients with cirrhosis and PVT, the investigators found a greater resolution of PVT at 6 months among patients treated with therapeutic doses of edoxaban relative to warfarin (INR goal 1.5 to 2.0) (70% vs. 20%). There was no significant difference in the incidence of bleeding between the 2 groups (62). The lower rates of thrombus resolution in patients treated with warfarin were attributed to subtherapeutic dosing.

These observational results should be interpreted with caution. The sample sizes were too small to be adequately powered to detect adverse events, the analyses were not adjusted for differences in characteristics among the treatment groups, and because of the observational design of these studies, residual confounding and bias cannot be excluded. These limitations underscore the unmet need for randomized clinical trial data in this high-risk group of patients.

TABLE 3 Hepatic Adverse Events Across Randomized Trials of NOACs Compared With Warfarin in patients With AF and VTE*

Trial	NOAC	NOAC	Warfarin	Odds Ratio (95% CI)*
AF trials				
RE-LY†	Dabigatran	13/6,076 (0.2)	21/6,022 (0.3)	0.61 (0.30–1.22)
ROCKET-AF	Rivaroxaban	33/7,111 (0.5)	35/7,125 (0.5)	0.94 (0.58–1.52)
ARISTOTLE	Apixaban	30/8,788 (0.3)	31/8,756 (0.4)	0.96 (0.58–1.59)
ENGAGE AF-TIMI 48‡	Edoxaban	15/7,012 (0.2)	10/7,012 (0.1)	1.50 (0.67–3.34)
VTE trials				
RE-COVER	Dabigatran	2/1,055 (0.2)	4/1,106 (0.4)	0.52 (0.09–2.86)
RE-MEDY	Dabigatran	2/1,430 (0.1)	1/1,426 (0.1)	1.99 (0.18–22.03)
EINSTEIN DVT	Rivaroxaban	2/1,682 (0.1)	4/1,648 (0.2)	0.48 (0.08–2.67)
HOKUSAI-VTE	Edoxaban	0/3,878	2/3,865 (0.05)	0.19 (0.009–4.15)

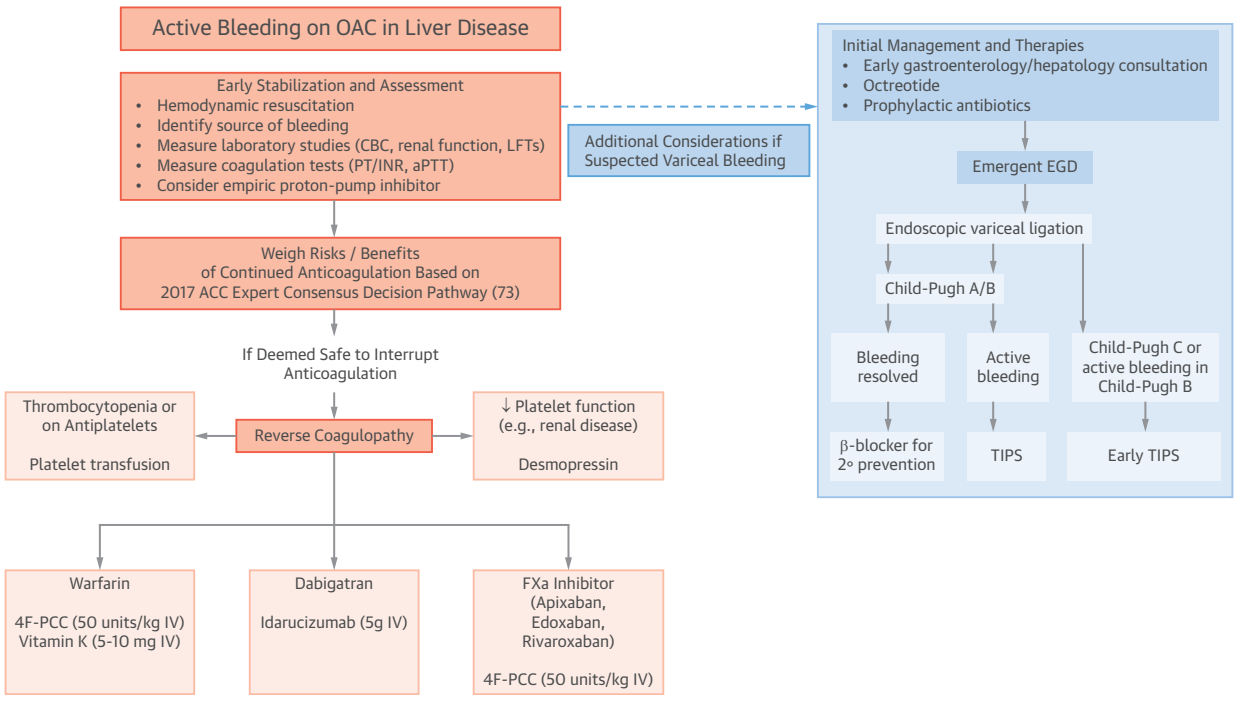
Values are n/N (%) unless otherwise indicated. *Hepatic adverse events were defined as alanine aminotransferase or aspartate aminotransferase >3 times upper limit of normal and total bilirubin >2 times upper limit of normal. All are p > 0.20. †These data apply to dabigatran 150 mg twice daily. ‡These data apply to the higher-dose edoxaban regimen.

ARISTOTLE = Apixaban for Reduction In STroke and Other ThromboembоLic Events in atrial fibrillation; EINSTEIN DVT = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis; ENGAGE AF-TIMI 48 = Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction Study 48; HOKUSAI-VTE = Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Tosylate (DU176b) Versus (LMW) Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; RE-COVER = Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-LY = Randomized Evaluation of Long-term Anticoagulation Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; CI = confidence interval; other abbreviations as in Table 2.

OACs AND THE RISK OF LIVER INJURY

The potential for hepatotoxicity with warfarin is rare and has been monitored during clinical use for several decades. However, given the more recent approval of NOACs, data (particularly over the long term) on the incidence of liver injury with NOACs are limited. The concern for risk of liver injury with NOACs started with ximelagatran, an oral direct thrombin inhibitor that was evaluated extensively for prevention of thromboembolism and was found to cause severe liver injury (alanine aminotransferase levels >3 times the upper limit of normal in 8% of treated patients) (63). Because of these concerns, further development of ximelagatran was halted, and it never entered the U.S. market; it was quickly withdrawn in Europe. The hepatic safety of warfarin and other NOACs has been closely monitored in all recent randomized trials of VTE and stroke prevention in AF. There was no difference in the incidence of hepatotoxicity between warfarin and currently marketed NOACs in these trials (**Table 3**). However, drug-induced liver injury is rare, and although randomized trials represent the gold standard for assessing drug efficacy, they are underpowered and may be too short to recognize rare adverse drugs reactions. Therefore, the potential for hepatotoxicity of NOACs needs to be closely monitored over the long term through dedicated post-marketing surveillance efforts. Currently, the European Heart

FIGURE 3 Management of Severe or Life-Threatening Bleeding in Patients With Liver Disease Who Are Taking OACs



ACC = American College of Cardiology; aPTT = activated partial thromboplastin time; CBC = complete blood count; EGD = esophagogastroduodenoscopy; FXa = factor Xa; INR = international normalized ratio; IV = intravenous; LFTs = liver function tests; OAC = oral anticoagulant agent; PT = prothrombin time; TIPS = transjugular intrahepatic portosystemic shunt; 4F-PCC = 4 factor-prothrombin complex concentrate; 2° = secondary.

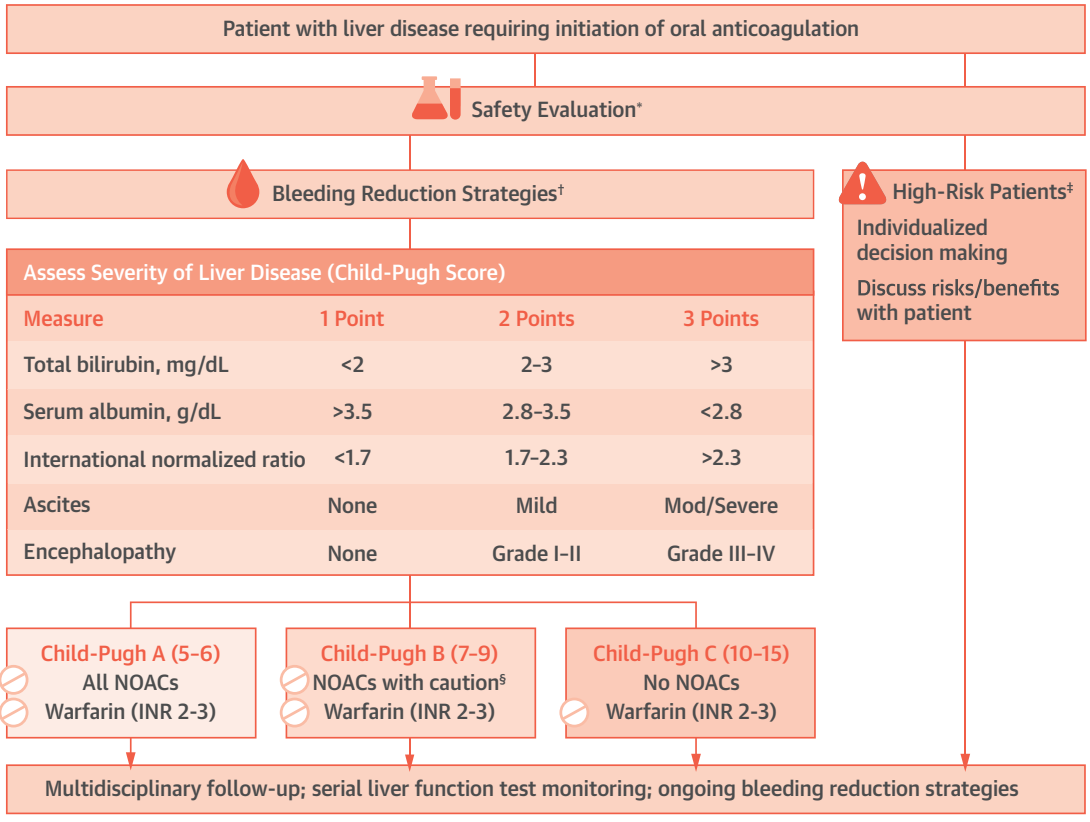
Rhythm Association guidelines recommend annual monitoring of liver function tests in patients treated with NOACs (64).

Following regulatory approval, the hepatic safety of NOACs has been closely followed and reported in clinical practice. All NOACs have been associated with elevations of transaminases. In an analysis of 113,717 patients with AF who were taking OACs (50% warfarin and 50% NOACs), there were 7 hospitalizations for liver injury per 1,000 person-years during a median follow-up of 14 months (65). Compared with patients taking warfarin, the incidence of liver injury was lower in patients taking NOACs (9 vs. 5 per 1,000 person-years). Among NOACs, dabigatran was associated with the lowest relative risk of liver injury. Similarly, a meta-analysis of 29 randomized trials comparing NOACs with standard anticoagulation therapy or placebo showed no increase in hepatic events with NOACs (66). Recently, a Canadian administrative database-linked cohort study examined the hepatic safety of OACs in 51,887 patients with AF (including 3,778 patients with comorbid liver disease) who were followed for 68,739 person-years (67). This study found no significant difference in the rates of serious liver injury with NOACs compared with warfarin in patients with or without liver disease. Although these results provide some reassurance about the hepatic safety of NOACs, the evaluation of hepatic safety of NOACs in patients with prevalent liver disease has not been performed in an adequately powered study.

GASTROPROTECTION IN PATIENTS WITH LIVER DISEASE WHO ARE TAKING OACs

Most bleeding in patients with liver disease is gastrointestinal in origin and may be attributed to varices, portal hypertensive gastropathy, peptic ulcer disease, and arteriovenous malformations. Bleeding is more frequent in patients with severe hepatic impairment (Child-Pugh C) compared with mild or moderate hepatic impairment (Child-Pugh A or B). Certain measures for gastroprotection in OAC-treated patients should be emphasized in the context of liver disease (68,69). According to American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association expert consensus recommendations on reducing upper gastrointestinal bleeding risks

CENTRAL ILLUSTRATION **Initiation of Oral Anticoagulation in Patients With Liver Disease**



Qamar, A. et al. J Am Coll Cardiol. 2018;71(19):2162–75.

*Measure baseline liver function tests, renal function, complete blood count, prothrombin time/INR, activated partial thromboplastin time, and screen for high-risk varices in cirrhosis. †Initiate proton-pump inhibitor therapy (especially if peptic ulcer disease), test for and eradicate *Helicobacter pylori* (as appropriate), provide alcohol cessation counseling, and minimize concomitant nonsteroidal anti-inflammatory drugs and antiplatelet use. ‡Recent major bleeding, active coagulopathy, severe thrombocytopenia, high-risk varices not amenable to intervention. §Except rivaroxaban. INR = international normalized ratio; NOAC = non-vitamin K-antagonist oral anticoagulants.

related to antithrombotic therapy, proton-pump inhibitors should be considered in patients with gastropathy or peptic ulcer disease who have an indication for antithrombotic therapy (70). Patients should be counseled regarding the specific hazards of concomitant alcohol intake or nonsteroidal anti-inflammatory drug use. Combination OAC use with 1 or more antiplatelet therapies should be limited in this high-risk group to the minimally indicated duration. Screening for *Helicobacter pylori* infection should be undertaken, and treatment should be administered as appropriate. Early collaboration with gastroenterologists may help guide screening and potential intervention of high-risk lesions (e.g., large esophageal varices) (71).

MANAGEMENT OF BLEEDING IN PATIENTS WITH LIVER DISEASE WHO ARE TAKING OACs

The optimal management of a patient with liver disease who has active bleeding while taking OACs depends on the severity of bleeding, the indication for anticoagulation therapy, and the underlying thrombotic risk (**Figure 3**); the approach should be similar to that used in patients without liver disease (72,73). The 2017 American College of Cardiology expert consensus decision pathway aims to assist clinicians in the management of bleeding complications in patients taking OACs (73). According to their recommendations, in patients with ongoing severe or life-threatening bleeding despite standard measures,

reversal of anticoagulation may be lifesaving. The anticoagulant effect of warfarin can be easily measured with the INR. For patients with life-threatening bleeding and an INR >2, an unactivated 4-factor prothrombin complex concentrate (PCC) and intravenous vitamin K should be administered. PCC is preferred over fresh frozen plasma because of the similar efficacy and lower incidence of adverse events with PCC (74). Subsequent INR values and the patient's clinical status should determine further requirements for PCC or vitamin K.

In patients taking NOACs, specific coagulation assays may help in measuring the extent of anticoagulation. Thrombin time and ecarin clotting time can measure the effect of dabigatran, whereas a calibrated anti-factor Xa chromogenic assay can quantify the effect of apixaban, rivaroxaban, and edoxaban. However, these tests are not widely available and are not routinely recommended before administering reversal agents. Idarucizumab, a humanized anti-dabigatran monoclonal antibody, is recommended when reversal of the anticoagulant effects of dabigatran is needed for life-threatening or uncontrolled bleeding (75). Currently, there is no specific commercially available antidote for the direct factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban). Until these antidotes become available, in patients with severe or life-threating bleeding that does not respond to conventional measures, a 4-factor PCC should be administered to reverse the anticoagulant effect of a factor Xa inhibitor (76). Activated charcoal should be administered if the anticoagulant was ingested within 2 h (77). Andexanet alfa (a factor Xa decoy) and ciraparantag (a nonspecific small molecule that reverses both factor IIa and Xa inhibitors) are currently being investigated as antidotes to NOACs (78,79).

Other specific management aspects may be relevant to limiting bleeding in patients with liver disease. Platelet transfusion may be considered in selected actively bleeding patients with severe thrombocytopenia (80). Early administration of intravenous proton-pump inhibitors, octreotide (a somatostatin analogue that reduces portal venous pressure), and antibiotics (as prophylaxis against spontaneous bacterial peritonitis) should be considered as appropriate. Early consideration for endoscopic management of actively bleeding varices should be undertaken. In patients with liver disease complicated by hepatorenal syndrome leading to uremia, desmopressin (an endothelial stimulant that increases factor VIII and von Willebrand factor) can be used to improve platelet function.

PRACTICAL APPROACH TO THE PRESCRIPTION OF OACs IN LIVER DISEASE

Given the lack of guideline recommendations or robust evidence from randomized trials, clinicians should follow current regulatory recommendations related to the use of OACs in patients with liver disease (**Central Illustration**). Potential OAC candidates for use in AF should be selected on the basis of traditional risk stratification tools, such as the CHA_2DS_2-VASc score (12,36). In all patients with or at risk of liver disease, liver function tests, platelet count, and coagulation profile should be measured before initiating OACs, and values should be serially monitored during treatment. Anticoagulation therapy should be avoided in the presence of severe thrombocytopenia (platelet counts of <50,000 to <70,000/μl), depending on the thrombotic risk of the patient (35,81). According to guidance by the American Association for the Study of Liver Diseases, all at-risk patients should be screened for varices and high-risk lesions before starting OACs (71). All patients with liver disease should be screened for alcohol use disorders, and cessation counseling should be instituted before starting OAC. Patients should be informed of the anticipated risks and benefits of OACs and should participate in shared decision making regarding the use and selection of a specific agent. Anticoagulation therapy decisions should be individualized in patients who have had a recent major bleeding complication, who have active coagulopathy, or who face clinically relevant bleeding risks (including high-risk variceal disease without the potential for intervention). Although warfarin has traditionally been used in most patients with liver disease who require OACs, NOACs (without dose adjustment) could be considered as safe alternatives in selected patients with mild hepatic impairment (Child-Pugh A). Warfarin is the only recommended OAC in patients with severe hepatic impairment (Child-Pugh C). In patients with moderate hepatic impairment (Child-Pugh B), apixaban, dabigatran, or edoxaban may be considered with caution when warfarin is not considered appropriate. Early collaboration among cardiologists, gastroenterologists or hepatologists, and hematologists may help optimize use of OACs in patients with liver disease, who simultaneously face high risks of bleeding and thrombosis.

CONCLUSIONS AND FUTURE DIRECTIONS

Patients with liver disease represent a challenging subgroup of patients requiring OACs as a result of

their increased thrombotic and bleeding risks. The old notion that patients with liver disease are "auto-anticoagulated" and protected from thrombotic events has not been substantiated by clinical data. The increasing prevalence of chronic cardiometabolic diseases such as obesity, diabetes mellitus, metabolic syndrome, and chronic alcoholism is expected to increase the burden of chronic liver disease further, particularly NAFLD, worldwide. AF and VTE, including PVT, are major causes of morbidity in patients with liver disease. Therefore, an optimal anticoagulation strategy in patients with liver disease with either warfarin or NOACs needs to be better defined. Data informing the safety and efficacy of OAC in patients with liver disease have been largely derived from pharmacokinetic studies in subjects with mild or moderate hepatic impairment (Child-Pugh A or B) or from observational studies that are limited by small sample sizes and residual confounding. Furthermore, current clinical guidelines do not offer specific recommendations for the use of OACs in this population.

An expert consensus panel with cross-specialty collaboration among cardiology, gastroenterology/hepatology, and hematology should be convened to guide clinicians prescribing OACs to patients with liver disease. Prospective and preferably randomized trials are needed to investigate the safety and efficacy of OACs in patients with liver disease across a diverse spectrum of thrombotic risk (AF, VTE, or PVT). The CIRROXABAN (Multicenter Prospective Randomized Trial of the Effect of Rivaroxaban on Survival and Development of Complications of Portal Hypertension in Patients With Cirrhosis; NCT02643212) trial is an ongoing placebo-controlled randomized trial with a target enrollment of 160 patients that is evaluating the role of rivaroxaban in preventing thrombotic complications in patients with liver disease and portal hypertension. Novel approaches using clinical characteristics and biomarkers should be developed to better stratify bleeding and thrombotic risk in patients with liver disease who require OACs. Given the rising prevalence of chronic liver disease and the associated challenging balance between bleeding and thrombosis, there is an unmet need to develop an evidence-based and practical approach to guide management of anticoagulation therapy in these high-risk patients.

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