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RECOMMENDATIONS AND GUIDELINES

Thromboprophylaxis for venous thromboembolism prevention in hospitalized patients with cirrhosis: Guidance from the SSC of the ISTH

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Abstract

Hospital-associated venous thromboembolism (HA-VTE) is a major cause of morbidity and mortality and is internationally recognized as a significant patient safety issue. While cirrhosis was traditionally considered to predispose to bleeding, these patients are also at an increased risk of VTE, with an associated increase in mortality. Hospitalization rates of patients with cirrhosis are increasing, and decisions regarding thromboprophylaxis are complex due to the uncertain balance between thrombosis and bleeding risk. This is further accentuated by derangements of hemostasis in patients with cirrhosis that are often considered contraindications to pharmacological thromboprophylaxis. Due to the strict inclusion and exclusion criteria of seminal studies of VTE risk assessment and thromboprophylaxis, there is limited data to guide decision making in this patient group. This guidance document reviews the incidence and risk factors for HA-VTE in patients with cirrhosis, outlines evidence to inform the use of thromboprophylaxis, and provides pragmatic recommendations on VTE prevention for hospitalized patients with cirrhosis. In brief, in hospitalized patients with cirrhosis:

1. We suggest inclusion of portal vein thrombosis as a distinct clinically important endpoint for future studies.

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2. We recommend against the use of thrombocytopenia and/or prolongation of prothrombin time/international normalized ratio as absolute contraindications to anticoagulant thromboprophylaxis.
3. We suggest anticoagulant thromboprophylaxis in line with local protocols and suggest low molecular weight heparin (LMWH) or fondaparinux over unfractionated heparin (UFH). In renal impairment, we suggest LMWH over UFH. For critically ill patients, we suggest case-by-case consideration of thromboprophylaxis.
4. We recommend research to refine VTE risk stratification, and to establish the optimal dosing and duration of thromboprophylaxis.

KEYWORDS
liver cirrhosis, liver diseases, prevention, thromboprophylaxis, venous thrombosis

1 | INTRODUCTION

Globally, hospital-associated venous thromboembolism (HA-VTE) is a common cause of morbidity and mortality, with an estimated 10 million events per annum.[1] Appropriate use of thromboprophylaxis in hospitalized patients significantly reduces the risk of HA-VTE by up to 60%.[2,3] VTE prevention is thus recognized as a major patient safety priority internationally. Hospitalization rates of patients with cirrhosis due to decompensating events, and for management of comorbid disease, are increasing.[4,5] Limited data and exclusion of patients with cirrhosis and abnormal hemostatic parameters from seminal thromboprophylaxis studies contributes to the uncertainty regarding its need and benefit in this patient group. Thrombocytopenia and prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) are common in patients with cirrhosis, and historically this has been interpreted by clinicians as predisposing to bleeding. Extensive laboratory work has demonstrated these patients have rebalanced hemostasis with hypercoagulable features predominating in those not critically ill.[6] Additionally, while variceal bleeding is of concern, it is now acknowledged as secondary to portal hypertension with little evidence that hemostatic alterations or the use of anticoagulant therapy modulates the risk or severity of variceal bleeding.[7,8]

All these issues raise challenges when weighing the need for thromboprophylaxis in patients with cirrhosis. Cohort studies of patients with cirrhosis indicate raised risks of both thrombosis and bleeding, discussed below.

Uptake of thromboprophylaxis in patients with cirrhosis is therefore challenging and has been additionally hampered by general under-utilization of thromboprophylaxis in acutely ill medical patients.[9] This guidance document reviews the epidemiological data for HA-VTE in patients with cirrhosis, the evidence and risks of thromboprophylaxis, and provides pragmatic recommendations on VTE prevention for hospitalized patients with cirrhosis.

2 | METHODS

Guidance statements were generated following review of the published literature. An initial search was conducted in PubMed using combinations of "liver cirrhosis," "liver diseases, "venous thrombosis," "deep vein thrombosis," "pulmonary embolism," "thromboprophylaxis," and "prevention." Relevant references from papers identified were also reviewed. Case reports and case series were excluded. There is a paucity of high quality randomized clinical trials in this area and thus the strength of guidance statements is based on review of available data and author consensus. Consensus was achieved by serial revision of proposed statements in response to coauthor feedback. The use of "we recommend" is based on consensus between authors combined with evidence from multiple larger clinical studies (that may be retrospective and uncontrolled) and reflects a strong guidance statement, where the clinician should adopt the practice in most cases. "We suggest" is based on consensus between authors but with a lack of multiple larger clinical studies and reflects a weak guidance statement, whereby the evidence to support the statement is not strong; the clinician may adopt the practice in some cases and an alternative practice may also be acceptable.

3 | Epidemiology of HA-VTE in patients with cirrhosis

3.1 | Deep vein thrombosis and pulmonary embolism

HA-VTE typically includes deep vein thrombosis (DVT) and pulmonary embolism (PE) as the most common manifestations of VTE. Retrospective observational cohort studies of patients with cirrhosis report the incidence of HA-VTE to range from 0.5% to 7%.[10-15] An early retrospective study reported an incidence of 1.9% for HA-VTE in those with cirrhosis ($n = 963$), compared to 1% in those without cirrhosis ($n = 12\,405$), contrasting with a 7% incidence in those with

chronic kidney disease ($n = 1692$), 6% with malignancy ($n = 673$), and 8% with cardiac failure ($n = 4489$).[10] A retrospective observational study investigating VTE incidence in critically ill patients reported an incidence of 2.7% and 7.6% in those with ($n = 75$) and without cirrhosis ($n = 723$), respectively; the incidence rate ratio was not significantly different after adjusting for baseline characteristics and use of low molecular weight heparin (LMWH; 0.64, 95% confidence interval [CI] 0.15–2.52).[16] Two Danish population-wide studies report an increased risk of VTE in patients with cirrhosis compared to matched controls. The first included 99 444 patients with VTE (compared to ~500 000 controls), and reported an increased risk of VTE in patients with cirrhosis (odds ratio [OR] 1.7, 95% CI 1.54–1.95). The second included 5854 patients with cirrhosis, and reported a VTE risk of 0.8% at 1 year, and 6.8% at 10 years.[17] Compared to 23 780 matched controls, cirrhosis was associated with a 2-fold increased risk of VTE (adjusted hazard ratio [aHR] 2.0, 95% CI 1.5–2.6). VTE was associated with increased mortality at 90 days (17% vs. 7% in those without VTE). A meta-analysis of 11 studies (including both in- and outpatient populations) reported an increased risk of VTE with an OR of 1.7 (95% CI 1.3–2.2) associated with cirrhosis.[18] Patients with cirrhosis and hepatocellular carcinoma are at additional risk of VTE[19] with a cumulative incidence of 6% in a single-center study, which reported hepatocellular carcinoma, multiple lesions, and distant metastases as independently associated with VTE.[20] VTE is associated with increased length of hospital stay and mortality in patients with cirrhosis.[12,20,21]

The predominant retrospective and observational nature of this data highlight the disparity of evidence compared to patient groups without cirrhosis. Use of thromboprophylaxis was low but variable (or not reported) across the above studies.

4 | Portal vein thrombosis

It is well established that patients with cirrhosis are at greater risk of portal vein thrombosis (PVT).[22] Prospective studies of PVT in patients with cirrhosis report an incidence ranging from 3.7%–24.5% at 1 year, with higher rates seen in cohorts including increased numbers of patients with decompensated disease.[22] A retrospective review of a large cohort of hospitalized patients with cirrhosis ($n = 7445$) reported 5.1% diagnosed with PVT and 1.3% VTE during hospitalization.[23] Hepatic encephalopathy (OR 14.0, 95% CI 10.8–14.1) and portal hypertensive changes at endoscopy (OR 1.3, 95% CI 1.03–1.8) were identified as independently associated with PVT, suggesting the risk increases in parallel with severity of liver disease. Additional risk factors included malignancy, diabetes, and abdominal surgery/invasive procedures. In this study, PVT did not impact length of stay or mortality. Given the association between PVT and severity of liver disease, it is perhaps unsurprising it is more commonly reported associated with hospitalization, particularly in association with critical illness.[24,25] Given PVT is highly prevalent in patients with cirrhosis, hospitalization may result in detection of a pre-existing event. A retrospective, observational cohort study of critically ill patients with cirrhosis ($n = 623$) attempts to address this by considering timing of diagnosis; overall VTE (including PVT) was identified in 20%. Early VTE (events prior to or within 48 h of admission) accounted for 13% and later VTE (diagnosed after 48 h) 7.2%, including PVT (DVT/PE in 2.7%).[25] Hepatocellular carcinoma, sepsis, and cryoprecipitate use were significantly associated with later VTE. PVT was not associated with mortality in this study, and its effect on mortality remains controversial in other settings such as those awaiting liver transplantation.[26-28] There remains uncertainty as to the efficacy of thromboprophylaxis in reducing PVT in hospital (see below) with a single randomized controlled trial of enoxaparin in ambulatory patients with decompensated cirrhosis reporting a significant reduction in PVT.[29] In future studies of thromboprophylaxis in patients with liver disease, PVT should be considered as a distinct clinical endpoint, in addition to DVT/PE to enable evaluation of its clinical significance and the effect (if any) of thromboprophylaxis.

5 | Risk assessment for VTE in patients with cirrhosis

5.1 | VTE risk assessment

VTE risk assessment is a recommended strategy to optimize in-hospital use of thromboprophylaxis enabling targeted provision to those most at risk, minimizing harm to those at low risk (by avoiding bleeding and heparin-induced thrombocytopenia) and increasing cost effectiveness.[30,31] There are a number of tools available with the PADUA and IMPROVE risk assessment models suggested by the American Society of Hematology clinical practice guidance for VTE prevention in medically ill patients.[30] Both tools give weighted scores for the presence of previous VTE, malignancy, increased age, known thrombophilia, reduced mobility, with PADUA including additional medical/surgical conditions.[32,33] The proportion of patients with liver disease included in the derivation of these scores was not reported by PADUA and <2% for IMPROVE.[32,33] A retrospective evaluation of PADUA in hospitalized patients with cirrhosis (32% received thromboprophylaxis) suggests this is an effective tool, with an incidence of VTE (including PVT) of 22% in the high risk strata.[34] Interestingly in the low risk group, few patients received thromboprophylaxis (2/91) with a VTE rate of 2%. The use of thromboprophylaxis was higher in those retrospectively assessed as high VTE risk with PADUA (70%), and was associated with a non-significant reduction in VTE (13% vs. 27%). A further small retrospective cohort study ($n = 98$ admissions) evaluated the IMPROVE risk assessment tool in patients with cirrhosis (with 76% receiving thromboprophylaxis), and reported VTE (including PVT) in 7.1% in those assessed as high risk versus 1.7% at low risk, among those receiving thromboprophylaxis.[35] This study suggested substantial over-prophylaxis in this cohort as only 19% of the cohort met IMPROVE criteria for thromboprophylaxis. Given the high rate of VTE within this small cohort despite thromboprophylaxis, IMPROVE may have inadequate sensitivity to VTE risk in patients with cirrhosis. While these small studies suggest some

discriminatory power in those with cirrhosis, both low risk groups in the above studies had VTE rates (with inclusion of PVT) above the threshold (1%) where thromboprophylaxis would be considered potentially beneficial.[36] Both PADUA and IMPROVE were developed to predict DVT and PE. Risk factors for PVT in cirrhosis are distinct with markers of portal hypertension severity (thrombocytopenia, reduced portal flow, and previous variceal bleeding) more important.[37] There is currently insufficient evidence to recommend the use of these risk assessment models in patients with cirrhosis; larger confirmatory studies are required. However, given the population data highlights increased VTE risk with laboratory studies supporting hypercoagulability in patients with cirrhosis (with caveats in the critically ill population),[6] we suggest hospitals apply their existing approach to VTE thromboprophylaxis to patients with cirrhosis. The variable inclusion of PVT within the VTE rate between studies highlights the need for this to be considered as a distinct endpoint, given the uncertainties discussed above.

5.2 | Bleeding risk assessment

A bleeding risk assessment model was also developed from a refined IMPROVE cohort (after exclusion of those with unknown bleeding histories and admission with bleeding), including 2% (n = 134) with "liver failure and INR>1.5."[38] While thrombocytopenia (platelet $<100\times10^9$/L) was an exclusion criterion for original study entry, this analysis reported 1.7% of patients with platelet counts $<50\times10^9$/L. Both thrombocytopenia and liver failure with international normalized ratio (INR) > 1.5 were associated with increased bleeding risk and are incorporated into the derived IMPROVE bleeding risk assessment tool. However, given patients with liver disease have a higher baseline risk of bleeding compared to other medically ill patients (particularly when critically ill),[39] and that the majority of bleeding relates to portal hypertension, the impact of pharmacological thromboprophylaxis on bleeding risk in this patient group remains uncertain. In the validation study of the IMPROVE bleeding risk score in acutely ill medical patients, use of anticoagulant prophylaxis was not associated with increased bleeding risk, but both thrombocytopenia and "liver failure with INR>1.5" were confirmed as associated with increased bleeding risk.[40] The IMPROVE bleeding tool has been evaluated in a single small prospective cohort of patients with cirrhosis with only 3% meeting the criteria for high bleeding risk.[35]

In critically ill patients with cirrhosis, most bleeding events are variceal in nature.[24,25,39] Factors identified as associated with increased bleeding risk include severity of liver disease, sepsis, renal impairment, bilirubin, prolonged coagulation times (particularly APTT), and low fibrinogen. Of note, the use of anticoagulants was not associated with increased bleeding.[25,39] Drolz et al. described "bleeding on admission" and the combination of "APTT >100s, platelet count $<30\times10^9$/L and fibrinogen<60 mg/dl" as the strongest predictors of (predominantly variceal) bleeding.[39] This contrasts with findings in the peri-procedural setting in which these parameters have not been found to influence bleeding risk, with neither thrombocytopenia or PT/INR predictive of bleeding.[41,42] This is reviewed in greater detail in the ISTH SSC guidance for periprocedural management of hemostasis in patients with cirrhosis.[42] Additionally, a recent study in hospitalized patients with cirrhosis and either acute decompensation or acute on chronic liver failure, found no relationship between hemostatic markers and non-portal hypertensive bleeding.[43] Thrombocytopenia has been paradoxically associated with increased PVT risk in ambulatory patients with cirrhosis, and may reflect severity of portal hypertension.[37] There is a need for further evaluation of bleeding risk stratification in patients with cirrhosis admitted to hospital.

6 | Thromboprophylaxis in patients with cirrhosis

The landmark studies of thromboprophylaxis in acutely ill medical patients included a highly selected cohort of patients with an anticipated extended admission duration, contrasting with the current short length of stay for the majority of medical admissions.[44] While these studies do not report the numbers of patients with cirrhosis, the exclusion criteria of thrombocytopenia (platelet $<100\times10^9$/L) and/or prolongation of PT or INR > 1.2 will have resulted in very few patients with cirrhosis being eligible, particularly those with acutely decompensated disease (data not reported).[2,3] There is limited study of the efficacy and safety of thromboprophylaxis within patients with cirrhosis and the available data are summarized in Table 1. None of the studies in hospitalized patients with cirrhosis identified a statistically significant reduction in HA-VTE associated with thromboprophylaxis use, although rates were numerically lower in three of the four studies incorporating PVT in the VTE definition.[34,35,45] Bleeding rates were higher than thrombosis rates in the majority of these studies; of note, in five of the six studies reporting bleeding outcomes, bleeding rates were numerically higher in patients not receiving thromboprophylaxis.[34,45,46,47,48] This may be explained by a higher baseline bleeding risk in the cohort not receiving thromboprophylaxis; for example, due to a past bleeding history and/or portal hypertension related bleeding.[45] Unfortunately there was inadequate detail presented regarding site/nature of bleeding events, particularly as to whether secondary to portal hypertension or not. In the single study reporting a numerically higher bleeding risk with thromboprophylaxis, a significantly increased risk of bleeding was identified associated with unfractionated heparin (UFH) but not LMWH.[46] Unfortunately, variable bleeding definitions and limited detail regarding site of bleeding limit further analysis. There are a number of additional limitations including the predominantly observational and retrospective nature, the variable inclusion of PVT as a clinical endpoint (four of seven studies), variable use of thromboprophylaxis (11.9%–76%), and variable definition of thromboprophylaxis use including as few as two consecutive doses being classified as "receiving thromboprophylaxis," and incomplete data regarding thromboprophylaxis agent used and dose prescribed.

TABLE 1 Summary of studies of anticoagulant thromboprophylaxis in patients with cirrhosis

Author	Time period	Study design	Admissions *n*	Thromboprophylaxis use *n* (%)	VTE *n* (%)	Bleeding *n* (%)
Critically ill patients only						
Al Dorzi et al.[16]	2006–2008	Retrospective observational cohort of critically ill patients	75	Overall: 24 (32) LMWH: 2 (2.7) UFH: 22 (29.3)	Overall: 2 (2.7) TP: 1 (1.4) No TP: 1 (1.4)	Not reported
Hospitalized patients						
Aldawood et al.[57]	2009	Retrospective observational cohort	226	Overall: 27 (11.9)	Overall: 6 (2.7) TP: 1 (3.7) No TP: 5 (2.2)	Not reported
Barclay et al.[45]	2008–2011	Retrospective observational cohort	1518	Overall: 392 (25.8) LMWH: 345 (22.7) UFH: 38 (2.5) Both: 9 (0.5)	Overall[a]: 23 (1.8) TP: 2 (0.5) No TP: 21 (1.8)	Overall: 131 (8.6) TP: 8 (2) No TP: 123 (10.3)
Bogari et al.[34]	2010–2013	Retrospective observational cohort	163	Overall: 52 (32)	Overall[a]: 18 (11) TP: 3 (5.8) No TP: 15 (13.5)	Overall: 5 (3.1) TP: 0 No TP: 5 (4.5)
Davis et al.[35]	Nov 2017-Mar 2018	Prospective observational cohort	98	Overall: 74 (76) LMWH: 35 (36) UFH: 39 (40)	Overall[a]: 4 (4.1) TP: 2 (2.7) No TP: 2 (8.3)	Overall: 1 (4.2) TP: 0 No TP: 1 (4.2)
Moorehead et al.[47]	2012–2013	Retrospective observational cohort	300	Overall[c]: 157 (52)	Overall[a]: 33 (11) TP[c]: 19 (12.1) No TP: 14 (9.8)	Overall: 96 (32) TP: 47 (30) No TP: 49 (34.3)
Shatzel et al.[46]	2007–2012	Retrospective observational cohort	600	Overall: 296 (49) Enoxaparin 40 mg od: 134 (22) UFH 5000 U bd/tds: 141 (23.5) Both: 21 (3.5)	Overall: 12 (2.0) TP: 7 (2.4) No TP: 5 (1.7)	Overall: 41 (6.8) TP: 24 (8.1) No TP: 17 (5.5)
Yerke et al.[48]	2008–2015	Retrospective propensity matched observational cohort	1806	Overall[b]: 903 (50)	Overall: 37 (2.0) TP[b]: 20 (2.2) No TP[b]: 17 (1.9)	Overall: 88 (4.9) TP[b]: 26 (2.9) No TP[b]: 62 (6.9)
Ambulatory patients						
Villa et al.[29]	2008–2010	Prospective randomized controlled trial	70	Enoxaparin 40 mg od: 34 (49)	Enoxaparin[a]: 0 No TP[a]: 6 (16.6)	Enoxaparin: 2 (5.8) No TP: 1 (2.7)

Abbreviations: bd, twice daily; LMWH, low molecular weight heparin; tds, three times daily; TP, thromboprophylaxis; UFH, unfractionated heparin; VTE, venous thromboembolism; od, once daily.

[a]Includes portal vein thrombosis.

[b]Defined "TP use" if given for >50% of stay and as 'no TP use' if <50% of stay and included UFH bd or tds, enoxaparin 40 mg once daily or 30 mg bd or fondaparinux 2.5 mg once daily.

[c]Defined "TP use" if at least two consecutive doses given and included UFH 5000 units bd or tds or dalteparin 5000 units once daily.

Thrombocytopenia and prolonged PT have been reported as associated with reduced uptake of thromboprophylaxis in patients with cirrhosis.[16,49,50] The studies summarized in Table 1, and small studies focused on patients with cirrhosis receiving in-hospital thromboprophylaxis, report predominantly low rates of bleeding (accepting the limitations above).[8,51] Expert consensus recommends temporary discontinuation of anticoagulation during variceal bleeding;[52] it would be appropriate to adopt this approach for thromboprophylaxis. Re-initiation can be considered following definitive treatment, for example post endoscopic variceal band ligation.

A single, small randomized controlled study ($n = 74$) of prophylactic enoxaparin compared to placebo (for 48 weeks) in ambulatory patients with decompensated liver disease (Child Pugh B7-C10) demonstrated a significant reduction in PVT and further decompensating events, with no significant increase in bleeding.[29] While small, this provides the most compelling evidence for both efficacy and safety of LMWH in patients with cirrhosis. The results of a further randomized controlled trial investigating prophylactic rivaroxaban versus placebo in decompensation-free survival in the ambulatory setting is awaited (NCT02643212).

Given most bleeding events in patients with cirrhosis are secondary to portal hypertension, and the lack of an apparent increase in bleeding associated with thromboprophylaxis in the limited data available, we suggest hospitals apply their existing approach to VTE thromboprophylaxis to patients with cirrhosis. Where the existing approach involves the use of PADUA/IMPROVE risk assessment models, clinicians should be aware of the limitations above and further consider thromboprophylaxis on a case-by-case basis. For those admitted to critical care settings, particularly with acute on chronic liver failure, we suggest consideration of thromboprophylaxis on a case-by-case basis.

7 | Choice of pharmacological thromboprophylaxis in patients with cirrhosis

For acutely ill medical patients, VTE prevention guidelines generally agree LMWH, UFH, and fondaparinux are similarly efficacious.[30,31] LMWH and fondaparinux are associated with a lower incidence of

TABLE 2 Comparison of societal recommendations for VTE prevention in patients with cirrhosis

	ISTH 2022	EASL 2022[56]	ACG 2020[58]
VTE risk assessment	Insufficient evidence to support use of VTE risk assessment models to guide thromboprophylaxis use.	Clinical prediction scores, such as PADUA or IMPROVE can be used to identify patients at high risk of VTE in hospital.	No recommendation
Bleeding risk assessment	Do not consider thrombocytopenia and/or prolonged PT/INR as absolute contraindications to thromboprophylaxis.	No recommendation	No recommendation
Thromboprophylaxis recommendation	Suggest use of anticoagulant thromboprophylaxis in line with local protocols and suggest the use of LMWH or fondaparinux over UFH. In patients with renal impairment, we suggest the use of LMWH over UFH. Suggest case-by-case consideration in critically ill patients (especially with acute on chronic liver failure).	In patients with cirrhosis at risk of DVT/PE, thromboprophylaxis with LMWH can be recommended as it has a reasonable safety profile, but efficacy is unclear. In patients with cirrhosis at risk of DVT/PE, thromboprophylaxis with DOACs can be recommended in patients with Child-Pugh class A/B as DOACs have a reasonable safety profile, but efficacy data are still limited. In patients with Child-Pugh C cirrhosis DOACs are not recommended.	Pharmacological prophylaxis for DVT prevention appears safe in hospitalized cirrhotic patients in the absence of bleeding or platelet count $<50\times10^9$/L
Research recommendations	• Include portal vein thrombosis as a distinct clinical endpoint in future studies of HA-VTE in patients with cirrhosis. • Further studies of VTE risk stratification in hospitalized patients with cirrhosis. • Investigation of optimal dosing and duration of anticoagulant thromboprophylaxis in hospitalized patients with cirrhosis.	• Large observational studies to collect data on validity of risk assessment models for VTE in patients with cirrhosis. • Large observational studies, or ideally randomized controlled trials to evaluate the safety and efficacy of LMWH or DOACs in hospitalized patients with cirrhosis at high risk of VTE.	

Abbreviations: ACG, American College of Gastroenterology; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; EASL, European Association for the Study of the Liver; HA-VTE, hospital-associated venous thromboembolism; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low molecular weight heparin; PE, pulmonary embolism; PT, prothrombin time; UFH, unfractionated heparin; VTE, venous thromboembolism.

heparin-induced thrombocytopenia and injection burden compared to UFH, and are generally favored.[31] There have been concerns raised from preclinical studies regarding efficacy of these agents in patients with cirrhosis due to their indirect mechanism of action via potentiation of antithrombin, which is reduced in cirrhosis.[53] However, a recent study comparing the anticoagulant effect of prophylactic LMWH/UFH prescribed to patients with and without cirrhosis suggested a similar anticoagulant effect of heparins in patients with cirrhosis.[54] There is no need for routine laboratory monitoring in this setting. As highlighted above and in Table 1, not all studies reported the pharmacological agent and/or doses utilized, so specific recommendations regarding preferred agent/dose cannot be made. Of note, fondaparinux has a longer half-life, is contraindicated in renal insufficiency (creatinine clearance of <30 ml/min), and lacks a direct reversal agent.[55] To our knowledge there are no direct comparisons between pharmacological agents in patients with cirrhosis.

8 | Comparison with other societal documents

Other societal recommendations are summarized in Table 2. Of note, while European Association for the Study of the Liver suggests the use of direct oral anticoagulants in patients with cirrhosis (excluding Child-Pugh C),[56] these agents are not licensed or routinely used for thromboprophylaxis in hospitalized patients with the exception of major joint arthroplasty and within specific localities (e.g., North America), we therefore do not specifically consider these agents in this guidance document.

9 | Recommendations

1. We suggest inclusion of PVT as a distinct clinically important endpoint for future studies of thromboprophylaxis in patients with cirrhosis.
2. We recommend against the use of thrombocytopenia and/or prolongation of PT/INR as absolute contraindications to anticoagulant thromboprophylaxis in patients with cirrhosis.
3. For hospitalized patients with cirrhosis, we suggest the use of anticoagulant thromboprophylaxis in line with local protocols and suggest the use of LMWH or fondaparinux over UFH. In patients with renal impairment, we suggest the use of LMWH over UFH. For critically ill patients (particularly with acute on chronic liver failure), we suggest case-by-case consideration of thromboprophylaxis.
4. We recommend further research to refine VTE risk stratification within hospitalized patients with cirrhosis, and to establish the optimal dosing and duration of thromboprophylaxis.

AUTHOR CONTRIBUTIONS

LNR 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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This guidance was developed by the Subcommittee Working Group on Hemostatic Management of Patients with Liver Disease; please see member contributions below. The manuscript was reviewed and approved by the Guidelines and Guidance Committee of ISTH.

CONFLICTS OF INTEREST

We have no conflicts of interest to report.

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