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CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guideline on the Management of Coagulation Disorders in Patients With Cirrhosis

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Cirrhosis is a disease state that is accompanied by significant alterations in laboratory parameters, such as platelet count (PLT) and prothrombin time/international normalized ratio (PT/INR), routinely used to estimate clotting. Based on this measured thrombocytopenia and coagulopathy, it has traditionally been assumed that these results convey a high risk of bleeding and, therefore, significantly increased risk for patients undergoing invasive procedures. However, it has become clear that this understanding underestimates the balanced nature of alterations in hemostasis associated with end-stage liver disease, and that neither thrombocytopenia nor elevated PT/INR necessarily predicts bleeding outcomes in most of these patients.[1] Moreover, the severity of coagulopathy estimated by these parameters is not predictive of bleeding complications in patients with cirrhosis, including major complications, such as variceal hemorrhage.[2] Although these patients are at risk for thrombosis—including deep vein thrombosis, pulmonary embolism, splanchnic vein thrombosis, or stroke—there has been some trepidation on the part of clinicians to treat them with conventional anticoagulants, such as vitamin K antagonists (VKAs).

Furthermore, testing strategies using PT/INR to estimate the likelihood of bleeding and monitor treatment end points in patients taking VKAs might not be relevant in patients with cirrhosis who have derangements of both procoagulant and anticoagulant factors. More recently, investigators have tested the utility of a more integrative approach using measurements of fibrin clot formation and lysis to try and capture the full spectrum of abnormalities seen in cirrhosis.

Scope and Purpose

This guideline aims to provide recommendations for pertinent clinically relevant questions related to hemostasis of bleeding, as well as prevention and treatment of thrombosis in patients with cirrhosis. Recognizing that prediction of bleeding or thrombotic events in this population is challenging, a detailed understanding of the current evidence in this field is vital to deliver the safest and most effective care to this vulnerable patient population. This guideline is accompanied by a technical review (TR)[3] in which a systematic review and meta-analysis of the evidence are summarized for the following questions:

Bleeding-related questions:

1. What testing strategy for bleeding risk assessment is most beneficial for patients with cirrhosis?
2. Does preprocedure prophylaxis to correct coagulation parameters and/or PLT level reduce the risk of bleeding in patients with cirrhosis?

Thrombosis-related questions:

3. Is venous thromboembolism (VTE) prophylaxis indicated in hospitalized patients with cirrhosis?
4. Should patients with cirrhosis be screened for nontumoral portal vein thrombosis (PVT)?
5. What are the data on specific anticoagulant therapies for nontumoral PVT in patients with cirrhosis?
6. In patients with atrial fibrillation and cirrhosis, is anticoagulation safe and effective?

Target Audience

The target audience of these guidelines includes primary care providers, gastroenterologists, hepatologists, advanced practice providers, nurses, and other health care professionals. Patients, as well as policy makers, can also benefit from these guidelines. These guidelines are not intended to impose a standard of care for individual institutions, health care systems, or countries. They provide

Abbreviations used in this paper: **AGA, American Gastroenterological Association Institute; CI, confidence interval; DOAC, direct-acting oral anticoagulant; ERCP, endoscopic retrograde cholangiopancreatography; FFP, fresh frozen plasma; INR, international normalized ratio; PICO, patient, intervention, comparator, outcome; PLT, platelet; PT, prothrombin time; PVT, portal vein thrombosis; RCT, randomized controlled trial; RR, relative risk; TPO-RA, thrombopoietin receptor agonist; TR, technical review; VET, visco-elastic testing; VKA, vitamin K antagonist; VTE, venous thromboembolism.**

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the basis for rational, informed decisions for clinicians, patients, and other health care professionals.

Methods

This document presents the official recommendations of the American Gastroenterological Association Institute (AGA) on the management of coagulation disorders in patients with cirrhosis. The guideline was developed by the AGA Institute's Clinical Guideline Committee and approved by the AGA Governing Board. It is accompanied by a TR that provides a detailed synthesis of the body of evidence from which these recommendations were formulated.

Optimal understanding of this guideline will be enhanced by reading applicable portions of the TR.[3] The guideline was developed using a process outlined elsewhere.[4] Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation methodology[5] and best practices as outlined by the Institute of Medicine (now National Academy of Medicine).[6] The certainty of the evidence supporting each statement is described as high, moderate, low, or very low (Table 1). A very low rating indicates great uncertainty regarding the estimate of effect. The strength of a recommendation reflects an understanding of the balance of the certainty of the evidence, the likelihood of desirable and undesirable effects, variability in patient values and preferences, as well as resource allocation (Table 2).[7] The adoption of this methodology, and the rigorous application of these standards to the specific PICO (patient, intervention, comparator, outcome) questions, distinguishes this guideline from other published work that have relied more heavily on expert opinion to provide guidance or chosen other specific questions for review.[8–11]

Guideline Panel Composition, Funding, and Conflicts of Interest

Members of the Guideline Panel and TR Panel were selected by the AGA Governing Board and Chair of the Clinical Guidelines Committee with careful consideration of conflict of interest. The Guideline Panel included gastroenterologists and hepatologists, Grading of Recommendations Assessment, Development and Evaluation methodologists, and a hematologist. Development of this guideline and the accompanying TR was fully funded by the AGA Institute without additional outside funding. The TR and guideline underwent independent peer review and a 30-day open public comment period. A patient was also asked to review this guideline and provide feedback. Panel members disclosed all potential conflicts of interest according to the AGA Institute policy. These disclosure statements are maintained at the AGA Institute headquarters in Bethesda, Maryland. No Guideline Panel member was excused from participation in the process owing to disqualifying conflict.

Formulation of Clinical Questions

The authors of the TR and this guideline, with input from the AGA governing board, identified critical areas of clinical need. Clinically relevant questions were structured into the PICO framework with the identified populations and intervention under consideration, the comparator against which the intervention was assessed, and the outcomes. Questions were developed for defined populations and were broadly divided into issues related to bleeding risk, particularly around procedures, and issues related to risk of clotting and anticoagulation in patients with cirrhosis. This clinical practice guideline addresses the specific questions summarized in Table 3.

Development of Recommendations

The Guideline Panel and the authors of the TR met virtually on January 8, 2021. The information in the TR was discussed in a systematic manner, facilitating subsequent creation of the guideline recommendations for or against each intervention. The Guideline Panel independently formulated the guideline recommendations. The certainty of available evidence and strength of recommendation are provided for each recommendation statement. The strength of each recommendation was rated as either strong or conditional. The words "we recommend" indicate a strong recommendation and "we suggest" indicate a conditional recommendation. Recommendations might be accompanied by qualifying comments or remarks, which serve to highlight variability in patient values or to help facilitate implementation.

Table 1. Grading of Recommendations Assessment, Development and Evaluation Definitions for Certainty of the Evidence

Certainty of evidence	Definition
High	We are very confident that the true effect lies close to the estimate of the effect
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low	Our confidence in the estimate is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect
Evidence gap	Available evidence is insufficient to determine true effect

Table 2. Grading of Recommendations Assessment, Development and Evaluation Definitions on Strength of Recommendation and Guide to Interpretation

Strength of recommendation	Wording in the guideline	For the patient	For the clinician
Strong	"The AGA recommends…"	Most individuals in this situation would want the recommended course and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests…"	The majority of individuals in this situation would want the suggested course, but many would not.	Different choices would be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
No recommendation	"The AGA makes no recommendation…"		The confidence in the effect estimate is so low that any effect estimate is speculative at this time.

Consideration of Health Equity

Using the health disparities and minority health search strategy,[12] applicable studies were searched for in Medline to evaluate for health disparities and effects on health equity.

External Review

The guideline and the accompanying TR underwent independent peer review and a 30-day open public comment period. All comments were collected by AGA staff. The comments were reviewed and addressed by the Guideline Panel and TR Panel and/or incorporated into a revised document. All comments were acknowledged in a response document, which was created for internal tracking purposes.

Plans for Updating This Guideline

In accordance with the Clinical Guidelines Committee policies, all guidelines are reviewed annually by the AGA Clinical Guideline Committee for new information. The need for an update will be determined no later than 3 years from publication (in 2024).

Recommendations

A summary of the recommendations in this guideline is provided in Table 3.

PICO Question 1: What testing strategy for bleeding risk assessment is most beneficial for patients with cirrhosis?

This question is aimed at the estimation of incremental cirrhosis-related bleeding risk associated with nonsurgical procedures (either bleeding or mortality). The authors broke this question into 2 components:

PICO Question 1A: Should visco-elastic testing (VET) be performed in patients with cirrhosis before procedures?

PICO Question 1B: Should PLT and PT/INR testing be done before procedures to predict procedure-related bleeding?

Recommendation for PICO Question 1A: In patients with stable cirrhosis undergoing common gastrointestinal procedures, the AGA makes no recommendation regarding VET before procedures to predict bleeding risk. (No recommendation, knowledge gap)

Recommendation for PICO Question 1B: In patients with stable cirrhosis (with known baseline abnormal coagulation parameters) undergoing common gastrointestinal procedures (eg, paracentesis, thoracentesis, variceal banding, colonic polypectomy, ERCP, and liver biopsy), the AGA suggests against the use of extensive preprocedural testing, including repeated measurements of PT/INR or PLT count. (Conditional recommendation, very low certainty evidence)

Summary of the Evidence

The role of PT/INR and PLT testing before invasive procedures is not well-defined and accumulating evidence suggests that these are not relevant markers for assessment of bleeding risk. Thromboelastography has received growing attention as an alternative marker for bleeding risk. Thromboelastogram has been used in clinical practice in surgery for upwards of 3 decades[13] and reviewed in multiple studies as a predictor of procedure-related bleeding risk. The authors of the TR identified a total of 5 randomized controlled trials (RCTs),[14–18] which studied the effect of using VET, either thromboelastogram or rotational thromboelastometry, vs standard of care before procedures (3

Table 3. Summary of Recommendations

PICO question	Recommendations	Strength of recommendation	Quality of evidence
1. What testing strategy for bleeding risk assessment is most beneficial for patients with cirrhosis?			
1A. Should VET be performed in patients with cirrhosis before procedures?	In patients with stable cirrhosis undergoing common gastrointestinal procedures, the AGA makes no recommendation regarding VET before procedures to predict bleeding risk.	No recommendation	Knowledge gap
1B. Should PLT and PT/INR testing be done before procedures to prevent procedure-related bleeding?	In patients with stable cirrhosis (with known baseline abnormal coagulation parameters) undergoing common gastrointestinal procedures (eg, paracentesis, thoracentesis, variceal banding, colonic polypectomy, ERCP, and liver biopsy), the AGA suggests against the use of extensive preprocedural testing, including repeated measurements of PT/INR or PLT count.	Conditional recommendation	Very low certainty evidence
2. Does preprocedure prophylaxis (ie, using blood product transfusion or TPO-RAs) to correct coagulation parameters and/or PLT level reduce the risk of bleeding in patients with cirrhosis?			
2A. Should preprocedural PLT and/or FFP transfusions be given to cirrhosis patients with thrombocytopenia or prolonged PT/INR to prevent procedure-related bleeding?	In patients with stable cirrhosis undergoing common gastrointestinal procedures (eg, paracentesis, thoracentesis, variceal banding, colonic polypectomy, ERCP, and liver biopsy), the AGA suggests against the routine use of blood products (eg, FFP and PLT) for bleeding prophylaxis Comment: This recommendation applies to the majority of patients with stable cirrhosis who usually do not have severe thrombocytopenia or severe coagulopathy. In patients with severe derangements in coagulation or thrombocytopenia undergoing a procedure that is high risk for bleeding, decisions about prophylactic blood transfusions should include discussions about potential benefits and risks (including transfusion reactions and delay of procedure) in consultation with a hematologist.	Conditional recommendation	Very low certainty evidence
2B. Should TPO-RAs be given to patients with cirrhosis and thrombocytopenia before procedures to prevent procedure-related bleeding?	In patients with thrombocytopenia and stable cirrhosis undergoing common procedures (and in particular, "low-risk" procedures), the AGA suggests against the routine use of TPO-RAs for bleeding prophylaxis. Comment: Patients who place a high value on the uncertain reduction of procedural bleeding events and a low value on the increased risk for PVT can reasonably select a TPO-RA.	Conditional recommendation	Very low certainty evidence

Table 3. Continued

PICO question	Recommendations	Strength of recommendation	Quality of evidence
3. Is VTE prophylaxis with anticoagulation indicated in hospitalized patients with cirrhosis?	In hospitalized patients with cirrhosis and who otherwise meet standard guidelines for the use of VTE prophylaxis, the AGA suggests standard anticoagulation prophylaxis over no anticoagulation.	Conditional recommendation	Very low certainty evidence
4. Should patients with cirrhosis be screened for PVT?	In patients with cirrhosis, the AGA suggests against routine screening for PVT. Comment: Patients who put a high value on the uncertain benefits of PVT screening and a low value on the potential downsides and harms related to treatment would reasonably select screening. This does not apply to patients who are listed for liver transplantation.	Conditional recommendation	Very low certainty evidence
5. What, if any, specific anticoagulation therapies should be offered for treatment of PVT in patients with cirrhosis: low-molecular-weight heparin, DOACs, or VKAs?	In patients with cirrhosis and acute or subacute nontumoral PVT, the AGA suggests using anticoagulation over no anticoagulation for treatment of PVT. Comment: Patients who put high value on the bleeding risk on anticoagulation and lower value on uncertain benefits of anticoagulation would reasonably choose no anticoagulation.	Conditional recommendation	Very low certainty evidence
6. Should patients with atrial fibrillation and cirrhosis be treated with anticoagulation?	In patients with cirrhosis and atrial fibrillation with an indication for anticoagulation, the AGA suggests using anticoagulation over no anticoagulation. Comment: Patients, particularly those with more advanced cirrhosis (Child-Turcotte-Pugh class C) and or low CHA2DS2-VASC scores who put high value on avoiding the bleeding risk on anticoagulation and lower value on the stroke reduction could reasonably choose no anticoagulation.	Conditional recommendation	Very low certainty evidence

RCTs) or during bleeding events (2 RCTs) in patients with cirrhosis and coagulopathy. Coagulopathy was typically defined as INR >1.8 and/or PLT <50,000/mL. Outcomes that were studied included bleeding after procedures, transfusion requirements, and mortality.

The use of VET did not impact post-procedural bleeding compared with standard of care in the 3 studies (relative risk [RR], 0.33; 95% CI, 0.01–7.87) and, similarly, was not helpful in predicting failure to control bleeding or prevent rebleeding. Preprocedural risk assessment using VET was not associated with long-term mortality, assessed for up to 90 days after the procedures (RR, 1.05; 95% CI, 0.45–2.44). There was a clear trend toward lower use of blood products in patients who were managed with VET, but these studies used variable thresholds for blood product transfusions, making comparisons difficult. No other impact was seen on clinically relevant outcomes. Two studies that examined the role of VET in management of bleeding events in patients with cirrhosis and demonstrated no clear benefit in ability to control bleeding or prevent rebleeding.

There was no direct comparative evidence from RCT or cohort studies of preprocedural laboratory testing with PLT and PT/INR or preprocedural prophylaxis with PLT and fresh frozen plasma (FFP) transfusion and the outcome of risk of procedural bleeding. Indirect evidence was examined from case series of consecutive patients and single-arm cohort studies that examined bleeding outcomes during or after the procedure in cirrhosis patients with elevated PT/INR and low PLT, in whom no prophylactic administration of PLT or FFP was given.

Certainty of the Evidence

The certainty of evidence was low or very low across the majority of outcomes as there were few events that led to serious imprecision, issues with inconsistency (heterogeneity), and issues with indirectness (the outcomes of delayed bleeding or mortality were more likely related to the underlying liver disease severity).

Discussion

The risk of periprocedural bleeding in patients with cirrhosis is variable and characteristics unique to cirrhosis, such as presence of advanced Child-Turcotte-Pugh cirrhosis or presence of acute-on-chronic liver failure contribute greatly to bleeding risk.[19–22] Furthermore, other factors can enhance or modify procedural bleeding risk in patients with cirrhosis, such as acute kidney injury.[21] Based on the TR, there was no direct evidence that conventional laboratory tests, including INR or PLT count, accurately predict bleeding risk in patients with cirrhosis. Although in vitro evidence suggests that a PLT count >55,000/mL provides adequate substrate for thrombin generation in patients with cirrhosis,[23] the TR authors found no direct clinical evidence supporting PLT count cutoff across various thresholds in predicting bleeding events. Based on the very low certainty evidence and the limited benefits, the Panel made a conditional recommendation against traditional coagulation testing.

VETs are an attractive alternative to traditional coagulation testing, as they are dynamic tests that measure clot formation, clot strength, and dissolution over time. VETs have the unique ability to parse out different components of the coagulation system, PLTs, and fibrinolytic system and measure the effective contribution of each to clot formation. The TR authors identified RCTs investigating procedural bleeding management strategies, which compared traditional coagulation measurement with VET protocol; however, because of the limitations of the evidence (rare bleeding events and no routine use of restrictive arms to establish baseline risk of bleeding without administration of prophylaxis), the Panel made no recommendation regarding VETs and labeled this question as an important evidence gap.

PICO Question 2: Does preprocedure prophylaxis (ie, using blood product transfusion or thrombopoietin receptor agonists [TPO-RAs]) to correct coagulation parameters and/or PLT level reduce the risk of bleeding in patients with cirrhosis?

This question is aimed to evaluate the effects of preprocedural prophylaxis with blood product transfusion or TPO-RAs on bleeding or mortality outcomes in patients with cirrhosis undergoing nonsurgical procedures. The authors broke this question into 3 components:

PICO Question 2A: Should preprocedural PLT and/or FFP transfusions be given to cirrhosis patients with thrombocytopenia or prolonged PT/INR to prevent procedure-related bleeding?

PICO Question 2B: Should preprocedural TPO-RAs be given to cirrhosis patients with thrombocytopenia to prevent procedure-related bleeding?

Recommendation for PICO Question 2A: In patients with stable cirrhosis undergoing common gastrointestinal procedures (eg, paracentesis, thoracentesis, variceal banding, colonic polypectomy, endoscopic retrograde cholangiopancreatography [ERCP], and liver biopsy), the AGA suggests against the routine use of blood products (eg, FFP or PLTs) for bleeding prophylaxis. (Conditional recommendation, very low certainty evidence)

Comment: This recommendation applies to the majority of patients with stable cirrhosis who usually do not have severe thrombocytopenia or severe coagulopathy. In patients with severe derangements in coagulation or thrombocytopenia undergoing a procedure that is high risk for bleeding, decisions about prophylactic blood transfusions should include discussions about potential benefits and risks (including transfusion reactions and delay of procedure) in consultation with a hematologist.

Recommendation for PICO Question 2B: In patients with thrombocytopenia and stable cirrhosis undergoing common procedures (and in particular, "low-risk" procedures), the AGA suggests against the routine use of TPO-RAs for bleeding prophylaxis. (Conditional recommendation, very low certainty evidence)

Comment: Patients who place a high value on the uncertain reduction of procedural bleeding events and a low value on the increased risk for PVT may reasonably select a TPO-RA.

Summary of the Evidence

The authors of the TR reviewed the literature in reference to 6 common procedures, including paracentesis, thoracentesis, esophagogastroduodenoscopy with banding, ERCP, colonoscopy with polypectomy, and liver biopsy. They found no RCTs using traditional coagulation testing such as PT/INR or PLT to either predict procedural bleeding or guide prophylactic blood product administration in patients with cirrhosis. Furthermore, no RCTs were found that used conventional coagulation tests to guide clinical management of post-procedure bleeding events.

The authors of the TR also performed a systematic review of studies that reported on the utility of standard laboratory tests, defined as PT/INR and PLT, for prediction of bleeding risk and found no direct evidence of an abnormal PT/INR or PLT threshold that predicts bleeding risk. The majority of the studies that reported bleeding rates were retrospective cohort studies that chose varying definitions of bleeding and/or thresholds to transfuse patients.

Many of the low-risk interventions reported either no bleeding or very low bleeding rates: 7 observational studies, including 1 retrospective case series,[24] 1 case-control,[22] and 5 cohort studies[25–29] examined patients undergoing paracentesis and 1 case-control[30] and 2 retrospective cohort studies)[31,32] examined thoracentesis. There was no clear threshold for standard coagulation parameters that defined an unacceptable risk, although 1 study suggested acute kidney injury might predispose to bleeding.[21] Similarly, in patients undergoing esophagogastroduodenoscopy with banding (4 case-control, retrospective, and prospective cohort studies),[20,33–35] colonoscopy with polypectomy (4 retrospective cohort studies),[36–39] or ERCP with sphincterotomy (3 retrospective studies),[40–42] a specific value of PLT or PT/INR that identified patients at an increased bleeding risk was not defined. Rather, progressive decompensation (as defined by the Child-Turcotte-Pugh score) was a more likely marker for bleeding after variceal banding, colonoscopic polypectomy (especially for larger polyps), or endoscopic sphincterotomy. Lastly, retrospective cohort studies[43–49] of patients undergoing liver biopsy did not routinely report interventions before biopsy or complication rates based on severity of liver disease. In the few studies that specifically reported on outcomes in patients with cirrhosis, there was no clear difference in risk of bleeding compared with patients without cirrhosis and no specific PT/INR threshold that defined a high-risk group, but a trend of lower PLT counts correlated with higher bleeding risk. See Supplementary Table 1.

The TR identified 5 RCTs that compared the use of PLT transfusions to TPO-RAs (including avatrombopag and lusutrombopag),[50–54] which have been US Food and Drug Administration–approved for the treatment of thrombocytopenia in cirrhotic patients undergoing a procedure. These studies assessed the impact of the TPO-RAs on PLT counts in patients with cirrhosis and thrombocytopenia before planned procedures, which typically were low risk (primarily dental procedures and diagnostic endoscopies). Study end points were increases in PLT counts (avoidance of fixed protocol PLT transfusion) rather than clinical bleeding, as well as rates of adverse events, including PVT.

No studies compared the use of TPO-RAs to a restrictive strategy of no TPO-RAs. Overall, there was a low rate of bleeding and multiple methodologic concerns existed (use of surrogate markers rather than direct evidence, lack of comparison groups who did not receive transfusion, as well as the low event rates). The risk of thrombotic events at 30 days was approximately 1% for avatrombopag and lusutrombopag.

Certainty of the Evidence

The certainty of evidence was very low across all outcomes, as observational studies without comparison group and indirect evidence (studies that did not report on PLT/plasma transfusion but used coagulopathy markers, such as INR and PLT) was examined. Furthermore, the evidence for TPO-RAs were derived from RCTs; however, indirectness on multiple levels decreased the certainty in the evidence (eg, indirect, surrogate outcome was used for procedural bleeding; PLT cutoff or need for transfusion to reach certain PLT cutoff and there was indirectness on comparator; there was no comparison group of patients with thrombocytopenia who did not receive either TPO or PLT transfusion before procedures). In addition, there were few events that led to serious imprecision.

Discussion

The data suggest that the baseline bleeding risk for common nonsurgical procedures is generally low. Although procedures are routinely grouped empirically by perceived risk, defined by the likelihood of bleeding based on the intervention or on the potential magnitude of bleeding, there are insufficient data to justify cut points of standard coagulation parameters to identify specific risk groups. It is important to acknowledge that this recommendation pertains to patients typically seen in practice; those with profoundly abnormal laboratory results (eg, patients who have concomitant bleeding disorders unrelated to their liver disease) may be at a different level of risk, and they were not typically included in the studies in this literature.

The TR authors stratified procedure-related bleeding risk into low or high using a threshold of 1.5%, based on literature review and expert interpretation of indirect evidence. In patients with severe thrombocytopenia or coagulopathy undergoing high-risk procedures, decisions about prophylactic blood transfusions should include potential benefits and risks, such as transfusion reactions and alloimmunization. The threshold for severe thrombocytopenia or coagulopathy could not be clearly defined from the literature and remains a matter of clinical judgment. In many cases, clinical care of these patients should be managed in collaboration with an expert hematologist.

The utility of PLT counts to predict bleeding in patients with cirrhosis is uncertain, and low PLT counts may reflect progression and severity of the underlying liver disease,

accompanying portal hypertension, and hypersplenism to a greater extent than bleeding risk at baseline.[55,56] Despite this, PLTs are commonly transfused in patients with cirrhosis and thrombocytopenia before invasive procedures. This strategy poses some risk to patients, given the short half-life of the transfusions, cost, and the possibility of alloimmunization and other adverse reactions. In the absence of direct comparative evidence, it is not possible to conclude that clinically relevant bleeding events during or after nonsurgical procedures could be prevented by transfusing blood products or TPO-RAs in patients with cirrhosis and decreased PLT count/increased INR. The Panel made a conditional recommendation against the routine use of blood products (eg, FFP and PLTs) for bleeding prophylaxis and TPO-RAs for bleeding prophylaxis, acknowledging the limited clinically relevant benefit, and low baseline bleeding risk that appeared to be independent of preprocedure bleeding prophylaxis.

PICO Question 3: Is VTE prophylaxis with anticoagulation indicated in hospitalized patients with cirrhosis?

Recommendation: In hospitalized patients with cirrhosis and who otherwise meet standard guidelines for the use of VTE prophylaxis, the AGA suggests standard anticoagulation prophylaxis over no anticoagulation. (Conditional recommendation, very low certainty of evidence)

Summary of the Evidence

Despite clear evidence of increased risk for VTE, hospitalized patients with cirrhosis have not been typically included in most studies of thromboprophylaxis with anticoagulation, and no RCTs were found comparing outcomes of prophylactic anticoagulation in patients with cirrhosis. Review of the literature by the TR identified only 5 retrospective studies[57–61] that examined the risk of thrombotic events in patients with cirrhosis. Given the observational and retrospective design, without well-defined outcomes (all thrombotic events, ie, deep venous thrombosis, pulmonary embolism, and PVT, were considered together) and lack of systematic screening for VTE, the TR team explored data from well-done RCTs in the general medical population, as well as previously published guidelines.[62] There was a reduction in symptomatic deep venous thrombosis (RR, 0.47; 95% CI, 0.22–1.00), but no effect in nonfatal pulmonary embolism (RR, 0.61; 95% CI, 0.23–1.67) with the use of prophylactic anticoagulation in hospitalized patients.

Systematic search by the TR team identified 3 retrospective cohort studies reporting on bleeding rates in patients with cirrhosis. Major bleeding was reported in 2 of the studies and all 3 studies reported on all bleeding events (overall number of major and minor bleeds). Pooled estimate did not show an association between prophylactic anticoagulation and major bleeding events (RR, 1.07; 95% CI, 0.37–3.06) or overall bleeding events (RR, 1.57; 95% CI, 0.73–3.37).

Certainty of the Evidence

The certainty of evidence was low across the benefit outcomes and very low for harms. The key concern was imprecision due to low number of events. Studies evaluating harms were judged to have serious risk of bias due to residual confounding, such as comorbidities or antiplatelet therapies in intervention vs controls that may have had an impact on the risk of bleeding independent from prophylactic anticoagulation and/or patient selection. Lastly, there was serious indirectness in the studies evaluating the benefits of anticoagulation because they were not done in the cirrhotic population. Overall certainty of evidence was very low.

Discussion

Patients with acute medical illnesses are at high risk of developing VTE; a recent policy statement from the American Heart Association points out that the risk of VTE is 1 to 2 per 1000 adult patients annually, but possibly as high as 1 in 100 annually among elderly patients and even higher among subgroups with risk factors. VTE contributes to increasing length of stay and is the leading cause of preventable hospital death in the United States and worldwide.[63] Similarly, it has been increasingly recognized that patients with cirrhosis are at significant risk of VTE, with typical incidence rates of 0.5%–1.9%, but in some studies, considerably higher.[64]

The VTE risks are best estimated by the use of several risk assessment models, most recently including the Padua Prediction score[65] and the IMPROVE VTE risk assessment model. These have been developed and widely applied. It is recommended that clinicians should incorporate both VTE and bleeding risk assessments into clinical decision making. The IMPROVE investigators developed a risk assessment model incorporating liver disease as a risk factor for bleeding (defined as an INR $>$ 1.5), which conveyed an increase in RR of 2.18.[66–68] The TR analysis pooled data from 3 retrospective cohort studies and did not detect an increase in the risk of bleeding in patients with cirrhosis treated with anticoagulation in these studies.

Given the strength of the data supporting the use of anticoagulation in acutely ill hospitalized medical patients, the evidence of similar VTE risk among patients with cirrhosis, and the very low certainty of evidence of an increased bleeding risk with pharmacologic VTE prophylaxis, the Panel made a conditional recommendation for use of anticoagulation prophylaxis.

PICO Question 4: Should patients with cirrhosis be screened for PVT?

Recommendation: In patients with cirrhosis, the AGA suggests against routine screening for PVT. (Conditional recommendation, very low certainty evidence)

Comment: Patients who put a high value on the uncertain benefits of PVT screening and a low value on the potential downsides and harms related to treatment would reasonably select screening. This does not apply to patients who are listed for liver transplantation.

Summary of the Evidence

PVT is a common occurrence in patients with cirrhosis; however, no direct comparative evidence from RCT or cohort studies has been derived to evaluate the utility of screening interventions for nontumoral PVT on patient important outcomes, such as hepatic decompensation and/or transplant-free survival. After a systematic search, the TR team was able to identify 4 single-arm prospective studies of patients with cirrhosis undergoing systematic imaging in the outpatient setting reporting the incidence of nontumoral PVT.[69–72] All studies used ultrasonography as a screening modality and had variable patient follow-up time (between 1 and 8 years). Patients also underwent serial imaging at varying screening intervals, which described an incidence ranging from 3.5% to 4.6% at 1 year and up to 11% during a 5-year course of follow-up.

Certainty of the Evidence

The certainty of evidence was very low, derived from single-arm studies with a serious risk of bias, and serious indirectness at the level of the outcome. Authors used nontumoral PVT detection as a surrogate outcome, and the impact on screening on patient important outcomes (eg, hepatic decompensation and mortality) remains unknown.

Discussion

The clinical impact of nontumoral PVT, however, is uncertain and likely reflects the progression of liver disease; whether PVT acts as a precipitant for worsening liver disease is debated. In patients with PVT who undergo liver transplantation, outcomes might be worse, and PVT has been characterized as conveying an increased risk of early mortality and graft failure. As a result, some authorities recommend screening for PVT at regular intervals,[73] as well as treating all newly diagnosed PVT. Several studies have demonstrated an increased likelihood of recanalization in patients with PVT treated with anticoagulation.[74] In addition, meta-analyses and systematic reviews of observational studies of anticoagulation do not describe an increased risk of bleeding; in fact, several studies describe a possibly lower rate of portal hypertension-related bleeding.[75,76] However, no comparative efficacy data from RCTs exist to guide therapy in either the transplant or nontransplant populations. Given the lack of data on the clinical significance of nontumoral PVT and limited data about treatment outcomes, the benefit of routine screening for PVT remains uncertain and the Panel made a conditional recommendation against routine screening.

PICO Question 5: What, if any, specific anticoagulation therapies should be offered for treatment of PVT in patients with cirrhosis: low-molecular-weight heparin, direct-acting oral anticoagulants (DOACs), or VKAs?

Recommendation: In patients with cirrhosis and acute or subacute nontumoral PVT, the AGA suggests using anticoagulation over no anticoagulation for treatment of PVT. (Conditional recommendation, very low certainty evidence)

Comment: Patients who put a higher value on the bleeding risk on anticoagulation and a lower value on the uncertain benefits of anticoagulation would reasonably choose no anticoagulation.

Summary of the Evidence

The TR identified 12 studies in adult patients with PVT treated with anticoagulation that reported recanalization rates; anticoagulation strategies included low-molecular-weight heparin or VKA. No studies of DOACs were identified that met the inclusion criteria. There was a substantially increased rate of complete or partial recanalization in patients treated with anticoagulation compared to untreated patients (RR, 2.27; 95% CI, 1.73–2.98). The studies distinguished patients with tumor-related vs nontumoral and acute vs chronic PVT. Higher rates of recanalization were noted in treated patients with acute or sub-acute PVT, defined as recent thrombosis in the absence of signs of chronic PVT, which were mostly asymptomatic. Although the certainty of evidence was very low, the overall rates of bleeding in patients treated with anticoagulation did not appear to be elevated compared with controls. Moreover, there was a decreased risk of portal hypertensive bleeding in patients who were anticoagulated compared to patients in the control group who were not anticoagulated (RR, 0.34; 95% CI, 0.16–0.75).

Certainty of the Evidence

The certainty of evidence was very low across all outcomes, including benefits and harms. The key concern across all of the outcomes was imprecision because the pooled estimates were based on sparse data and low event rate. In addition, for bleeding outcomes, data from single-arm cohort studies were used with a concern for serious risk of bias due to lack of comparator, assessment of outcome was poorly described (there was not a clear definition of bleeding) and there were studies with inadequate follow-up time. Recanalization was used as a surrogate outcome for patient important outcomes (eg, hepatic decompensation and mortality), necessitating rating down for indirectness.

Discussion

Based in the current literature, there is no direct comparative evidence regarding PVT treatment with anticoagulation and the effects on mortality and/or liver-related morbidity. Furthermore, published studies lack standard bleeding definitions and most did not distinguish portal hypertensive bleeding from other bleeding sources. However, despite the limitations, there is very low certainty evidence that using anticoagulation will promote recanalization and even decrease bleeding. The latter finding is potentially explained by reduced incidence of bleeding from esophageal varices in the anticoagulation group as a potential benefit of therapy to reduce portal pressure by promoting recanalization. Taking all this into consideration, the Panel made a conditional recommendation for use of anticoagulation. Lastly, there are no data to support the use

of one anticoagulant over another, as no comparative studies between anticoagulants exist. In addition, the TR team did not evaluate nonpharmacologic treatment, such as transjugular intrahepatic portosystemic shunt. This recommendation is in line with the treatment of PVT with anticoagulation in liver transplantation candidates.

PICO Question 6: Should patients with atrial fibrillation and cirrhosis be treated with anticoagulation?

Recommendation: In patients with cirrhosis and atrial fibrillation with an indication for anticoagulation, the AGA suggests using anticoagulation over no anticoagulation. (Conditional recommendation, very low quality evidence)

Comment: Patients, particularly those with more advanced cirrhosis (Child-Turcotte-Pugh class C) and/or low CHA2DS2-VASC scores, who put a higher value on avoiding the bleeding risk on anticoagulation and lower value on the stroke reduction could reasonably choose no anticoagulation.

Summary of the Evidence

The TR team explored established evidence for the benefit of oral anticoagulation in patients with atrial fibrillation described in the CHEST guideline.[77] This evidence is derived from well-done and large RCTs in the noncirrhotic population. In patients with cirrhosis and atrial fibrillation treated with anticoagulation compared with untreated patients, there was a reduction in mortality (RR, 0.72; 95% CI, 0.55–0.94). The risk of nonfatal stroke appeared to be lower in patients treated with DOACs compared with warfarin (RR, 0.81; 95% CI, 0.73–0.91). Bleeding risk was evaluated in 7 cohort studies that evaluated outcomes in patients treated with VKAs vs untreated controls or patients treated with DOACs; a higher risk of bleeding was seen in patients who were anticoagulated vs untreated controls (rate ratio, 1.91; 95% CI, 1.85–2.26), although the risk was lower among patients treated with DOACs vs VKAs (RR, 0.62; 95% CI, 0.45–0.85).

Similar trends were also seen in estimating risk of intracranial hemorrhage (rate ratio, 3.5; 95% CI, 3.30–4.0) comparing incidence in patients treated with VKAs to untreated controls, with a lower rate in patients treated with DOACs vs VKAs (RR 0.7; 95% CI, 0.58–0.84). The overall benefits of anticoagulation appear to outweigh the risk of bleeding in patients with cirrhosis and atrial fibrillation with a CHA2DS2-VASC score $\geq$2.

Certainty of the Evidence

The certainty of evidence was moderate across the benefit outcomes and very low across potential harms. There are well-done, large RCTs in the noncirrhotic population that were used to inform the benefit outcomes (reduction in mortality and nonfatal stroke), but because those studies did not include patients with cirrhosis, the evidence was rated down for indirectness. Single-arm cohort studies with a serious risk of bias and imprecision due to low event rate were used to inform the potential harms (major bleeding events and intracranial hemorrhage). The overall certainty of evidence was very low due to the uncertain harms.

Discussion

The overall mortality rate and the risk of nonfatal stroke are well defined in noncirrhotic populations with atrial fibrillation. Both outcomes are significantly reduced in patients who were treated with anticoagulation compared to those who were not treated, with the magnitude of the risk reduction related to the underlying risk estimated by the CHA2DS2-VASC score.[78] Patients with cirrhosis are equally at risk for morbidity from atrial fibrillation. However, patients with cirrhosis are routinely excluded from clinical trials with anticoagulation due to concerns for bleeding and, therefore, the exact benefit is unknown, but it is likely similar to the general population. Major bleeding was increased in cirrhotic patients treated with anticoagulation compared with cirrhotic patients who were not treated (rate ratio, 1.91). Most of the studies reporting on major bleeding were performed in patients with well-compensated cirrhosis and just a small percentage had advanced liver disease. Point estimates with a moderate certainty suggest a substantial improvement in risk of mortality and nonfatal stroke, especially with higher CHA2DS2-VASC scores. However, there is very low certainty in the magnitude of undesirable effects (bleeding) that was considered to be small. Therefore, the balance between desirable and undesirable effects probably favors the use of anticoagulation, especially in patients with higher CHA2DS2-VASC scores and compensated liver cirrhosis.

Equity

The Panel did not identify any recommendations that can worsen health equities but acknowledged that many of the TPO-RAs were expensive and might not be routinely covered by insurance and thus underinsured individuals can be disadvantaged.

Future Research Needs and Evidence Gaps

The TR and Guideline Panels identified multiple knowledge gaps and areas for future research in the management of coagulation and thrombosis in patients with cirrhosis. Although the understanding of the delicate balance between procoagulant and anticoagulant factors in cirrhosis has advanced significantly, this knowledge has yet to translate directly into evidence-based recommendations for clinical care, and multiple highly significant questions and knowledge gaps remain. Future research should focus on the best strategies to identify patients at risk for bleeding or thrombosis, to appropriately provide prophylaxis using blood product transfusion or TPO-RAs in patients at risk for clinically significant bleeding, to screen for and treat PVT, and to prevent clinically significant thromboembolic events. Additional RCTs and well-done cohort studies in these areas are urgently needed, given the ongoing large burden of chronic fibrotic liver diseases.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2021.08.015

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Conflicts of interest
All members were required to complete the disclosure statement. These statements are maintained at the American Gastroenterological Association (AGA) headquarters in Bethesda, Maryland, and pertinent disclosures are published with this report. Panel members disclosed all potential conflicts of interest according to the AGA Institute policy.

Supplementary Table 1. Procedure Risk Stratification

Low-risk procedures[a]	High-risk procedures[b]
Cardiac catheterization	Chest tube placement
Central line placement (including PICC line placement)	Endoscopy Coagulation or ablation of tumors, vascular lesions EMR or ESD ERCP with biliary or pancreatic sphincterotomy EUS with FNA Large polypectomy, polyp >1 cm PEG placement
Dental extraction	Dialysis access (tunneled)
Dialysis access (non-tunneled)	Liver biopsy (transjugular or percutaneous)
Endoscopy Diagnostic endoscopy with or without biopsy ERCP without sphincterotomy EUS without FNA Variceal band ligation Uncomplicated polypectomy, polyp ≤1cm	Lumbar puncture
Endotracheal intubation	Percutaneous solid organ biopsy or deep non-organ biopsy
Paracentesis	PTC placement
Percutaneous biopsy of superficial non-organ biopsy	TIPS placement
Thoracentesis	Transarterial or percutaneous HCC therapies

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; FNA, fine-needle aspirate; HCC, hepatocellular carcinoma; PEG, percutaneous endoscopic gastrostomy; PICC, peripherally inserted central catheter; PTC, percutaneous transhepatic cholangiography; TIPS, transjugular intrahepatic portosystemic shunt.
[a]A <1.5% bleed risk.
[b]A ≥1.5% bleed risk or bleeding risk into a vulnerable area.