Venous Thromboembolism Management in Special Cases

High VTE Risk in Liver Diseases: An Emerging Concern

In patient with cirrhosis and 'autoanticoagulation', elevated international normalized ratio (INR) may not protect from thrombosis. Thus, thromboprophylaxis should be considered in such patients.

	In-hospital VTE incidence[2]	VTE-related mortality[2]	Length of stay/ hospitalization cost[3]
Compensated cirrhosis	21% higher	7.6% higher	52% higher*
Decompensated cirrhosis	39% higher	11.1% higher	

*Compared to hospitalized patients without liver disease; data from the Nationwide Inpatient Sample (NIS) for the year 2005. NIS is the largest all-payer inpatient database in the United States and contains data from almost 1,000 hospitals from the 37 participating states.

Clinical Challenges of VTE Management in Liver Diseases

Patients with cirrhosis are at high risk for bleeding and thrombotic complications due to dysregulated hemostasis.[2]

Complications of encephalopathy, edema, ascites, immobility, liver cancer, and venous stasis of the portal vein further contribute to increased risk for thrombosis.[4]

Cirrhosis affects procoagulant/ anticoagulant factors, thus increasing INR/activated partial thromboplastin time levels and decreasing anti-factor Xa (anti-Xa) levels. Therefore, determining when to institute prophylactic anticoagulation and optimal therapeutic monitoring becomes challenging.[5,6]

VTE Management in Hospitalized Patients With Cirrhosis

Screening

Patients with cirrhosis should undergo periodical screening endoscopy to assess varices and risk of bleeding.[1]

Recent expert consensus

Hospitalized patients with cirrhosis should be considered for thromboprophylaxis and treatment unless absolutely contraindicated (Figure 1).[2]

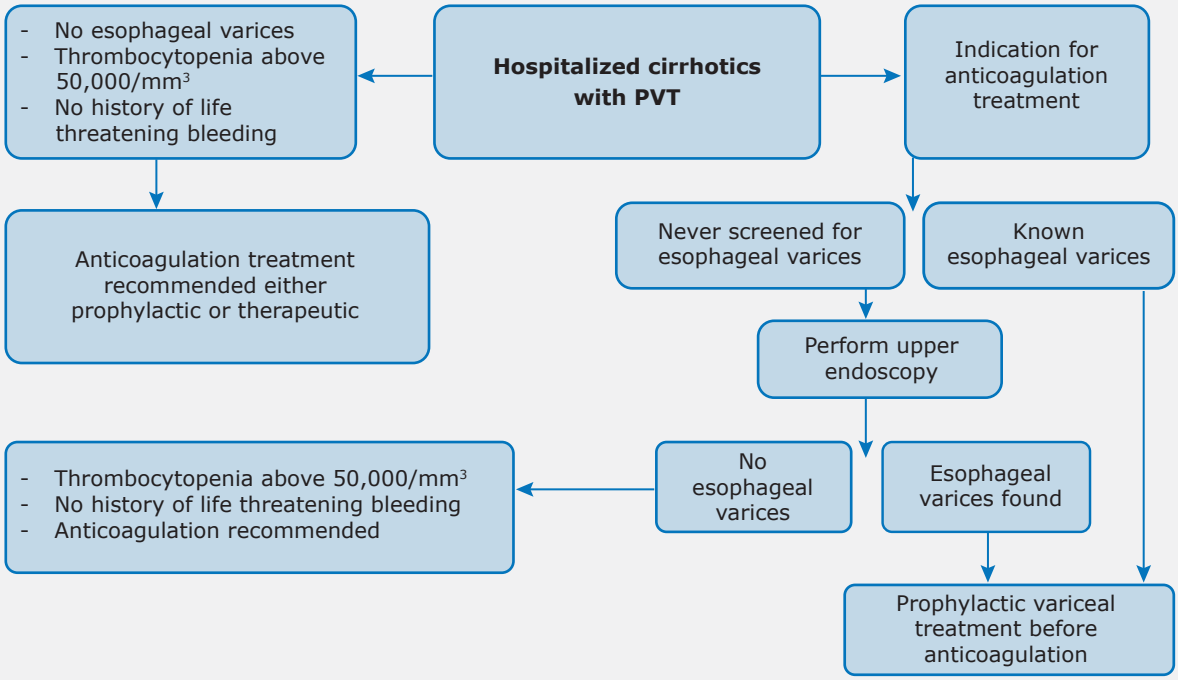
Treatment

VTE treatment should be used in patients with minimal varices, no evidence of clinical bleeding, and appropriate clinical indication.[1]

Monitoring

Patients with cirrhosis should be monitored closely for signs and symptoms of bleeding and thrombosis.[5]

Figure 1: VTE management in hospitalized patients with cirrhosis



PVT, portal vein thrombosis.

Pharmacological VTE Management in Liver Diseases

Low molecular weight heparins (LMWHs) as treatment of choice:
For the prevention and treatment of deep vein thrombosis(DVT)/pulmonary embolism (PE)/portal vein thrombosis (PVT) in patients with cirrhosis[5]

Unfractionated heparins (UFHs) as alternative anticoagulant therapy:
In patients with cirrhosis for shorter-term use and in patients with severe renal dysfunction and/or hemodynamic instability[5]

Direct oral anticoagulants (DOACs) contraindicated:
Rivaroxaban and apixaban contraindicated in severe hepatic diseases due to impaired metabolic inactivation[7]

Guideline Recommendations for VTE Management in Liver Diseases

The latest guidelines recommend using anticoagulation in acutely ill patients for both VTE prophylaxis and treatment in carefully selected patients with cirrhosis (Table 1).

Table 1: Guideline recommendations for pharmacological VTE management in liver diseases

ACCP (2012)	ASH (2016, 2020)	AGA (2021)
For thromboprophylaxis in acutely ill patients with high risk for bleeding (patients with cirrhosis and high-risk varices), mechanical thromboprophylaxis with graduated compression stockings or intermittent pneumatic compression is recommended.[7,8]	• Hepatic insufficiency must be considered prior to the selection of anticoagulant.[9] • When choosing particular anticoagulants in patients with the liver disease, LMWHs offer advantage of fixed, weight-adjusted dosing without monitoring.[4] • Standard dosages of LMWHs can be used in patients with cirrhosis.[4] • DOACs are not recommended for moderate to severe liver disease.[9] • Anti-Xa heparin level monitoring considered in patients receiving long-term treatment.[4]	In hospitalized patients with cirrhosis and who otherwise meet standard guidelines for the use of VTE prophylaxis, standard anticoagulation prophylaxis is recommended over no anticoagulation.[10]

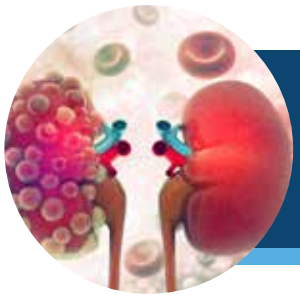
ACCP, American College of Chest Physicians; AGA, American Gastroenterological Association; ASH, American Society of Hematology; DOACs, direct oral anticoagulants; LMWHs, low molecular weight heparins; VTE, venous thromboembolism.

LMWHs for VTE Management in Patients with Cirrhosis

Standard LMWH dosing may be used in patients with cirrhosis, but serum creatinine may be falsely low in decompensated patients.[5]

Monitoring of anti-Xa is useful in patients with cirrhosis to ensure sufficient anticoagulation by LMWH for prophylactic or therapeutic indications.[11]

Prophylactic use of LMWH (enoxaparin 40 mg daily) is clinically proven to be safe in patients with cirrhosis.[11]



High VTE Risk in Chronic Kidney Disease (CKD)

2X increased VTE risk in patients with chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] 15–59 mL/min/1.73 m^2) than patients with normal renal function (eGFR >90 mL/min/1.73 m2).[12]

≥12 times higher mortality rate ratio of PE in patients receiving dialysis than general population.[4]

2X increased risk of bleeding in patients with eGFR <30 mL/min.[4]

Higher recurrent VTE rates in patients with moderate to severe CKD (6.6 events per 100 person-years) than in patients with mild to no CKD (5 events per 100 person- years).[13]

Clinical Challenges of VTE Management in CKD

No thromboembolic and hemorrhagic risk scores adequately define individual VTE risk in patients with CKD.[14]

The need for anticoagulants is much higher in patients with CKD due to a fragile balance between the high risk of thromboembolic events and bleeding.[14]

Several anticoagulants increase the risk of bleeding due to impaired renal functions.[9] In contrast, the initiation of anticoagulation in severe CKD and end-stage renal disease is still debatable. Uncertainty is also higher in VTE management, as there are no specific guidelines for patients with CKD.[14]

Pharmacological VTE Management in CKD

LMWHs are preferred for pharmacokinetic predictability and ease of administration without the need for monitoring. However, dose adjustment is required in CKD stages 4 and 5. For dosage adjustment, it is recommended to monitor anti-Xa activity to avoid under dosage and achieve optimal therapeutic levels.[14]

UFH is preferred as a short half-life allows the anticoagulant effect to wear off within 1 to 4 hours, even in patients with severe renal dysfunction at high hemorrhagic risk.[14]

DOACs as anticoagulant therapy constitute a therapeutic option in CKD. However, in renal dysfunction, their use makes dose adjustment mandatory, as there is a variable degree of renal clearance.[14]

Guideline Recommendations for VTE Management in CKD

- There is no consensus regarding preferred anticoagulation for VTE prophylaxis and treatment in CKD.[14]
- Due to limited data, clinicians need practical clues for monitoring and optimizing the VTE treatment in CKD.[14]
- The latest guideline recommends considering the benefit-risk ratio of anticoagulants on a case-by-case basis for VTE prevention and treatment in patients with CKD (Table 2).

Table 2: Guideline recommendations for pharmacological VTE management in CKD

ACCP (2012)	ASH (2020)	ISH (2022)
• Renal function should be considered when making decisions about the use and/or the dose of LMWH, fondaparinux, and other antithrombotic drugs that are cleared by the kidneys, particularly in the elderly, patients with diabetes, and those at high risk for bleeding.[8] • **Depending on the circumstances, one of the following options is recommended in this situation[8]:** — Avoiding the use of anticoagulant that bioaccumulates in the presence of renal impairment — Using a lower dose of the agent — Monitoring drug level or its anticoagulant effect	• DOACs are not recommended in patients with renal insufficiency (CrCl <30 mL/min).[9]	• LMWH is recommended for initial treatment of established VTE in patients with cancer when CrCl is ≥30 mL/min.[15] • In severe renal failure (CrCl <30 mL/min), use unfractionated heparin, followed by early vitamin K antagonists (possible from day 1) or LMWH adjusted to anti-Xa concentration for the treatment of established VTE.[15] • In patients with severe renal failure, an external compression device can be applied, and pharmacological prophylaxis could be considered on a case-by-case basis.[15]

ACCP, American College of Chest Physicians; ASH, American Society of Hematology; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; ISH, International Society on Thrombosis and Haemostasis; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

LMWHs for VTE Management of Patients in CKD

- Enoxaparin is the most studied LMWH in patients with renal dysfunction, primarily due to its licensed dose reduction (1 mg/kg once daily) for patients with severe renal disease (CrCl <30 mL/min).[16]
- There are limited clinical data for dalteparin and tinzaparin in severe CKD.[14]
- The recommended dosing of enoxaparin for VTE management in renal impairment is shown in Table 3.[17]

Table 3: Enoxaparin dosing for VTE management in renal impairment

In moderate (CrCl: 30–50 mL/min)/ mild (CrCl: 50–80 mL/min) renal impairment	No dose adjustment is recommended; however, careful clinical monitoring is advised.[17]	
In severe renal impairment (CrCl <30 mL/min)[17]		
VTE management	**Standard dose**	**Adjusted dose in renal impairment**
Prophylactic dosing	40 mg SC once daily	20 mg SC once daily
	20 mg SC once daily	20 mg SC once daily
Therapeutic dosing	1 mg/kg SC twice daily	1 mg/kg SC once daily
	1.5 mg/kg SC once daily	1 mg/kg SC once daily

CrCl, creatinine clearance; SC, subcutaneous; VTE, venous thromboembolism.

VTE and Bleeding Risk Assessment in Hospitalized Patients With Liver/Renal Diseases

No specific VTE risk assessment models (RAMs) have been recommended in hospitalized patients with liver/renal diseases.[7,14]

The ACCP (2012) recommends the Padua prediction scoring system, and the ASH (2018) refers to Padua and IMPROVE as VTE RAMs for predicting thrombosis and bleeding risk in medically ill patients.[18]

Padua predictor score that is widely used to assess VTE risk in hospitalized medically ill patients has also shown to be helpful in the subpopulation of patients with liver/renal diseases.[18,19]

When choosing pharmacological VTE prophylaxis, the risk of major bleeding with IMPROVE-BLEED risk score should be considered in acutely ill medical patients with liver/renal diseases.[18]

Medically ill patients with liver/renal diseases with Padua VTE score of ≥4 or IMPROVE-VTE score of ≥3, provided that their IMPROVE-BLEED risk score is <7, should be offered pharmacologic prophylaxis during the hospital stay.[18]

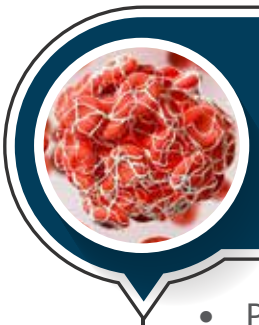
VTE and Bleeding Risk Assessment in Patients With Liver/Renal Diseases Undergoing Surgery

No specific VTE RAMs have been recommended in patients with liver/renal diseases undergoing surgery.[14]

The ACCP (2012) recommends the Caprini prediction scoring system for assessing VTE risk in patients undergoing surgery, which can also be used in the subpopulation of patients with liver/renal diseases.[20]

When choosing pharmacological VTE prophylaxis, the risk of major bleeding with IMPROVE-BLEED risk score should be considered in patients with liver/renal diseases undergoing surgery.[18]

Surgical patients with liver/renal diseases: CAPRINI VTE score of ≥3 and IMPROVE-BLEED risk score <7, should be offered pharmacologic prophylaxis.[20]



Key Points

- Patients with significant renal or hepatic diseases have a dual increased risk of thrombosis and bleeding; thus, VTE management is challenging.
- To assess VTE risk in patients with liver/renal diseases, the Padua RAM can be used in medically ill patients and Caprini RAM can be used in patients undergoing surgery.
- To implement pharmacological VTE prophylaxis in patients with liver/renal diseases, the risk of major bleeding with an IMPROVE-BLEED risk score should also be considered in medically ill patients or in patients undergoing surgery.
- LMWHs and UFHs can be used for the management of VTE in cirrhosis; however, DOACs are contraindicated in cirrhosis.
- LMWHs, UFHs, and DOACs can be used for the management of VTE in CKD; however, dose adjustment is required in severe CKD.

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