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ISTH GUIDANCE AND GUIDELINES

Anticoagulation for stroke prevention in atrial fibrillation and treatment of venous thromboembolism and portal vein thrombosis in cirrhosis: guidance from the SSC of the ISTH

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Abstract

While advanced liver disease was previously considered to be an acquired bleeding disorder, there is increasing recognition of an associated prothrombotic state with patients being at higher risk of atrial fibrillation (AF) and stroke and venous thromboembolism (VTE) including portal vein thrombosis (PVT). We review the available literature on epidemiology, pathophysiology, and risk factors and provide guidance on anticoagulant management of these conditions in adults with cirrhosis. In patients with

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Child–Pugh A or B cirrhosis and AF, we recommend anticoagulation with standard-dose direct oral anticoagulants (DOACs) in accordance with cardiology guideline recommendations for patients without liver disease. In those with Child–Pugh C cirrhosis, there is inadequate evidence with respect to the benefit and risk of anticoagulation for stroke prevention in AF. In patients with cirrhosis and acute deep vein thrombosis or pulmonary embolism, we recommend anticoagulation and suggest use of either a DOAC or low-molecular-weight heparin (LMWH)/vitamin K antagonist (VKA) in Child-Pugh A or B cirrhosis and LMWH alone (or as a bridge to VKA in patients with a normal baseline international normalized ratio) in Child-Pugh C cirrhosis. We recommend anticoagulation for patients with cirrhosis and symptomatic PVT. We suggest anticoagulation for those with asymptomatic, progressing PVT and recommend continuing extended anticoagulation for liver transplant candidates with PVT.

KEYWORDS
anticoagulation, atrial fibrillation, liver cirrhosis, portal vein, venous thrombosis

1 | INTRODUCTION

Patients with advanced liver disease are at an increased risk of bleeding and were historically considered to be "auto-anticoagulated" on the basis of abnormal coagulation tests. More recent data support the presence of a "rebalanced," yet fragile, hemostatic system that simultaneously increases the risks of bleeding and thrombosis due to changes in primary and secondary hemostasis and the fibrinolytic system [1]. Laboratory data have demonstrated progressive changes in many of these parameters with advancing Child–Pugh scores [2].

With respect to primary hemostasis, thrombocytopenia is common in patients with cirrhosis with 80% of patients having platelet counts below the lower limit of normal [3]. Severe thrombocytopenia ($<50 \times 10^9$/L) is uncommon in ambulatory patients with compensated disease but increases in those with decompensated disease and is frequently encountered in hospitalized patients with critical illness [4,5]. Platelet counts of $<30 \times 10^9$/L remain infrequent even in those with advanced disease. Mechanisms for thrombocytopenia in cirrhosis include reduced production secondary to bone marrow suppression from underlying disease (eg, alcohol or viral hepatitis), reduced thrombopoietin production and/or activity, increased destruction (autoantibodies against platelet surface antigens), and possible sequestration in the spleen [3]. Evidence is conflicting with respect to the impact of liver disease on platelet function with some studies showing decreased and others demonstrating increased platelet function. However, there are significant data to suggest that thrombocytopenia is not a predictor of procedural bleeding risk in patients with liver disease [6]. This may be a result of mechanisms counteracting thrombocytopenia including increased levels of von Willebrand factor (VWF) and decreased ADAMTS-13 levels [7].

Secondary hemostasis in liver disease is altered secondary to reduced coagulation factor (F)II, FV, FVII, FIX, FX, and FXI and hypofibrinogenemia but is counteracted by increased FVIII and VWF levels and decreased production of natural anticoagulants including protein C, protein S, and antithrombin.

Global hemostatic assays have demonstrated an enhanced thrombin-generating capacity in cirrhosis [8], and there is evidence of enhanced thrombin generation *in vivo* [9]. Fibrinolysis is increased by reduced alpha2-antiplasmin, FXIII, and thrombin activatable fibrinolysis inhibitor and elevated tissue plasminogen activator levels. Conversely, fibrinolysis is reduced by reduced plasminogen and increased plasminogen activator inhibitor-1 levels [1]. Global fibrinolytic tests indicate preserved fibrinolytic potential in compensated patients, but both hypofibrinolysis and hyperfibrinolysis in more advanced disease [10].

In addition to changes in hemostatic mechanisms, the treatment of thrombosis in advanced liver disease may be further complicated by altered anticoagulant pharmacodynamic and pharmacokinetic effects including reductions in coagulation factors, antithrombin levels, protein binding, metabolism, and excretion. These factors in combination with the limited, primarily observational data in this field present a challenge to the clinician in determining if, when, and how to anticoagulate the patient with advanced liver disease. As patients with advanced liver disease may experience thrombosis at higher rates than those without advanced liver disease, these questions arise at relatively high frequency in clinical practice. This document summarizes the limited available evidence and provides guidance recommendations for anticoagulation for stroke prevention in atrial fibrillation (AF) and venous thromboembolism (VTE) including portal vein thrombosis (PVT) in patients with cirrhosis.

2 | METHODS

Guidance statements were written after review of the published literature. An initial search was conducted in PubMed using

combinations of "liver cirrhosis," "liver diseases," "atrial fibrillation," "portal veins," "venous thrombosis," "risk factors," "incidence," "anticoagulation," "coumarins," and "direct acting oral anticoagulants." Reference lists of publications identified in the search were reviewed and articles retrieved where relevant. Randomized controlled trials or observational studies that addressed the epidemiology, pathophysiology, risk factors, and treatment of thrombosis in adults with liver disease were included. Heterogeneity in severity of liver disease of the patients included in many studies (particularly in AF) did not allow search to be restricted specifically to cirrhosis. For clarity, throughout the guidance document, we use the terms presented in each respective primary study (eg, liver disease, advanced liver disease, and cirrhosis). Due to limited clinical data on direct oral anticoagulants (DOACs), pharmacokinetic studies of DOACs in patients with liver disease with *in vivo* data were also reviewed. Case reports were excluded. Consensus was achieved by serial revision of proposed statements in response to co-author feedback. "We recommend" is used when consensus between authors was achieved in combination with evidence from multiple higher quality clinical studies with greater certainty of evidence; it indicates a strong guidance statement, where clinicians should generally implement the guidance recommendation. "We suggest" is based on author consensus but with a lack of higher quality clinical studies with lower certainty of evidence; it indicates a weak guidance statement, whereby strong evidence to support the statement is lacking; and the clinician may implement the guidance recommendation in some situations, but an alternative practice may also be appropriate.

3 | ANTICOAGULATION IN PATIENTS WITH ADVANCED LIVER DISEASE

Low-molecular-weight heparins (LMWHs), vitamin K antagonists (VKAs), and DOACs are the most commonly used anticoagulants, including in patients with liver disease. Their use and considerations in patients with advanced liver disease are summarized below.

3.1 | LMWHs

These agents were the traditional anticoagulants of choice in the treatment of thrombosis in patients with advanced liver disease. However, they act by potentiating the effect of antithrombin, a glycoprotein often reduced in patients with advanced liver disease, possibly resulting in an altered anticoagulant effect in this population [11]. Further, volume overload and hepatorenal syndrome associated with advanced liver disease may affect drug absorption, distribution, and clearance [12–14]. Additionally, LMWHs are expensive in many jurisdictions and many patients find them to be inconvenient for long-term use. The optimal dosing and monitoring of LMWH in patients with advanced liver disease require further investigation for situations in which they are still required.

3.2 | VKAs

For many years, VKAs were the only oral anticoagulant treatment option. As such, there is significant clinical experience with their use, including in patients with advanced liver disease. However, their use is challenging in this population who may have altered medication absorption, distribution, and hepatic metabolism as well as lower baseline factor levels and elevated international normalized ratios (INRs); as such, the optimal INR therapeutic range in these patients is unknown [15]. Moreover, patients with chronic liver disease may have lower time in therapeutic range, which may result in reduced efficacy and safety [16].

3.3 | DOACs

DOACs are now the preferred anticoagulants for stroke prevention in AF and for the prevention and treatment of thrombosis in most patient populations [17–19]. Their similar or improved efficacy and safety profiles as compared with LMWHs or VKAs, fixed dosing, lesser drug-drug and drug-food interactions as compared to VKAs, and ease of administration make these agents particularly desirable. However, DOACs are subject to variable degrees of non-renal elimination (apixaban, 75%; rivaroxaban, 65%; edoxaban, 50%; and dabigatran, 20%) [20], and as such, patients with advanced liver disease may experience altered pharmacokinetic and clinical effects secondary to reductions in coagulation factors, plasma protein binding, metabolism and renal excretion in hepatorenal syndrome. The available *in vivo* pharmacokinetic data in cirrhosis for each DOAC are summarized below and the available clinical data are subsequently discussed in the respective AF, VTE, and PVT sections.

3.4 | Dabigatran

In a study of 24 patients (12 healthy volunteers and 12 patients with Child–Pugh B cirrhosis) who were administered a single dose of dabigatran 150 mg, the mean concentration–time curve, terminal half-life, activated partial thromboplastin time, ecarin clotting time, and thrombin time did not differ between groups. However, there was a greater increase in INR in patients with cirrhosis [21].

3.5 | Rivaroxaban

A study of 32 patients (8 each Child–Pugh A and B cirrhosis and 16 controls) who were administered a single dose of rivaroxaban 10 mg found that moderate, but not mild hepatic impairment increased rivaroxaban exposure and prothrombin time compared to controls [22].

3.6 | Apixaban

A study including 32 patients (8 each with Child–Pugh A and B cirrhosis and 16 controls) who were administered a single dose of

apixaban 5 mg found similar apixaban maximal concentration and area under the concentration–time curve values in all patients [23]. In a study of 12 patients with cirrhosis, those with Child–Pugh B or C disease had numerically higher anti-Xa levels (median peak, 297 vs 138 ng/mL; P = .073) [24].

3.7 | Edoxaban

A study of 32 patients (8 each with Child–Pugh A and B cirrhosis and 16 controls) who were administered a single dose of edoxaban 15 mg found similar exposure to edoxaban and its primary active metabolite, M4, in all patients [25]. In a more recent study with repeated dosing, 32 patients (15 with Child–Pugh A cirrhosis, 1 with Child–Pugh B cirrhosis, and 16 controls) were administered edoxaban 60 mg daily for 7 days. Despite similar edoxaban-calibrated anti-Xa levels, edoxaban resulted in lesser reductions in endogenous thrombin potential and D-dimer levels in patients than in controls [26]. In a study of 23 patients with cirrhosis, those with Child–Pugh B or C cirrhosis compared with those with Child–Pugh A cirrhosis had higher anti-Xa levels (median peak, 226 vs 137 ng/mL [P = .301] in patients receiving any dose and 345 vs 137 ng/mL [P = .048] in patients receiving on-label dosing) and lower thrombin generation [24].

3.8 | Anticoagulant reversal

Patients with advanced liver disease receiving anticoagulants who experience major bleeding or who require reversal prior to urgent surgery to ensure adequate hemostasis for the procedure may receive reversal and/or hemostatic agents (idarucizumab, andexanet alfa, vitamin K, and/or prothrombin complex concentrate) in accordance with the evidence and guideline recommendations in patients without liver disease [27–30]. Specific recommendations regarding additional hemostatic therapies in patients with liver disease and major bleeding are outside the scope of this guidance document and hematology consultation is advised for patient-specific suggestions in these complex scenarios. Specific recommendations for periprocedural patients with cirrhosis with abnormal coagulation parameters and thrombocytopenia are summarized in detail in a separate ISTH guidance document [31].

3.9 | Hepatotoxicity of DOACs

Ximelagatran, the first oral direct thrombin inhibitor, was withdrawn from the market in 2006 secondary to hepatotoxicity. Postmarketing surveillance of the subsequently approved DOACs has revealed rare cases of liver injury. In a French database study of AF patients comparing DOAC with VKA use, DOAC use was not associated with an increased risk of serious acute liver injury (ALI) including hospitalization for ALI or liver transplantation. However, dabigatran use in patients with chronic alcoholism was associated with an increased risk of serious ALI (hazard ratio [HR], 2.86; 95% CI, 1.73-4.75), although its use was associated with a protective effect with respect to the ancillary outcome of increased liver enzymes (HR, 0.54; 95% CI, 0.38-0.75) [32].

4 | AF IN PATIENTS WITH LIVER DISEASE

4.1 | Epidemiology

In a large meta-analysis of 385 866 patients with cirrhosis, the overall prevalence of AF was 5.0% (95% CI, 2.8%-8.6%) [33]. The prevalence of AF is higher with greater liver disease severity as measured with the model for end-stage liver disease (MELD) score; the AF prevalence is 3.7% in patients with MELD scores of 10 or less as compared with 20.2% in patients with scores over 30 [34]. Importantly, in patients with AF, cirrhosis is not protective against ischemic stroke. In fact, the risk of ischemic and hemorrhagic stroke in AF in patients with CHA_2DS_2VASc scores of 2 or higher not receiving antithrombotic medications may be higher in those with cirrhosis as compared to those without cirrhosis (HR, 1.10; 95% CI, 1.00-1.20; and HR, 1.20; 95% CI, 1.01-1.42, respectively) [35]. Further, AF in patients with cirrhosis is associated with increased mortality (odds ratio [OR], 1.44; 95% CI, 1.36-1.53) [33].

4.2 | Pathophysiology

A complex interplay of shared risk factors, complications, and treatments for cirrhosis may contribute to the increased risk of AF in patients with liver disease. Steatotic liver disease, the current leading cause of cirrhosis, is associated with risk factors independently associated with AF including hypertension, heart failure, obesity, and obstructive sleep apnea [36,37]. Alcohol can further contribute to AF secondary to electrical, autonomic, and structural atrial remodeling [38]. Another less common etiology of cirrhosis, alpha-1 antitrypsin deficiency, can also cause severe emphysema, increasing the risk of AF secondary to pulmonary hypertension and atrial remodeling [39]. Additionally, chronic iron overload associated with hemochromatosis may lead to cardiomyopathy, altered electrical conduction, and AF [40].

Complications of advanced liver disease including cirrhotic cardiomyopathy, portal hypertension, portosystemic collaterals, and imbalanced vascular tone lead to renin–angiotensin–aldosterone system (RAAS) activation. The resultant expansion of plasma volume and increased left atrial volume are associated with AF [41,42]. Intestinal congestion with gut bacterial translocation, hepatorenal syndrome, and autonomic dysfunction with increased sympathetic tone all contribute to a chronic systemic proinflammatory state, leading to increased risk of cardiac cell fibrosis and apoptosis [41]. Similarly, endotoxins and increased bile acids contribute to cardiac ion channel remodeling, increasing the risk of arrhythmias [43]. Hepatorenal syndrome, diuretics and mineralocorticoid receptor antagonists for

ascites, lactulose for hepatic encephalopathy, and trimethoprim–sulfamethoxazole for the prevention and treatment of spontaneous bacterial peritonitis may also lead to electrolyte imbalances and increased risk of AF [44].

4.3 | Anticoagulation

Anticoagulation for AF in patients with liver disease with VKAs or DOACs appears to reduce the risk of stroke and mortality in patients with Child–Pugh A, B and C cirrhosis in cohort studies (data for Child–Pugh C cirrhosis published in abstract form only). The available literature does not suggest an increased risk of bleeding with anticoagulation in these patients; however, this finding is inconsistent with that of other populations and data are limited to observational studies at significant risk of selection bias and confounding as summarized in Table 1 [45–48].

4.3.1 | DOACs vs VKA

All pivotal phase III stroke prevention in AF trials comparing DOACs with warfarin excluded patients with active liver disease. A post-hoc analysis of ENGAGE AF-TIMI 48 compared edoxaban with warfarin in 1083 patients with a history of mild liver disease or liver enzymes greater than or equal to 2 times the upper limit of normal with preserved liver function. In this trial, edoxaban 60 mg daily (or 30 mg daily in patients with reduced renal function, weight, or concomitant use of potent P-glycoprotein inhibitors) had similar treatment effects to warfarin with respect to prevention of ischemic and hemorrhagic stroke in patients with a history of liver disease as compared with those without (P interaction = 0.28 and 0.94, respectively) [49].

Additional data for the efficacy and safety of DOACs compared with VKAs in liver disease is primarily derived from observational studies including primarily patients with less advanced disease without cirrhosis [50–53]. The studies are at significant risk of selection bias and confounding including frequent use of reduced DOAC dosing. Additional data include a small randomized controlled trial including 56 patients with AF and Child–Pugh A or B cirrhosis, which compared dabigatran 110 mg twice daily with warfarin. No thrombotic events were reported in either group. Dabigatran was found to have lower rates of bleeding than warfarin (17% vs 46%; P = .038) [54]. Notably, the study used a reduced dose of dabigatran, baseline creatinine level of patients in the warfarin group was higher than that of those in the dabigatran group (P = .02), and time in therapeutic range in the warfarin group was not reported. These factors may have biased the bleeding results in favor of dabigatran. Taken together, however, the available data suggest that DOACs may be at least as effective as warfarin for stroke prevention in AF in liver disease and may be associated with a lower risk of major bleeding, gastrointestinal bleeding, and intracranial hemorrhage (ICH) (Table 2) [48–54].

Clinical data for DOAC use in patients with higher Child–Pugh scores are extremely limited. An abstract presented at a recent American Association for the Study of Liver Diseases meeting reported the results of a cohort study from an international registry comparing DOAC with warfarin use in 8477 patients with AF and Child–Pugh C cirrhosis [48]. The authors reported no difference in ischemic stroke or mortality between groups, but found lower rates of gastrointestinal bleeding and ICH with DOAC than with warfarin use (2.0% vs 2.4%; P = .0001; 6.6% vs 8.7%; P = .004, respectively). Possible confounders including differences in comorbidities and MELD scores between groups and DOAC dosing were not reported. Importantly, this work remains unpublished and has not yet been subjected to peer review.

4.3.2 | Rivaroxaban vs apixaban

Two cohort studies discussed above also compared outcomes in patients receiving rivaroxaban with those receiving apixaban. No difference was found between agents with respect to ischemic stroke, transient ischemic attack, or systemic embolism but rivaroxaban increased major bleeding and major gastrointestinal bleeding compared with apixaban, although bleeding rates were similar in the subgroup of patients with cirrhosis [52,53].

4.3.3 | Prescribing trends

The use of oral anticoagulation for stroke prevention in AF in patients with cirrhosis is increasing. In a cohort study that included 32 487 American patients from 2012 to 2019, the proportion of oral anticoagulant users increased from 39% to 49%; among anticoagulant users, there was a marked increase in DOAC use from 20% to 77% over this same period. Increasing trends in DOAC use over time among anticoagulant users were observed in patients with decompensated cirrhosis (increased from 12% in 2012 to 76% in 2019) as well as in those with compensated cirrhosis (increased from 25% in 2012 to 79% in 2019). The most frequently prescribed DOAC was apixaban, which constituted 68% of DOAC use in this population in 2019 [55]. Persistence to anticoagulation in AF patients with cirrhosis is low, but higher in DOAC than in VKA users (31% and 9%, respectively, at 5 years in a UK cohort study) [56].

4.3.4 | Guideline recommendations

The 2021 European Heart Rhythm Association Practical Guide on the Use of Non-VKA Oral Anticoagulants in Patients with AF and the 2023 American College of Cardiology/American Heart Association/American College of Chest Physicians/Heart Rhythm Society Guidelines for the Diagnosis and Management of AF state that all DOACs can be safely used in Child–Pugh A cirrhosis; that dabigatran, apixaban, and edoxaban can be used with caution in patients with Child–Pugh B cirrhosis; and that all DOACs should be avoided in Child–Pugh C cirrhosis [17,20]. The 2021 American Gastroenterological

TABLE 1 Anticoagulation compared with no anticoagulation for stroke prevention in AF in liver disease.

Study	Design	Population	Child–Pugh or MELD score	Effectiveness	Safety
Chokesuwattanaskul et al., 2019 [45]	Meta-analysis of 7 retrospective cohort studies; mean, 3.1-11-y follow-up	*N* = 17 798 with AF and cirrhosis from 4 countries (United States, Italy, South Korea, and Taiwan)	Not reported	Stroke: HR, 0.58; 95% CI, 0.35-0.96	Bleeding: HR, 1.45; 95% CI, 0.96-2.17
Serper et al., 2020 [46]	Multicenter retrospective cohort study; median, 4.6-y follow-up	*N* = 2694 with AF and cirrhosis from 128 United States veterans' centers	Child–Pugh A: 77%; Child–Pugh B: 22%; Child–Pugh C: 1%	IS: warfarin: HR, 0.29; 95% CI, 0.09-0.90 DOACs: HR, 0.23; 95% CI, 0.07-0.79 Death: warfarin: HR, 0.54; 95% CI, 0.40-0.73 DOACs: HR, 0.50; 95% CI, 0.31-0.81	Bleeding[a]: warfarin: HR, 1.29; 95% CI, 0.74-2.26 DOACs: HR, 0.37; 95% CI, 0.13-1.07
Steensig et al., 2022 [47]	Nationwide register-based cohort study; maximum 5-y follow-up	*N* = 1238 with AF (CHA_2DS_2-VASc-score ≥1 in men and ≥2 in women) and liver disease from Denmark	Median MELD: 9	Composite TE (IS, TIA, or VTE): - Patients with a CHA_2DS_2-aVASc-score of >2 in men and of >3 for women: RR, 0.66; 95% CI, 0.45-0.87; *P* = .001 - Men or women with scores of 1-2 or 2-3, respectively: RR, 1.19; 95% CI, 0.22-2.16	Composite bleeding risk[b] (RR, 1.08; 95% CI, 0.58-1.58; and RR, 0.88; 95% CI, 0.47-1.29) Patients with cirrhosis (median MELD score, 11) vs noncirrhotic liver disease (RR, 0.72; 95% CI, 0.28-1.15)
Ayoub et al., 2023 [48]	Cohort study from international database	*N* = 16 029 with AF and cirrhosis	Child–Pugh C: 100%	IS: 0.9% vs 0.5%; *P* = 0.03 3-y mortality: 47.4% vs 71.2%; *P* = .00001	GIB: 18.8% vs 19.5%; *P* = .3 ICH: 3% vs 2.7%; *P* = .19

AF, atrial fibrillation; GIB, gastrointestinal bleeding; HR, hazard ratio; ICH, intracranial hemorrhage; IS, ischemic stroke; MELD, model for end-stage liver disease; TE, thromboembolism; TIA, transient ischemic attack; RR, risk ratio; VTE, venous thromboembolism.

[a] (1) ≥2 g/dL hemoglobin drop on 2 consecutive laboratory tests within a 90-day period; (2) any International Classification of Diseases-9-Clinical Modification/International Classification of Diseases-10-Clinical Modification codes for intracranial bleeding, including hemorrhagic stroke; (3) admission requiring any packed red blood cell transfusion; or (4) primary discharge diagnosis codes of gastrointestinal bleeding, hemarthrosis, or other bleeding.

[b] Composite of gastrointestinal, intracerebral, or urogenital bleeding requiring hospitalization or epistaxis requiring emergency department visit or hospital admission.

TABLE 2 Direct oral anticoagulants compared with warfarin for stroke prevention in AF in liver disease.

Study	Design	Population	Child–Pugh or MELD score	Efficacy	Bleeding
Qamar, 2019 [49]	Post-hoc analysis of multicenter, international ENGAGE AF-TIMI 48 RCT	*N* = 1083 with AF and a history of prior liver disease or liver enzymes >2 ULN	Child–Pugh A	Edoxaban 60 mg ↔ vs warfarin IS: HR, 1.00; 95% CI, 0.83-1.19; *P* interaction between those with prior liver disease and those without = 0.28	Edoxaban 60 mg ↓ vs warfarin: hemorrhagic stroke: HR, 0.54; 95% CI, 0.38-0.77; *P* interaction between those with prior liver disease and those without = 0.94
Lee, 2019 [50]	Retrospective cohort study	Subgroup of *N* = 4942 with AF and significant active liver disease	Not reported	DOACs ↓ vs warfarin IS: HR, 0.45; 95% CI, 0.31-0.64	DOACs ↓ vs warfarin Hospitalization for MB: HR, 0.62; 95% CI, 0.44-0.87 ICH: HR, 0.42; 95% CI, 0.24-0.72 NB: 51% of patients on DOACs used reduced dosing
		Subgroup of *N* = 768 with AF and cirrhosis	Not reported	DOACs ↔ vs warfarin IS: HR, 0.62; 95% CI, 0.25-1.46	DOACs ↔ vs warfarin Hospitalization for MB: HR, 0.79; 95% CI, 0.35-1.75 ICH: HR, 0.48; 95% CI, 0.15-1.40 NB: 58% of patients on DOACs used reduced dosing
Menichelli, 2020 [51]	Meta-analysis of 7 studies (5 retrospective cohort studies, 1 prospective cohort study and 1 RCT)	*N* = 40 809 with AF and advanced liver disease	Not reported	DOACs ↔ vs warfarin IS: HR, 0.89; 95% CI, 0.62-1.27 DOACs ↓ vs warfarin All-cause death: HR, 0.77; 95% CI, 0.61-0.96	DOACs ↓ vs warfarin MB: HR, 0.63; 95% CI, 0.43-0.93 ICH: HR, 0.49; 95% CI, 0.40-0.59
Lawal, 2023 [52]	Retrospective cohort study	*N* = 10 029 with AF and chronic liver disease	Not reported	DOACs ↓ vs warfarin IS/SE: HR, 0.64; 95% CI, 0.46-0.90 NB: 80% of patients using standard DOAC dosing	DOACs ↓ vs warfarin MB: HR, 0.69; 95% CI, 0.58-0.82
		Subgroup of *N* = 2940 with AF and cirrhosis		DOACs ↔ vs warfarin IS/SE: HR, 0.90; 95% CI, 0.51-1.57 DOACs ↓ vs warfarin All-cause death: HR, 0.75; 95% CI, 0.62-0.91	DOACs ↓ vs warfarin MB: HR, 0.70; 95% CI, 0.53-0.93
Douros, 2024 [53]	Retrospective cohort study	*N* = 11 881 with AF and acute, chronic and/or severe liver disease	Not reported	DOACs ↔ vs warfarin IS/TIA: HR, 1.01; 95% CI, 0.76-1.34 All-cause death: HR, 0.90; 95% CI, 0.81-1.01	DOACs ↓ vs warfarin MB: HR, 0.87; 95% CI, 0.77-0.99 ICH: HR, 0.49; 95% CI, 0.28-0.88
		Subgroup of *N* = 2683 with AF and cirrhosis		DOACs ↔ vs warfarin IS/TIA: HR, 1.20; 95% CI, 0.69-2.08 All-cause death: HR, 0.85; 95% CI, 0.69-1.05	DOACs ↔ vs warfarin MB: HR, 0.84; 95% CI, 0.67-1.07

(Continues)

TABLE 2 (Continued)

Study	Design	Population	Child–Pugh or MELD score	Efficacy	Bleeding
Baylo, 2023 [54]	RCT: dabigatran 110 mg bid vs warfarin	*N* = 56 with AF and cirrhosis	Child–Pugh A: 43%, Child–Pugh B: 57%	IS/SE: no events in either group	Dabigatran ↔ vs warfarin MB: 0% vs 4%; *P* = .944 Dabigatran ↓ vs warfarin All bleeding: 17% vs 46%; *P* = .038
Ayoub, 2023 [48]	Retrospective cohort study	*N* = 8477 with AF and cirrhosis	Child–Pugh C: 100%	DOACs ↔ vs warfarin IS/SE: 1.2% vs 1.4%; *P* = 0.63 3-y mortality: 42% vs 44%; *P* = .2	DOACs ↓ vs warfarin GIB: 2 vs 2.4%; *P* = .0001 ICH: 6.7% vs 8.7%; *P* = .004

↑, increased; ↓, reduced; ↔ equivalent; AF, atrial fibrillation; DOAC, direct oral anticoagulant; GIB, gastrointestinal bleeding; HR, hazard ratio; ICH, intracranial hemorrhage; IS, ischemic stroke; MB, major bleeding; RCT, randomized controlled trial; SE, systemic embolism; ULN, upper limit of normal.

Association Clinical Practice Guideline on the Management of Coagulation Disorders in Patients with Cirrhosis suggest anticoagulation for stroke prevention in AF in compensated cirrhosis in patients with higher CHA_2DS_2VASc scores and state that patients with Child–Pugh C cirrhosis and/or low CHA_2DS_2VASc scores could reasonably choose no anticoagulation [57].

4.4 | Left atrial appendage occlusion

Two randomized controlled trials, PROTECT-AF and PREVAIL, found that percutaneous implantation of a WATCHMAN device for left atrial appendage occlusion (LAAO) for stroke prevention in AF was superior or non-inferior to warfarin, respectively [58,59]. Patients with liver disease were not explicitly excluded from these trials; however, it is unclear how well this population was represented as this information was not reported.

In a retrospective cohort study of 54 897 hospitalizations for LAAO including 905 patients with cirrhosis, patients with cirrhosis as compared with those without cirrhosis had higher rates of procedural complications but no difference in ischemic stroke, gastrointestinal bleeding, or ICH after adjusted multivariate logistic regression [60]. In another retrospective cohort study of 62 005 patients with AF admitted for LAAO including 1160 patients with cirrhosis, after multivariable logistic regression analysis, cirrhosis was an independent predictor for higher in-hospital mortality (OR, 8.6; 95% CI, 4.1-17.9) and other complications including ICH (OR, 4.3; 95% CI, 1.7-10.7), retroperitoneal hemorrhage (OR, 8.0; 95% CI, 2.7-24.0), transient ischemic attack (OR, 6.9; 95% CI, 2.6-18.1), and VTE (OR, 1.9; 95% CI, 1.75-4.89) [61].

4.5 | Guidance recommendations

1. We recommend that patients with Child–Pugh A or B cirrhosis with AF and CHA_2DS_2VASc score of 2 or greater in males and of 3 or greater in females be anticoagulated for stroke prevention as per current guideline recommendations in patients without cirrhosis unless otherwise contraindicated. There is inadequate evidence with respect to the benefit and risk of anticoagulation in patients with Child–Pugh C cirrhosis.
2. We suggest that patients with Child–Pugh A or B cirrhosis with AF and CHA_2DS_2VASc score of 1 in males and of 2 in females be anticoagulated for stroke prevention as per current guideline recommendations in patients without cirrhosis unless otherwise contraindicated. There is inadequate evidence with respect to the benefit and risk of anticoagulation in patients with Child–Pugh C cirrhosis.
3. We suggest that DOACs at standard doses are used in patients with AF and Child–Pugh A or B cirrhosis in preference to VKAs based on available evidence suggesting greater efficacy and safety with DOACs as compared with VKAs.

4. There is inadequate *in vivo* pharmacokinetic or clinical evidence to recommend for or against specific DOACs for stroke prevention in AF in cirrhosis.
5. We suggest a case-by-case consideration of LAAO in select patients with AF and cirrhosis at high risk of stroke who are not candidates for, or who have failed, anticoagulation and who are expected to have a reasonable life expectancy (ie, patient awaiting transplant).

5 | DEEP VEIN THROMBOSIS/PULMONARY EMBOLISM IN PATIENTS WITH LIVER DISEASE

VTE is classically described as comprising deep vein thrombosis (DVT) and pulmonary embolism (PE). In patients with cirrhosis, VTE most commonly manifests as PVT. In this guidance document, we discuss DVT/PE separately from PVT.

The increased risk of VTE associated with cirrhosis was first described less than 20 years ago in a retrospective case-control study of hospitalized patients with cirrhosis, challenging the previous concept of cirrhosis as an acquired bleeding disorder [62]. While abnormal hemostatic parameters such as prolonged prothrombin time (PT), activated partial thromboplastin time, and thrombocytopenia are common, in the absence of active bleeding, anticoagulation remains the mainstay of DVT/PE treatment. In this section, we review the epidemiology, risk factors, and treatment options for DVT/PE and propose pragmatic management strategies.

5.1 | Epidemiology

Population-based studies from Denmark report a 10-year risk of DVT/PE in patients with cirrhosis of 2.5% (HR, 2.0; 95% CI, 1.5-2.6) as compared with an age- and sex-matched cohort without cirrhosis [63]. This is similar to an earlier analysis reporting an increased risk of unprovoked DVT/PE in patients with cirrhosis (HR, 2.06; 95% CI, 1.79-2.38) [64]. Of note, DVT/PE was associated with increased mortality in those with cirrhosis (17% vs 7%), and patients with chronic liver disease (CLD) were far less commonly treated with anticoagulation (37% vs 77%) [63]. In a meta-analysis of 695 012 patients with cirrhosis across 11 studies, cirrhosis was associated with an increased risk of DVT/PE (OR, 1.7; 95% CI, 1.3-2.2). The analysis further confirmed an elevated risk when specifically considering both DVT (OR, 2.0; 95% CI, 1.8-2.3) and PE (OR, 1.7; 95% CI, 1.0-2.6) [65].

5.2 | Risk factors

Hospitalization increases the risk of DVT/PE and is further discussed in detail in a previous SSC guidance document on VTE prevention [66]. The population studies discussed above report an increased risk of DVT/PE in those with alcohol-related CLD [63] with conflicting data regarding the impact of sex on DVT/PE risk [63,65].

5.3 | Anticoagulation

Anticoagulation is the mainstay of therapy for DVT/PE. There are limited data evaluating the optimal anticoagulant in patients with cirrhosis. While DOACs are now widely accepted as the preferred agent for management of DVT/PE in the general population, patients with liver disease were excluded from pivotal phase III trials confirming their clinical effectiveness and safety [18,67–71]. The randomized controlled trials of apixaban (AMPLIFY) and dabigatran (RECOVER) compared with enoxaparin/warfarin for the treatment of DVT/PE did not specifically exclude patients with cirrhosis, whereas this was a prespecified exclusion in the rivaroxaban (EINSTEIN) and edoxaban (HOKUSAI) DVT/PE trials. The AMPLIFY trial, however, excluded patients with active and clinically significant liver disease such as hepatorenal syndrome, while the RECOVER trial excluded patients with clinically significant liver disease with transaminases more than twice the upper limit of normal. A recent large retrospective cohort study of patients with CLD and DVT/PE utilized American claims data to compare rates of hospitalization for recurrent VTE or major bleeding between propensity matched pairs of DOAC–warfarin (n = 2361), apixaban-warfarin (n = 895), rivaroxaban–warfarin (n = 2161), and apixaban–rivaroxaban (n = 895) treated patients. The risk of the composite outcome was lower for DOAC, apixaban, and rivaroxaban than that for warfarin, but not significantly different between apixaban and rivaroxaban. The risk of hospitalization for major bleeding was lower for DOAC (HR, 0.69; 95% CI, 0.57-0.84), apixaban (HR, 0.43; 95% CI, 0.30-0.63), and rivaroxaban (HR, 0.72; 95% CI, 0.58-0.89) than for warfarin, with no difference seen between apixaban and rivaroxaban. The risk of recurrent VTE was lower for apixaban vs warfarin (HR, 0.47; 95% CI, 0.26-0.86), with no difference reported between other comparisons. Subgroup analyses of those with cirrhosis and decompensated cirrhosis comparing DOAC with warfarin with respect to the primary outcome were limited by the small sample size but were consistent with the primary findings [72].

5.3.1 | Management of anticoagulation in patients with thrombocytopenia

Much of the data and recommendations for VTE management in patients with thrombocytopenia pertain to patients with cancer-associated thrombosis. The consensus in this patient group is to provide full-dose anticoagulation where the platelet count is >40 to 50 × 10^9/L and to consider supporting the platelet count to enable this in the initial 30 days following VTE. Beyond this time period, a reduced dose of anticoagulation may be offered provided the platelet count is >25 × 10^9/L [73]. Dose reductions might also be more suitable for patients in the initial 30 days with a limited thrombus burden; for example, a distal DVT or small volume PE. There is no direct evidence from patients with liver disease to inform recommendations. Thus, an individualized approach is suggested incorporating evaluation of the potential risk of thrombus extension and embolization, bleeding risk factors, and patient preference.

5.4 | Guidance recommendations

1. We recommend that patients with cirrhosis and acute DVT/PE are offered treatment with anticoagulation barring a contraindication such as active bleeding, in keeping with current guideline recommendations for patients without cirrhosis.
2. We suggest the use of either DOAC or LMWH with/without VKA for patients with Child–Pugh A or B cirrhosis based on patient preference.
3. We suggest LMWH alone (or as a bridge to VKA in patients with a normal baseline INR) in patients with Child–Pugh C cirrhosis.
4. We suggest that anticoagulation should not be withheld in patients with moderate thrombocytopenia secondary to advanced liver disease. A case-by-case decision should be made when the platelet count is $<50 \times 10^9$/L, based on site and extent of thrombosis, risk of thrombus extension, patient preference, and presence of active bleeding/additional bleeding risk factors.

6 | PORTAL VEIN THROMBOSIS IN PATIENTS WITH CIRRHOSIS

6.1 | Epidemiology

PVT is uncommon in the general population with an incidence of approximately 1.7 to 3.8 per 100 000 [74]. It is, however, extremely common in patients with CLD, with an annual incidence ranging from 1.6% to 24.4% in prospective observational cohorts [75–77]. PVT is often identified on screening investigations for hepatocellular carcinoma or upon investigation of decompensated liver disease. Severity of liver disease is an important modulator of risk, with the incidence lower in cohorts with predominantly compensated cirrhosis. A population-based study in Germany suggested increased detection of PVT over time, with a 2.3-fold increase in PVT prevalence in patients with cirrhosis over the 14 year study period, with a parallel increase in the use of imaging [78].

6.2 | Pathophysiology

The pathogenesis of PVT is thought to differ from more common venous thrombotic diseases. The portal venous system is very different from other deep venous systems as the portal vein does not drain blood to the heart, but to hepatic sinusoids in the liver, and perhaps more significantly, the portal vein does not have venous valves [79], which are important in the development of DVT [80]. In liver disease, development of fibrosis can lead to portal hypertension resulting in enlargement of the portal vein and formation of portosystemic collateral vessels. The increase in portal vein diameter and "steal effect" from the portocollateral circulation ultimately leads to a reduction of portal blood flow and risk of PVT. It has been proposed that the risk of PVT may also be increased secondary to endothelial dysfunction from portal hypertension and bacterial translocation, which may induce endothelial expression of VWF and FVIII with a consequent hypercoagulable state in the portal vein [81]. However, accumulating evidence argues against a primary role of hypercoagulability in the development of PVT [82].

Recently, histological features of cirrhotic non-malignant PVT have been reported [83]. Remarkably, portal vein thrombi had a very different appearance compared with that of venous thrombi from patients with DVT and PE. Whereas "classic" venous thrombi are fibrin-rich structures, rich in polyhedral red blood cells [84], portal vein thrombi were frequently devoid of fibrin. Rather, portal vein thrombi were characterized by a thickening of the portal vein vessel wall. This portal vein intimal hyperplasia was accompanied by fibrin-rich structures in some patients. In those patients in whom the portal vein thrombus contained fibrin, there was a notable absence of polyhedral red blood cells. These findings reinforce the notion that hypercoagulability is not central to the pathogenesis of PVT. Rather, portal hypertension-related development of portal vein intimal hyperplasia may be a more important contributor.

6.3 | Risk factors

The risk of PVT is predominantly modulated by severity of liver disease and portal hypertension [85–90]. A recent prospective observational study of 369 patients with cirrhosis (72% Child–Pugh A) with detailed clinical and laboratory profiling reported portal blood flow velocity, thrombocytopenia, and prior variceal bleeding as the strongest predictors of PVT [77]. An extensive selection of hemostatic and inflammatory markers measured at study enrolment was not associated with PVT. Platelet count was reported as a predictor of PVT in the PRO-LIVER study, with a platelet count $<75 \times 10^9$/L associated with a HR of 3.6 (95% CI, 1.7-7.2) compared with a platelet count $>125 \times 10^9$/L [76]. In this study, previous PVT was additionally found to be a strong predictor of further PVT (HR, 4.2; 95% CI, 2.5-7.2).

The underlying etiology of cirrhosis and patient characteristics also affect the risk of PVT, with metabolic dysfunction–associated steatohepatitis (MASH), metabolic syndrome, and obesity reported as risk factors [88,90–93]. Heritable and acquired thrombophilia have not been consistently associated with risk of PVT in patients with cirrhosis [75]. ABO blood type, a well-established genetic risk factor for development of DVT and PE, is not a modulator of risk for PVT as evidenced in a study of over 80 000 patients [94]. Routine thrombophilia testing for evaluation of VTE risk or following a confirmed VTE/PVT is not recommended [19,95].

6.4 | Anticoagulation

Although portal vein thrombi often lack classic thrombus components, anticoagulant therapy is central to the management of non-malignant PVT in patients with cirrhosis. A small study demonstrated that long-term anticoagulant therapy with LMWH is effective in preventing the development of PVT [96]; however, larger studies are required and

the value of thromboprophylactic therapy aimed at primary prevention of PVT is unclear. Treatment of PVT using anticoagulant therapy is safe and effective, as evidenced by multiple meta-analyses [97–99]. Interestingly, multiple studies have found that bleeding risk is not increased by anticoagulant treatment [99,100], and some studies even suggest a reduction in variceal bleeding [97]. The reduced risk of variceal bleeding in patients receiving anticoagulant therapy may relate to a reduction in portal pressure by anticoagulant-induced recanalization. Of note, these data stem from observational studies with small numbers of patients, and hence, are subject to a risk of bias. Furthermore, anticoagulation does not have a detrimental effect on the outcomes of patients who experience gastrointestinal bleeding [101]. The lack of an increased bleeding risk associated with anticoagulant therapy in cirrhosis may reflect a simultaneous decrease in variceal and increase in non-variceal bleeding. Of note, although anticoagulant therapy is reasonably effective in achieving recanalization (~70% of patients), spontaneous recanalization occurs in a significant proportion of patients (~30%) [97,102]. While anticoagulant therapy does not seem to be associated with a significant bleeding risk, it remains uncertain whether patients benefit from portal vein recanalization. It has been argued that portal vein recanalization may slow disease progression and offer a survival benefit [103], but studies have shown that development of PVT does not lead to faster progression of disease [87]. The clinical scenario where PVT is known to have a detrimental impact on patient outcomes is in liver transplantation. Presence of PVT at the time of liver transplantation increases 1-year mortality (OR, 1.38; 95% CI, 1.14-1.66). When compared with partial PVT, patients whose PVT was occlusive had a higher 30-day pooled mortality rate (OR, 5.65; 95% CI, 2-15.96; $P < .0001$) and 1-year mortality rate (OR, 2.48; 95% CI, 0.99-6.17; $P = .38$) [104]. Moreover, PVT preventing physiological portal vein anastomosis is associated with increased all-cause graft loss and persistence of portal hypertension [105]. Therefore, maintaining a patent PV system is a priority in liver transplantation candidates.

Recent data from an individual patient data meta-analysis of 500 patients (IMPORTAL study) demonstrated that anticoagulant therapy for PVT is associated with a survival benefit (adjusted subdistribution HR, 0.59; 95% CI, 0.49-0.70). Interestingly, the survival benefit was independent of portal vein recanalization [102]. This observation suggests that anticoagulant therapy has beneficial effects that are unrelated to the thrombus itself. Such effects may relate to dampening of intrahepatic activation of coagulation. Intrahepatic coagulation has been shown to lead to progression of disease by various mechanisms including activation of hepatic stellate cells by coagulation proteases and ischemia in the microvasculature by microthrombus formation [106]. The observation that recanalization by anticoagulant therapy but not recanalization by placement of a transjugular intrahepatic portosystemic shunt (TIPS) is associated with a survival benefit [98] also supports the concept that anticoagulation has effects beyond thrombus resolution. In addition, 2 randomized controlled trials in patients with cirrhosis without PVT have demonstrated beneficial effects of anticoagulation on progression of disease [96,107]. However, a number of limitations exist with respect to the IMPORTAL study. Included studies were largely retrospective and heterogeneous with respect to PVT severity and location and type of anticoagulation. Also, the study did not specify whether the PVT was chronic or acute. Importantly, no patients treated with DOACs were included, and there was no information provided regarding anticoagulant dosage. In addition, although the study was an individual patient data meta-analysis and data were adjusted for confounders, residual confounding cannot be excluded as most of the studies were retrospective. Finally, patients included in the IMPORTAL study were relatively young and many may have been transplant candidates with a clear indication for anticoagulation, which limits extrapolation of the findings to all patients with cirrhosis and PVT.

There are very limited data available evaluating DOACs in comparison with LMWH/VKA for treatment of PVT in patients with cirrhosis. A recent systematic review identified 11 studies of anticoagulation in PVT of which only 1 was a randomized controlled trial (which has since been retracted) [108]. There are several limitations to many of the eligible studies including retrospective study design, small patient numbers, selective inclusion criteria, and suboptimal management in the VKA arms (ie, no overlapping of LMWH until INR in therapeutic range). Notwithstanding these limitations, the available data suggest that DOACs are as effective as LMWH/VKA in PVT recanalization without an increased risk of bleeding, but well-designed studies are required particularly in patients with more advanced CLD.

6.4.1 | Symptomatic PVT

PVT that is associated with ischemic symptoms requires therapeutic anticoagulation with the aim of preventing thrombus extension and bowel ischemia. Fortunately, this potentially catastrophic complication is rare in patients with advanced liver disease with portal hypertension due to decompression from portosystemic collaterals [19]. In patients that do not respond to anticoagulant therapy or in whom anticoagulant therapy is contraindicated, TIPS placement may be considered. Such a strategy requires multidisciplinary assessment including hepatology, interventional radiology, and hematology specialists.

6.4.2 | Asymptomatic PVT

Asymptomatic PVT may be acute (<6 months) or chronic (>6 months) [19], although the age of the thrombus is difficult to estimate using routine imaging techniques. The presence of cavernoma is indicative of an older thrombus. Studies have suggested that treatment of acute thrombi with anticoagulant therapy has a higher recanalization rate than treatment of chronic thrombi [109,110].

The benefits of treating asymptomatic PVT remain unclear as it is unknown whether successful recanalization decreases disease progression and liver-related mortality. In patients with a thrombus that shows progression over time, treatment aimed at halting thrombus progression is likely indicated, particularly if there is concern for

development of bowel ischemia. In patients with PVT who are transplant candidates, treatment of PVT aimed at recanalization is indicated as a patent portal vein facilitates physiological portal vein anastomoses during transplantation, which improves surgical outcomes [109]. In patients with PVT who are not transplant candidates, the benefits of attempting to achieve portal vein recanalization are unclear. However, given the favorable effect of anticoagulation on survival independent of portal vein recanalization in the IMPORTAL study, there may be benefit to anticoagulating all patients with PVT, unless there are clear contraindications to anticoagulant therapy. Additional studies are required to provide a definitive answer as to the role of anticoagulation for PVT in patients who are not liver transplant candidates.

6.4.3 | Guideline recommendations

Recommendations from the American Gastroenterology Association (AGA), the American Association for the Study of Liver Diseases (AASLD), and the Baveno Faculty (endorsed by the European Association for the Study of the Liver) with respect to indications and recommended agents for therapeutic anticoagulation in patients with cirrhosis and PVT are summarized in Table 3 [19,111,112]. All guidelines recommend anticoagulation for acute complete main PVT or progressive thrombosis. AASLD and Baveno Faculty also recommend anticoagulation for acute partial main PVT. Conflicting guidance is provided in the setting of asymptomatic or chronic PVT; AGA recommends anticoagulation for chronic PVT under selected circumstances, while AASLD recommends against anticoagulation in chronic complete occlusion of the main portal vein or cavernous transformation of the portal vein with established collaterals. Both AGA and Baveno Faculty recommend anticoagulation for PVT in liver transplant candidates. All guidelines endorse the use of LMWH or VKA, with the most recent publications (AASLD and Baveno Faculty) also endorsing DOAC use.

6.5 | Guidance recommendations

1. We recommend anticoagulation for all patients with cirrhosis with symptomatic PVT for a minimum of 6 months.
2. We suggest anticoagulation for all patients with cirrhosis with asymptomatic, but progressing PVT for a minimum of 6 months, unless there are clear contraindications to anticoagulation.
3. We recommend continuing extended anticoagulation for all patients with cirrhosis and PVT who are candidates for liver transplantation unless patients are actively bleeding.
4. Anticoagulation may be considered in patients with cirrhosis and asymptomatic PVT who are not candidates for liver transplantation on a case-by-case basis as anticoagulation may be associated with a survival benefit. If anticoagulation is initiated, we recommend regular reassessment of bleeding risk (eg, at 6-monthly intervals) and withdrawal of anticoagulation in the event of active bleeding or with significant increase in bleeding risk.
5. We recommend evaluating for the presence of varices and ensuring adequate management prior to initiation of anticoagulant therapy and reference to other guidance documents for recommended strategies [112].
6. We suggest the use of either DOAC or LMWH with/without VKA for patients with Child–Pugh A or B cirrhosis.
7. We suggest LMWH alone (or as a bridge to VKA in patients with a normal baseline INR) in patients with Child–Pugh C cirrhosis.

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TABLE 3 Indications and recommended agents for therapeutic anticoagulation for PVT in patients with cirrhosis.

Guideline (year of publication)	AGA (2020) [111]	AASLD (2021) [19]	Baveno VII (2022) [112]
Indications	Acute complete occlusion of main portal vein Chronic PVT with: 1. Progression of thrombus or SMV involvement 2. History of bowel ischemia 3. Inherited thrombophilia - PVT in patients awaiting liver transplant	Recent occlusive or partially occlusive (>50%) thrombosis of main portal vein Progression of recent thrombus of small intrahepatic subbranches of portal vein or minimally occlusive (<50%) thrombus of main portal vein	Recent (<6 mo) completely or partially occlusive (>50%) thrombosis of portal vein trunk Minimally occlusive (<50%) thrombosis of portal vein trunk that progresses on short-term follow-up (1-3 mo) or compromises SMV Symptomatic PVT PVT in potential liver transplant candidates
Recommended agents	Initial: UFH or LMWH Maintenance: LMWH, VKA	LMWH, VKA, or DOAC	Initial: preferably LMWH Maintenance: LMWH, VKA, or DOAC

AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; PVT, portal vein thrombosis; SMV, superior mesenteric vein; UFH, unfractionated heparin; VKA, vitamin K antagonist.

Committee (SSC) Subcommittee on Hemostatic Management of Patients with Liver Diseases and SSC Subcommittee on Control of Anticoagulation. This manuscript was reviewed and approved by the Guidelines and Guidance Committee of ISTH.

AUTHOR CONTRIBUTIONS

S.C., L.R., and T.L. drafted the manuscript. All authors provided intellectual input, critically reviewed, and agreed to the guidance recommendations. All authors approved the final document.

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S.C. has received speaker or advisory board fees from AstraZeneca, BMS/Pfizer, Fresenius Kabi, Leo Pharma, and Servier. A.C. has served as a consultant for MingSight Pharmaceuticals, the New York Blood Center, Sanofi, and Synergy, and has received authorship royalties from UpToDate. A.G. has received travel/conference awards from Octapharma and CSL Behring. N.G. has received consulting fees or travel awards from Bayer, Bristol-Myers Squibb/Pfizer, LEO Pharma, and Diagnostica Stago. V.H.G. has received speaker fees from Cook Medical and Gore Medical. K.M. has received speaker fees from Alexion, Bayer, and CSL Behring; fees for participation in trial steering committees for Bayer and AstraZeneca; consulting fees from uniQure and Therini, and fees for participation in data monitoring and endpoint adjudication committee for Octapharma. D.M.S. has received honoraria paid indirectly to her research institute from AstraZeneca, BMS-Pfizer, Roche, and Servier for educational presentations. D.M.S. is supported by a Tier 2 Canada Research Chair in Anticoagulant Management of Cardiovascular Disease. L.R. has received speaker or advisory fees from Chugai and Hemab. S.S. and T.L. have no competing interests to disclose.

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REFERENCES

[1] Lisman T, Hernandez-Gea V, Magnusson M, Roberts L, Stanworth S, Thachil J, Tripodi A. The concept of rebalanced hemostasis in patients with liver disease: communication from the ISTH SSC working group on hemostatic management of patients with liver disease. *J Thromb Haemost*. 2021;19:1116–22.

[2] Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, Colombo M, Mannucci PM. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. *Gastroenterology*. 2009;137:2105–11.

[3] Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, Weksler B, Esteban R. Thrombocytopenia associated with chronic liver disease. *J Hepatol*. 2008;48:1000–7.

[4] Drolz A, Horvatits T, Roedl K, Rutter K, Staufer K, Kneidinger N, Holzinger U, Zauner C, Schellongowski P, Heinz G, Perkmann T, Kluge S, Trauner M, Fuhrmann V. Coagulation parameters and major bleeding in critically ill patients with cirrhosis. *Hepatology*. 2016;64:556–68.

[5] Ow TW, Fatourou E, Rabinowich L, van den Boom B, Nair S, Patel VC, Hogan B, McPhail M, Roberts LN, Bernal W. Prevalence of bleeding and thrombosis in critically ill patients with chronic liver disease. *Thromb Haemost*. 2022;122:1006–16.

[6] Zanetto A, Campello E, Senzolo M, Simioni P. The evolving knowledge on primary hemostasis in patients with cirrhosis: a comprehensive review. *Hepatology*. 2024;79:460–81.

[7] Lisman T, Bongers TN, Adelmeijer J, Janssen HLA, de Maat MPM, de Groot PG, Leebeek FWG. Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology*. 2006;44:53–61.

[8] Lebreton A, Sinegre T, Lecompte T, Talon L, Abergel A, Lisman T. Thrombin generation and cirrhosis: state of the art and perspectives. *Semin Thromb Hemost*. 2020;46:693–703.

[9] Elvers FL, Stamouli M, Adelmeijer J, Jeyanesan D, Bernal W, Maas C, Patel VC, Lisman T. In vivo generation of thrombin in patients with liver disease without apparent evidence of activation of the intrinsic or extrinsic pathway of coagulation. *J Thromb Haemost*. 2023;21:2078–88.

[10] von Meijenfeldt FA, Lisman T. Fibrinolysis in patients with liver disease. *Semin Thromb Hemost*. 2021;47:601–9.

[11] Bechmann LP, Sichau M, Wichert M, Gerken G, Kröger K, Hilgard P. Low-molecular-weight heparin in patients with advanced cirrhosis. *Liver Int*. 2011;31:75–82.

[12] Rommers MK, Van der Lely N, Egberts TCG, van den Bemt PMLA. Anti-Xa activity after subcutaneous administration of dalteparin in ICU patients with and without subcutaneous oedema: a pilot study. *Crit Care*. 2006;10:R93.

[13] Haas CE, Nelsen JL, Raghavendran K, Mihalko W, Beres J, Ma Q, Forrest A. Pharmacokinetics and pharmacodynamics of enoxaparin in multiple trauma patients. *J Trauma*. 2005;59:1336–43.

[14] Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol*. 2008;64:1147–61.

[15] Turco L, de Raucourt E, Valla DC, Villa E. Anticoagulation in the cirrhotic patient. *JHEP Rep*. 2019;1:227–39.

[16] Efird LM, Mishkin DS, Berlowitz DR, Ash AS, Hylek EM, Ozonoff A, Reisman JI, Zhao S, Jasuja GK, Rose AJ. Stratifying the risks of oral anticoagulation in patients with liver disease. *Circ Cardiovasc Qual Outcomes*. 2014;7:461–7.

[17] Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, Deswal A, Eckhardt LL, Goldberger ZD, Gopinathannair R, Gorenek B, Hess PL, Hlatky M, Hogan G, Ibeh C, Indik JH, Kido K, Kusumoto F, Link MS, Linta KT, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2024;149:e1–156.

[18] Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, Thurston C, Vedantham S, Verhamme P, Witt DM, D Florez I, Izcovich A, Nieuwlaat R, Ross S, Schünemann H J, Wiercioch W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4:4693–738.

[19] Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, Lisman T, Valla DC. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;73:366–413.

[20] Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Vanassche T, Potpara T, Camm AJ, Heidbuchel H, External reviewers. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace*. 2021;23:1612–76.

[21] Stangier J, Stähle H, Rathgen K, Roth W, Shakeri-Nejad K. Pharmacokinetics and pharmacodynamics of dabigatran etexilate, an

oral direct thrombin inhibitor, are not affected by moderate hepatic impairment. *J Clin Pharmacol*. 2008;48:1411–9.

[22] Kubitza D, Roth A, Becka M, Alatrach A, Halabi A, Hinrichsen H, Mueck W. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct factor Xa inhibitor. *Br J Clin Pharmacol*. 2013;76:89–98.

[23] Frost CE, Ly V, Garonzik SM. Apixaban pharmacokinetics and pharmacodynamics in subjects with mild or moderate hepatic impairment. *Drugs R D*. 2021;21:375–84.

[24] Semmler G, Pomej K, Bauer DJM, Balcar L, Simbrunner B, Binter T, Hartl L, Becker J, Pinter M, Quehenberger P, Trauner M, Mandorfer M, Lisman T, Reiberger T, Scheiner B. Safety of direct oral anticoagulants in patients with advanced liver disease. *Liver Int*. 2021;41:2159–70.

[25] Mendell J, Johnson L, Chen S. An open-label, phase 1 study to evaluate the effects of hepatic impairment on edoxaban pharmacokinetics and pharmacodynamics. *J Clin Pharmacol*. 2015;55:1395–405.

[26] Bos S, Schreuder T, Blokzijl H, Adelmeijer J, Lisman T, Kamphuisen PW. Anticoagulant activity of edoxaban in patients with cirrhosis. *Blood*. 2020;136:1561–4.

[27] Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377:431–41.

[28] Milling TJ Jr, Middeldorp S, Xu L, Koch B, Demchuk A, Eikelboom JW, Verhamme P, Cohen AT, Beyer-Westendorf J, Gibson CM, Lopez-Sendon J, Crowther M, Shoamanesh A, Coppens M, Schmidt J, Albaladejo P, Connolly SJ, ANNEXA-4 Investigators. Final study report of andexanet alfa for major bleeding with factor Xa inhibitors. *Circulation*. 2023;147:1026–38.

[29] Abraham NS, Barkun AN, Sauer BG, Douketis J, Laine L, Noseworthy PA, Telford JJ, Leontiadis GI. American College of Gastroenterology-Canadian Association of Gastroenterology clinical practice guideline: management of anticoagulants and antiplatelets during acute gastrointestinal bleeding and the periendoscopic period. *Am J Gastroenterol*. 2022;117:542–58.

[30] Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, Hemphill JC 3rd, Johnson R, Keigher KM, Mack WJ, Mocco J, Newton EJ, Ruff IM, Sansing LH, Schulman S, Selim MH, Sheth KN, Sprigg N, Sunnerhagen KS, American Heart Association/American Stroke Association. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2022;53:e282–361.

[31] Roberts LN, Lisman T, Stanworth S, Hernandez-Gea V, Magnusson M, Tripodi A, Thachil J. Periprocedural management of abnormal coagulation parameters and thrombocytopenia in patients with cirrhosis: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2022;20:39–47.

[32] Maura G, Bardou M, Billionnet C, Weill A, Drouin J, Neumann A. Oral anticoagulants and risk of acute liver injury in patients with nonvalvular atrial fibrillation: a propensity-weighted nationwide cohort study. *Sci Rep*. 2020;10:11624.

[33] Chokesuwattanaskul R, Thongprayoon C, Bathini T, O'Corragain OA, Sharma K, Preechawat S, Wijarnpreecha K, Kroner PT, Ungprasert P, Cheungpasitporn W. Epidemiology of atrial fibrillation in patients with cirrhosis and clinical significance: a meta-analysis. *Eur J Gastroenterol Hepatol*. 2019;31:514–9.

[34] Huang WA, Dunipace EA, Sorg JM, Vaseghi M. Liver disease as a predictor of new-onset atrial fibrillation. *J Am Heart Assoc*. 2018;7:e008703.

[35] Kuo L, Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Lip GYH, Chen SA. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? *J Am Heart Assoc*. 2017;6:e005307.

[36] Vandenberk B, Altieri MH, Liu H, Raj SR, Lee SS. Review article: diagnosis, pathophysiology and management of atrial fibrillation in cirrhosis and portal hypertension. *Aliment Pharmacol Ther*. 2023;57:290–303.

[37] Long MT, Ko D, Arnold LM, Trinquart L, Sherer JA, Keppel SS, Benjamin EJ, Helm RH. Gastrointestinal and liver diseases and atrial fibrillation: a review of the literature. *Therap Adv Gastroenterol*. 2019;12:1756284819832237.

[38] Voskoboinik A, Prabhu S, Ling LH, Kalman JM, Kistler PM. Alcohol and atrial fibrillation: a sobering review. *J Am Coll Cardiol*. 2016;68:2567–76.

[39] Suri A, Patel D, Teckman JH. Alpha-1 antitrypsin deficiency liver disease. *Clin Liver Dis*. 2022;26:391–402.

[40] Rose RA, Sellan M, Simpson JA, Izaddoustdar F, Cifelli C, Panama BK, Davis M, Zhao D, Markhani M, Murphy GG, Striessnig J, Liu PP, Heximer SP, Backx PH. Iron overload decreases CaV1.3-dependent L-type Ca^{2+} currents leading to bradycardia, altered electrical conduction, and atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2011;4:733–42.

[41] Zardi EM, Abbate A, Zardi DM, Dobrina A, Margiotta D, Van Tassell BW, Afeltra A, Sanyal AJ. Cirrhotic cardiomyopathy. *J Am Coll Cardiol*. 2010;56:539–49.

[42] Iwakiri Y, Trebicka J. Portal hypertension in cirrhosis: pathophysiological mechanisms and therapy. *JHEP Rep*. 2021;3:100316.

[43] Mozos I. Arrhythmia risk in liver cirrhosis. *World J Hepatol*. 2015;7:662–72.

[44] Ng CKF, Chan MHM, Tai MHL, Lam CWK. Hepatorenal syndrome. *Clin Biochem Rev*. 2007;28:11–7.

[45] Chokesuwattanaskul R, Thongprayoon C, Bathini T, Torres-Ortiz A, O'Corragain OA, Watthanasuntorn K, Lertjitbanjong P, Sharma K, Prechawat S, Ungprasert P, Kroner PT, Wijarnpreecha K, Cheungpasitporn W. Efficacy and safety of anticoagulation for atrial fibrillation in patients with cirrhosis: a systematic review and meta-analysis. *Dig Liver Dis*. 2019;51:489–95.

[46] Serper M, Weinberg EM, Cohen JB, Reese PP, Taddei TH, Kaplan DE. Mortality and hepatic decompensation in patients with cirrhosis and atrial fibrillation treated with anticoagulation. *Hepatology*. 2021;73:219–32.

[47] Steensig K, Pareek M, Krarup AL, Sogaard P, Maeng M, Tayal B, Lee CJ, Torp-Pedersen C, Lip GY, Holland-Fischer P, Kragholm KH. Thromboembolism and bleeding in patients with atrial fibrillation and liver disease - a nationwide register-based cohort study: thromboembolism and bleeding in liver disease. *Clin Res Hepatol Gastroenterol*. 2022;46:101952.

[48] Ayoub M, Tomanguillo Chumbe J, Koontz M, Daglilar E, Anwar N, Naravadi V. The liver meeting: Boston, Massachusetts Nov 10-14, 2023. *Hepatology*. 2023;78:S1–2154.

[49] Qamar A, Antman EM, Ruff CT, Nordio F, Murphy SA, Grip LT, Greenberger NJ, Yin OQP, Choi Y, Lanz HJ, Mercuri MF, Braunwald E, Giugliano RP. Edoxaban versus warfarin in patients with atrial fibrillation and history of liver disease. *J Am Coll Cardiol*. 2019;74:179–89.

[50] Lee SR, Lee HJ, Choi EK, Han KD, Jung JH, Cha MJ, Oh S, Lip GYH. Direct oral anticoagulants in patients with atrial fibrillation and liver disease. *J Am Coll Cardiol*. 2019;73:3295–308.

[51] Menichelli D, Ronca V, Di Rocco A, Pignatelli P, Marco Podda G. CAR. Direct oral anticoagulants and advanced liver disease: a systematic review and meta-analysis. *Eur J Clin Invest*. 2021;51:e13397.

[52] Lawal OD, Aronow HD, Shobayo F, Hume AL, Taveira TH, Matson KL, Zhang Y, Wen X. Comparative effectiveness and safety of direct oral anticoagulants and warfarin in patients with atrial

fibrillation and chronic liver disease: a nationwide cohort study. *Circulation*. 2023;147:782–94.
[53] Douros A, Cui Y, Platt RW, Filion KB, Sebastiani G, Renoux C. Effectiveness and safety of direct oral anticoagulants among patients with non-valvular atrial fibrillation and liver disease: a multinational cohort study. *Thromb Res*. 2024;237:71–8.
[54] Baylo A, Cherniavskyi V, Reshotko D. Assessment of the efficiency and safety of anti-coagulation therapy in patients with liver cirrhosis and atrial fibrillation. *Clin Exp Hepatol*. 2023;9:265–71.
[55] Simon TG, Schneeweiss S, Singer DE, Sreedhara SK, Lin KJ. Prescribing trends of oral anticoagulants in US patients with cirrhosis and nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2023;12:e026863.
[56] Douros A, Cui Y, Platt RW, Filion KB, Sebastiani G, Renoux C. Utilization and long-term persistence of direct oral anticoagulants among patients with nonvalvular atrial fibrillation and liver disease. *Br J Clin Pharmacol*. 2022;88:994–1009.
[57] O'Shea RS, Davitkov P, Ko CW, Rajasekhar A, Su GL, Sultan S, Allen AM, Falck-Ytter Y. AGA clinical practice guideline on the management of coagulation disorders in patients with cirrhosis. *Gastroenterology*. 2021;161:1615–27.e1.
[58] Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P, PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374:534–42.
[59] Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64:1–12.
[60] Mir T, Rawasia WF, Uddin M, Sheikh M, Munir MB, Balla S. Left atrial appendage closure device outcomes among cirrhosis patients with atrial fibrillation: a United States national cohort study. *Europace*. 2023;25:1408–14.
[61] Thotamgari SR, Sheth AR, Patel HP, Bretzman J, Ward RC, Thakkar S, Patel JT, Asirvatham SJ, Holmes DR Jr, Egbe A, Deshmukh A, DeSimone CV. Liver cirrhosis is independently associated with increased in-hospital mortality in patients undergoing left atrial appendage occlusion device implantation. *Heart Rhythm*. 2022;19:1392–3.
[62] Northup PG, McMahon MM, Ruhl AP, Altshuler SE, Volk-Bednarz A, Caldwell SH, Berg CL. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. *Am J Gastroenterol*. 2006;101:1524–8.
[63] Jepsen P, Tapper EB, Deleuran T, Kazankov K, Askgaard G, Sorensen HT, Vilstrup H, West J. Risk and outcome of venous and arterial thrombosis in patients with cirrhosis: a Danish nation-wide cohort study. *Hepatology*. 2021;74:2725–34.
[64] Søgard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. *Am J Gastroenterol*. 2009;104:96–101.
[65] Ambrosino P, Tarantino L, Di Minno G, Paternoster M, Graziano V, Petitto M, Nasto A, Di Minno MN. The risk of venous thromboembolism in patients with cirrhosis. A systematic review and meta-analysis. *Thromb Haemost*. 2017;117:139–48.
[66] Roberts LN, Hernandez-Gea V, Magnusson M, Stanworth S, Thachil J, Tripodi A, Lisman T. Thromboprophylaxis for venous thromboembolism prevention in hospitalized patients with cirrhosis: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2022;20:2237–45.
[67] National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing guideline. London: National Institute for Health and Care Excellence; 2020.
[68] EINSTEIN–PE Investigators, Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–97.
[69] Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ, the RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342–52.
[70] Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–15.
[71] Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808.
[72] Lawal OD, Aronow HD, Hume AL, Shobayo F, Matson KL, Barbour M, Zhang Y, Wen X. Venous thromboembolism, chronic liver disease and anticoagulant choice: effectiveness and safety of direct oral anticoagulants versus warfarin. *Res Pract Thromb Haemost*. 2024;8:102293.
[73] Samuelson Bannow BT, Lee A, Khorana AA, Zwicker JI, Noble S, Ay C, Carrier M. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2018;16:1246–9.
[74] Ageno W, Dentali F, Pomero F, Fenoglio L, Squizzato A, Pagani G, Re R, Bonzini M. Incidence rates and case fatality rates of portal vein thrombosis and Budd–Chiari syndrome. *Thromb Haemost*. 2017;117:794–800.
[75] Senzolo M, Garcia-Tsao G, García-Pagán JC. Current knowledge and management of portal vein thrombosis in cirrhosis. *J Hepatol*. 2021;75:442–53.
[76] Violi F, Corazza GR, Caldwell SH, Talerico G, Romiti GF, Napoleone L, Perticone F, Bolondi L, Pietrangelo A, Vestri AR, Raparelli V, Basili S, PRO-LIVER Collaborative Group. Incidence and recurrence of portal vein thrombosis in cirrhotic patients. *Thromb Haemost*. 2019;119:496–9.
[77] Turon F, Driever EG, Baiges A, Cerda E, García-Criado Á, Gilabert R, Bru C, Berzigotti A, Nuñez I, Orts L, Reverter JC, Magaz M, Camprecios G, Olivas P, Betancourt-Sanchez F, Perez-Campuzano V, Blasi A, Seijo S, Reverter E, Bosch J, et al. Predicting portal thrombosis in cirrhosis: a prospective study of clinical, ultrasonographic and hemostatic factors. *J Hepatol*. 2021;75:1367–76.
[78] Gu W, Hortlik H, Erasmus HP, Schaaf L, Zeleke Y, Uschner FE, Ferstl P, Schulz M, Peiffer KH, Queck A, Sauerbruch T, Brol MJ, Rohde G, Sanchez C, Moreau R, Arroyo V, Zeuzem S, Welsch C, Trebicka J. Trends and the course of liver cirrhosis and its complications in Germany: nationwide population-based study (2005 to 2018). *Lancet Reg Health Eur*. 2022;12:100240.
[79] Okudaira M. Anatomy of the portal vein system and hepatic vasculature. In: Okuda K, Benhamou JP, eds. *Portal hypertension*. Tokyo: Springer; 1991.
[80] Karino T, Motomiya M. Flow through a venous valve and its implication for thrombus formation. *Thromb Res*. 1984;36:245–57.
[81] Violi F, Pignatelli P, Castellani V, Carnevale R, Cammisotto V. Gut dysbiosis, endotoxemia and clotting activation: a dangerous trio for portal vein thrombosis in cirrhosis. *Blood Rev*. 2023;57:100998.
[82] Anton A, Campreciós G, Pérez-Campuzano V, Orts L, García-Pagán JC, Hernández-Gea V. The pathophysiology of portal vein

thrombosis in cirrhosis: getting deeper into Virchow's triad. *J Clin Med*. 2022;11:800.

[83] Driever EG, von Meijenfeldt FA, Adelmeijer J, de Haas RJ, van den Heuvel MC, Nagasami C, Weisel JW, Fondevila C, Porte RJ, Blasi A, Heaton N, Gregory S, Kane P, Bernal W, Zen Y, Lisman T. Nonmalignant portal vein thrombi in patients with cirrhosis consist of intimal fibrosis with or without a fibrin-rich thrombus. *Hepatology*. 2022;75:898–911.

[84] Chernysh IN, Nagaswami C, Kosolapova S, Peshkova AD, Cuker A, Cines DB, Cambor CL, Litvinov RI, Weisel JW. The distinctive structure and composition of arterial and venous thrombi and pulmonary emboli. *Sci Rep*. 2020;10:5112.

[85] Zocco MA, di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani FR, Riccardi L, Lancellotti S, Santoliquido A, Flore R, Pompili M, Rapaccini GL, Tondi P, Gasbarrini GB, Landolfi R, Gasbarrini G. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. *J Hepatol*. 2009;51:682–9.

[86] Noronha Ferreira C, Marinho RT, Cortez-Pinto H, Ferreira P, Dias MS, Vasconcelos M, Alexandrino P, Serejo F, Pedro AJ, Gonçalves A, Palma S, Leite I, Reis D, Damião F, Valente A, Xavier Brito L, Baldaia C, Fatela N, Ramalho F, Velosa J. Incidence, predictive factors and clinical significance of development of portal vein thrombosis in cirrhosis: a prospective study. *Liver Int*. 2019;39:1459–67.

[87] Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, Plessier A, Roulot D, Chaffaut C, Bourcier V, Trinchet JC, Valla DC, Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. *Hepatology*. 2015;61:660–7.

[88] Gaballa D, Bezinover D, Kadry Z, Eyster E, Wang M, Northup PG, Stine JG. Development of a model to predict portal vein thrombosis in liver transplant candidates: the portal vein thrombosis risk index. *Liver Transpl*. 2019;25:1747–55.

[89] Stine JG, Wang J, Shah PM, Argo CK, Intagliata N, Uflacker A, Caldwell SH, Northup PG. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: a matched case-control study. *Liver Int*. 2018;38:94–101.

[90] Abdel-Razik A, Mousa N, Elhelaly R, Tawfik A. De-novo portal vein thrombosis in liver cirrhosis: risk factors and correlation with the model for end-stage liver disease scoring system. *Eur J Gastroenterol Hepatol*. 2015;27:585–92.

[91] Stine JG, Shah NL, Argo CK, Pelletier SJ, Caldwell SH, Northup PG. Increased risk of portal vein thrombosis in patients with cirrhosis due to nonalcoholic steatohepatitis. *Liver Transpl*. 2015;21:1016–21.

[92] Ayala R, Grande S, Bustelos R, Ribera C, García-Sesma A, Jimenez C, Moreno E, Martinez-Lopez J. Obesity is an independent risk factor for pre-transplant portal vein thrombosis in liver recipients. *BMC Gastroenterol*. 2012;12:114.

[93] Hernández-Conde M, Llop E, Fernández-Carrillo C, Perelló C, López-Gómez M, Abad J, Martínez-Porras JL, Fernández-Puga N, Calleja JL. Visceral fat is associated with cirrhotic portal vein thrombosis. *Expert Rev Gastroenterol Hepatol*. 2019;13:1017–22.

[94] Scheiner B, Northup PG, Gruber AB, Semmler G, Leitner G, Quehenberger P, Thaler J, Ay C, Trauner M, Reiberger T, Lisman T, Mandorfer M. The impact of ABO blood type on the prevalence of portal vein thrombosis in patients with advanced chronic liver disease. *Liver Int*. 2020;40:1415–26.

[95] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. *J Hepatol*. 2022;76:1151–84.

[96] Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, Tata C, Zecchini R, Gitto S, Petta S, Lei B, Bernabucci V, Vukotic R, De Maria N, Schepis F, Karampatou A, Caporali C, Simoni L, Del Buono M, Zambotto B, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology*. 2012;143:1253–60.e4.

[97] Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. *Gastroenterology*. 2017;153:480–7.e1.

[98] Davis JPE, Ogurick AG, Rothermel CE, Sohn MW, Intagliata NM, Northup PG. Anticoagulation and transjugular intrahepatic portosystemic shunting for treatment of portal vein thrombosis in cirrhosis: a systematic review and meta-analysis. *Clin Appl Thromb Hemost*. 2019;25:1076029619888026.

[99] Yao C, Zhao M, Ibrahim B, Saab S. Anticoagulation for the treatment of portal vein thrombosis in cirrhosis: a systematic review and meta-analysis of comparative studies. *J Clin Exp Hepatol*. 2023;13:404–13.

[100] Zhang Z, Zhao Y, Han B, Zhu Z, Sun L, Cui X. The efficacy and safety of anticoagulants in the treatment of cirrhotic portal vein thrombosis: a systematic review and meta-analysis. *Clin Appl Thromb Hemost*. 2022;28:10760296221104797.

[101] Cerini F, Gonzalez JM, Torres F, Puente Á, Casas M, Vinaixa C, Berenguer M, Ardevol A, Augustin S, Llop E, Senosiain M, Villanueva C, de la Pena J, Banares R, Genesca J, Sopena J, Albillos A, Bosch J, Hernandez-Gea V, Garcia-Pagan JC. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. *Hepatology*. 2015;62:575–83.

[102] Guerrero A, Campo LD, Piscaglia F, Scheiner B, Han G, Violi F, Ferreira CN, Tellez L, Reiberger T, Basili S, Zamora J, Albillos A. Baveno Cooperation: an EASL consortium. Anticoagulation improves survival in patients with cirrhosis and portal vein thrombosis: the IMPORTAL competing-risk meta-analysis. *J Hepatol*. 2023;79:69–78.

[103] Noronha Ferreira C, Reis D, Cortez-Pinto H, Tato Marinho R, Gonçalves A, Palma S, Leite I, Rodrigues T, Pedro AJ, Alexandrino P, Serejo F, Sobral Dias M, Ferreira P, Vasconcelos M, Damiao F, Xavier Brito L, Baldaia C, Fatela N, Ramalho F, Velosa J. Anticoagulation in cirrhosis and portal vein thrombosis is safe and improves prognosis in advanced cirrhosis. *Dig Dis Sci*. 2019;64:2671–83.

[104] Zanetto A, Rodriguez-Kastro KI, Germani G, Ferrarese A, Cillo U, Burra P, Senzolo M. Mortality in liver transplant recipients with portal vein thrombosis - an updated meta-analysis. *Transpl Int*. 2018;31:1318–29.

[105] Fundora Y, Hessheimer AJ, Del Prete L, Maroni L, Lanari J, Barrios O, Clarysse M, Gastaca M, Barrera Gomez M, Bonadona A, Janek J, Bosca A, Alamo Martinez JM, Zozaya G, Lopez Garnica D, Magistri P, Leon F, Magini G, Patrono D, Nicovsky J, et al. Alternative forms of portal vein revascularization in liver transplant recipients with complex portal vein thrombosis. *J Hepatol*. 2023;78:794–804.

[106] Anstee QM, Dhar A, Thursz MR. The role of hypercoagulability in liver fibrogenesis. *Clin Res Hepatol Gastroenterol*. 2011;35:526–33.

[107] Sanchez AP, Turon F, Martinez J, Fortea JI, Hernandez-Guerra M, Alvarado-Tapias E, Pons M, Magaz M, Llop E, Álvarez-Navascués C, Alonso JC. Rivaroxaban improves survival and decompensation in cirrhotic patients with moderate liver dysfunction. Double-blind, placebo-controlled trial. *J Hepatol*. 2023;78:S2–3.

[108] Koh JH, Liew ZH, Ng GK, Liu HT, Tam YC, De Gottardi A, Wong YJ. Efficacy and safety of direct oral anticoagulants versus vitamin K antagonist for portal vein thrombosis in cirrhosis: a systematic review and meta-analysis. *Dig Liver Dis*. 2022;54:56–62.

[109] Rodriguez-Castro KI, Vitale A, Fadin M, Shalaby S, Zerbinati P, Sartori MT, Landi S, Pettinari I, Piscaglia F, Han G, Burra P, Simioni P, Senzolo M. A prediction model for successful anticoagulation in cirrhotic portal vein thrombosis. *Eur J Gastroenterol Hepatol*. 2019;31:34–42.

[110] Senzolo M, Sartori TM, Rossetto V, Burra P, Cillo U, Boccagni P, Gasparini D, Miotto D, Simioni P, Tsochatzis E, Burroughs KA. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. *Liver Int*. 2012;32:919–27.

[111] Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG clinical guideline: disorders of the hepatic and mesenteric circulation. *Am J Gastroenterol*. 2020;115:18–40.

[112] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C. Baveno VII Faculty. Baveno VII - renewing consensus in portal hypertension. *J Hepatol*. 2022;76:959–74.