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AGA Technical Review on Coagulation in Cirrhosis

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The coagulation system of healthy individuals has evolved to maintain a secure balance of pro- and antihemostatic systems. This fine-tuned balance promotes rapid coagulation during vessel breach, yet simultaneously preserves local control of thrombosis during vascular remodeling.[1] Patients with cirrhosis acquire a unique global alteration in the coagulation and fibrinolytic system (Figure 1).[2,3] As patients with cirrhosis develop progressive hepatic decompensation, coagulation protein synthesis is affected, thrombocytopenia worsens, and venous collaterals expand with portal hypertension. These changes were once thought to combine to promote bleeding tendencies and thereby protect against thrombosis. However, we now recognize the hemostatic system in patients with cirrhosis is a "rebalanced" state.[4–8]

Although patients with cirrhosis often have traditional markers of coagulopathy, with thrombocytopenia and elevation in international normalized ratio (INR), these laboratory values do not predict bleeding.[9,10] With the development of global coagulation assays, such as viscoelastic testing (VET) and thrombin generation assay, our understanding of this complex system in cirrhosis has progressed significantly. Early translational studies demonstrated that the decline in procoagulant proteins is balanced by a decline in anticoagulant proteins, such as activated protein C,[4] indicating the hemostatic system remains functional in cirrhosis and rebalanced. This complicated system is vulnerable to imbalance with disease progression and simultaneous bleeding, and thrombosis may be encountered.[11,12] Alterations that can tip this balance include both internal disease state progression (eg, worsening hepatic decompensation) and other factors, such as infection or renal failure.[13–15]

Understanding this paradigm in hemostasis is essential when caring for patients with cirrhosis who vary from well-compensated to acutely decompensated disease with acute on chronic liver failure (ACLF). When patients develop decompensated disease, clinicians measure the integrity of the hemostatic system and often rely on laboratory tests to explain episodes of bleeding, predict bleeding before invasive procedures, and direct hemostatic therapy. The most common conventional tests used to assess the hemostatic system include INR and coagulation factor assays (eg, fibrinogen). In addition, levels of platelets are often measured to screen for thrombocytopenia, which may be a risk factor for bleeding in some situations. These conventional tests of hemostasis are imprecise, and global coagulation assays, such as VETs, can more accurately predict risk.[16]

The role of anticoagulation has been increasingly studied in patients with cirrhosis, as risk and prevalence of venous thromboembolism (VTE) and nontumoral portal vein thrombosis (PVT) is now established.[17] In hospitalized patients with cirrhosis, the benefit and risk of VTE thromboprophylaxis is not well understood. Yet clinicians must make a choice daily when caring for patients with cirrhosis to administer or withhold VTE prophylaxis.[18] PVT is common in cirrhosis and it is not clear whether detection or treatment affects outcomes.[19] Yet, in certain circumstances, treatment with anticoagulation has been shown to be effective and safe.[20] The risk of stroke in atrial fibrillation (AF) is well recognized, and patients with cirrhosis are treated increasingly with anticoagulation.[21]

Our knowledge of the hemostatic system in cirrhosis has greatly expanded, and we now recognize that prediction of bleeding or thrombotic events in this population remains challenging.[22] Therefore, 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.

Objectives of the Review

This technical review (TR) focuses on pertinent clinically relevant questions related to hemostasis of bleeding, as well as prevention and treatment of thrombosis in patients with

Abbreviations used in this paper: **ACLF, acute on chronic liver failure; AF, atrial fibrillation; CI, confidence interval; CTP, Child-Turcotte-Pugh; DOAC, direct-acting oral anticoagulant; DVT, deep vein thrombosis; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; EVL, esophageal variceal ligation; FFP, fresh frozen plasma; GEV, gastroesophageal varices; GI, gastrointestinal; GRADE, Grading of Recommendation, Assessment, Development and Evaluation; ICH, intracranial hemorrhage; INR, international normalized ratio; PICO, population, intervention, comparator, outcome; PVT, portal vein thrombosis; RCT, randomized controlled trial; ROTEM, rotational thromboelastometry; RR, relative risk; SOC, standard of care; TEG, thromboelastography; TPO, thrombopoietin; TR, technical review; VET, viscoelastic testing; VKA, vitamin K antagonist; VTE, venous thromboembolism.**

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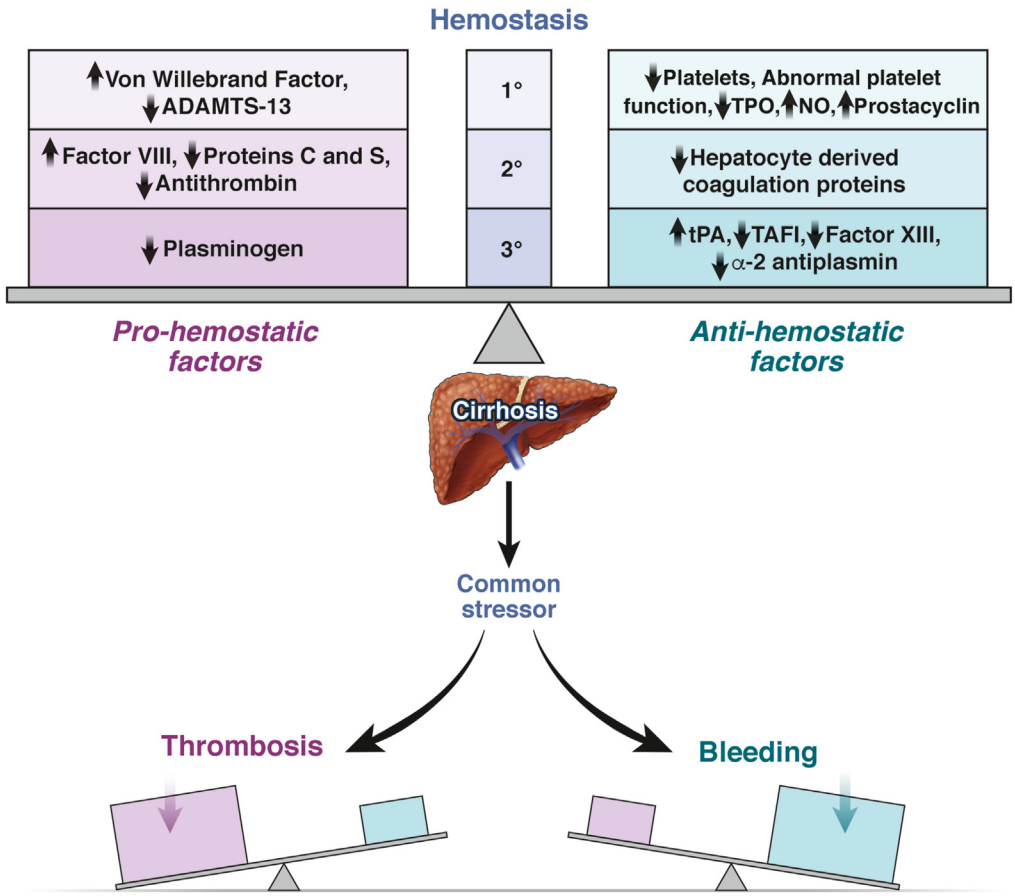

Figure 1. Overview of the hemostatic system in patients with cirrhosis. NO, nitric oxide; TAFI, thrombin activatable fibrinolysis inhibitor; tPA, tissue plasminogen activator.

cirrhosis. The goal of this TR was to provide an evidence-based framework for clinicians to base important therapeutic decisions for patients with cirrhosis. In this review, key deficiencies in the current literature relating to this topic are exposed, which should guide future investigations.

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 platelet level reduce the risk of bleeding in patients with cirrhosis?

Thrombosis-Related Questions

3. Is VTE prophylaxis with anticoagulation indicated in hospitalized patients with cirrhosis?
4. Should patients with cirrhosis be screened for nontumoral PVT?
5. What are the data on specific anticoagulant therapies for nontumoral PVT in patients with cirrhosis?
6. In patients with AF and cirrhosis, is anticoagulation safe and effective?

Methods

Overview

The TR was developed by the American Gastroenterological Association to support the accompanying guideline on coagulation in patients with cirrhosis. The team included content experts, methodologists, and a research librarian to assist with the systematic review. The Guideline Panel and the TR team initially developed several clinical questions aimed at the general care of patients with cirrhosis in relationship to clinical problems involving hemostasis and thrombosis. The TR team then used the PICO (population, intervention, comparator, and outcome) format to generate important clinically relevant questions. The PICO format provides a framework that guides evidence assessment and analysis profiles[23] (Table 1). The TR Panel then identified patient-important outcomes and systematically reviewed the literature for each PICO question. In addition, the TR Panel reviewed the literature for indirect evidence that could assist the Guideline Panel in making informed decisions for PICO questions 1 and 2. This indirect evidence included single-arm cohort studies that examined bleeding outcomes after various procedures in patients with cirrhosis. This evidence was used (1) to evaluate platelet and INR testing in patients with cirrhosis undergoing nonsurgical procedures and to inform on the role of platelet transfusion and plasma transfusion and (2) in the prophylaxis of nonsurgical procedural bleeding. Furthermore, indirect evidence from randomized controlled

Table 1. PICO Questions

Question no.	Informal question for diagnosis/ risk assessment	PICO question			
		Population	Intervention	Comparator	Outcome
1	What testing strategy for bleeding risk assessment is most beneficial for patients with cirrhosis?	Patients with cirrhosis undergoing invasive procedures	INR Platelets VET (TEG or ROTEM)	Usual care	Post-procedural bleeding Mortality Failure to control bleeding Failure to prevent rebleeding Blood product transfusion
2	Does preprocedure prophylaxis to correct coagulation parameters and/or platelet level reduce the risk of bleeding in patients with cirrhosis?	Patients with cirrhosis undergoing invasive procedures (eg, paracentesis, thoracentesis, EGD with variceal banding, ERCP, colonoscopy with polypectomy, and liver biopsy)	Platelet transfusion Plasma transfusion TPO agonists	Placebo	Reduction in procedural bleeding Bleeding
3	Is VTE prophylaxis with anticoagulation indicated in hospitalized patients with cirrhosis?	Hospitalized patients with cirrhosis	Heparin, LMWH	No intervention	VTE events Bleeding
4	Should patients with cirrhosis be screened for PVT?	Patients with cirrhosis: Transplantation candidates and nontransplantation candidates	Imaging	No screening	Incident PVT Mortality
5	What are the data on specific anticoagulation therapies for nontumoral PVT in patients with cirrhosis?	Patients with cirrhosis and PVT	LMWH, DOACs, warfarin	No intervention	Recanalization of PVT Progression of PVT Bleeding
6	In patients with AF and cirrhosis, is anticoagulation safe and effective?	Patients with cirrhosis and AF	Anticoagulation	No intervention	Mortality Stroke Bleeding ICH

AF, atrial fibrillation; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde pancreaticogram; ICH, intracranial hemorrhage; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PVT, portal vein thrombosis; ROTEM, rotational thromboelastometry; TEG, thromboelastography; TPO, thrombopoietin agonist; VTE, venous thrombotic events.

trials (RCTs) in the general population (noncirrhotic) was used to inform the benefits in PICO questions 3 and 6. Weekly meetings were held with the TR group throughout the process and evidence was summarized and graded for outcomes in each PICO. The GRADE (Grading of Recommendation, Assessment, Development and Evaluation) framework was used throughout the process to guide question formation, literature search, evidence grading, and profiles.[24]

Formulating the Clinical Questions and Outcome Measures

Initially, 26 questions were identified among the TR team and Guideline Panel, which were subsequently distilled into 6 separate PICO questions (Table 1). The questions and final PICOs were approved by the American Gastroenterological Association Governing Board. Among the most important outcomes considered were those directly related to clinical care with respect to assessment of bleeding risk in relationship to common procedures (PICO questions 1 and 2), efficacy of anticoagulation for the prevention of VTE (PICO question 3), need for screening patients with cirrhosis for PVT and the safety and treatment of PVT (PICO questions 4 and 5), and the safety and efficacy of prophylactic anticoagulation for prevention of stroke in AF (PICO question 6). This topic of investigation presents several challenging aspects when comparing outcomes, as the literature is largely limited to observational single-arm cohort studies with high risk of bias and use of nonstandardized outcome definitions. As such, certain PICOs were amenable only to qualitative descriptive analysis without quantitative evidence-based profiles due to severe deficiencies in the literature (PICO questions 1, 2, and 4), highlighting the need for future, methodologically rigorous, prospective investigation.

Systematic Review Process

The systematic review is reported in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Meta-Analysis of Observational Studies in Epidemiology proposal.[25] A protocol was developed a priori by the TR Panel in conjunction with the Guideline Panel to steer the systematic review.

Literature Search Strategy

Guided by the TR Panel, a medical librarian conducted a comprehensive search in April 2020, using the following databases: MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Embase Classic, Embase, and Wiley's Cochrane Library. The search was limited to English language and human adults. We conducted 4 different searches, all with different criteria. The PICO question 1 search was conducted for the 3 most used tests in patients with cirrhosis, that is, platelet count, INR, and VET. We used an RCT search filter and excluded case reports, editorials, letters, comments, and notes. Similarly, RCT and comparative design (case-control and comparative cohort) search filters were used for PICO question 2, and we searched for platelet, plasma transfusion, and thrombopoietin (TPO) agonists before nonsurgical procedures. Furthermore, all study designs except case reports, editorials, and letters, were used when conducting a search for PICO question 4. Lastly, 1 search without design filters was conducted for PICO questions 3, 5, and 6. We also queried content experts and hand-searched for indirect evidence and ongoing, yet to be published studies. When necessary, we contacted the authors of the pertinent conference abstracts published after 2017. We excluded conferences and congresses abstracts published before 2018. The final strategy is available in Supplementary Figure 1. The reference lists of previously published systematic reviews, prior guidelines, and the included references were also searched to identify relevant studies that might have been missed by our search strategy.

Eligibility Criteria

The inclusion and exclusion criteria were based on the formulated clinical questions and discussed for each individual PICO question.

Study Selection

The references identified using the above search strategy were reviewed according to the standard systematic review methods. The title and abstract of each identified reference were reviewed by 2 blinded independent investigators for eligibility and full-text retrieval. When disagreement was encountered at this stage, the reference was included for full-text retrieval. Each full-text article was then evaluated by 2 independent blinded investigators. Disagreement was solved by consensus between the 2 investigators and if it was not resolved, a third investigator from the team was consulted.

Data Analysis

For comparative studies, we expected these to originate from diverse populations and from heterogeneous settings, therefore, we used the random-effects model to pool the relative risks (RRs). When the number of included studies was 3 or fewer, we used the fixed-effect model due to the instability of between-study variance.[26] For incidence data, we used the Freeman-Tukey transformation and then pooled the results using the inverse-variance, fixed-effects model.[27] We presumed that larger studies were more likely to be more inclusive and representative of the general population. The fixed-effects model will give such studies, appropriately, higher weights in the pooled estimates. We used the I^2 statistic to quantify statistical heterogeneity.[28] Categorical variables were reported as RRs. The statistical analyses were conducted using RevMan, version 5.3.[29] When meta-analysis was not feasible, we presented data narratively and using descriptive statistics.

Certainty of Evidence

We used the GRADE framework to assess the quality of evidence derived from the systematic review and meta-analysis.[24] In this approach, the evidence is graded for each outcome as high, moderate, low, or very low. Evidence derived from RCTs starts as high quality and evidence derived from observational studies starts as low quality. Subsequently, the evidence can be rated down for risk of bias, inconsistency, indirectness, imprecision, publication bias, and/or other factors. The evidence can be rated up when there is a large magnitude of effect or dose–response relationship.

Evidence-to-Decision Framework

Because this TR was used to inform the development of clinical guidelines alongside a comprehensive risk-to-benefit analysis and the accompanying quality of evidence, information about additional factors, such as patients' preferences and values, resource utilization, and cost-effectiveness, were considered and noted when available.

PICO Question 1: What Testing Strategy for Bleeding Risk Assessment Is Most Beneficial for Patients With Cirrhosis?

Results

A total of 5 RCTs assessing the role of using VET (thromboelastography [TEG] and rotational thromboelastometry [ROTEM]) vs standard of care (SOC) before procedures (3 RCTs[16,30,31]) or during bleeding events (2 RCTs[32,33]) were identified (Table 2).

Inclusion criteria. Adults with cirrhosis and severe coagulopathy, defined as INR>1.8 and/or platelet count <50,000/mL, were included. Participants in the VET arm received fresh frozen plasma (FFP) and/or platelets according to study protocols. Participants in the SOC arm received FFP or platelets per medical center guidelines or SOC.

Exclusion criteria. Exclusion criteria were ongoing bleeding, previous or current thrombotic events, antiplatelet or anticoagulant therapy in the previous 7 days, infection or sepsis, hemodialysis, disseminated intravascular coagulation, or acute liver failure.

The Role of Traditional Coagulation Testing (eg, International Normalized Ratio and Platelet Count) in Assessment of Bleeding Risk Before or Clinical Management of Post-Procedure Bleeding Events

We found no RCTs using traditional coagulation testing alone, such as INR or platelet count, to either predict procedural bleeding or guide prophylactic blood product administration in patients with cirrhosis. We also found no RCTs that used conventional coagulation tests alone to systematically guide clinical management of post-procedure bleeding events.

The Role of Viscoelastic Testing in Assessment of Bleeding Risk Before Procedures in Cirrhosis

Three RCTs included patients with cirrhosis undergoing both low- and high-risk procedures. Overall, there were a total of 78 patients enrolled in each arm. The outcomes analyzed were post-procedural bleeding, blood product transfusion, and mortality. The study by Rocha et al[30] used ROTEM and the other 2 studies[16,31] used TEG to guide the transfusion protocol in the intervention arm.

Post-procedural bleeding. The use of VET to assess procedural bleeding risk had no impact on post-procedural bleeding (RR, 0.33; 95% confidence interval [CI], 0.01–7.87) (Supplementary Figure 2). However, the confidence in this estimate is very low because it is based on a single bleeding event that occurred in a solitary study. The lack of bleeding events in either arm in the other 2 studies rendered the RR not estimable.

Blood product transfusion. The number of patients who received blood products before an invasive procedure was lower in the VET cohort than in patients undergoing transfusions in the SOC condition (n = 26 vs 72). The use of VET to assess bleeding risk before procedures was associated with a trend toward administration of fewer preprocedural blood products for bleeding risk prophylaxis (RR, 0.37; 95% CI, 0.12–1.18) (Figure 2).

Mortality post procedure. Mortality was assessed for up to 90 days after the procedures. There were a total of 8 post-procedure deaths in each of the 2 arms, all associated with progressive liver failure and unrelated to post-procedure bleeding. Preprocedure bleeding risk assessment using VET was not associated with risk of death (RR, 1.05; 95% CI, 0.45–2.44) (Supplementary Figure 3).

The Role of Viscoelastic Testing in the Clinical Management of Bleeding Events in Patients With Cirrhosis

Two RCTs assessed the impact of VET use (79 patients) vs SOC (77 patients) in the management of variceal and nonvariceal bleeding events in patients with cirrhosis and severe coagulopathy.[32,33] Reported outcomes included failure to control bleeding, failure to prevent rebleeding after initial hemostasis, blood product transfusion, and mortality.

Failure to control bleeding. Failure to control bleeding by day 5 occurred in 12 vs 18 patients in the VET and SOC groups, respectively. Use of VET during management of bleeding events in patients with cirrhosis was not associated with a failure to control bleeding (RR, 0.64; 95% CI, 0.34–1.23) (Supplementary Figure 4).

Failure to prevent rebleeding (days 6–42). Of the 62 and 49 patients in the VET and SOC groups, respectively, who had controlled bleeding by day 5, failure to prevent rebleeding between days 6 and 42 occurred in 22 vs 19 patients. Rebleeding was defined as a single episode of clinically significant melena or hematemesis resulting in any of the following: hospital admission, blood transfusion, 3 g drop in hemoglobin, or death within 6 weeks. Use of VET at initial presentation of bleeding did not impact this late composite outcome (RR, 0.98; 95% CI, 0.63–1.51) (Supplementary Figure 5).

Blood product transfusion. Patients in the VET group received blood components using VET-based criteria with cutoffs that varied per each individual study protocol. The type of product administration based on VET results also varied. Kumar et al[32] used VET-based criteria to administer FFP, platelets, or cryoprecipitate, and Rout et al[33] administered FFP or platelets only. Similarly, the criteria for transfusion in the SOC groups were based on INR and platelet counts in both studies, but with different cutoffs. For this reason, pooled comparisons of the amount of blood products or transfusion-related adverse effects between the 2 groups could not be reasonably performed. A total of 46 of 79 patients in the VET group and 77 of 77

Table 2. GRADE Evidence Profile for PICO Question 1: What Testing Strategy for Bleeding Risk Assessment Is Most Beneficial for Patients With Cirrhosis?

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	SOC	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
Post-procedure bleeding 3	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	0/78 (0.0)	1/78 (1.3)	0.33 (0.01–7.87)	9 fewer per 1000 (from 13 fewer to 88 more)	⊕⊕◯◯ LOW	CRITICAL
Proportion with FFP or platelet transfusion received preprocedure 3	Randomized trials	Not serious	Serious[b]	Serious[c]	Serious[d]	None	26/78 (33.3)	72/78 (92.3)	0.37 (0.12–1.18)	582 fewer per 1000 (from 812 fewer to 166 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Mortality post-procedure 3	Randomized trials	Not serious	Not serious	Very serious[e]	Very serious[f]	None	8/59 (13.6)	8/59 (13.6)	1.05 (0.45–2.44)	7 more per 1000 (from 75 fewer to 195 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure to control bleeding at 5 d 2	Randomized trials	Not serious	Not serious	Serious[c]	Serious[d]	None	12/79 (15.2)	18/77 (23.4)	0.64 (0.34–1.23)	84 fewer per 1000 (from 154 fewer to 54 more)	⊕⊕◯◯ LOW	CRITICAL
Failure to prevent rebleeding after d5 (d6–42) 2	Randomized trials	Not serious	Not serious	Serious[g]	Serious[d]	None	22/62 (35.5)	19/49 (38.8)	0.98 (0.63–1.51)	8 fewer per 1000 (from 143 fewer to 198 more)	⊕⊕◯◯ LOW	IMPORTANT
Blood product transfusion received for bleeding (either of FFP, platelets, or cryoprecipitate) 2	Randomized trials	Not serious	Serious[b]	Serious[c]	Serious[f]	None	46/79 (58.2)	77/77 (100.0)	0.58 (0.48–0.71)	420 fewer per 1000 (from 520 fewer to 290 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT

Table 2. Continued

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	SOC	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
Mortality after bleeding (42 d)												
2	Randomized trials	Not serious	Not serious	Very serious[h]	Serious[d]	None	31/79 (39.2)	39/77 (50.6)	0.77 (0.56–1.06)	116 fewer per 1000 (from 223 fewer to 30 more)	⊕◯◯◯ VERY LOW	IMPORTANT

[a]Post-procedure bleeding occurred only in 1 study (1 event).
[b]$I^2 > 90\%$.
[c]Indirectness of comparator. Only a minority of patients would have received transfusions in an SOC practice.
[d]Small number of events, wide 95% CI.
[e]6-week mortality after procedure is less likely directly related to the procedure.
[f]Low number of events.
[g]Rebleeding after initial control is less likely to be impacted by blood product transfusion during initial bleeding event.
[h]Mortality after 42 days is less likely to be impacted by FFP or platelet transfusion during initial bleed and more likely to be related to liver-disease severity.

patients in the SOC group received transfusion of blood products (platelets, FFP, or cryoprecipitate, alone or in combination). Use of VET was associated with a lower risk of receiving blood product transfusion (RR, 0.58; 95% CI, 0.48–0.71) (Supplementary Figure 6).

Mortality after bleeding. A total of 31 of 79 patients in the VET group and 39 of 77 patients in the SOC group died within 6 weeks of the bleeding event. Use of VET was not associated with mortality after the bleeding event (RR, 0.77; 95% CI, 0.56–1.06) (Supplementary Figure 7).

Certainty of Evidence

The level of certainty was low or very low in most of the outcomes. The small number of events led to serious or very serious imprecision. We downgraded for inconsistency (I^2 >90%) in the outcomes related to blood product transfusion. Furthermore, we downgraded for indirectness of comparator in the outcomes related to blood product transfusion because only a minority of patients would have received transfusions in SOC practice. In the outcomes related to mortality or rebleeding, the evidence was downgraded for indirectness because these delayed outcomes are more likely to be related to liver disease severity than interventions.

Discussion

Clinicians must frequently assess bleeding risk in patients with cirrhosis and develop strategies to prevent bleeding or react to bleeding in the periprocedural period. Many other factors beyond coagulation tests contribute to bleeding risk in patients with cirrhosis undergoing invasive procedures. The risk of bleeding with procedures is variable and based on the characteristics of the specific procedure and other operator-dependent features. Guidance on stratification of bleeding risk for procedures has historically been based on decisions regarding the management of anticoagulant therapy in the periprocedural period (Supplementary Table 1).[34–37] However, patients with cirrhosis are diverse and vary across a wide spectrum. Characteristics unique to cirrhosis, such as presence of advanced Child-Turcotte-Pugh (CTP) cirrhosis or presence of ACLF, contribute greatly to bleeding risk.[11,13,38,39] Furthermore, other factors may enhance or modify procedural bleeding risk in patients with cirrhosis, such as acute kidney injury.[14] Given the complexity of bleeding risk assessment in patients with cirrhosis, we sought to analyze different laboratory testing strategies in this patient population.

Traditional coagulation testing. Based on our systematic review of the literature, we found no direct evidence that conventional laboratory tests, including INR or platelet count, accurately predict bleeding risk in patients with cirrhosis. Although in vitro evidence suggests that a platelet count >55,000/mL provides adequate substrate for thrombin generation in patients with cirrhosis,[40] we found no direct clinical evidence supporting platelet count cutoff across various thresholds in predicting bleeding events. The available literature examining bleeding risk in patients with

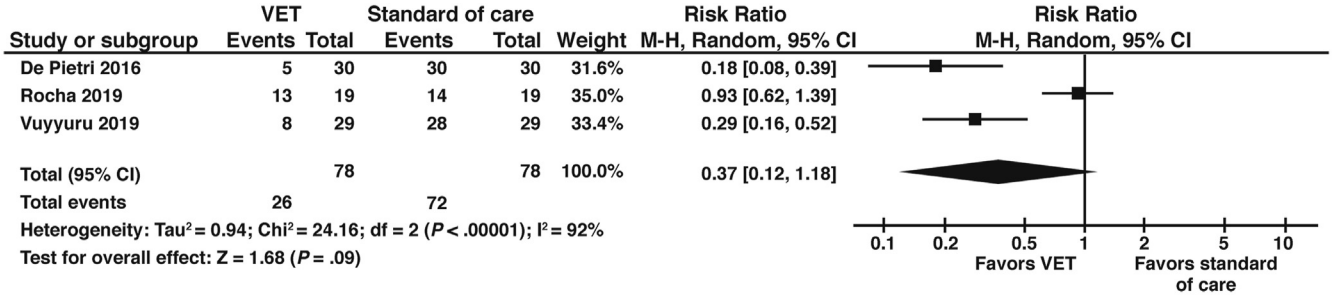

Figure 2. VET and preprocedural blood product transfusion.

cirrhosis is of very low quality, without either RCTs or large prospective cohort studies adequately powered to detect clinically relevant bleeding events, and suffers from a high degree of heterogeneity.

Viscoelastic testing. Given the limitations of a single test in measuring the complicated hemostatic system in patients with cirrhosis, a multiparameter assessment of global coagulation with VET is an attractive alternative.[41] VETs 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, platelets, and fibrinolytic system and measure the effective contribution of each to clot formation. Currently, data do not demonstrate the ability of VETs to predict bleeding events or to affect mortality in patients with cirrhosis. We identified 3 RCTs investigating procedural bleeding management strategies that compared traditional coagulation measurement with VET protocol.[16,30,31] Bleeding events were rare and there was no routine use of restrictive arms to establish baseline risk of bleeding without administration of prophylaxis. Although the use of VET before procedures clearly reduces platelet and plasma transfusion compared with traditional testing, there is no current direct evidence that VET provides more accurate assessment of bleeding risk per se. Future investigation focusing on patient-centered outcomes, while using restrictive arms when prophylaxis is not administered, are now essential to better understand the role of VET in bleeding risk assessment.

PICO Question 2: Does Preprocedure Prophylaxis to Correct Coagulation Parameters and/or Platelet Level Reduce the Risk of Bleeding in Patients With Cirrhosis?

Methods

As procedural risk is inherent to the specific characteristics of the procedure itself (see PICO question 1), we chose to analyze the most common procedures that patients with cirrhosis are likely to undergo. This TR found prospective RCTs grouping procedures together to analyze the utility of VET[16,30,31] and the efficacy and safety of TPO agonists.[42–46] However, our systematic search did not reveal RCTs for cohorts undergoing one of the selected specific procedures and, therefore, we searched the literature individually for observational studies pertaining to patients with cirrhosis undergoing the following procedures: paracentesis, thoracentesis, esophagogastroduodenoscopy (EGD) with esophageal variceal band ligation (EVL), endoscopic retrograde cholangiopancreatography (ERCP), colonoscopy with polypectomy, and liver biopsy.

Results

Paracentesis. We identified 8 retrospective case series, case-control, and cohort studies examining patients with cirrhosis undergoing paracentesis for ascites.[14,39,47–52] In general, the majority of studies do not indicate whether bleeding prophylaxis was administered before paracentesis. Patient characteristics are also not uniformly reported; however, the majority of patient characteristics would be similar, given the presence of ascites is typical of decompensated cirrhosis. The largest studies performed to date that provide preprocedure values for INR and platelets reviewed a total of 4216 paracenteses.[47,52] In the study by Grabau et al,[47] the majority of patients had INR >1.5 (n = 823 of 1100) and platelet count <50,000/mL (n = 598 of 1100) and reported no bleeding events. A more recent study examining 3116 paracenteses found a total of 6 bleeding events.[52] In general, preprocedure bleeding prophylaxis was not given (mean platelet count was 121,000/mL and INR was 1.6). A study restricted to patients with ACLF and propensity-matched controls (mean platelet was 90,000/mL and INR was 2.2) identified a total of 18 bleeding events, defined as blood present in the ascites.[39] There was no significant difference in mean platelets count or INR between the 2 groups in a case-control study examining patients with hemoperitoneum after paracentesis compared with a control population of patients suspected of bleeding (but ruled out with computed tomography) after paracentesis.[14] On multivariate analysis, acute kidney injury was associated with bleeding risk (odds ratio, 4.3; 95% CI, 1.3–13.5); however, Model for End-Stage Liver Disease score, platelet count, and INR were not significant predictors.

Thoracentesis. We found 3 studies investigating bleeding outcomes in patients with cirrhosis undergoing thoracentesis.[53–55] These studies vary in cohort inclusion criteria and study design, therefore, direct comparison between studies was not possible. Prophylaxis before thoracentesis was reported in 2 studies. The largest retrospective cohort examined patients with coagulopathy,

as defined by platelet count <50,000/mL and INR >1.6.[53] The study does not clearly define the percentage of patients in the cohort with liver disease. The authors examined 1009 thoracenteses and compared patients that received prophylaxis to correct INR and platelets to patients who did not and found no difference in bleeding-related events (n = 0 of 706 in no prophylaxis vs 4 of 303 in prophylaxis).[53] These data are limited, given the lack of information on the underlying risk factors of the cohort, and are at risk for misclassification bias and selection bias. A retrospective case-control study compared thoracentesis in patients with cirrhosis and those without cirrhosis reported 3 major bleeding events (1.8%) in the group with cirrhosis.[55]

Upper endoscopy with esophageal variceal band ligation. A total of 4 studies reported bleeding outcomes in patients undergoing EGD with EVL.[13,56–58] Study designs included case-control, retrospective, and prospective cohort studies. One study examined the risk of bleeding in patients undergoing EVL while on anticoagulation. None of the studies clearly reported provision of pre-EGD prophylaxis with plasma or platelet transfusion. One study retrospectively examined 150 patients with cirrhosis undergoing EVL and found 11 post-EVL ulcer bleeding events.[13] When comparing the group with bleeding to patients without bleeding, there was no significant association between platelet count <50,000/mL and INR >1.5. Notably, transfusion requirements were similar between groups with elevated coagulation parameters (INR >1.5 and platelet count <50,000/mL) and those with low-risk parameters. A case-control study compared 17 cases of post-EVL ulcer bleeding to 84 controls without bleeding and reported platelet levels before EVL to be similar in cases and controls (98,000/mL cases and 101,000/mL controls).[56] This study reported associations with prothrombin index and aspartate transaminase to platelet ratio index with bleeding risk, but did not correlate values of prothrombin time or platelet count to bleeding risk. The largest study to date prospectively collected 24 cases of post-EVL ulcer bleeding of 521 total EGD procedures.[58] Platelet count was similar between the groups (121,000/mL in bleeding subjects vs 118,000/mL in controls) and prothrombin time/INR was elevated (1.8 in bleeding subjects vs 1.5 in control). Of note, Model for End-Stage Liver Disease was significantly higher in the group that developed post-EVL ulcer bleeding in this study.

Colonoscopy with polypectomy. We reviewed 4 studies examining bleeding outcomes in patients with cirrhosis undergoing colonoscopy with polypectomy.[38,59–61] All studies were retrospective cohort or case-control design. The studies almost exclusively included compensated patients with CTP A cirrhosis. Three studies did not report information on preprocedure bleeding prophylaxis. The largest study retrospectively examined 814 patients undergoing colonoscopy (700 with CTP A) and identified 10 delayed bleeding events within 30 days (5 in CTP A cirrhosis [0.7%] and 5 in CTP B/C cirrhosis [4.4%]).[38] Mean platelet count was 85,000/mL and mean INR was 2.2 in patients with CTP C cirrhosis. If patients received prophylaxis before colonoscopy, the values of corrected INR and platelets were reported accordingly. Multivariable analysis showed CTP B or C cirrhosis and polyp size to be significant risk factors for delayed bleeding. Thrombocytopenia was not significantly associated with delayed post-polypectomy bleeding. The remainder of the studies analyzed did not report information on correction of coagulation parameters before colonoscopy, however, they did report significantly low rates of delayed post-polypectomy bleeds. In 1 retrospective cohort of 307 patients with cirrhosis (85.7% CTP A), only 1 bleeding event was reported.[60] Similarly, a retrospective case-control study examining 89 patients with cirrhosis (CTP A 84.3%) and 348 controls without cirrhosis found only 2 delayed post-polypectomy bleeds in patients with cirrhosis compared with 1 in controls without cirrhosis.[61]

Endoscopic retrograde cholangiopancreatography. We identified 3 retrospective studies examining bleeding risk in patients with cirrhosis undergoing ERCP.[62–64] Two studies did not report preprocedure bleeding prophylaxis[62,63]; 1 study included only patients who had intervention to correct INR and platelets.[64] One study examined 129 ERCPs in patients with cirrhosis undergoing ERCP compared with 392 ERCPs in patients without cirrhosis.[62] In the cohort with cirrhosis, 74% were CTP B or C with a median Model for End-Stage Liver Disease score of 14.[62] Thirty-five patients with cirrhosis underwent biliary sphincterotomy. Of the patients with cirrhosis, 8 developed bleeding after ERCP compared with 121 who did not. Both platelet count and INR were not significantly different between the groups. Patients with gastrointestinal (GI) bleeding more commonly underwent sphincterotomy (n = 5 of 8 [63%] GI bleeds vs 30 of 121 [25%] no GI bleeds). Overall, there was no difference in incidence of GI bleeding when comparing patients with cirrhosis to controls without cirrhosis. A large retrospective case-control study compared 3228 patients with cirrhosis who underwent ERCP (80.6% with decompensated cirrhosis) and found a post-procedural bleeding incidence of 2.1% compared with 1.2% in matched noncirrhotic controls ($P < .01$).[63] On multivariable analysis, decompensated cirrhosis, therapeutic ERCP, and biliary sphincterotomy were independently associated with bleeding; however, coagulation parameters and use of preprocedure bleeding prophylaxis were not included in the model. A multicenter retrospective study examining outcomes in 538 ERCP in patients with cirrhosis found 6 cases of bleeding (1.1% incidence rate).[64] Of note, all patients included in this study received bleeding prophylaxis if INR >1.5 or platelet count <50,000/mL.

Two studies were reviewed that directly compared procedural methods in ERCP and bleeding risk.[65,66] One study randomized patients with CTP A/B cirrhosis and common bile duct stones to undergo sphincterotomy with either mechanical lithotripsy or large balloon dilation.[65] Patients with platelet count <50,000/mL and "severe coagulopathy" were excluded and use of prophylaxis was not reported. There were a total of 98 patients enrolled and 5 "mild" bleeding events were reported (4 in the group undergoing lithotripsy). Another study retrospectively examined patients with cirrhosis undergoing ERCP with

sphincterotomy with 2 separate types of electrocautery (alternating current vs blended current).[66] Prophylaxis was provided for patients with platelet count <50,000/mL and INR >1.5. A total of 29 patients were examined and 3 bleeding events (1 major) were identified in the group using blended current compared with 0 events in the group using alternating current. These 2 studies highlight the complexities of analyzing bleeding in patients undergoing ERCP when numerous factors particular to the procedure play a significant role in modifying bleeding risk.

Liver biopsy. We reviewed 7 retrospective studies examining bleeding complications after percutaneous[67–70] and transjugular liver[68,71–73] biopsies. There was no report of prophylaxis administration before liver biopsy in any of the reviewed studies. Overall, these cohorts were heterogeneous and included both patients with and without cirrhosis (majority of patients did not have cirrhosis). We did not identify a study specifically evaluating bleeding from liver biopsy in patients with cirrhosis only. Two studies that investigated transjugular liver biopsy[71,73] included patients with severe coagulopathy for whom percutaneous liver biopsy was contraindicated. Overall rates of major bleeding were low, ranging from 0.2% to 0.6%. One prospective study compared patients undergoing percutaneous vs transjugular liver biopsy.[68] Of the total cohort, only 8 of 68 (11.8%) in the percutaneous group and 22 of 75 (29.3%) in the transjugular group had cirrhosis. One bleeding event occurred (subcapsular hematoma) in the group undergoing percutaneous biopsy; however, it was not reported whether they had cirrhosis.

We reviewed 3 large retrospective study cohorts examining patients undergoing percutaneous biopsy.[67,69,70] One study examined 4275 procedures from 1994 to 2002.[67] No information on prophylaxis, patient characteristics, presence of cirrhosis, or coagulation parameters was provided for the overall cohort. Bleeding was reported in 0.4% of cases, with 5 deaths related to bleeding events (15 patients, 33% with cirrhosis). A large retrospective study in patients with chronic liver diseases examined 3357 patients (12% with cirrhosis) and found bleeding events in 21 (0.6%) patients after biopsy.[70] When comparing the patients without complications to patients with bleeding, there was no significant difference between groups in platelet count, prothrombin time, or partial thromboplastin time. The group with bleeding more commonly had a platelet count <60,000/mL (4.8%) vs only 0.3% in the nonbleeding group; however, this did not reach statistical significance. In multivariable analysis, platelet count <100,000/mL was an independent predictor of bleeding (odds ratio, 4.1; 95% CI, 1.5–11.1; $P < .01$). Seef et al[69] evaluated complications in patients with chronic hepatitis C undergoing percutaneous liver biopsy from 2000 to 2006. Patients with decompensated cirrhosis and platelet count <50,000/mL were excluded. Of note, there was center variability for minimal platelet level required before biopsy. Bleeding occurred in 0.5% (n = 16 of 2740) of patients, with no statistically significant difference in percent of patients with cirrhosis in the nonbleeding cohort (39.9%; n = 1068 of 2677) vs in the bleeding cohort (50%; n = 8 of 16). Preprocedure INR was the same between groups, however, mean platelet level was significantly lower in the bleeding group (121,000/mL) compared with the nonbleeding group (158,000/mL). In the bleeding group, 26.7% of patients had a platelet count <60,000/mL and 50% had a platelet count >100,000/mL. Similar to other studies in this field, no data were provided regarding administration of prebiopsy prophylaxis.

Randomized Controlled Trial in Patients With Cirrhosis Undergoing Invasive Grouped Procedures

Viscoelastic studies. Several RCTs have been conducted in patients with cirrhosis comparing the use of VET with traditional coagulation parameters to guide prophylaxis before invasive procedures.[16,30,31] The 3 studies identified vary in study design, bleeding definitions, and types of procedures included. One study randomized 60 patients undergoing both low- and high-risk procedures to SOC prophylaxis (FFP for INR >1.8 and platelet transfusion if platelet count <50,000/mL) vs prophylaxis based on predetermined VET parameters.[16] A significant reduction in both platelet transfusion and FFP transfusion was found in the VET cohort compared with SOC. Bleeding occurred in 1 patient undergoing paracentesis in the SOC arm who received FFP transfusion prior. Another study randomized patients with cirrhosis undergoing central venous catheter placement to SOC (FFP for INR >1.5 and platelet transfusion if platelet count <50,000/mL), prophylaxis based on ROTEM, or a restrictive strategy with no prophylaxis.[30] There were no major bleeding events reported in the entire cohort with a significant reduction in transfusion in the ROTEM vs SOC groups. A study examining prophylaxis based on SOC vs TEG parameters in high-risk procedures found similar results with reduction in transfusion in the group assigned to TEG and no bleeding events in either cohort.[31]

Thrombopoietin agonists. We identified 5 RCTs examining TPO agonists compared with platelet transfusion in patients with cirrhosis and thrombocytopenia before undergoing an invasive procedure.[42–46] Procedural type was heterogeneous. These studies included primarily low-risk procedures and included both medical and surgical procedures. All studies focus on preprocedure prophylaxis for thrombocytopenia and do not report use of other concurrent prophylaxis, such as an INR or fibrinogen target. There was no study comparing outcomes with a group of patients with thrombocytopenia who did not receive either TPO or platelet transfusion before procedures (eg, restrictive arm).

Two large RCTs examined the efficacy of avatrombopag to raise platelets in patients with thrombocytopenia and cirrhosis before planned procedures.[43] Patients were given placebo or avatrombopag and platelet count was measured the day of procedure. Patients received transfusion if platelet count was <50,000/mL. The majority of procedures performed in these studies were low risk (61%, n = 248 of 407). The most common procedures performed were diagnostic and therapeutic EGD (52%; n = 212 of 407). The predefined combined primary end point was no need for

platelet transfusion or rescue therapy for bleeding, and it favored the treatment group with an RR of 2.46 (95% CI, 1.77–3.41) for patients in the high platelets group that received 40 mg avatrombopag (Supplementary Figure 8) and RR of 2.36 (95% CI, 1.67–3.32) for patients in the low platelets group that received 60 mg avatrombopag (Supplementary Figure 10). In both studies, avatrombopag met the primary end point at high and low dose with a significant reduction in platelet transfusion. There was no reporting of the number of patients who received rescue therapy, however, bleeding rates were low in the entire cohort (3.5%; n = 15 of 430), with no statistically significant differences between groups. No difference was reported for incidence of thrombotic events (RR, 0.28; 95% CI, 0.03–3.02) (Supplementary Figure 9). A similar study examined lusutrombopag to raise platelet counts in patients with thrombocytopenia and cirrhosis before planned procedures.[44] Patients were given placebo or lusutrombopag and platelet count was measured the day of procedure and patients received transfusions if <50,000/mL. Patients in the lusutrombopag group achieved platelet count >50,000/mL more often compared with the placebo group (RR, 3.60; 95% CI, 1.72–7.57) and there was no difference in thrombotic events (RR, 0.55; 95% CI, 0.12–2.64) (Supplementary Figures 11 and 12; Supplementary Table 4). The majority of procedures performed in this study were low risk (66%; n = 121 of 185). Endoscopies were the most common procedures performed and constituted all of the low-risk procedures. Lusutrombopag significantly reduced the need for platelet transfusions compared with placebo (71% in placebo vs 35% in lusutrombopag). Two patients required intervention for rescue bleeding (1 patient underwent colonoscopy with polypectomy in placebo group and received platelet transfusion prior and the other underwent surgical mastoidectomy and had received platelet transfusion). A total of 9 bleeding events (4.2%; n = 9 of 214) were reported (5.6% in placebo vs 2.8% in lusutrombopag).

Certainty of Evidence

The overall certainty of evidence was very low (Supplementary Table 2). For platelet and plasma transfusion, indirect observational evidence from single-arm cohort studies that examined post-procedure bleeding outcomes in patients with elevated INR and thrombocytopenia was identified. None of the studies reported on preprocedural platelet or plasma transfusion. Thus, the evidence was rated down for indirectness. Furthermore, there was very serious risk of bias because none of the studies had a comparison group, bleeding outcomes were poorly defined, and the intervention was not always defined or standardized (Supplementary Table 1). Regarding the TPO agonist studies, the evidence was rated down for serious indirectness because surrogate outcomes (eg, transfusion before or after the procedure) were used instead of post-procedural bleeding. In addition, there was no comparison group of patients with thrombocytopenia who did not receive either TPO agonist or platelet transfusion before procedures. Lastly, in the TPO agonist studies, the event rate was very low and we rated down for imprecision (Supplementary Tables 3 and 4).

Discussion

The risk of bleeding in patients with cirrhosis undergoing procedures is challenging to quantify and involves multiple factors related to patient disease state and specific features inherent to the procedure itself. Clinical study designs that examine patients undergoing a specific procedure are mainly small retrospective cohorts. These studies often do not address the use of preprocedure prophylaxis (eg, plasma or platelet transfusions) and have substantial risk for selection bias. Other studies have looked at cohorts undergoing multiple different types of procedures to derive conclusions about overall general bleeding risks.[74,75] RCTs in this field have amalgamated multiple different procedures together (both low and high risk). These studies either analyzed the utility of VET compared with traditional testing[16,30,31] or compared TPO agonist use vs platelet transfusions.[42–46] With the exception of 1 small study,[30] these studies do not include restrictive strategy cohorts in which patients do not receive any preprocedure prophylaxis. As such, it is not possible to fully understand whether prophylaxis provides harm or benefit with respect to the outcome of bleeding, as prophylaxis was generally given in these studies before procedures.

Low-risk procedures. Patients with cirrhosis commonly undergo low-risk procedures, including paracentesis, thoracentesis, and EGD with EVL. We found no strong correlation of bleeding risk and abnormal coagulation parameters, including thrombocytopenia, elevated INR, and abnormal VET parameters. The evidence analyzed is based on observational studies and of very low certainty, owing to serious risk of bias and indirectness. Single cohort retrospective studies demonstrate a correlation between bleeding risk and more advanced cirrhosis, independent of platelet count or INR.[38,58] This suggests there may be other factors unique to the individual patient that increase bleeding risk, including ACLF or sepsis. The 2 largest trials comparing TPO agonists with standard platelet transfusion for thrombocytopenia (platelet count <50,000/mL) before procedures included mostly low-risk procedures and found very low bleeding rates.[43,44] Overall, bleeding events are very rare in patients with cirrhosis undergoing low-risk procedures and appear to be independent of preprocedure bleeding prophylaxis. The current literature is limited by the rarity of bleeding events, nonstandardization of outcome definitions, combination of different types of procedures for analysis, and the lack of a control arm without use of prophylaxis.

High-risk procedures. We analyzed high-risk procedures including colonoscopy with polypectomy, ERCP, and liver biopsy. We found a low certainty of evidence that is limited by a serious risk of bias and indirectness. We found no strong correlation between bleeding risk and abnormal coagulation parameters, including thrombocytopenia, elevated INR, and abnormal VET parameters. In 2 prospective RCTs comparing VET with traditional prophylaxis, there were a total of 3 endoscopies with polypectomy, 2 ERCPs with sphincterotomy, and 51 percutaneous liver biopsies performed with no bleeding events.[16,31] The 2 largest trials comparing TPO agonists with platelet

transfusion included only 25 total liver biopsies, 18 colonoscopies with polypectomy, and no ERCPs. Bleeding events in these studies were presented in a composite outcome (both low- and high-risk procedures) and overall were very low in both studies. Similar to low-risk procedures, the literature for high-risk procedures is also limited by a very low certainty of evidence for the efficacy of preprocedure bleeding prophylaxis to reduce bleeding.

PICO Question 3: Is Venous Thromboembolism Prophylaxis With Anticoagulation Indicated in Hospitalized Patients With Cirrhosis?

Results

We included studies of hospitalized patients with cirrhosis receiving prophylactic anticoagulation that reported major bleeding and venous thromboembolic events. We excluded studies that lacked a control arm, included surgical patients only, did not have a clear definition of prophylactic anticoagulation, or included patients without cirrhosis.

Benefit assessment: incident venous thromboembolism. There were no RCTs comparing incidence of VTE in recipients of prophylactic anticoagulation vs a control group in hospitalized patients with cirrhosis. There were 5 retrospective cohort studies reporting VTE events in hospitalized patients with cirrhosis receiving prophylactic anticoagulation.[18,76–79]

VTE events were defined as deep vein thrombosis (DVT) or pulmonary embolism (PE) or PVT and presented as composite end points in most studies, irrespective of symptom presence. The retrospective nature of the studies without systematic screening for VTE limits robust interpretation to support clinical guidance. Hence, we used prospective data from RCTs in the general medical population published previously.[80] These studies use well-defined outcomes of symptomatic DVT (4 RCTs) and nonfatal PE (6 RCTs). In these studies, the use of prophylactic anticoagulation in hospitalized patients reduced the risk of symptomatic DVT (RR, 0.47; 95% CI, 0.22–1.00), but not that of nonfatal PE (RR, 0.61; 95% CI, 0.23–1.67).

Harms assessment: bleeding. There were no RCTs comparing harms due to prophylactic anticoagulation with a control group in hospitalized patients with cirrhosis. There were 3 retrospective cohort studies reporting bleeding events in those with vs without prophylactic anticoagulation during hospitalization.[18,78,79] *All bleeding events* was defined as the overall number of major and minor bleeds reported in the study. *Major bleeding* (reported in 2 studies) was defined per the International Society on Thrombosis and Haemostasis.[81]

In pooled analysis of the 3 studies, bleeding events (major and minor) occurred in 38 of 450 patients (8.4%) in the prophylactic anticoagulation group and 31 of 504 patients (6.2%) in the control group. Prophylactic anticoagulation was not associated with an increased risk of overall bleeding events (RR, 1.57; 95% CI, 0.73–3.37) (Figure 3). In the 2 studies reporting major bleeding events, these occurred in 4 of 154 patients on anticoagulation and 6 of 200 not on anticoagulation. Prophylactic anticoagulation was not associated with major bleeding (RR, 1.07; 95% CI, 0.37–3.06) (Supplementary Figure 13). Bleeding events from esophageal varices were not described separately in all studies, therefore, they could not be analyzed.

Certainty of Evidence

Evidence from large RCTs was used to explore the benefits from prophylactic anticoagulation in hospitalized patients with cirrhosis (Table 3). Because these studies included a general medical population and are not limited to cirrhosis, the evidence was rated down for indirectness. In addition, the small number of VTE events resulted in serious imprecision. Consequently, the certainty of evidence appraising the outcomes benefit was low. To explore harms of prophylactic anticoagulation in hospitalized patients with cirrhosis, observational evidence from retrospective cohort studies was used. The results were limited by serious risk of bias due to lack of blind randomization and by serious or very serious imprecision due to a small number of bleeding events. The certainty of evidence assessing the harms analysis was very low.

Discussion

Patients with cirrhosis are at a significantly increased risk to develop VTE compared with patients without cirrhosis.[82] The rebalanced coagulation system in cirrhosis can transform to a hypercoagulable state.[83–85] VTE risk factors, such as malignancy, immobility, and critical illness, are common in patients with cirrhosis and development of VTE increases risk of mortality.[86] Current guidelines for

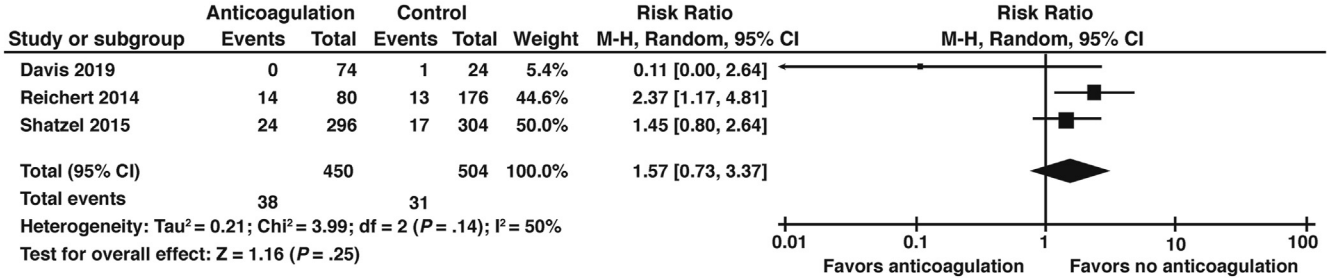

Figure 3. VTE prophylaxis and all bleeding events.

Table 3. GRADE Evidence Profile for PICO Question 3: Is Venous Thromboembolism Prophylaxis With Anticoagulation Indicated in Hospitalized Patients With Cirrhosis?

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anticoagulation	No anticoagulation	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
Major bleeding 2	Observational studies	Serious[a]	Not serious	Not serious	Very serious[b]	None	4/154 (2.6)	6/200 (3.0)	1.07 (0.37–3.06)	2 more per 1000 (from 19 fewer to 62 more)	⊕◯◯◯ VERY LOW	CRITICAL
All bleeding events 3	Observational studies	Serious[a]	Not serious	Not serious	Serious[c]	None	38/450 (8.4)	31/504 (6.2)	1.57 (0.73–3.37)	35 more per 1000 (from 17 fewer to 146 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Symptomatic DVTd 4	Randomized trials	Not serious	Not serious	Serious[d]	Serious[c]	None	13/2805 (0.5)	40/2870 (1.4)	0.47 (0.22–1.00)	7 fewer per 1000 (from 11 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL
Nonfatal PEd 6	Randomized trials	Not serious	Not serious	Serious[d]	Serious[c]	None	7/9993 (0.1)	21/10163 (0.2)	0.61 (0.23–1.67)	1 fewer per 1000 (from 2 fewer to 1 more)	⊕⊕◯◯ LOW	CRITICAL

[a]No detailed reports of other confounders, such as comorbidities or antiplatelet therapies, in cases vs controls that may impact the risk of bleeding independent from prophylactic anticoagulation and may have impacted patient selection
[b]Only 10 events total.
[c]Fewer than 300 events total.
[d]The studies were not designed specifically for patients with cirrhosis.[80]

medical patients admitted to the hospital recommend VTE prophylaxis with anticoagulation for patients at high risk to develop VTE.[80] Risk stratification should be performed with risk assessment models, such as the Padua Prediction Score, to determine which patients are at highest risk and would benefit from prophylaxis.[87,88] Risk assessment models have been applied successfully to cohorts with cirrhosis in smaller retrospective observational studies.[18,89]

Prior prospective RCTs examining anticoagulation for prevention of VTE in medical patients exclude patients with cirrhosis. It remains unclear whether patients with cirrhosis may benefit from medical VTE prophylaxis, given the potential for increased risk of bleeding. Nevertheless, clinicians are obligated to provide or withhold VTE prophylaxis in patients with cirrhosis admitted to the hospital based on existing current evidence. We therefore sought to assess the evidence for the efficacy and safety of medical VTE prophylaxis in hospitalized patients with cirrhosis.

Due to the limitations discussed above, we applied the evidence of RCTs conducted in the nonsurgical medical cohort from guidelines published previously.[80] Although these studies typically exclude patients with cirrhosis, it is unlikely that a properly powered RCT will be performed in patients with cirrhosis, as incidence of VTE is low. These results suggest that patients who are at high risk to develop VTE when hospitalized should be treated with anticoagulation prophylaxis, as there is a clear reduction in incident DVT and PE. Only 3 retrospective observational studies met criteria to analyze risk of bleeding in patients with cirrhosis receiving anticoagulation for prophylaxis compared with patients who did not receive prophylaxis. When both major and all bleeding events were assessed, there was no significant increased risk of bleeding when patients with cirrhosis receive anticoagulation for VTE prophylaxis. The rarity of events and low number of studies severely limit any firm conclusion regarding the risk of bleeding with anticoagulation. These studies are all small with significant selection bias, as treatment was not assigned randomly.

It can be expected that use of anticoagulation for VTE prophylaxis would increase the overall risk of bleeding in hospitalized patients, and data in patients with cirrhosis are too sparse to know with certainty the balance of risk and benefit. However, it is clear that patients with cirrhosis are at risk to develop VTE and, if they develop VTE, there is a high risk of mortality.[86] Future prospective studies examining outcomes and pharmacokinetics of prophylactic anticoagulation in patients with cirrhosis are needed to better inform the benefits and risks of this practice.

PICO Question 4: Should Patients With Cirrhosis Be Screened for Portal Vein Thrombosis?

Results

We searched for prospective studies of patients with cirrhosis evaluated serially in the outpatient setting with imaging (ultrasound or cross-sectional with computed tomography or magnetic resonance imaging) every 3–6 months reporting the development of incident nontumoral PVT. We excluded studies of patients who underwent imaging due to hospitalization, presence of malignancy (eg, hepatocellular carcinoma), or known nontumoral PVT. Retrospective cohort studies, case reports, comments, editorials, letters, notes, and abstracts published before 2017 were excluded.

There were no studies designed to compare the impact on nontumoral PVT incidence between an intervention cohort undergoing systematic screening for nontumoral PVT and a cohort undergoing no screening. Therefore, the published literature is not adequate to support evidence of the comparative effectiveness of systematic screening vs no screening for nontumoral PVT in the outpatient management of patients with cirrhosis.

The current literature consists of single-arm prospective studies of patients with cirrhosis undergoing systematic imaging in the outpatient setting reporting the incidence of nontumoral PVT. We identified 3 published studies[90–92] and 1 abstract.[93] All studies included patients with cirrhosis, followed with imaging every 3 or 6 months in the outpatient setting. The site (eg, trunk, branch, or both), degree of occlusion (eg, nonocclusive or occlusive), duration and presentation (eg, recent, chronic, asymptomatic, or symptomatic), or extent of PV system occlusion (eg, portal vein, splenic vein, or superior mesenteric vein) of incidental nontumoral PVT was not described in all studies either descriptively or with a formal classification system.[94,95] In addition, the length of follow-up was variable (between 1 and 8 years). The reported incidence of nontumoral PVT in included studies varied between 3.5% and 4.6% at 1 year. The greatest incidence of nontumoral PVT was 10.7% at 5 years.[92] There were no uniform reports of additional nontumoral PVT-related outcomes sufficient for pooled analyses.

Certainty of Evidence

The GRADE evidence profile is illustrated in Supplementary Table 5. The risk of bias was serious because there are no comparative studies between systematic screening and SOC. The indirectness was serious because the impact of nontumoral PVT detection on important patient outcomes, such as mortality remains unclear.

In summary, no comparative effectiveness estimates are available to determine the benefits or harms of ultrasound screening compared with no screening. In addition, the impact of nontumoral PVT on liver disease progression, including hepatic decompensation or transplant-free survival, was inconsistently reported among studies and mortality outcomes are absent.

Discussion

Nontumoral PVT is common in patients with cirrhosis, with a 5-year cumulative incidence rate of 11%.[91] Risk factors for nontumoral PVT in patients with cirrhosis are well described, with the strongest factor likely being advanced portal hypertension and reduced portal blood

flow.[96–99] The impact of nontumoral PVT on clinical outcomes remains controversial, especially in patients who are not candidates for liver transplantation. One large French study demonstrated that nontumoral PVT is a result of the natural history of cirrhosis progression rather than a cause of hepatic decompensation.[91] However, other studies conclude that nontumoral PVT is associated with greater risk of hepatic decompensation and mortality.[100–103] In candidates for liver transplantation, nontumoral PVT may negatively impact post-transplantation survival by affecting perioperative management.[102,104,105] Consequently, previous consensus statements and guideline recommendations suggest screening for nontumoral PVT in patients with cirrhosis listed for liver transplantation in order to guide perioperative management.[22,106–108] In light of these recommendations and current variation in clinical practice, we sought to evaluate the quality of the evidence with respect to the benefit of systematic screening for nontumoral PVT in all patients with cirrhosis.

To date, there are no RCTs comparing patients with cirrhosis undergoing screening for nontumoral PVT to patients who are not screened in either the general or liver transplantation populations. We identified 4 single-arm observational prospective studies that investigated screening for nontumoral PVT in patients with cirrhosis. With the limitations posed by these study designs, no comparative effectiveness estimates are available at this time to determine the benefits or harms of screening compared with usual care. All studies included in our analysis employed ultrasound at various screening intervals to detect nontumoral PVT. Current consensus and guideline statements suggest 6-month interval screening coinciding with hepatocellular carcinoma screening intervals. As even the role of screening remains unclear, there is no current evidence to support an optimal interval for screening. Confirmation with cross-sectional imaging (eg, computed tomography or magnetic resonance imaging) was not universally performed throughout the studies assessed.

In summary, no comparative effectiveness estimates are available to determine the benefits or harms of systematic screening compared with no screening. The impact of nontumoral PVT on liver disease progression is unknown. Prospective trials following patients who undergo screening compared with those who do not will be necessary to assess the benefits of screening, subsequent need for therapy, and to determine the overall effect of nontumoral PVT on disease progression and mortality.

PICO Question 5: What Are the Data on Specific Anticoagulant Therapies for Nontumoral Portal Vein Thrombosis in Patients With Cirrhosis?

Results

Benefits. For efficacy of anticoagulation for nontumoral PVT in patients with cirrhosis, there was no direct evidence from either RCT or large comparative cohort studies or indirect comparative evidence informing on patient important outcomes, such as mortality and/or hepatic decompensation. However, we identified comparative cohort studies that inform on the effects of anticoagulation on nontumoral PVT outcome, including degree of recanalization (partial or complete), no response or nontumoral PVT progression, both of which can affect important patient-centered outcomes (Table 4).

A total of 12 studies met inclusion criteria and reported recanalization in adult patients with cirrhosis and nontumoral PVT who were treated with anticoagulation.[90,109–119] We excluded studies reporting on malignant PVT or those that included treatments other than anticoagulation, including transjugular intrahepatic portosystemic shunt. Six of the 12 studies were comparative retrospective cohorts in which the anticoagulation group was treated with low-molecular-weight heparin and/or a vitamin K antagonist (VKA) and the control group did not receive any treatment.[90,112–114,117,118] Mean age was between 45 and 59 years in the anticoagulation group and between 48 and 61 years in the control group. Advanced liver disease (CTP class B and C) was reported in all 6 studies and ranged from 47% to 89% in the anticoagulation group and between 50% and 80% in the control group. Total median follow-up time was between 19 and 44 months and median anticoagulation time ranged from 4 to 13 months.

Among patients with cirrhosis and nontumoral PVT from the 6 comparative studies (n = 391), the RR of complete and partial recanalization was 2.27 (95% CI, 1.73–2.98) for those patients who received anticoagulation treatment compared with no treatment (Figure 4). We further explored rates of complete or partial recanalization in single-arm studies that analyzed anticoagulation treatment in patients with cirrhosis and nontumoral PVT. There were 12 studies (n = 514) that assessed the effect of anticoagulation therapy. The rate of complete/partial recanalization was 63% (95% CI, 59%–68%). When limiting to the 6 comparative studies, the rate of complete/partial recanalization in the control group receiving no treatment (n = 208) was 21% (95% CI, 16%–27%) (Supplementary Figures 14 and 15).

Six comparative cohort studies evaluated nontumoral PVT nonresponse or progression. The RR was 0.57 (95% CI, 0.48–0.68) for those patients who received anticoagulation treatment compared with no treatment. Rates of nonresponders/progression of PVT pooled from 12 single-arm cohort studies (n = 514) was 34% (95% CI, 30%–38%) and 79% (95% CI, 73%–84%) for the control group pooled from 6 studies (n = 209) (Supplementary Figures 16 and 17).

Harms. Evidence regarding bleeding was sparse and most of the studies did not adhere to standard definitions for major bleeding. In most cases, included studies reported only all bleeds generally, regardless of severity or those related to portal hypertension. A total of 12 studies met the same inclusion criteria as the benefits analysis and reported on both recanalization and bleeding.[90,109–119] Five of the 12 studies had a comparative retrospective cohort design and the anticoagulation group was treated with low-molecular-weight heparin and/or VKA and the control group did not

Table 4. GRADE Evidence Profile for PICO Question 5: What Are the Data on Specific Anticoagulant Therapies for Nontumoral Portal Vein Thrombosis in Patients With Cirrhosis?

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LWMH/ warfarin and DOAC	No therapy	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
Complete/partial recanalization of PVT as a surrogate outcome for patient-important outcomes (reduction in mortality, decompensation in cirrhosis 6	Observational studies	Not serious[a]	Not serious	Serious[b]	Serious[c]	None	102/183 (55.7)	51/208 (32.7)	2.27 (1.73–2.98)	309 more per 1000 (from 179 more to 485 more)	⊕◯◯◯ VERY LOW	CRITICAL
Nonresponders/ progression of PVT 6	Observational studies	Not serious[a]	Not serious	Serious[b]	Serious[c]	None	78/183 (42.6)	158/209 (75.6)	0.57 (0.47–0.68)	325 fewer per 1000 (from 401 fewer to 242 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Major bleed not related to portal hypertension bleed 4	Observational studies	Serious[d]	Not serious	Not serious	Very serious[e]	None	1/79 (1.3)	2/96 (2.1)	0.74 (0.12–4.48)	5 fewer per 1000 (from 18 fewer to 73 more)	⊕◯◯◯ VERY LOW	CRITICAL
All bleeds including portal hypertension bleeding 5	Observational studies	Serious[d]	Not serious	Not serious	Very serious[e]	None	14/160 (8.8)	35/254 (13.8)	0.86 (0.45–1.63)	19 fewer per 1000 (from 74 fewer to 87 more)	⊕◯◯◯ VERY LOW	CRITICAL
Esophageal variceal bleed 5	Observational studies	Serious[d]	Not serious	Not serious	Very serious[e]	None	6/160 (3.8)	36/255 (14.1)	0.34 (0.15–0.75)	93 fewer per 1000 (from 120 fewer to 35 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Table 4. Continued

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LWMH/ warfarin and DOAC	No therapy	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
Mortality/ decompensation in cirrhosis[f]												

LMWH, low-molecular-weight heparin.
[a]Newcastle-Ottawa Scale was used and no serious risk of bias was identified, just unclear selection bias in the smaller studies.
[b]Indirect outcome, recanalization as a surrogate outcome for patient-important outcomes (eg, mortality, decompensation in cirrhosis).
[c]Based on sparse data and low event rate.
[d]In the majority of the studies, the assessment of outcome was not well described (there was no clear definition of bleeding) and there were studies with inadequate follow-up time.
[e]Based on very sparse data, just few events.
[f]No evidence was identified that reported on mortality and or decompensation in cirrhosis.

receive any treatment.[90,112,113,117,118] Due to very sparse events in the comparative cohort studies, we used single-arm retrospective cohort studies to determine the incidence of bleeding per 100 patient-years. Four comparative studies (n = 175) informed on major bleeding not related to gastroesophageal varices (GEVs), as defined by established guidelines from the International Society on Thrombosis and Haemostasis.[90,112,113,117] The RR of major bleeding not related to GEVs was 0.74 (95% CI, 0.12 to 4.48) for those patients who received anticoagulation treatment compared with no treatment (Supplementary Figure 18). However, this RR was based on 3 events, with 1 of 79 major bleeds in the anticoagulation group and 2 of 96 in the control group. Therefore, we explored the incidence of major bleeding per 100 patient-years from single-arm retrospective cohort studies. The incidence of major bleeding with anticoagulation treatment was 0.03 (95% CI, 0.01 to 0.05) per 100 patient-years and was pooled from 9 studies (n = 347) (Supplementary Figure 19). In the control group, the incidence was 0.02 (95% CI, –0.01 to 0.05) per 100 patient-years, pooled from 4 studies (n = 96) (Supplementary Figure 20).

Five comparative studies (n = 414) informed on all bleeding events, including major and minor bleeding, as well as those related to GEVs or not.[90,112,113,117,118] The RR of all bleeding was 0.86 (95% CI, 0.45–1.63) for those patients who received anticoagulation treatment compared with no treatment (Figure 5). For GEV bleeds, the RR of major bleeding per year was 0.34 (95% CI, 0.16–0.75) in patients treated with anticoagulation vs those who were not treated (Figure 6). Furthermore, the incidence of all bleeding events per 100 patient-years from single-arm retrospective cohort studies in patients treated with anticoagulation was 0.05 (95% CI, 0.03–0.07) per 100 patient-years and was pooled from 12 studies (n = 523) (Supplementary Figure 21). In the control group, the incidence was 0.12 (95% CI, 0.08–0.15) per 100 patient-years, pooled from 5 studies (n = 254) (Supplementary Figure 22).

Certainty of Evidence

Evidence from a comparative retrospective cohort was used to inform on the benefits and harms of anticoagulation treatment in patients with cirrhosis and nontumoral PVT. The risk of bias was assessed by using the Newcastle-Ottawa Scale for observational studies and, when applied for the outcomes of recanalization, no serious bias was identified. There was minimal uncertainty regarding selection bias in the smaller studies. However, because recanalization can be theorized to surrogate for patient-important outcomes, such as mortality and/or decompensation in cirrhosis, the evidence was rated down for indirectness. Furthermore, there was serious imprecision due to a low event rate. The certainty of evidence informing benefit outcomes was very low.

To inform on harms of anticoagulation in patients with cirrhosis and nontumoral PVT, observational evidence from comparative and single-arm cohort studies was used. Within these studies, a serious risk of bias was identified because

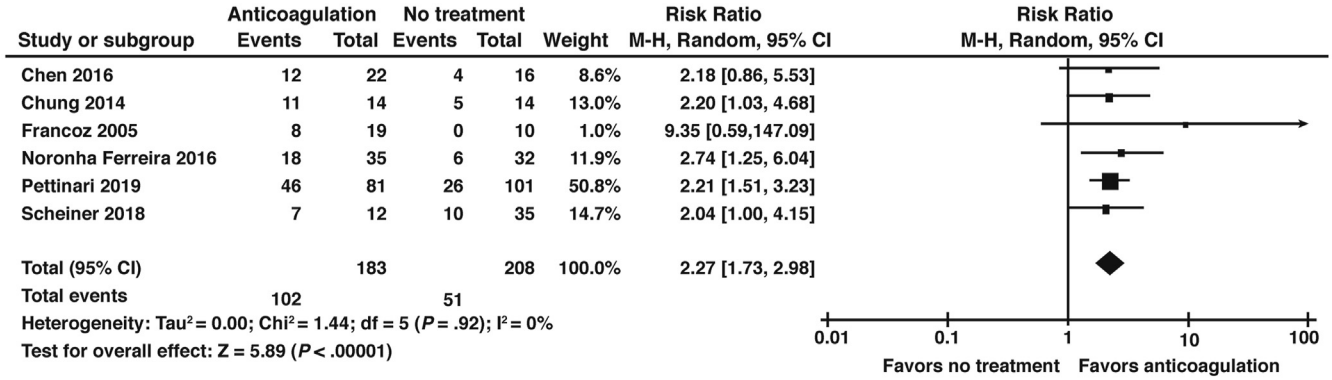

Figure 4. Complete or partial portal vein recanalization, comparison of anticoagulation vs no treatment.

the assessment of outcomes was not well-described (there was not a clear definition of bleeding) and studies with inadequate follow-up time were included. In addition, there was very serious imprecision due to a very small number of events. The certainty of evidence for the harms analysis was also very low.

Taken collectively, the overall certainty of evidence was very low, as quality of the evidence from both the benefits and the harms was very low.

Discussion

There is considerable controversy regarding the clinical significance of nontumoral PVT in patients with cirrhosis and whether this contributes to worsening hepatic decompensation (see PICO question 4).[19] Treatment of PVT with anticoagulation in candidates for liver transplantation has been recommended in some cases.[106,107] Given this controversy, we sought to evaluate the quality of the evidence supporting the use of anticoagulation to treat nontumoral PVT.

Anticoagulation is effective in treating nontumoral PVT in patients with cirrhosis. Anticoagulation promotes portal recanalization in patients treated for nontumoral PVT compared with patients who are not treated (RR, 2.27; 95% CI, 1.72–2.98). In patients who were not treated with anticoagulation, the rate of recanalization was 21% (95% CI, 16%–27%), which was much lower than in patients treated with anticoagulation 64% (95% CI, 59%–68%).

Although the current literature demonstrates anticoagulation as an effective treatment for nontumoral PVT in patients with cirrhosis, bleeding remains a feared consequence of therapy. A major limitation in the literature is the lack of randomization and formal standardization of bleeding definitions, making comparisons across studies difficult. When assessing for major bleeding events, pooled incidence from both single and comparator treatment arms revealed an incidence of 0.03 (95% CI, 0.01 to 0.05) per 100 patient-years compared with a similar incidence of bleeding in the control groups 0.02 (95% CI, –0.01 to 0.05) per 100 patient-years. When examining all reported bleeding events in patients treated with anticoagulation compared with the control group, the incidence of all bleeding events was lower in the group treated with anticoagulation. This finding is potentially explained by reduced incidence of bleeding from GEV in the anticoagulation group, with an RR for bleeding from GEV of 0.34 (95% CI, 0.16 to 0.75) when comparing patients treated with anticoagulation with those who were not. This finding may support a potential benefit of therapy to reduce portal pressure by promoting recanalization and thereby reducing risk of GEV bleeding. However, due to selection bias in these studies, other factors, such as aggressive endoscopy with EVL before initiation of anticoagulation therapy, may alternatively explain this finding. Nonetheless, overall bleeding risk with anticoagulation appears to be similar to patients with nontumoral PVT not treated with anticoagulation.

Although we were unable to compare individual anticoagulants directly in terms of both safety and efficacy, the

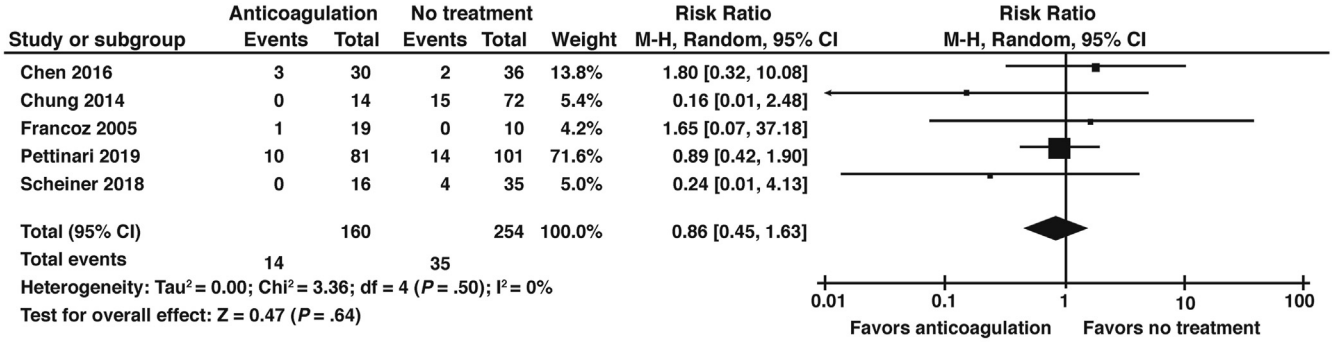

Figure 5. All bleeding events, comparison of anticoagulation vs no treatment.

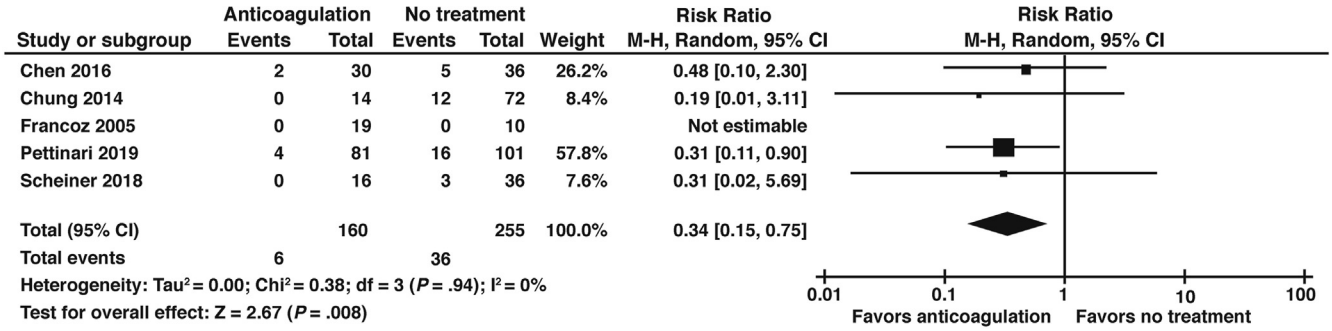

Figure 6. Esophageal variceal bleeding events, comparison of anticoagulation vs no treatment.

choice of anticoagulant remains a decision best made on an individual basis. Few studies to date have analyzed DOACs in patients with cirrhosis and we did not identify any such studies that met our inclusion criteria. Each anticoagulant has inherent strengths and limitations.[22] In addition, although this TR was limited to medical therapies to treat nontumoral PVT, transjugular intrahepatic portosystemic shunt placement with or without anticoagulation is a nonpharmacologic alternative with similar rates of PV recanalization.[120–122]

In summary, despite the significant limitations of the available literature, anticoagulation to treat nontumoral PVT in patients with cirrhosis appears to be safe and effective, even in advanced liver disease. Prospective, randomized trials that systematically assess benefits and harms of anticoagulation are required to better understand the role of specific types of anticoagulation and to aid the clinician managing nontumoral PVT.

PICO Question 6: In Patients With Atrial Fibrillation and Cirrhosis, Is Anticoagulation Safe and Effective?

Results

The benefit of oral anticoagulation in patients with AF is well established. Guideline recommendations support the use of oral anticoagulation in patients with stroke risk factors for AF.[123] The decision to treat patients with anticoagulation is based on use of a risk assessment model, CHA2DS2-VASc, which defines risk factors for thromboembolic stroke.[124] This TR identified 6 high-quality RCTs with more than 200 events that informed on overall mortality and stroke outcomes. Although the specific focus of PICO question 6 was to assess the benefits and harms specific to patients with cirrhosis, we did not identify direct comparative evidence from RCTs or comparative cohort studies that would inform on the effects of anticoagulation on stroke prevention and mortality. Thus, we used higher-quality data from these guidelines to inform these outcomes. Given the risk of bleeding is likely a unique outcome in cirrhosis, we conducted a systematic review that included direct evidence from observational cohort studies that evaluated the outcomes of major bleeding and intracranial hemorrhage (ICH) in patients with cirrhosis.

Mortality. Among patients with AF, based on data from 6 RCTs (n = 2850), the RR of mortality was 0.72 (95% CI, 0.55–0.94) for those patients who received anticoagulation treatment compared with no treatment (Table 5).

Nonfatal stroke. Within the same 6 RCTs (n = 2850), the RR of nonfatal stroke was 0.34 (95% CI, 0.23–0.49) for those patients with AF who received anticoagulation treatment with VKA compared with no treatment (Table 5). Absolute risk was variable, depending on the population baseline risk, ranging from 15 fewer per 1000 in patients with CHA2DS2-VASc 0–1, to 63 fewer per 1000 in CHA2DS2-VASC >2. When patients treated with DOAC were compared with patients treated with VKA, the RR of nonfatal stroke was 0.81 (95% CI, 0.73–0.91) in favor of DOAC treatment (Table 6).

Major bleed. The evidence informing major bleeding risk is derived from single-arm cohort studies that either used DOAC or VKA in patients with cirrhosis and AF. Included studies defined cirrhosis as any of the following: cirrhosis diagnosed by clinical, radiographic, or histologic testing; International Classification of Diseases, Ninth Revision codes for cirrhosis; and noninvasive markers of fibrosis (eg, Fibrosis-4 Index > 3.25). All studies reporting outcomes in patients with chronic liver disease without cirrhosis were excluded. We accepted major bleeding definition by established guidelines from the International Society on Thrombosis and Haemostasis or equivalent report of bleeding that met this definition.[81] Studies that did not clearly define cirrhosis or bleeding events according to these definitions were excluded.

Seven studies met the inclusion criteria and were included in the final analysis.[125–131] All 7 studies were comparative cohort studies and all of them had 1 group of subjects that was treated with VKA. Three of the studies contained a control group or subjects that did not receive anticoagulation,[125,126,131] and 5 studies had a group of subjects treated with DOAC.[127–131] Given the limited number of studies and events that directly compared treatment with anticoagulation vs no treatment, we pooled the bleeding incidence from a single-arm cohort, for each group separately and then calculated the RR between the 2 cohorts. Incidence of bleeding was reported in 100 patient-years. Furthermore, we identified 5 comparative cohort studies that compared subjects treated with VKA and DOAC.[127–131] Data from all the studies was pooled and RR and rate ratio were then calculated.

Table 5. GRADE Evidence Profile for PICO Question 6: In Patients With Atrial Fibrillation and Cirrhosis, Is Anticoagulation Safe and Effective?

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA	No therapy	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
Death[a] 6	RCT	Not serious	Not serious	Serious[a]	Not serious	None	103/1425 (7.2)	136/1425 (9.5)	0.72 (0.55–0.94)	27 fewer per 1000 (from 43 fewer to 6 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Nonfatal strokea 6	RCT	Not serious	Not serious	Serious[a]	Not serious	None	36/1425 (2.5)	CHA2DS2-VASC 0–1: (2.2)	0.34 (0.23–0.49)	15 fewer per 1000 (from 17 fewer to 11 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
								CHA2DS2-VASC 2: (4.5)		30 fewer per 1000 (from 35 fewer to 23 fewer)		
								CHA2DS2-VASC >2: (9.6)		63 fewer per 1000 (from 74 fewer to 49 fewer)		
Major bleed 7	Observational	Serious[b]	Not serious	Not serious	Serious[c]	None	106/2334 (4.2)	45/2030 (2.1)	1.91 (1.85–2.26)	38 more per 1000 (from 36 more to 53 more)	⊕◯◯◯ VERY LOW	CRITICAL
ICH 6[d]	Observational	Serious[b]	Not serious	Not serious	Serious[c]	None	35/2882 (1.2)	12/2473 (0.4)	3.5 (3.3–4)	53 more per 1000 (from 48 more to 63 more)	⊕◯◯◯ VERY LOW	CRITICAL

[a]Data from VKA compared with no therapy for VTE prevention in patient with AF and no cirrhosis was used.[123]
[b]No comparison group single-arm studies were analyzed separately.
[c]Low number of events ($n < 200$).
[d]High rates are probably due to hemorrhagic transformation of underlying cerebrovascular attack.

Table 6. GRADE Evidence Profile for PICO Question 6: Comparison of Direct Oral Anticoagulants vs Vitamin K Antagonists in Patients With Atrial Fibrillation and Cirrhosis

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOAC	VKA	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
Nonfatal stroke[a]												
4	RCT	Serious[b]	Not serious	Seriousa	Not serious	None	911/29,312 (3.1)	1107/29,229 (3.8)	0.81 (0.73–0.91)	6 fewer per 1000 (from 3 fewer to 8 fewer)	⊕⊕◯◯ LOW	CRITICAL
Major bleed												
5	Observational	Serious[c]	Not serious	Not serious	Serious[d]	None	67/2171 (3.0)	93/2113 (4.4)	0.62 (0.45–0.85)	15 fewer per 1000 (from 18 fewer to 13 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
ICH												
4[e]	Observational	Serious[c]	Not serious	Not serious	Serious[d]	None	22/2096 (1.04)	23/1955 (1.18)	0.70 (0.58–0.84)	6 fewer per 1000 (from 9 fewer to 3 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

[a]VKA compared with no therapy for VTE prevention in patient with AF and no cirrhosis.[123]
[b]Issues with allocation concealment and blinding of participants and personnel.
[c]Selection bias.
[d]n < 200 events.
[e]High rates are probably due to hemorrhagic transformation of underlying cerebrovascular attack.

Age throughout the studies ranged from a mean age of 62 years to a mean age of 77 years. Advanced liver disease (CTP class B and C) was reported in 5 studies and ranged from 27% to 64% in the VKA group, from 10% to 36% in the DOAC group, and from 10% to 28% in the control group. Pooled incidence of major bleeding in the VKA group per 100 patient-years was 4.2 (95% CI, 3.4–5.0) (Supplementary Figure 23). Three studies had a control group.[125,126,131] One study had 2 control groups, 1 control group was a VKA-matched cohort and the other was a DOAC-matched cohort.[131] Pooled incidence of major bleeding in the control group per 100 patient-years was 2.1 (95% CI, 1.5–2.7) (Supplementary Figure 24). Five studies included patients who were treated with DOAC.[127–131] Pooled incidence of major bleeding in the DOAC group per 100 patient-years was 2.7 (95% CI, 2.0–3.4) (Supplementary Figure 25).

Patients with cirrhosis and AF who were treated with VKA had more major bleeding events compared with patients who did not receive anticoagulation (rate ratio, 1.91; 95% CI, 1.85–2.26) (Table 5). Patients with cirrhosis and AF treated with DOAC had fewer major bleeding events compared with patients with cirrhosis and AF treated with VKA (RR, 0.62; 95% CI, 0.45–0.85) (Figure 7).

Intracranial hemorrhage. Evidence informing the risk of ICH is derived from 6 single-arm cohort studies that either used DOAC or VKA in patients with liver cirrhosis and AF.[125,128–132] Definitions for cirrhosis were the same as described above. Included studies provided a specific report of ICH defined by clinical documentation or International Classification of Diseases, Ninth Revision code.

Similar to the major bleeding outcome, for the VKA and control comparison we pooled data from each group separately and for the VKA vs DOAC we used comparative data. Pooled incidence of ICH in the VKA group per 100 patient-years was 0.7 (95% CI, 0.4–1.0) (Supplementary Figure 26). Three studies had a control group; 1 study had 1 control group that was a VKA-matched cohort and the other was a DOAC-matched cohort.[125,131,132] Pooled incidence of ICH in the control group per 100 patient-years was 0.2 (95% CI, 0.1–0.3) (Supplementary Figure 27). Four studies included patients who were treated with DOAC.[128–131] Pooled incidence of ICH in the DOAC group per 100 patient-years was 0.6 (95% CI, 0.3–0.9) (Supplementary Figure 28).

Patients with cirrhosis and AF who were treated with VKA had more ICHs compared with patients with cirrhosis and AF who did not receive any treatment (rate ratio, 3.5; 95% CI, 3.3–4) (Table 5). Patients with cirrhosis and AF, when treated with DOAC, had fewer ICHs compared with patients with

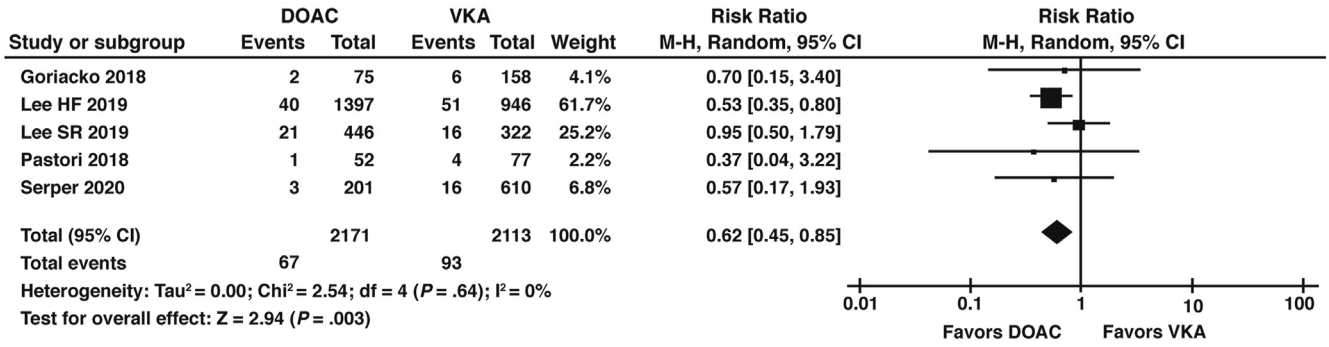

Figure 7. Anticoagulation and AF major bleeding events, comparison of VKAs vs DOACs.

cirrhosis and AF treated with VKA (RR, 0.7; 95% CI, 0.58–0.84) (Table 6).

Certainty of Evidence

Evidence from large RCTs was used to inform the benefits from anticoagulation treatment in patients with AF and cirrhosis. Because these data came from a population of patients without cirrhosis, the evidence was rated down for indirectness. As a result, the certainty of evidence informing benefit outcomes was moderate. To inform on the harms of anticoagulation in patients with cirrhosis and AF, observational evidence from single-arm cohort studies was used. Within these studies, a serious risk of bias was identified due to lack of comparison, in addition to serious imprecision due to a small number of events. The certainty of evidence for the harms analysis was very low. The overall certainty of evidence was very low, as it is driven by the quality of the evidence from the harms.

Discussion

AF is a common cardiac arrhythmia and can lead to significant morbidity in patients with increased risk of thromboembolic stroke. Guideline recommendations based on high-quality RCT support the use of oral anticoagulation in patients with risk factors for stroke (eg, CHA2DS2-VASc risk factors).[123] Patients with cirrhosis are at risk for AF and clinicians increasingly face decisions regarding the management of these patients.[133,134] However, patients with cirrhosis are routinely excluded from clinical trials with anticoagulation due to concerns about bleeding and, therefore, risk-to-benefit assessment is challenging.

Due to the lack of prospective comparator studies examining anticoagulation in patients with cirrhosis, we used data from high-quality RCTs obtained from current guidelines.[123] It is unlikely that properly powered RCTs in patients with cirrhosis will be conducted to firmly establish stroke reduction with anticoagulation. Based on the data presented, anticoagulation reduces mortality and stroke in patients treated with oral anticoagulation at risk for stroke. The benefit of anticoagulation relies on the underlying thrombotic risk, as determined by CHA2DS2-VASc score and patients with 1 or more risk factors. Therefore, patients with cirrhosis and elevated CHA2DS2-VASc score should obtain a similar benefit from anticoagulation. Specifically, DOACs appear more effective compared with VKA in the general population. However, the pharmacodynamics of both VKA and DOAC in patients with cirrhosis remain unclear.[135,136] Whether similar rates of efficacy are achievable in patients with cirrhosis, particularly decompensated cirrhosis, is not currently known, and metabolism and potency of anticoagulants in cirrhosis need further study.

The risk of bleeding on anticoagulation in patients with cirrhosis is presumed to be higher than in the general population. In some situations, this risk might potentially outweigh the benefits of anticoagulation. In the observational studies we reviewed, the overall incidence of major bleeding in patients on VKA for AF was found to be 4.2 per 100 patient-years compared with 2.1 per 100 patient-years in patients not treated with VKA. Several recent trials examining DOAC compared with VKA in patients without cirrhosis have been conducted and demonstrate rates of overall major bleeding of 2.1%–3.6% per year in DOAC and 3.1%–3.4% per year in VKA.[137–139]

Comparing rates of major bleeding in these observational, single-arm studies with cirrhosis patients is difficult, as these were not randomized and therefore subject to significant selection bias. The majority of studies included cohorts of primarily well-compensated patients with CTP A cirrhosis. The rate ratio of 1.91 in patients with cirrhosis treated with VKA compared with patients who were not treated with anticoagulation suggests an increased risk of bleeding is expected when anticoagulation is used. When comparing DOAC treatment to VKA in patients with cirrhosis, there appears to be a reduced incidence of major bleeding and ICH in patients treated with DOAC. This finding parallels data in the general medical population.[138]

In summary, in patients with well-compensated cirrhosis, AF, and elevated CHA2DS2-VASc stroke risk factors, oral anticoagulation is a safe therapy that likely reduces risk of stroke. Both VKA and DOAC likely place patients with cirrhosis at higher risk to develop major bleeding and ICH, however, the risk for major bleeding might be lower with DOAC. The literature is limited in this field, with significant risk of bias and lack of prospective comparative studies. In general, cohorts are highly selected patients with well-compensated cirrhosis and therefore application of these findings to patients with decompensated cirrhosis requires further study. In addition, as DOAC will likely overtake VKA for treatment of AF in the

general population, further study in patients with cirrhosis is needed to better understand the pharmacodynamics of DOAC in cirrhosis.

Future Directions

Although the last several years have seen significant gains in our knowledge of the nuanced coagulation system unique to patients with cirrhosis, the lack of both RCTs and standard outcome definitions continues to hinder expansion of understanding and promote ongoing clinical controversy. Despite current research efforts, multiple highly significant questions and knowledge gaps remain. We look to future trials to be designed with the highest rigor to answer these questions and bridge knowledge gaps about procedural bleeding risk prediction and appropriate prophylaxis, the role of global coagulation tests, the clinical outcomes in patients with nontumoral PVT, how to best prescribe VTE prophylaxis, and how to optimally dose therapeutic anticoagulants in patients with both compensated and decompensated cirrhosis.

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.2021.09.004.

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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.