AGA Technical Review on Coagulation in Cirrhosis

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Abbreviations:

TR: TR
AGA: American Gastroenterology Association
PICO: Population, Intervention, Comparator, Outcome
PRISMA: Preferred reporting Items for Systematic Reviews
MOOSE: Meta-analysis of Observational Studies in Epidemiology
RCT: Randomized controlled trial
RR: relative risk
CI: confidence interval
INR: international normalized ratio
VET: viscoelastic testing
TGA: thrombin generation assay
ACLF: acute on chronic liver failure
VTE: venous thromboembolism
PVT: portal vein thrombosis
AF: atrial fibrillation
TPO: thrombopoetin
LMWH: low molecular weight heparin
DOAC: direct acting oral anticoagulation
VKA: vitamin k antagonist
TEG: thromboelastography
ROTEM: rotational thromboelastometry
SOC: standard of care
FFP: fresh frozen plasma
CTP: Child-Turcotte-Pugh
EGD: esophagogastroduodenoscopy
EVL: esophageal variceal ligation
APRI : AST to platelet ratio index
MELD: model for endstage liver disease
ERCP: endoscopic retrograde cholaniopancreatogram
GI: gastrointestinal
DVT: deep venous thrombosis
PE: pulmonary embolism
ISTH: International Society of Thrombosis and Haemostasis
HCC: hepatocellular carcinoma
US: ultrasound
TIPS: transjugular portosystemic shunt
GEV: gastroesophageal varices
ICH: intracranial hemorrhage
AF: atrial fibrillation

Introduction

The coagulation system of healthy individuals has evolved to maintain a secure balance of pro and anti-hemostatic 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 recognized the hemostatic system in patients with cirrhosis is a “re-balanced” state.[4-8]

While 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 (TGA), our understanding of this complex system in cirrhosis has significantly progressed. Early translational studies demonstrated that the decline in *pro*coagulant proteins is balanced by a decline in *anti*coagulant 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 may tip this balance include both internal disease state progression (e.g., 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 prior to invasive procedures, and to direct hemostatic therapy. The most common conventional tests used to assess the hemostatic system include the INR and coagulation factor assays (e.g., fibrinogen). Additionally, 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, may 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 non-tumoral 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 if 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 increasingly treated 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 cirrhosis. The goal of this TR is to provide an evidence-based framework for clinicians to base important therapeutic decisions in 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 pre-procedure prophylaxis to correct coagulation parameters and/or platelet level reduce the risk of bleeding in patients with cirrhosis?***

Thrombosis related questions:

1. ***Is VTE prophylaxis indicated in hospitalized patients with cirrhosis?***
2. ***Should patients with cirrhosis be screened for non-tumoral PVT?***
3. ***What are the data on specific anticoagulant therapies for non-tumoral PVT in patients with cirrhosis?***
4. ***In patients with atrial fibrillation and cirrhosis is anticoagulation safe and effective?***

Methods

Overview. The TR was developed by the American Gastroenterology Association (AGA) to support the accompanying guideline on coagulation in patients with cirrhosis. The TR 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 "Population, Intervention, Comparator, and Outcome (PICO)" format to generate important clinically relevant questions. The PICO format provides a framework which then guides evidence assessment and analysis profiles.[23] The TR panel then identified patient-important outcomes and systematically reviewed the literature for each PICO question. Additionally, the TR panel reviewed the literature for indirect evidence that could assist the guideline panel in making informed decisions for the PICO 1 and PICO 2 questions. 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 non-surgical procedures, to inform on the role of platelet transfusion and plasma transfusion and (2) in the prophylaxis of non-surgical procedural bleeding. Furthermore, indirect evidence from published well-designed RCTs in the general population (non-cirrhotic) was used to inform the benefits in PICO 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 framework (Grading of Recommendation, Assessment, Development, and Evaluation) 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 six separate PICO questions (Table 1). The questions and final PICOs were approved by the AGA governing board. Among the most important outcomes considered were directly related to clinical care with respect to assessment of bleeding risk in relationship to common procedures (PICO 1 and 2), need for screening patients with cirrhosis for PVT (PICO 3), the safety and efficacy of anticoagulation for the prevention of VTE and treatment of PVT (PICO 4 and 5), and the use of prophylactic anticoagulation for prevention of stroke in AF (PICO 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 non-standardized 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 1, PICO 2 and PICO 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 (PRISMA) statement and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) 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 four different searches all with different criteria. (1) The PICO 1 search was conducted for the three most used tests in patients with cirrhosis: platelet count, INR, and VET. We used a randomized controlled trial (RCT) search filter and excluded: case reports, editorials, letters, comments and notes. (2) Similarly, RCT and comparative design (case-control and comparative cohort) search filters were used for PICO 2 and we searched for platelet, plasma transfusion, and thrombopoietin (TPO) agonists before non-surgical procedures. (3) Furthermore, all study designs except case reports, editorials, and letters, were used when conducting a search for PICO 4. (4) Lastly, one search without design filters was conducted for PICO 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/congresses abstracts published prior to 2018. The final strategy is available in (Supplementary Figure S-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 above formulated clinical questions and discussed for each individual PICO.

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 two 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 manuscript was then evaluated by two independent blinded investigators. Disagreement was solved by consensus between the two 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. When the number of included studies was three or less, 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 a relative risk (RR). The statistical analyses were conducted using RevMan 5.3.[29] When meta-analysis was not feasible, we presented data narratively and using descriptive statistics.

Quality of Evidence Assessment . 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 RCT starts as high-quality, while 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-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 1: What testing strategy for bleeding risk assessment is most beneficial for patients with cirrhosis?

Results

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

Inclusion criteria: Adults with cirrhosis and severe coagulopathy, defined as INR>1.8 and/or platelets <50,000 /mL. Participants in the TEG 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 standard of practice.

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

The role of traditional coagulation testing (e.g., INR 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 VET 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 while the other two 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%CI 0.01, 7.87) (Supplementary Figure S-2). However, the confidence in this estimate is very low because it is based on one single bleeding event which occurred in a solitary study. The lack of bleeding events in either arm in the other two studies rendered the risk ratio not estimable.

Blood product transfusion

The number of patients who received blood products prior to an invasive procedure was lower in the VET cohort than in patients undergoing transfusions in the SOC condition (26 versus 72). The use of VET to assess bleeding

risk prior to procedures was associated with a trend for administration of fewer pre-procedural 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 eight post-procedure deaths in each of the two arms, all associated with progressive liver failure, and unrelated to post-procedure bleeding. Pre-procedure bleeding risk assessment using VET was not associated with the risk of death (RR=1.05, 95% CI 0.45, 2.44) (Supplementary Figure S-3).

The role of VET in the clinical management of bleeding events in patients with cirrhosis

Two RCTs assessed the impact of VET use (79 patients) versus SOC (77 patients) in the management of variceal and non-variceal bleeding events in patients with cirrhosis and severe coagulopathy.[32, 34] Reported outcomes included failure to control bleeding, failure to prevent re-bleeding after initial hemostasis, blood product transfusion, and mortality.

Failure to control bleeding

Failure to control bleeding by day five occurred in 12 versus 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 S-4).

Failure to prevent re-bleeding (days 6-42)

Of the 62 and 49 patients in the VET and SOC groups respectively who had controlled bleeding by day five, failure to prevent re-bleeding between days 6-42 occurred in 22 versus 19 patients. Re-bleeding 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 six 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 S-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 whereas Rout *et al.*[34] administered only FFP or platelets. Similarly, the criteria for transfusion in the SOC groups were based on INR and platelet levels in both studies, but with different cutoffs. For this reason, pooled comparisons of the amount of blood products or transfusion-related side effects between the two groups could not be reasonably performed. A total of 46/79 patients in the VET group and 77/77 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 S-6).

Mortality after bleeding

A total of 31/79 patients in the VET group and 39/77 patients in the SOC group died within six 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 S-7).

Quality 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, since only a minority of patients would have received transfusions in SOC practice. In the outcomes related to mortality or re-bleeding the evidence was downgraded for indirectness because these delayed outcomes are more likely to be related to liver disease severity rather 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 peri-procedural 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 peri-procedural period (Supplementary Table S-1).[35-38] 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, 39, 40] 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. While *in vitro* evidence suggests that a platelet count >55,000/mL provides adequate substrate for thrombin generation in patients with cirrhosis[41], we found no direct *clinical* evidence supporting platelet count cut-off across various thresholds in predicting bleeding events. The available literature examining bleeding risk in patients with 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 multi-parameter assessment of global coagulation with VET is an attractive alternative.[42] 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. We identified three RCTs investigating procedural bleeding management strategies which compared traditional coagulation measurement to 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. While the use of VET prior to procedures clearly reduces platelet and plasma transfusion compared to traditional testing, there is no current direct evidence that VET provides more accurate assessment of bleeding risk per se. Future investigation using restrictive arms where prophylaxis is not administered are essential to better understand the role of VET in bleeding risk assessment in patients with cirrhosis.

PICO 2: Does pre-procedure 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 1), we chose to analyze the most common procedures patients with cirrhosis are likely to undergo. This TR found prospective, RCTs grouping procedures together to analyze the utility of VET[16, 31, 43] and the efficacy and safety of TPO agonists[44-48]. 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 cholangiopancreatogram (ERCP), colonoscopy with polypectomy, and liver biopsy.

Results

Paracentesis

We identified eight retrospective case series, case-control, and cohort studies examining patients with cirrhosis undergoing paracentesis for ascites.[14, 40, 49-54] In general, the majority of studies do not indicate if bleeding prophylaxis was administered prior to paracentesis. Patient characteristics are also not uniformly reported, however given the necessity of ascites for the procedure, it is presumed that the majority of patient characteristics would be similar and include decompensated cirrhosis. The largest studies performed to date which provide pre-procedure values for INR and platelets reviewed a total of 4,216 paracenteses.[49, 54] In the study by Grabau *et al.*, the majority of patients had INR > 1.5 (823/1100) and platelets < 50,000/mL (598/1100) and reported no bleeding events.[49] A more recent study examining 3,116 paracenteses found a total of six bleeding events.[54] In general, pre-procedure bleeding prophylaxis was not given (mean platelet count was of 121,000/mL and INR 1.6). A study restricted to patients with ACLF and propensity matched controls (mean platelet 90,000/mL, INR 2.2) identified a total of 18 bleeding events, defined as blood present in the ascites.[40] In a case-control study examining patients with hemoperitoneum after paracentesis compared to a control population of patients suspected of bleeding (but ruled out with CT) after paracentesis there was no significant difference in mean platelets level or INR between the two groups.[14] On multivariate analysis, AKI was associated with bleeding risk (OR 4.3, 95%CI 1.3, 13.5), however MELD score, platelet level, and INR were not significant predictors.

Thoracentesis

We found three studies investigating bleeding outcomes in patients with cirrhosis undergoing thoracentesis.[55-57] These studies vary in cohort inclusion criteria and study design, therefore direct comparison between studies is not possible. Prophylaxis prior to thoracentesis was reported in two studies. The largest retrospective cohort examined patients with “coagulopathy” as defined by platelet count < 50,000/mL and INR > 1.6.[55] The study does not clearly define the percentage of patients in the cohort with liver disease. The authors examined 1,009 thoracenteses and

compared patients that received prophylaxis to correct INR and platelets to patients who did not did not and found no difference in bleeding-related events (0/706 in no prophylaxis vs. 4/303 in prophylaxis).[55] These data are limited given the lack of information on the underlying cohort and are at risk for misclassification bias and selection bias. A retrospective case control study compared thoracentesis in patients with cirrhosis versus those without cirrhosis reported three major bleeding events (1.8%) in the group with cirrhosis.[57]

Upper endoscopy with esophageal variceal band ligation

A total of four studies reported bleeding outcomes in patients undergoing EGD with EVL.[13, 58-60] 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 <50,000/mL and INR>1.5. Notably, transfusion requirements were similar between groups with elevated coagulation parameters (INR>1.5 and platelet <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 prior to EVL to be similar in cases and controls (98,000/mL cases and 101,000/mL controls).[58] This study reported associations with prothrombin index and AST to platelet ratio index (APRI) with bleeding risk, but did not correlate values of PT or platelets to bleeding risk. The largest study to date prospectively collected 24 cases of post-EVL ulcer bleeding out of 521 total EGD procedures.[60] Platelet count was similar between the groups (121,000/mL bleeding subjects vs. 118,000/mL control) and PT/INR was elevated (1.8 bleeders vs. 1.5 control). Of note, model for endstage liver disease (MELD) was significantly higher in the group that developed post-EVL ulcer bleeding in this study.

Colonoscopy with polypectomy

We reviewed four studies examining bleeding outcomes in patients with cirrhosis undergoing colonoscopy with polypectomy.[39, 61-63] All studies were a retrospective cohort or case control design. The studies almost exclusively included compensated patients with CTP A cirrhosis. Three studies did not report information on pre-procedure bleeding prophylaxis. The largest study retrospectively examined 814 patients undergoing colonoscopy (700 with CTP A) and identified ten delayed bleeding events within 30 days [five in CTP A cirrhosis (0.7%) and five in CTP B/C cirrhosis (4.4%)].[39] Mean platelet level was 85,000/mL and mean INR was 2.2 in patients with CTP C cirrhosis. If patients received prophylaxis prior to colonoscopy, the values of corrected INR and platelets were reported accordingly. Multivariable analysis showed the 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 prior to colonoscopy, however reported significantly low rates of delayed post-polypectomy bleeds. In one retrospective cohort of 307 patients with cirrhosis (85.7% CTP A), only one bleeding event was reported.[62] Similarly, a retrospective case control study examining 89 patients with cirrhosis (CTP A 84.3%) and 348 controls

without cirrhosis found only two delayed post-polypectomy bleeds in patients with cirrhosis compared to one in controls without cirrhosis.[63]

ERCP

We identified three retrospective studies examining bleeding risk in patients with cirrhosis undergoing ERCP.[64-66] Two studies did not report pre-procedure bleeding prophylaxis;[64, 65] one study only included patients who had intervention to correct INR and platelets.[66] One study examined 129 ERCP in patients with cirrhosis undergoing ERCP compared to 392 ERCP in patients without cirrhosis.[64] In the cohort with cirrhosis, 74% were CTP B or C with a median MELD score of 14.[64] Thirty-five patients with cirrhosis underwent biliary sphincterotomy. Of the patients with cirrhosis, eight developed bleeding after ERCP compared to 121 who did not. Both platelet count and INR were not significantly different between the groups. Patients with GI bleeding more commonly underwent sphincterotomy (5/8 63% GI bleed vs. 30/121 25% no GI bleed). Overall there was no difference in incidence of GI bleeding comparing patients with cirrhosis to controls without cirrhosis. A large retrospective case control study compared 3,228 patients with cirrhosis who underwent ERCP (80.6% with decompensated cirrhosis) and found a post-procedural bleeding incidence of 2.1% compared to 1.2% in matched non-cirrhotic controls ($p<0.01$).[65] On multivariable analysis, decompensated cirrhosis, therapeutic ERCP, and biliary sphincterotomy were independently associated with bleeding, however coagulation parameters and use of pre-procedure bleeding prophylaxis were not included in the model. A multicenter retrospective study examining outcomes in 538 ERCP in patients with cirrhosis found six cases of bleeding (1.1% incidence rate).[66] Of note, all patients included in this study received bleeding prophylaxis if INR >1.5 or platelets <50,000/mL.

Two studies were reviewed which directly compared procedural methods in ERCP and bleeding risk.[67, 68] 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.[67] Patients with platelets <50,000/mL and “severe coagulopathy” were excluded and use of prophylaxis was not reported. There were a total of 98 patients enrolled and five “mild” bleeding events were reported (four in the group undergoing lithotripsy). Another study retrospectively examined patients with cirrhosis undergoing ERCP with sphincterotomy with two separate types of electrocautery (alternating current versus blended current).[68] Prophylaxis was provided for patients with platelets <50,000/mL and INR >1.5. A total of 29 patients were examined and three bleeding events (one major) were identified in the group using blended current compared to zero events in the group using alternating current. These two studies highlight the complexities of analyzing bleeding in patients undergoing ERCP where numerous factors particular to the procedure play a significant role in modifying bleeding risk.

Liver biopsy

We reviewed seven retrospective studies examining bleeding complications after percutaneous[69-72] and transjugular liver[70, 73-75] 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 only patients with cirrhosis. Two studies investigated transjugular liver biopsy[75] [73] included patients with severe coagulopathy where percutaneous liver biopsy was contraindicated. Overall rates of major bleeding were low, ranging from 0.2-0.6%. One prospective study compared patients undergoing percutaneous versus transjugular liver biopsy.[70] Of the total cohort only 8/68 (11.8%) in the percutaneous group and 22/75 (29.3%) in the transjugular group had cirrhosis. One bleeding event occurred (subcapsular hematoma) in the group undergoing percutaneous biopsy, however it is not reported if they had cirrhosis.

We reviewed three large retrospective study cohorts examining patients undergoing percutaneous biopsy.[69, 71, 72] One study examined 4,275 procedures from 1994-2002.[69] 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 five deaths related to bleeding events (15 patients, 33% with cirrhosis). A large retrospective study in patients with chronic liver diseases examined 3,357 patients (12% with cirrhosis) and found bleeding events in 21 (0.6%) patients after biopsy.[72] When comparing the patients without complications to patients with bleeding, there was no significant difference in platelet count, PT, or PTT between groups. The group with bleeding more commonly had a platelet level < 60,000/mL (4.8%) versus only 0.3% in the non-bleeding group, however this did not reach statistical significance. In multivariable analysis, platelet count < 100,000/mL was an independent predictor of bleeding (OR 4.1, CI 1.5-11.1, p<0.01). Seef *et al*.[71] evaluated complications in patients with chronic hepatitis C undergoing percutaneous liver biopsy from 2000-2006. Patients with decompensated cirrhosis and platelet counts < 50,000/mL were excluded. Of note, there was center variability for minimal platelet level required prior to biopsy. Bleeding occurred in 0.5% (16/2740) patients with no statistically significant difference in percent of patients with cirrhosis 1068/2677 (39.9%) in non-bleeding cohort versus 8/16 (50%) in the bleeding cohort. Pre-procedure INR was the same between groups, however mean platelet level was significant lower in the bleeding group (121,000/mL) compared to the non-bleeding group (158,000/mL). In the bleeding group 26.7% of patients had a platelet count < 60,000/mL and 50% had platelet counts greater than 100,000/mL. Similar to other studies in this field, no data was provided regarding administration of pre-biopsy prophylaxis.

RCT in patients with cirrhosis undergoing invasive grouped procedures

Viscoelastic studies

Several RCTs have been conducted in patients with cirrhosis comparing the use of VET to traditional coagulation parameters to guide prophylaxis prior to invasive procedures.[16, 30, 31] The three 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 standard of care prophylaxis (fresh frozen plasma for INR >1.8 and platelet transfusion if less than 50,000/mL) versus prophylaxis based on predetermined VET parameters.[16] A significant reduction in both platelet transfusion and FFP transfusion was found in the VET cohort compared to SOC. Bleeding occurred in one patient undergoing a 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 < 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 versus SOC groups. A study examining prophylaxis based on SOC versus 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]

TPO agonists

We identified five RCTs examining TPO agonists compared to platelet transfusion in patients with cirrhosis and thrombocytopenia prior to undergoing an invasive procedure.[44-48] Procedural type was heterogonous. These studies included primarily low-risk procedures and included both medical and surgical procedures. All studies focus on pre-procedure 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 prior to procedures (e.g., restrictive arm).

Two large RCTs examined the efficacy of avatrombopag to raise platelets in patients with thrombocytopenia and cirrhosis prior to planned procedures.[45] Patients were given placebo or avatrombopag and platelet count was measured the day of procedure. Patients were transfused if platelet count was less than 50,000/mL. The majority of procedures performed in these studies were low-risk (61%, 248/407). The most common procedures performed were diagnostic and therapeutic EGD (52%, 212/407). The predefined combined primary endpoint was no need for platelet transfusion or rescue therapy for bleeding and it favored the treatment group RR 2.46 (95% CI: 1.77, 3.41) for patients in high platelets group that received 40mg avatrombopag (Supplementary Figure S-8) and RR 2.36 (95%CI: 1.67, 3.32) for patients in low platelets group that received 60mg avatrombopag (Supplementary Figure S-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%, 15/430) 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 S-9). A similar study examined lusotrombopag to raise platelets in patients with thrombocytopenia and cirrhosis prior to planned procedures.[46] Patients were given placebo or lusotrombopag and platelet count was measured the day of procedure and patients were transfused if less than 50,000/mL. Patients in the lusotrombopag group achieved platelets > 50,000 /mL more compared to placebo group, RR 3.60 (95% CI: 1.72, 7.57) and there was no difference in the thrombotic events (RR 0.55, 95% CI: 0.12, 2.64) (Supplementary Figure S-12). The majority of procedures performed in this study were low-risk (66%, 121/185). Endoscopies were the most common procedures performed and constituted all of the low-risk procedures. Lusotrombopag significantly reduced the need for platelet transfusions compared to placebo (71% in placebo versus 35% in lusotrombopag). Two patients required intervention for rescue bleeding (one 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 nine bleeding events (4.2%, 9/214) were reported (5.6% in placebo versus 2.8% in lusotrombopag).

Quality of evidence

The overall certainty of evidence was very low. 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 pre-procedural 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 S-1). Regarding the TPO agonist studies, the evidence was rated down for serious indirectness because surrogate outcomes (e.g., transfusion prior to or after the procedure) were used instead of post-procedural bleeding. Additionally, there was no comparison group of patients with thrombocytopenia who did not receive either TPO agonist or platelet transfusion prior to procedures. Lastly, in the TPO agonist studies the event rate was very low and we rated down for imprecision (Supplementary Table S-2 and Table S-3).

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 which examine patients undergoing a specific procedure are mainly small retrospective cohorts. These studies often do not address the use of pre-procedure prophylaxis (e.g., 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.[76, 77] RCTs in this field have amalgamated multiple different procedures together (both low and high-risk). These studies either analyzed the utility of VET compared to traditional testing[16, 30, 31] or compared TPO agonist use versus platelet transfusions.[44-48] With the exception of one small study[30], these studies do not include restrictive strategy cohorts where patients do not receive any pre-procedure prophylaxis. As such, it is not possible to fully understand if prophylaxis provides harm or benefit in respect to the outcome of bleeding as prophylaxis was generally given in these studies prior to 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.[39, 60] This suggests there may be other factors unique to the individual patient that increase

bleeding risk, including ACLF or sepsis. The two largest trials comparing TPO agonists to standard platelet transfusion for thrombocytopenia (platelets <50,000/mL) prior to procedures included mostly low-risk procedures and found very low bleeding rates.[45, 46] Overall, bleeding events are very rare in patients with cirrhosis undergoing low-risk procedures and appear to be independent of pre-procedure bleeding prophylaxis. The current literature is limited by the rarity of bleeding events, non-standardization 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 two prospective RCTs comparing VET to traditional prophylaxis, there were a total of three endoscopies with polypectomy, two ERCP with sphincterotomy, and 51 percutaneous liver biopsies performed with no bleeding events.[16, 31] The two largest trials comparing TPO agonists to 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 was 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 pre-procedure bleeding prophylaxis to reduce bleeding.

PICO 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 which reported major bleeding and venous thromboembolic (VTE) events. We excluded studies which lacked a control arm, included only surgical patients, those which 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 versus a control group in hospitalized patients with cirrhosis. There were five retrospective cohort studies reporting VTE events in hospitalized patients with cirrhosis receiving prophylactic anticoagulation.[18, 78-81]

VTE events were defined as deep vein thrombosis (DVT) or pulmonary embolism (PE) or portal vein thrombus (PVT) and presented as composite endpoints 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 previously published.[82] These studies use well-defined outcomes of symptomatic DVT (four RCTs) and non-fatal PE (six 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 non-fatal PE (RR=0.61, 95%CI 0.23, 1.67).

Harms assessment: bleeding

There were no RCTs comparing harms due to prophylactic anticoagulation to a control group in hospitalized patients with cirrhosis. There were three retrospective cohort studies reporting bleeding events in those with versus without prophylactic anticoagulation during hospitalization.[18, 80, 81] *All bleeding events* were defined as the overall number of major and minor bleeds reported in the study. *Major bleeding* (reported in two studies) was defined per the International Society on Thrombosis and Hemostasis (ISTH).[83]

In pooled analysis of the three studies, bleeding events (major and minor) occurred in 38/450 (8.4%) patients in the prophylactic anticoagulation group and 31/504 (6.2%) patients 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 two studies reporting major bleeding events, these occurred in 4/154 patients on anticoagulation and 6/200 not on anticoagulation. Prophylactic anticoagulation was not associated with major bleeding (RR=1.07, 95% CI 0.37, 3.06) (Supplementary Figure S-13). Bleeding events from esophageal varices were not separately described in all studies, therefore they could not be analyzed.

Quality 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. Additionally, 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 significant increased risk to develop VTE compared to patients without cirrhosis.[84] The rebalanced coagulation system in cirrhosis can transform to a hypercoagulable state.[85-87] VTE risk factors, such as malignancy, immobility, and critical illness are common in patients with cirrhosis and development of VTE increases risk of mortality.[88] Current guidelines for medical patients admitted to the hospital recommend VTE prophylaxis with anticoagulation for patients at high-risk to develop VTE.[82] Risk stratification should be performed with risk assessment models, such as the Padua Prediction Score, to determine which patients are highest risk and would benefit from prophylaxis.[89, 90] Risk assessment models have been successfully applied to cohorts with cirrhosis in smaller retrospective observational studies.[18, 91]

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 to 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 non-surgical medical cohort from previously published guidelines.[82] While 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 while hospitalized should be treated with anticoagulation prophylaxis as there is a clear reduction in incident DVT and PE. Only three retrospective observational studies met criteria to analyze risk of bleeding in patients with cirrhosis receiving anticoagulation for prophylaxis compared to 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.[88] Future prospective study examining outcomes and pharmacokinetics of prophylactic anticoagulation in patients with cirrhosis is now needed to better inform the benefits and risks of this practice.

PICO 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 (US) or cross-sectional with computed tomography (CT) or magnetic resonance imaging (MRI)] every 3-6 months reporting the development of incident non-tumoral PVT. We excluded studies of patients who underwent imaging due to hospitalization, presence of malignancy [e.g., hepatocellular carcinoma (HCC)] or known non-tumoral PVT. Retrospective cohort studies, case reports, comments, editorials, letters, notes and abstracts published prior to 2017 were excluded.

There were no studies designed to compare the impact on non-tumoral PVT incidence between an intervention cohort undergoing systematic screening for non-tumoral PVT and a cohort undergoing no screening. Therefore, the published literature is not adequate to support evidence of the comparative effectiveness of systematic screening versus no screening for non-tumoral 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 non-tumoral PVT. We identified three published studies[92-94] and one abstract[95]. All studies included patients with cirrhosis, followed with imaging every three or six months in the outpatient setting. The site (e.g., trunk, branch or both), degree of occlusion (e.g., non-occlusive or occlusive), duration and presentation (e.g., recent, chronic, asymptomatic or symptomatic) or extent of PV system occlusion (e.g., portal vein, splenic vein, superior mesenteric vein) of incidental non-tumoral PVT was not described in all studies either descriptively or with a formal classification system.[96, 97] Additionally the length of follow-up was variable (between one and eight years). The reported incidence of non-tumoral PVT in included studies varied between 3.5%-4.6% at 1-year. The greatest incidence of non-tumoral PVT was 10.7% at 5-years.[94] There were no uniform reports of additional non-tumoral PVT related outcomes sufficient for pooled analyses.

Quality of evidence

The GRADE evidence profile is illustrated in Supplementary Table S-5. The risk of bias was serious because there are no comparative studies between systematic screening and standard-of-care. The indirectness was serious because the impact of non-tumoral 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 US screening compared to no screening. In addition, the impact of non-tumoral PVT on liver disease progression,

including hepatic decompensation or transplant-free survival, was inconsistently reported among studies and mortality outcomes are absent.

Discussion

Non-tumoral PVT is common in patients with cirrhosis with a 5-year cumulative incidence rate to 11%.[93] Risk factors for non-tumoral PVT in patients with cirrhosis are well described with the strongest factor likely being advanced portal hypertension and reduced portal blood flow.[98-101] The impact of non-tumoral PVT on clinical outcomes remains controversial, especially in patients who are not liver transplant candidates. One large French study demonstrated that non-tumoral PVT is a result of the natural history of cirrhosis progression rather than a cause of hepatic decompensation.[102] However, other studies conclude that non-tumoral PVT is associated with greater risk of hepatic decompensation and mortality.[103-106] In liver transplant candidates, non-tumoral PVT may negatively impact post-transplantation survival by affecting perioperative management.[105, 107, 108] Consequently, previous consensus statements and guideline recommendations suggest screening for non-tumoral PVT in patients with cirrhosis listed for liver transplantation in order to guide perioperative management.[22, 109-111] In light of these recommendations and current variation in clinical practice, we sought to evaluate the quality of the evidence in respect to the benefit of systematic screening for non-tumoral PVT in all patients with cirrhosis.

To date, there are no RCTs comparing patients with cirrhosis undergoing screening for non-tumoral PVT to patients who are not screened in either the general or liver transplant populations. We identified four single-arm observational prospective studies that investigated screening for non-tumoral 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 to usual care. All studies included in our analysis employed US at various screening intervals to detect non-tumoral PVT. Current consensus and guideline statements suggest 6-month interval screening coinciding with HCC 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 (e.g., CT or MRI) 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 to no screening. The impact of non-tumoral PVT on liver disease progression is unknown. Prospective trials following patients who undergo screening compared to those who do not will be necessary to assess benefits of screening, subsequent need for therapy, and to determine the overall effect of non-tumoral PVT on disease progression and mortality.

PICO 5: What are the data on specific anticoagulant therapies for non-tumoral PVT in patients with cirrhosis?

Results

Benefits

For efficacy of anticoagulation for non-tumoral 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 non-tumoral PVT outcome including degree of recanalization (partial or complete), no response or non-tumoral PVT progression, both of which may affect important patient-centered outcomes (Table 4).

A total of 12 studies met inclusion criteria and reported recanalization in adult patients with cirrhosis and non-tumoral PVT who were treated with anticoagulation.[92, 112-122] We excluded studies reporting on malignant PVT or those that included treatments other than anticoagulation, including transjugular intrahepatic portosystemic shunt (TIPS). Six of the 12 studies were comparative retrospective cohorts where the anticoagulation group was treated with low molecular weight heparin (LMWH) and or a vitamin K antagonist (VKA) and the control group did not receive any treatment.[92, 115-117, 120, 121] Mean age was between 45 years and 59 years in the anticoagulation group and between 48 years and 61 years in the control group. Advanced liver disease (CTP class B and C) was reported in all six studies and ranged from 47%-89% in the anticoagulation group and between 50-80% in the control group. Total median follow up time was between 19 and 44 months and median anticoagulation time ranged from four to 13 months.

Among patients with cirrhosis and non-tumoral PVT from the six comparative studies (n= 391), the relative risk of complete and partial recanalization was 2.27 (95% CI: 1.73, 2.98) for those patients who received anticoagulation treatment compared to 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 non-tumoral 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 six 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 S-14 and S-15).

Six comparative cohort studies evaluated non-tumoral PVT non-response or progression. The relative risk was 0.57 (95% CI: 0.48, 0.68) for those patients who received anticoagulation treatment compared to no treatment. Rates of non-responders/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 six studies (n=209) (Supplementary Figures S-16 and S-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.[92, 112-122] Five of the 12 studies had a comparative retrospective cohort design where the anticoagulation group was treated with LMWH and/or VKA and the control group did not receive any treatment.[92, 115, 116, 120, 121] Due to very sparse events in the comparative cohort studies, to determine the incidence of bleeding per 100 patient-years, we used single arm retrospective cohort studies. Four comparative studies (n=175) informed on major bleeding, not related to gastroesophageal varices (GEVs), as defined by established guidelines from the ISTH.[92, 115, 116, 120] The relative risk of major bleeding not related to GEVs was 0.74 (95% CI: 0.12, 4.48) for those patients who received anticoagulation treatment compared to no treatment (Supplementary Figure S-18). However, this relative risk was based on three events, with 1/79 major bleeds in the anticoagulation group and 2/96 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, 0.05) per 100 patient-years and was pooled from nine studies (n=347) (Supplementary Figure S-19). In the control group the incidence was 0.02 (95%CI: -0.01, 0.05) per 100 patient-years, pooled from four studies (n= 96) (Supplementary Figure S-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.[92, 115, 116, 120, 121] The relative risk of all bleeding was 0.86 (95% CI: 0.45, 1.63) for those patients who received anticoagulation treatment compared to no treatment (Figure 5). For GEV bleeds, the relative risk of major bleeding per year was 0.34 (95% CI:0.16, 0.75) in patients treated with anticoagulation versus 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 S-21). In the control group the incidence was 0.12 (95%CI: 0.08, 0.15) per 100 patient-years, pooled from five studies (n=254) (Supplementary Figure S-22).

Quality of evidence

Evidence from comparative retrospective cohort was used to inform on the benefits and harms of anticoagulation treatment in patients with cirrhosis and non-tumoral 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, due to a low event rate there was serious imprecision. The certainty of evidence informing benefit outcomes was very low.

To inform on harms of anticoagulation in patients with cirrhosis and non-tumoral PVT, observational evidence from comparative and single arm cohort studies was used. Within these studies a serious risk of bias was identified because the assessment of outcome was not well described (there was not 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 both quality of the evidence from the benefits and the harms was very low.

Discussion

There is considerable controversy regarding the clinical significance of non-tumoral PVT in patients with cirrhosis and whether this contributes to worsening hepatic decompensation (See PICO 4).[19] Treatment of PVT with anticoagulation in liver transplant candidates has been recommended in some cases.[109, 110] Given this controversy, we sought to evaluate the quality of the evidence supporting the use of anticoagulation to treat non-tumoral PVT.

Anticoagulation is effective in treating non-tumoral PVT in patients with cirrhosis. Anticoagulation promotes portal recanalization in patients treated for non-tumoral PVT compared to 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%).

While the current literature demonstrates anticoagulation as an effective treatment for non-tumoral 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, 0.05) per 100 patient-years compared to a similar incidence of bleeding in the control groups 0.02 (95%CI: -0.01, 0.05) per 100 patient-years. When examining all reported bleeding events in patients treated with AC compared to 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 a RR for bleeding from GEV of 0.34 (95% CI: 0.16, 0.75) when comparing patients treated with anticoagulation compared to 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 prior to initiation of anticoagulation therapy may alternatively explain this finding. Nonetheless overall bleeding risk with anticoagulation appears to be similar to patients with non-tumoral PVT not treated with anticoagulation.

While we were unable to directly compare individual anticoagulants directly in terms of both safety and efficacy, the choice of anticoagulant remains a decision best made on an individual basis. Few studies to date have analyzed direct oral anticoagulants (DOAC) in patients with cirrhosis and we did not identify any such studies which met our

inclusion criteria. Each anticoagulant has inherent strengths and limitations.[22] Additionally, while this TR was limited to medical therapies to treat non-tumoral PVT, TIPS placement with or without anticoagulation is a non-pharmacologic alternative with similar rates of PV recanalization.[123-125]

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

PICO 6: In patients with atrial fibrillation and cirrhosis is anticoagulation safe and effective?

Results

The benefit of oral anticoagulation in patients with atrial fibrillation (AF) is well established. Guideline recommendations support the use of oral anticoagulation in patients with stroke risk factors for AF.[126] 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.[127] This TR identified six high quality RCTs with more than 200 events that informed on overall mortality and stroke outcomes. Although the specific focus of PICO 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 which 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 six RCTs (n= 2850), the relative risk of mortality was 0.72, 95% CI: 0.55-0.94 for those patients who received anticoagulation treatment compared to no treatment. (Table 5).

Non-fatal stroke

Within the same six RCTs (n= 2850), the relative risk of non-fatal stroke was 0.34 (95% CI 0.23, 0.49) for those patients with AF who received anticoagulation treatment with VKA compared to 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 to patients treated with VKA the relative risk of non-fatal 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: (1) cirrhosis diagnosed by clinical/radiographic/histologic testing; (2) ICD-9 codes for cirrhosis; (3) non-invasive markers of fibrosis (e.g., Fibrosis-4 Index > 3.25). All studies reporting outcomes in chronic liver disease patients without cirrhosis were excluded. We accepted major bleeding definition by established guidelines from the ISTH or equivalent report of bleeding that met this definition.[83] 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.[128-134] All seven studies were comparative cohort studies and all of them had one group of subjects that was treated with VKA. Three of the studies contained a control group or subjects that did not receive anticoagulation[128, 129, 134], and five studies had a group of subjects treated with DOAC[130-134] 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 rate ratio between the two cohorts. Incidence of bleeding was reported in 100 patient years. Furthermore, we identified five comparative cohort studies that compared subjects treated with VKA and DOAC.[130-134] Data from all the studies was pooled and relative risk was then calculated.

Age throughout the studies ranged from a mean age of 62 to a mean age of 77. Advance liver disease CTP class B and C was reported in five studies and ranged from 27%-64% in the VKA group, 10-36% in the DOAC group and 10-28% 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 S-23) Three studies had a control group.[128, 129, 134] One study had two control groups, one control group was a VKA-matched cohort and the other was a DOAC-matched cohort.[134] Pooled incidence of major bleeding in the control group per 100 patient-years was 2.1 (95% CI 1.5, 2.7) (Supplementary Figure S-24) Five studies included patients who were treated with DOAC.[130-134] Pooled incidence of major bleeding in the DOAC group per 100 patient years was 2.7 (95% CI 2.0, 3.4) (Supplementary Figure S-25)

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

Intracranial hemorrhage

Evidence informing the risk of ICH is derived from six single arm cohort studies that either used DOAC or VKA in patients with liver cirrhosis and AF.[128, 131-135] Definitions for cirrhosis were the same as described above. Included studies provided a specific report of ICH defined by clinical documentation or ICD-9 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 S-26) Three studies had a control group, with one study having one control group which was a VKA-matched cohort and the other was a DOAC-matched cohort.[128, 134, 135] Pooled incidence of ICH in the control group per 100 patient-years was 0.2 (95% CI 0.1, 0.3). (Supplementary Figure S-27) Four studies included patients that were treated with DOAC.[131-134] Pooled incidence of ICH in the DOAC group per 100 patient-years was 0.6 (95% CI 0.3, 0.9). (Supplementary Figure S-28)

Patients with cirrhosis and AF who were treated with VKA had more ICH when compared to patients with cirrhosis and AF that did not received any treatment with a rate ratio of 3.5 (95% CI 3.3, 4). (Table 5) Patients with cirrhosis

and AF when treated with DOAC had less ICH compared to patients with cirrhosis and AF treated with VKA, RR of 0.7 (95% CI 0.58, 0.84). (Table 6)

Quality of evidence

Evidence from large RCTs was used to inform the benefits from anticoagulation treatment in patients with AF and cirrhosis. Because this 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 in 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 (e.g., CHA2DS2-VASc risk factors).[126] Patients with cirrhosis are at risk for AF and clinicians increasingly face decisions regarding the management of these patients.[136, 137] However, patients with cirrhosis are routinely excluded from clinical trials with anticoagulation due to concerns for bleeding and therefore risk 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.[126] It is unlikely that properly powered RCTs in patients with cirrhosis will be conducted to firmly establish stroke reduction with anticoagulation. Based on these 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 greater than or equal to one risk factor. Therefore, patients with cirrhosis and elevated CHA2DS2-VASc score should obtain a similar benefit from anticoagulation. Specifically, DOAC appear more effective when compared to VKA in the general population. However, the pharmacodynamics of both VKA and DOAC in patients with cirrhosis remain unclear.[138, 139] 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 needs 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 may potentially outweigh 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 to 2.1 per 100 patient years in patients not treated with VKA. Several recent trials

examining DOAC compared to 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.[140-142]

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 primarily of well compensated patients with CTP A cirrhosis. The rate ratio of 1.91 in patients with cirrhosis treated with VKA compared to 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.[141]

In summary, in patients with well compensated cirrhosis, AF, and elevated CHA2DS2-VASc stroke risk factors, oral anticoagulation is a safe therapy which 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 may 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. Additionally, 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, a lack of both RCTs and standard outcome definitions continue 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 non-tumoral PVT, how to best prescribe VTE prophylaxis and how to optimally dose therapeutic anticoagulants in patients with both compensated and decompensated cirrhosis.

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Supplementary Tables and Figures

Table S-1: Procedure risk stratification

Low-risk procedures (<1.5% bleed risk)	High-risk procedures (≥1.5% bleed risk or bleeding risk into a vulnerable area)
Cardiac catheterization	Chest tube placement
Central line placement (including PICC line placement)	Endoscopy Coagulation or ablation of tumors, vascular lesions EMR or ESD ERCP with biliary or pancreatic sphincterotomy EUS with FNA Large polypectomy- polyp >1cm PEG placement
Dental extraction	Dialysis access (tunneled)
Dialysis access (non-tunneled)	Liver biopsy (transjugular or percutaneous)
Endoscopy Diagnostic endoscopy with or without biopsy ERCP without sphincterotomy EUS without FNA Variceal band ligation Uncomplicated polypectomy- polyp ≤1cm	Lumbar puncture
Endotracheal intubation	Percutaneous solid organ biopsy or deep non-organ biopsy
Paracentesis	PTC placement
Percutaneous biopsy of superficial non-organ biopsy	TIPS placement
Thoracentesis	Transarterial or percutaneous HCC therapies

EMR=endoscopic mucosal resection; ERCP=endoscopic retrograde cholangiopancreatography; ESD=endoscopic submucosal dissection; EUS=endoscopic ultrasound; FNA=fine needle aspirate; HCC=hepatocellular carcinoma; PEG=percutaneous endoscopic gastrostomy; PICC=peripherally inserted central catheter; PTC=percutaneous transhepatic cholangiography; TIPS=transjugular intrahepatic portosystemic shunt;

Figure S-1: PRISMA flow diagram

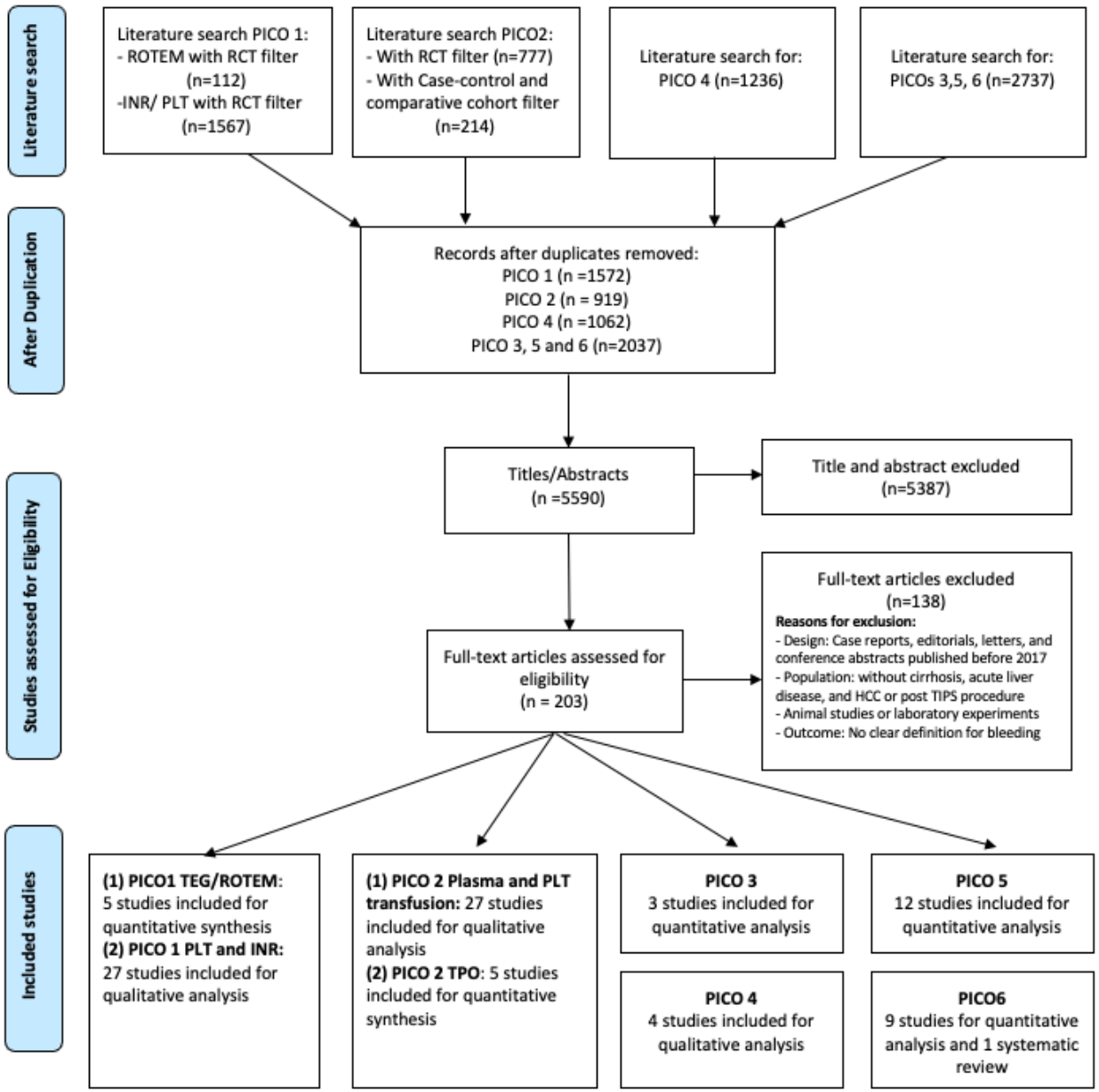

Figure S-2: Post-procedure bleeding comparing TEG to SOC

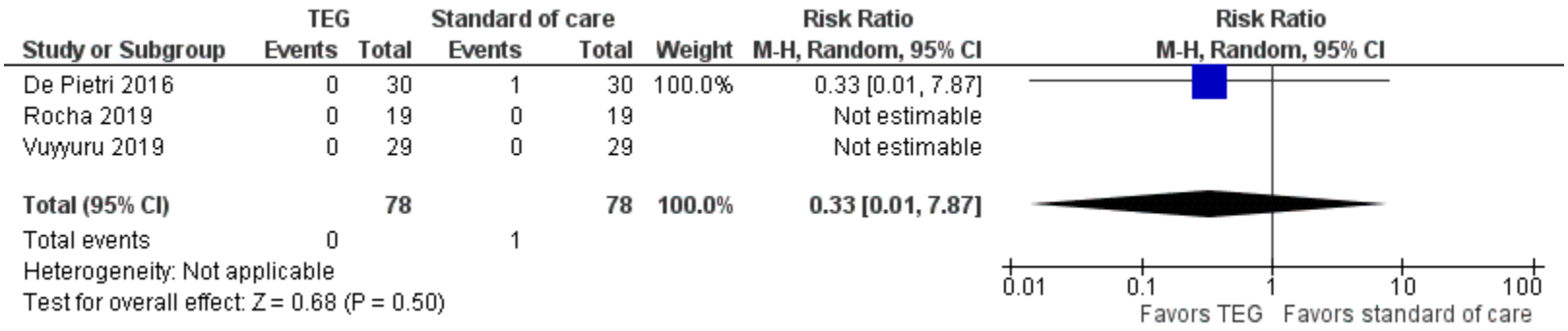

Figure S-3: Post-procedural mortality (up 90 days) comparing TEG to SOC

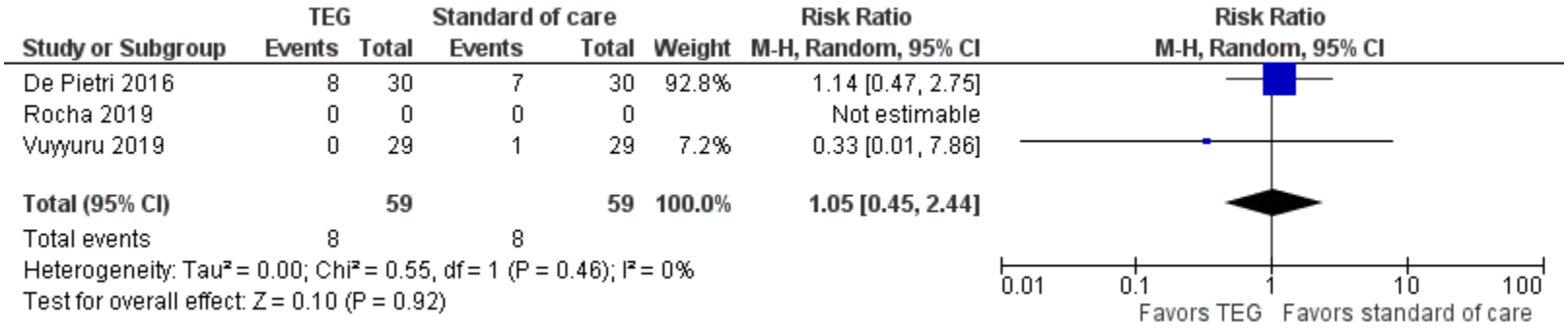

Figure S-4: Failure to control bleeding at five days comparing TEG to SOC

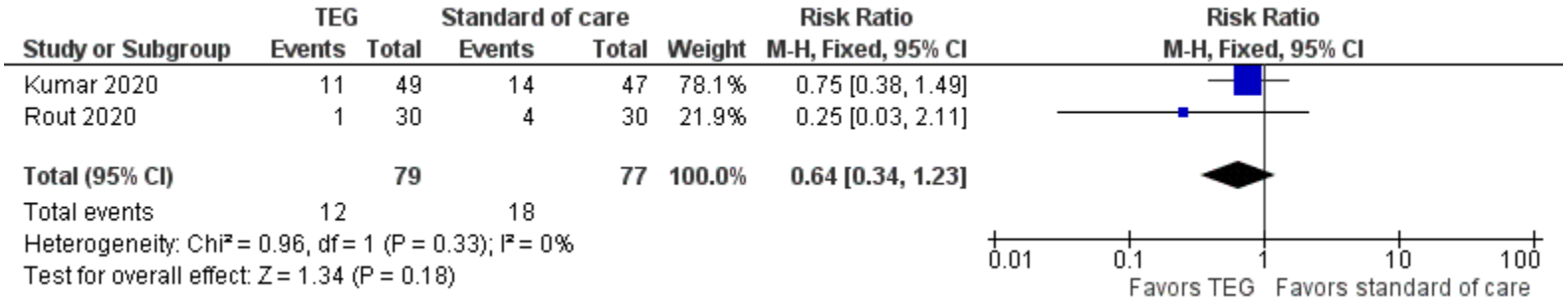

Figure S-5: Failure to prevent re-bleeding (days 6-42) comparing TEG to SOC

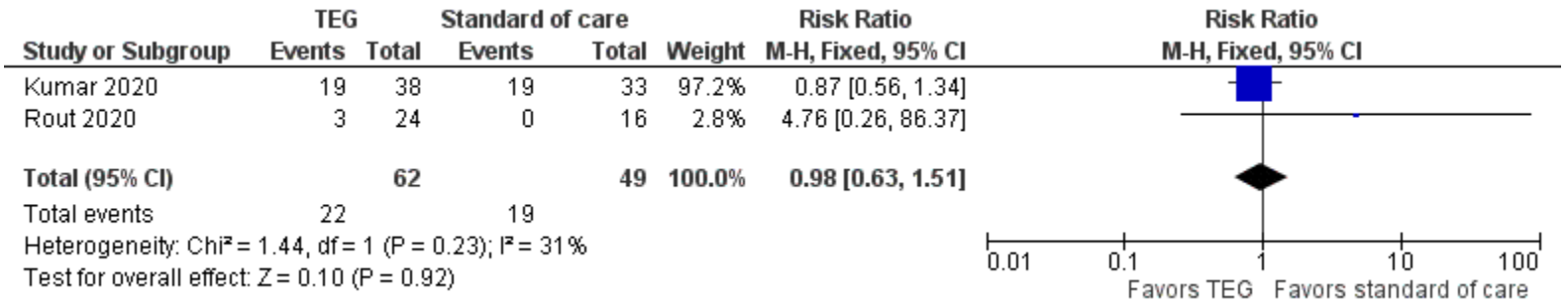

Figure S-6: Blood product transfusion for bleeding comparing TEG to SOC

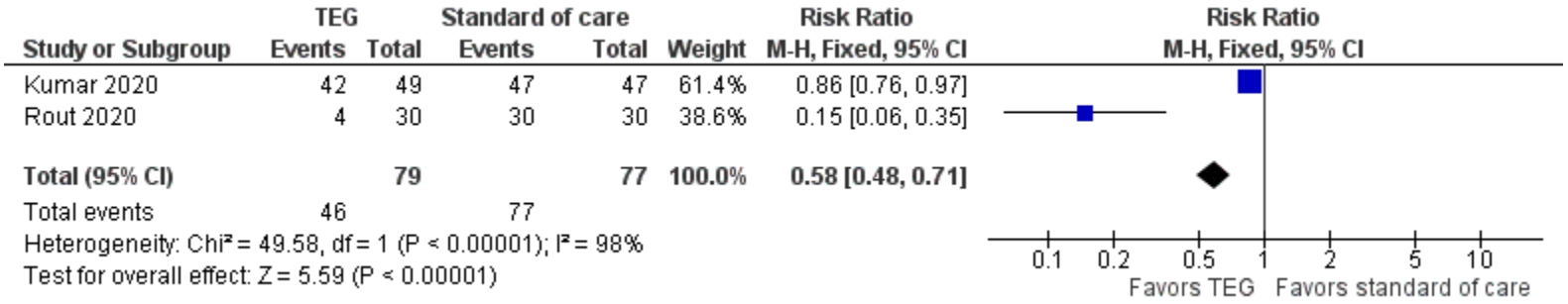

Figure S-7: Mortality at 42 days after bleeding comparing TEG to SOC

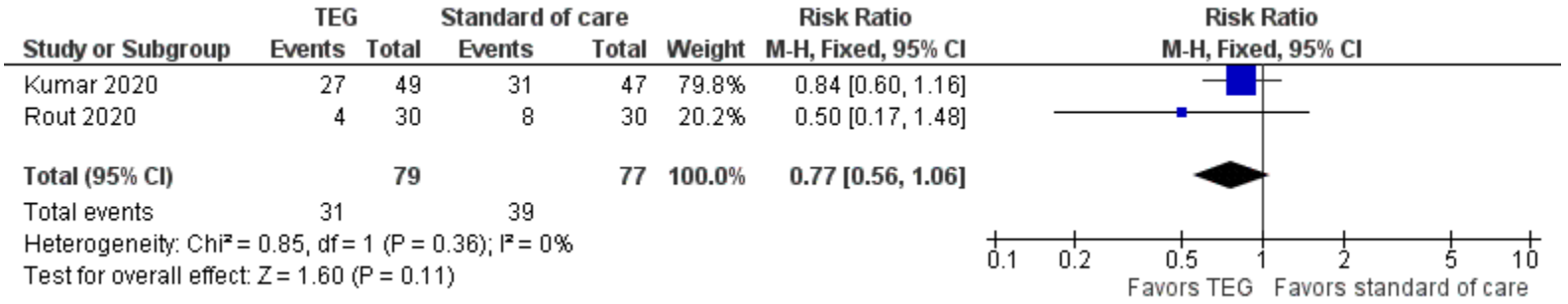

Table S-2: Post-procedural bleeding summarized by individual procedure

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Impact
Post-Paracentesis bleeding	(8 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]	No direct comparative evidence from RCT or cohort studies was found in regards to pre-procedural prophylaxis with PLT and plasma transfusion and effect on procedural bleeding. However, indirect evidence was examined from case series of consecutive patients case-control and single arm cohort studies that examined bleeding outcomes during or after the procedure in patients with elevated INR and thrombocytopenia from cirrhosis in whom no prophylactic administration of platelets or plasma was given. None of the studies reported on pre-procedural PLT or plasma transfusion. In large retrospective cohort study [Grabau 2004], 75% (823/1100) of patients with INR> 1.5 and 54% (598/1100) patients with platelets < 50,000, no bleeding events were observed. In a recent study of 3116 paracenteses of patients with mean platelet count of 122,000 (12% of patient had PLT < 50,000) and mean INR 1.6 (14% had INR >2), there were 6/3116 (0.2%) bleeding events requiring transfusion. In univariate analysis to determine risk factors for hemorrhage, INR and platelet count failed to predict bleeding [Rowley 2019]. A study restricted to patients with ACLF undergoing paracentesis with mean platelet 90,000, and INR of 2.2, identified a total of 18/602 (2.9%) bleeding events, but no formal definition of bleeding severity was used in this study. Patients with bleeding events had mean platelet count of 63,300 and INR of 3.1 [Lin 2016]. In a smaller study of 304 procedures in 205 patients with mean platelets 38,400 and mean INR 1.6, 3/304 (1%) major GI bleeds were identified. Patients with the major bleeds had PLT of 41-46 g/l [Kurup 2014]. In a prospective cohort study of 515 procedures in 171 patients with around 10% of patients having platelet count < 50,000 and 53.4% with INR > 1.5, identified 5/515 (1%) major bleeds and 12/515 (2.3%) minor/ self limited bleeds. There were 2 studies reporting on major bleeding events 9/4729 (0.2%) [Pache 2005] and 8/489 (1.6%) [Gilani 2009], but they both did not provide details regarding platelet count and INR. In a small case-control study of 24 post paracentesis bleeding cases compared to 66 controls showed no difference in mean platelets level or INR between the two groups [Hung 2018]. In summary, due to the very low baseline risk (and absence of comparative evidence) there is very low certainty evidence that in patients with cirrhosis and decreased platelet count / increased INR, clinically relevant bleeding events during or after paracentesis could be prevented by transfusing blood products
Post-Thoracentesis bleeding	(3 observational studies)	⊕◯◯◯ VERY LOW [c,d,e]	No direct comparative evidence from RCT was found in regards to pre-procedural prophylaxis with PLT and plasma transfusion and effect on procedural bleeding. However, we identified a large retrospective cohort study of 1009 thoracenteses and compared groups that either received prophylaxis to correct INR and platelets or did not receive prophylaxis and found no difference in bleeding related events (0/706 in no prophylaxis vs. 4/303 in prophylaxis) [**Hibbert 2013**]. A retrospective case control study compared thoracentesis in cirrhotic versus non-cirrhotic patients and reported only 3 major bleeding events (1.8%) in the group with cirrhosis that had a mean platelet count of 119,000 and mean INR 1.7 [**Shojaee 2018**]. There was no report on transfusion and the unadjusted odds ratio for bleeding if PLT were <50,000 vs. PLT >50,000 was (OR = 9.67, 95%CI = 1.16–80.42). Furthermore, in small retrospective cohort study with 312 patients, 16/312 (5.1%) had PLT <50, 000 and 44/312 (14%) had INR >1.6, there were no bleeding events reported [**Puchalski 2013**]. In summary, due to the very low baseline risk, there is very low certainty evidence that in patients with cirrhosis and decreased platelet count / increased INR, clinically relevant bleeding events during or after thoracentesis could be prevented by transfusing blood products.
Post- EGD for esophageal varices banding bleeding	(3 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]	No direct comparative evidence from RCT or cohort studies was found in regards to pre-procedural prophylaxis with PLT and plasma transfusion and effect on procedural bleeding. However, indirect evidence from single arm cohort studies that examined bleeding outcomes after the procedure in patients with elevated INR and thrombocytopenia was identified. None of the studies reported on pre-procedural PLT or plasma transfusion. One study retrospectively examined 150 patients with cirrhosis undergoing EBL and found 11 post EBL ulcer bleeding events. When comparing the group with bleeding to patients without bleeding there was no significant association between PLT<50,000 and INR>1.5. There was 1/28 (3.5%) bleeds in patients with PLT < 50,000 vs. 10/132 (7.6%) in patients with PLT>50,000 and 3/28 (10.7%) bleeds in patients with INR >1.5 vs 8/122 (6.6%) in patients with INR <1.5 [**Rocha 2009**]. A case control study compared 17 cases of EBL ulcer bleeding to 84 controls and reported platelet levels prior to EBL to be similar in cases and controls 98,300 and 101,400 [**Vanbiervliet 2010**]. The largest study to date prospectively collected 24 cases of post-banding ulcer bleeding out of 521 total EGD procedures. Platelet count was similar between the groups (120.7

			bleeders vs. 118.2 control) and PT/INR was elevated (1.75 bleeders vs. 1.52 control) [**Due˜nas 2020**]. In summary, due to absence of comparative evidence, there is very low certainty evidence that in patients with cirrhosis and decreased platelet count / increased INR, clinically relevant bleeding events during or after esophageal varices band ligation could be prevented by transfusing blood products.
Post-Colonoscopy with polypectomy bleeding	(4 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]	No direct comparative evidence was found. However, indirect evidence from single arm cohort studies that examined bleeding outcomes after the procedure in patients with elevated INR and thrombocytopenia was identified. None of the studies reported on pre-procedural PLT or plasma transfusion. The largest study retrospectively examined 814 patients with cirrhosis undergoing colonoscopy and identified 10 delayed bleeding events (5 in patients with CTP A cirrhosis (0.7%) and 5 in CTP B/C cirrhosis (4.4%). Mean platelet level was 85,000 and mean INR was 2.2 in patients with CTP C cirrhosis. Multivariate analysis showed that thrombocytopenia was not significantly associated with delayed post polypectomy bleed [**Soh 2019**]. Three other studies analyzed did not report information on correction of coagulation parameters prior to colonoscopy, however reported significantly low rates of delayed post polypectomy bleeds. In one retrospective cohort of 307 patients with cirrhosis undergoing colonoscopy (85.7% CTP A), only 1 bleeding event was reported [**Huang 2016**]. Similarly a retrospective case control study examining 89 patients with cirrhosis (CTP A 84.3%) and 348 controls found only 2 delayed polypectomy bleeds [**Lee 2016**]. Additionally, in small retrospective cohort study with 30 mostly compensated cirrhosis patients (70% CTP A), there were no delayed polypectomy bleeds reported [**Won Jeon 2015**]. In summary, in absence of comparative evidence, there is very low certainty evidence that in patients with cirrhosis and decreased platelet count / increased INR, clinically relevant bleeding events during or after polypectomy could be prevented by transfusing blood products.
Post ERCP bleeding	(5 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]	No direct comparative evidence was found. However, indirect evidence from single arm cohort studies that examined bleeding outcomes after the procedure in patients with elevated INR and thrombocytopenia was identified. None of the studies reported on details regarding pre-procedural PLT or plasma transfusion. One study examined 129 ERCP in patients with cirrhosis undergoing ERCP, 74% were CTP B or C, 8/129 (6.2%) developed GI bleeding after ERCP. Both platelet count and INR were not significantly different between patients developing bleeding vs. no bleeding group and in a multivariable analysis were not predicting bleeding [**Adike 2017**]. A large retrospective control study with 3228 patients with cirrhosis who underwent ERCP (80.6% with decompensated cirrhosis) and found post procedural bleeding incidence of 2.1% compared. However, coagulation parameters and use of prophylaxis were not available to include in the model [**Navaneethan 2017**]. A multicenter retrospective review examining outcomes in 538 ERCP in patients with cirrhosis found 6 cases of bleeding (1.1% incidence rate). All patients included in this study received prophylaxis if INR>1.5 or platelets<50,000 **[Adler 2016**]. Similarly, another smaller retrospective cohort study of 29 subjects where prophylaxis was provided for patients with platelets<50,000 /mL and INR >1.5prior the ERCP, reported on 1/29 (3.4%) major bleed event [**Parlak 2016**]. Lastly, a RCT comparing different procedural methods in ERCP excluded patients with platelets<50,000 /mL and “severe coagulopathy” and reported only on 5/98 (5.1%) “mild” bleeding events [**Radwan 2019**]. In summary, absence of comparative evidence, there is very low certainty evidence that in patients with cirrhosis and decreased platelet count / increased INR, clinically relevant bleeding events during or after ERCP could be prevented by transfusing blood products.
Post- percutaneous liver biopsy bleeding	(4 observational studies)	⊕◯◯◯ VERY LOW [a,c,f]	No direct comparative evidence was found. In addition, no indirect evidence from single arm cohort studies that examined bleeding outcomes after the procedure in patients with elevated INR and thrombocytopenia was identified nor studies that would reported on details regarding pre-procedural PLT or plasma transfusion were identified. Indirect evidence from studies including mixed population reporting on incidence of bleeding events and then evaluate a risk factors of bleeding such as cirrhosis, PLT and INR. Large database study of 4275 percutaneous liver biopsies had 15/4275 (0.35%) bleeding events and 5 deaths related to bleeding events (33% of the bleeding events were patients with cirrhosis and no coagulopathy reported) [Meyers 2007]. Similarly, 21/3357 (0.6%) bleeding events where reported in a large cohort study 341/3357 (12%) had cirrhosis. Additionally, there was no significant difference in platelets, PT, or aPTT between the bleeding and non-bleeding group. The group with bleeding had a higher percentage of platelet level less than 60,000 (4.8%) versus only 0.3% in the non-bleeding group, however this did not reach statistical significance [Takyar 2016]. Furthermore, in another cohort study with bleeding occurred in 0.5% (16/2740) patients with no significant difference in mean percent of patients with cirrhosis 1068/2677 (39.9%) in non-bleeding cohort versus 8/16 (50%) in the bleeding cohort. However patients with decompensated cirrhosis and platelet count less than 50,000 were excluded. Pre-procedure INR was the same between groups and in the bleeding group 26.7% of patients had a platelet count less than 60,000 and 50% had platelet counts greater than 101,000 [Seeff 2010]. In summary, due to the very low baseline risk (and absence of comparative evidence) there is very low certainty evidence that in patients with cirrhosis and decreased platelet count / increased INR, clinically relevant bleeding events during or after percutaneous liver biopsy could be prevented by transfusing blood products.
Post Transjugular liver biopsy (TJLB) bleeding	(3 observational studies)	⊕◯◯◯ VERY LOW [c,f,g]	No direct comparative evidence was found. However, indirect evidence from single arm cohort studies that examined bleeding outcomes after the procedure in patients with elevated INR and thrombocytopenia was identified. None of the studies reported on details regarding pre-procedural PLT or plasma transfusion, just incidence of bleeding events in coagulopathic population. A systematic review of case series of TJLB reported on major bleeding events: hepatic hematoma 4/7469 (0.05%) and intraperitoneal hemorrhage 15/7469 (0.2%), 85% of the total population had PT>3s over control value and PTL<60,000 [Kalambokis 2007].

			Furthermore, a retrospective cohort study on patients with severe coagulopathy (define as PT>6s greater than control value Plt <70,000), reported intraperitoneal bleeding in 2/341 (0.6%) [Dohan 2015]. Additionally small cohort study report 0/22 bleeding events but in this study there was no information on INR or PLT [Procopet 2012]. In summary, due to the very low baseline risk (and absence of comparative evidence) there is very low certainty evidence that in patients with cirrhosis and decreased platelet count / increased INR, clinically relevant bleeding events during or after transjugular liver biopsy could be prevented by transfusing blood products.

Explanations

a. **Very serious Risk of bias**: No comparison group, bleeding outcomes poorly defined, Intervention not always defined (most studies does not report if prophylaxes was given)
b. **Serious indirectness:** There is an indirectness on the level of intervention, most studies does not report if PLT/plasma transfusions were given; they just report INR levels and PLT count
c. Unable to assess for imprecision since outcome cannot be measured
d. **Serious Risk of bias:** No comparison group in one of the studies, poorly defined intervention and bleeding outcomes serious selection bias in the largest study as cohort poorly described
e. **Very serious indirectness**: The largest study does not clearly define the percentage of patients in the cohort with liver disease indirectness in intervention most studies did not report on PLT/plasma transfusion but used coagulopathy markers such as INR and PLT
f. **Very serious indirectness:** Multilevel indirectness suspected: Studies had mixt population not only cirrhotic patients, indirectness in intervention studies did not report on PLT/plasma transfusion but used coagulopathy markers such as INR and PLT
g. **Very serious Risk of bias:** No comparison group, bleeding outcomes poorly defined, Intervention not always defined (most studies does not report if prophylaxes was given) come of the case series in the SR may not have been on consecutive patients

Table S-3: Evidence Profile for Avatrombopag RCTs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Avatrombopag	Placebo	Relative (95% CI)	Absolute (95% CI)		
Patients not requiring platelet transfusion or rescue procedures for bleeding up to 7 days after scheduled procedure in high PLT group [d, e, g]												
2	randomized trials	not serious	not serious	very serious [a]	serious [b]	none	103/117 (88.0%)	24/67 (35.8%)	RR 2.46 (1.77 to 3.41)	**523 more per 1,000** (from 276 more to 863 more)	⊕◯◯◯ VERY LOW	CRITICAL
Patients not requiring platelet transfusion or rescue procedures for bleeding up to 7 days after scheduled procedure in low PLT group [d, f, g]												
2	randomized trials	not serious	not serious	very serious [a]	serious [b]	none	107/160 (66.9%)	26/91 (28.6%)	RR 2.36 (1.67 to 3.32)	**389 more per 1,000** (from 191 more to 663 more)	⊕◯◯◯ VERY LOW	CRITICAL
Thrombotic events within 30 days of use												
2	randomized trials	not serious	not serious	very serious [c]	very serious [h]	none	1/117 (0.9%)	2/67 (3.0%)	RR 0.28 (0.03 to 3.02)	**21 fewer per 1,000** (from 29 fewer to 60 more)	⊕◯◯◯ VERY LOW	CRITICAL

a. Multilevel indirectness: Indirect / surrogate outcome for procedural bleeding and there was indirectness on comparator (there was no comparison group of patients with thrombocytopenia who did not receive either TPO or platelet transfusion prior to procedures)
b. Low event rate <200 events
c. There was indirectness on comparator (there was no comparison group of patients with thrombocytopenia who did not receive either TPO or platelet transfusion prior to procedures)
d. 60.8% (248/435) of participants across both trials underwent a low-bleeding risk procedure, such as a paracentesis, endoscopy, or colonoscopy. 22.1% (90/435) of participants underwent a high-bleeding risk procedure, such as a dental procedure, laparoscopic intervention, radiofrequency ablation, or vascular catheterization. 17.2% (70/435) of participants underwent a moderate-bleeding risk procedure, such as a liver biopsy, ethanol ablation, or chemoembolization for hepatocellular carcinoma.
e. In ADAPT-1, 231 patients met eligibility criteria; based on baseline platelet count, 59 patients were randomized to avatrombopag 40 mg and 34 patients were randomized to matching placebo. In ADAPT-2, 204 patients met eligibility criteria; based on baseline platelet count, 58 patients were randomized to avatrombopag 40 mg and 33 patients were randomized to matching placebo.
f. In ADAPT-1, 231 patients met eligibility criteria; based on baseline platelet count, 90 patients were randomized to avatrombopag 60 mg and 48 patients were randomized to matching placebo. In ADAPT-2, 204 patients met eligibility criteria; based on baseline platelet count, 70 patients were randomized to avatrombopag 60 mg and 43 patients were randomized to matching placebo.
g. There is no reporting of number of patients who received rescue therapy, however bleeding rates were low in the entire cohort (3.5%, 15/430) with no statistically significant differences between groups
h. There were only 3 events

Table S-4: Evidence profile for Lusutrombopag RCTs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lusutrombopag 3mg	Placebo	Relative (95% CI)	Absolute (95% CI)		
Patient achieving platelet count >50,000/mL following Lusutrombopag administration												
3	randomized trials	not serious [a]	not serious	very serious [b]	serious [c]	none	121/172 (70.3%)	40/172 (23.3%)	RR 3.588 (1.747 to 7.368)	**602 more per 1,000** (from 174 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
Thrombotic events												
3	randomized trials	not serious	not serious	not serious	very serious [d]	none	2/172 (1.2%)	4/170 (2.4%)	RR 0.547 (0.111 to 2.703)	**11 fewer per 1,000** (from 21 fewer to 38 more)	⨁⨁◯◯ LOW	CRITICAL

a. Tateishi *et al*. 2018 has reporting bias
b. Multilevel indirectness: Indirect / surrogate outcome for procedural bleeding and there was indirectness on comparator (there was no comparison group of patients with thrombocytopenia who did not receive either TPO or platelet transfusion prior to procedures)
c. Low event rate <200 events
d. There were only 6 events

Figure S-8: Patients not requiring platelet transfusion (or rescue procedures for bleeding) up to seven days after scheduled procedure in high platelet count group following TPO administration

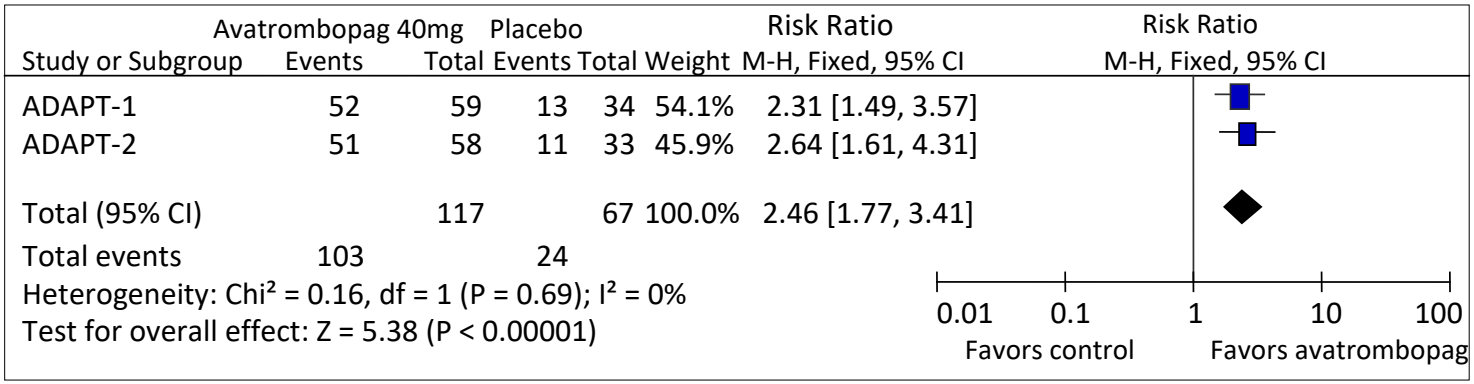

Figure S-9: Thrombotic events within 30 days of TPO agonist use

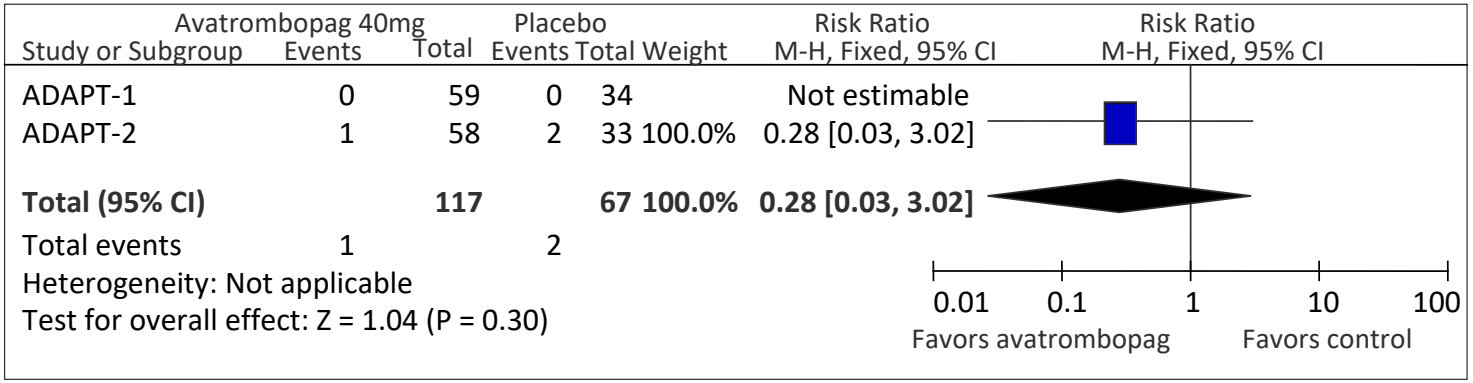

Figure S-10: Patients not requiring platelet transfusion (or rescue procedures for bleeding) up to seven days after scheduled procedure in low platelet count group following TPO agonist administration

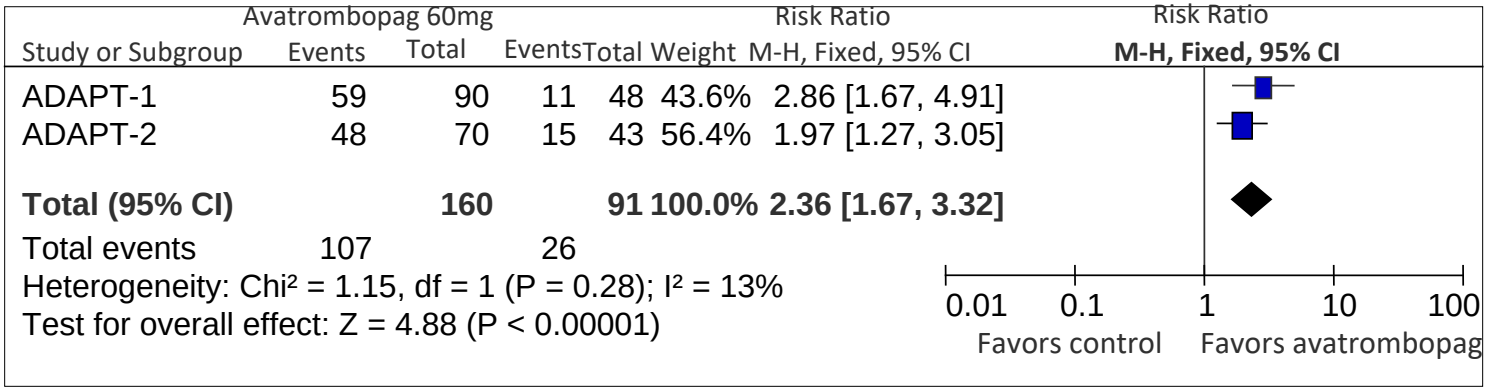

Figure S-11: Patient achieving platelet count >50,000/mL following Lusutrombopag administration

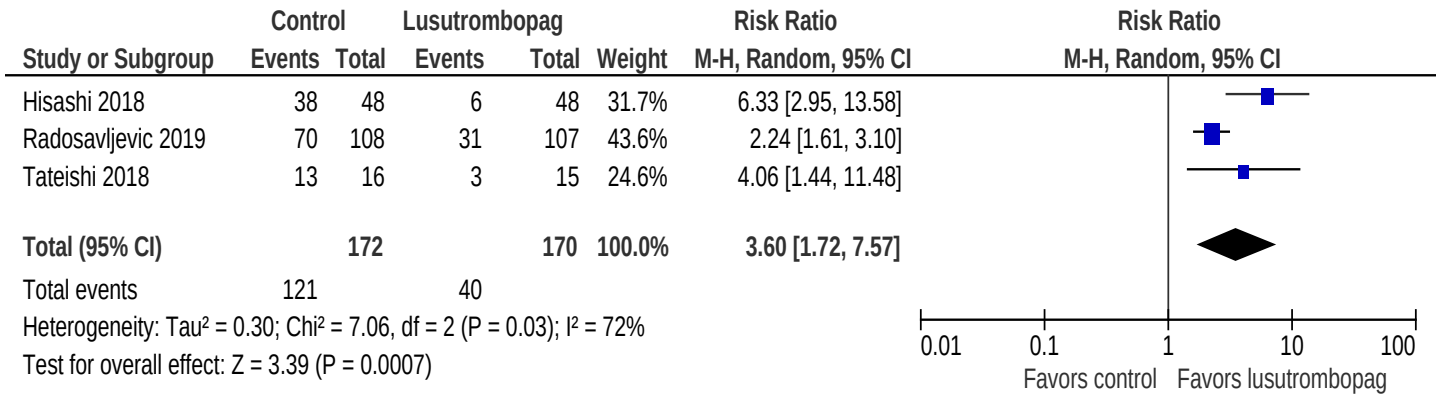

Figure S-12: Thrombotic events following Lusutrombopag administration

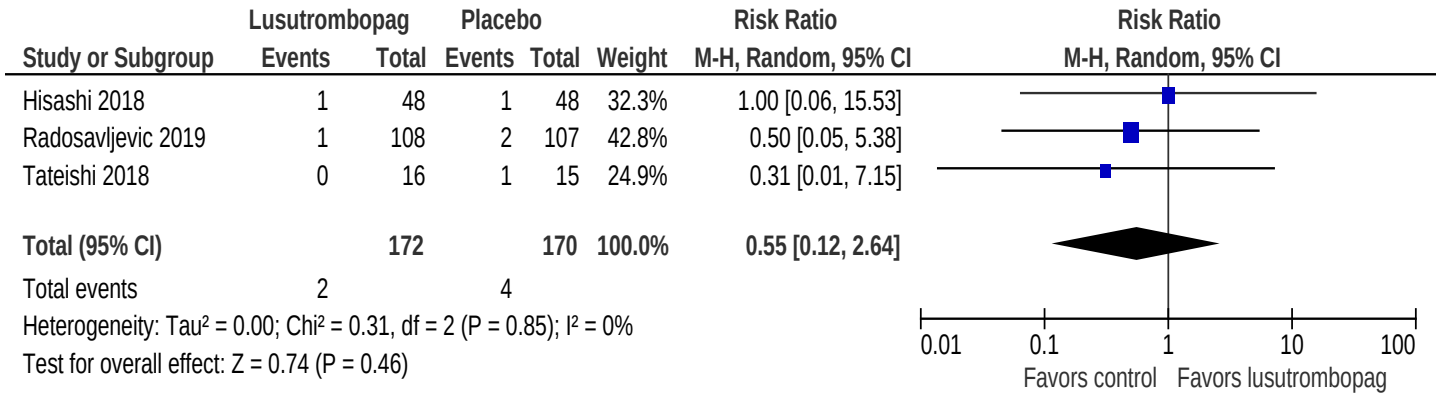

Figure S-13: Major bleeding events when prescribing pharmacologic VTE prophylaxis

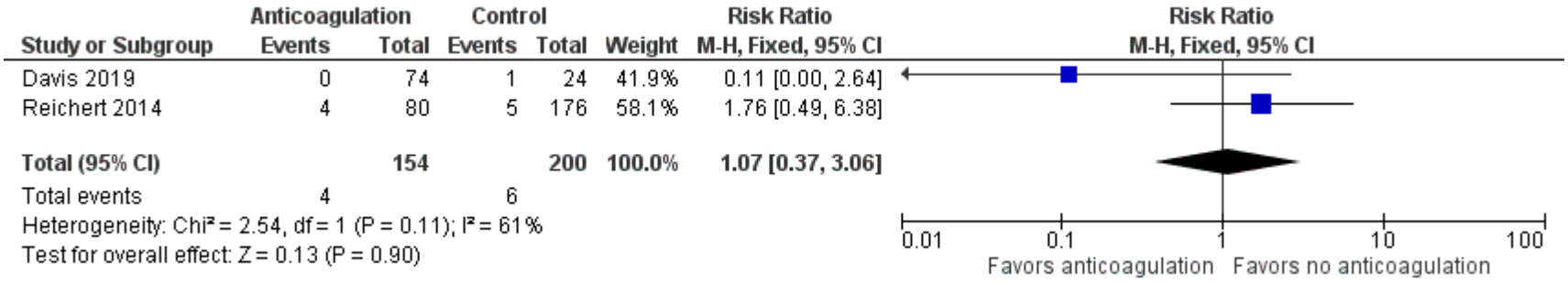

Table S-5: Evidence profile for PICO4

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Incident PVT									
4	observational studies	serious [a]	not serious	serious [b]	N/A	none	There are no studies with 2 arms comparing imaging to standard of care for incident PVT in cirrhosis. The available literature describes outcomes in single-arm observational cohorts who underwent serial imaging with US. Systematic screening for PVT in patients with cirrhosis detected PVT with an incidence between 3.5-4.6% at 1 year and 10.7% at 5 years. There was no difference in PVT incidence between 3 versus 6-monthly US.	⊕◯◯◯ VERY LOW	CRITICAL

[a]Comparator with no screening was not available

[b]The impact of PVT detection on patient important outcomes such as mortality is unclear

Figure S-14: Complete/partial recanalization with anticoagulation (single arm analysis)

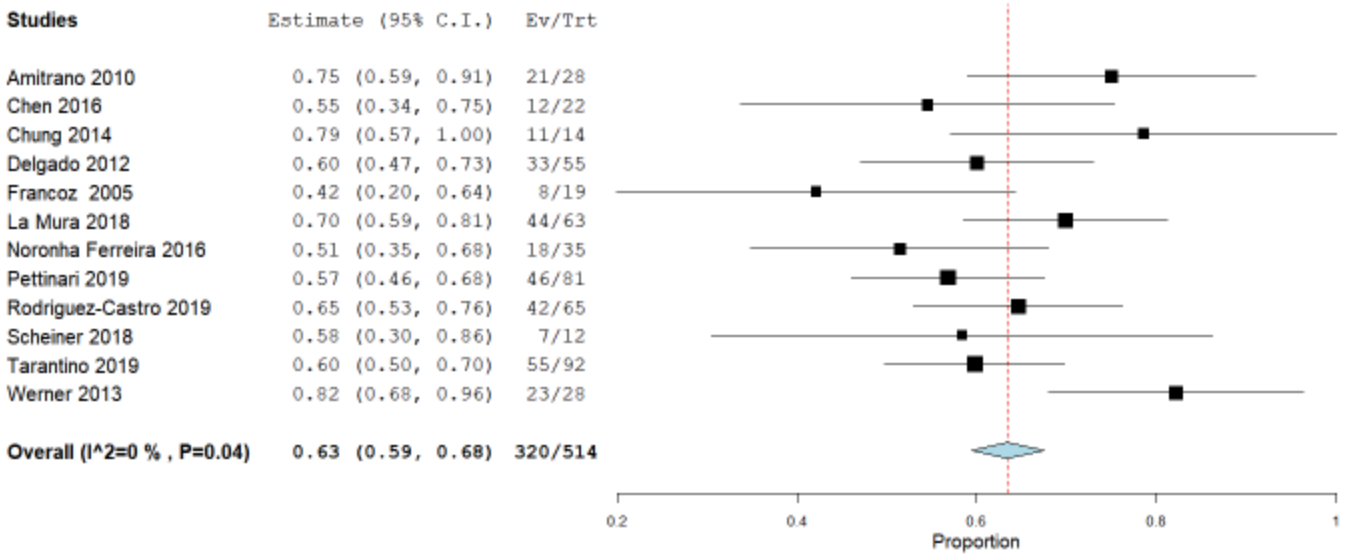

Figure S-15: Complete/partial recanalization with no treatment (single arm analysis)

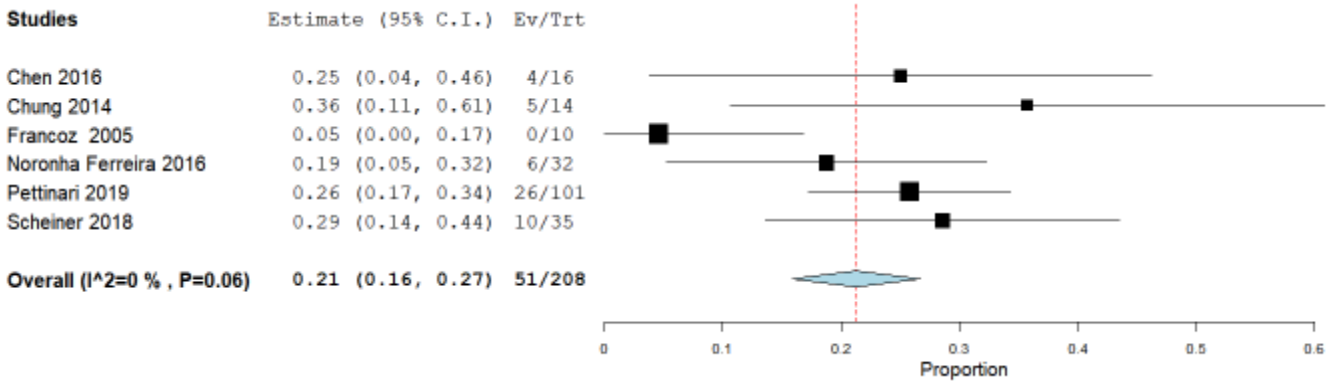

Figure S-16: Non-response/progression of PVT following anticoagulation (single arm analysis)

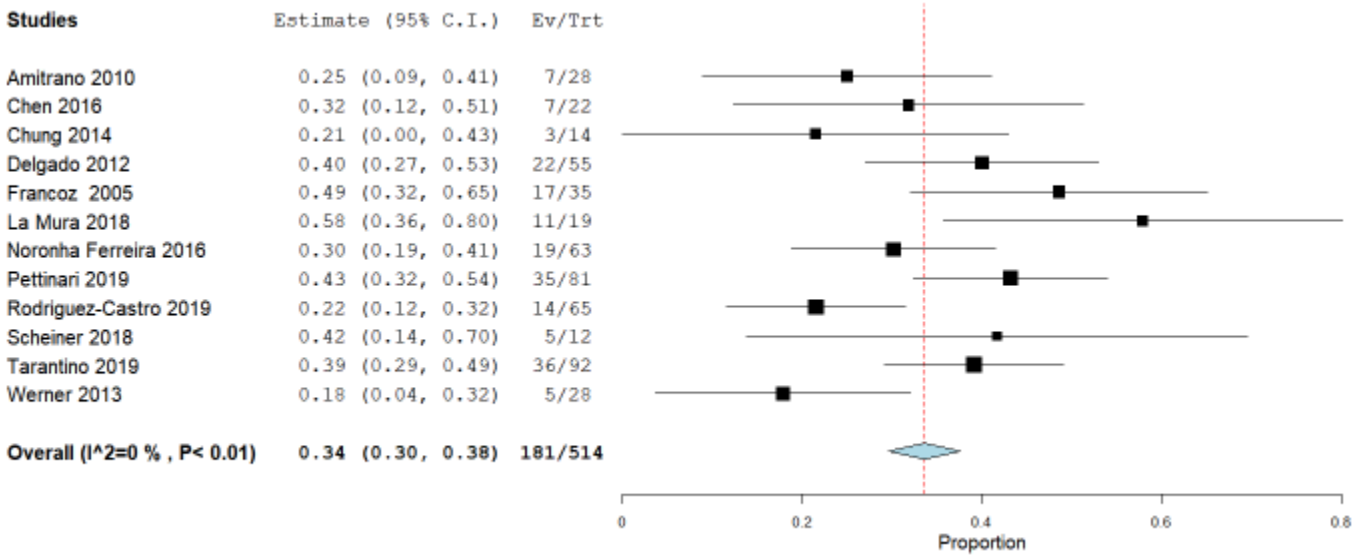

Figure S-17: Non-response/progression of PVT with no treatment (single arm analysis)

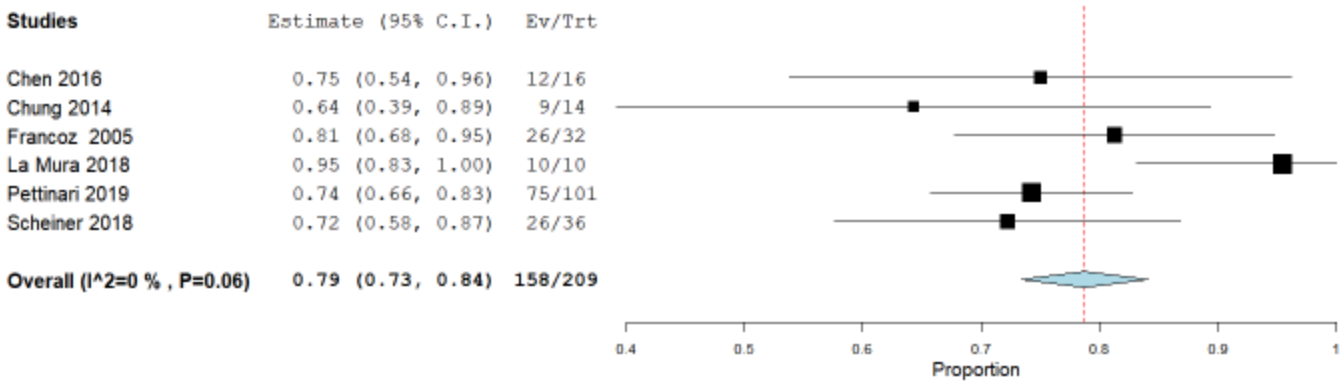

Figure S-18: Major bleeding risk comparative anticoagulation vs. no treatment

Study or Subgroup	Anticoagulation Events	Anticoagulation Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2016	0	30	0	36		Not estimable
Chung 2014	0	14	1	14	33.5%	0.33 [0.01, 7.55]
Francoz 2005	1	19	0	10	33.6%	1.65 [0.07, 37.18]
Scheiner 2018	0	16	1	36	32.9%	0.73 [0.03, 16.91]
Total (95% CI)		**79**		**96**	**100.0%**	**0.74 [0.12, 4.48]**
Total events	1		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.78); I² = 0%

Test for overall effect: Z = 0.33 (P = 0.74)

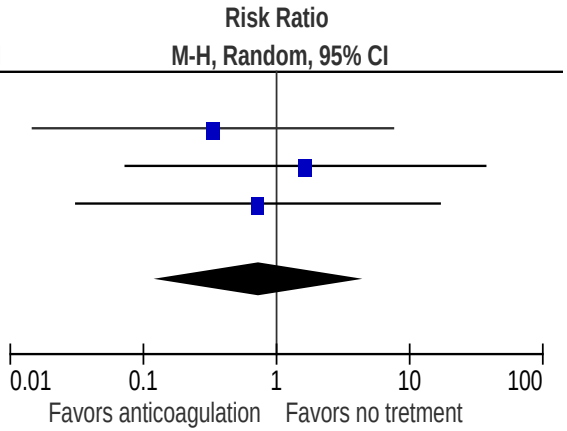

Figure S-19: Major bleeding with anticoagulation to treat PVT (single arm analysis)

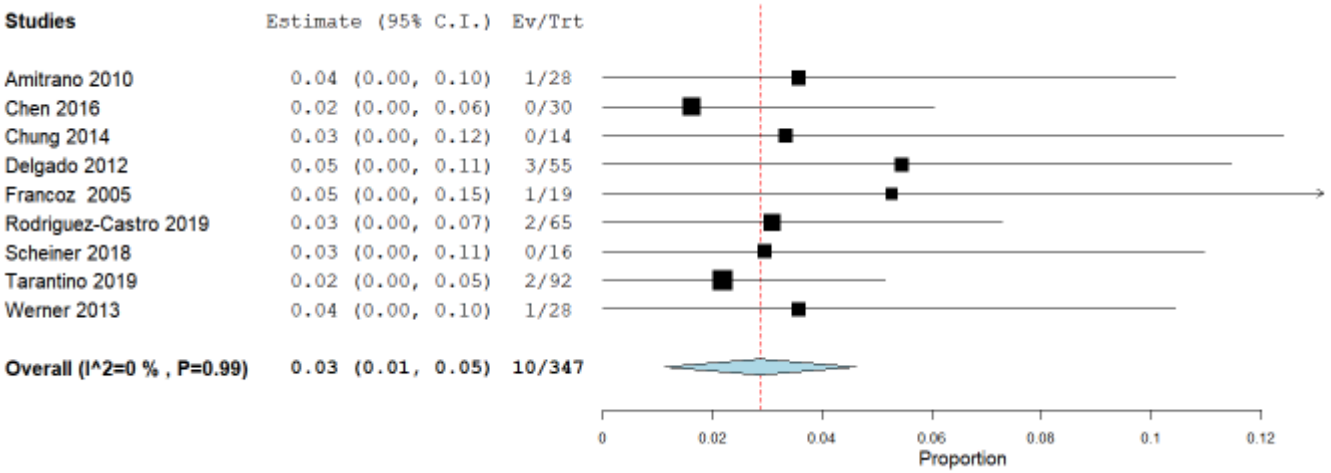

Figure S-20: Major bleeding with no treatment of PVT (single arm analysis)

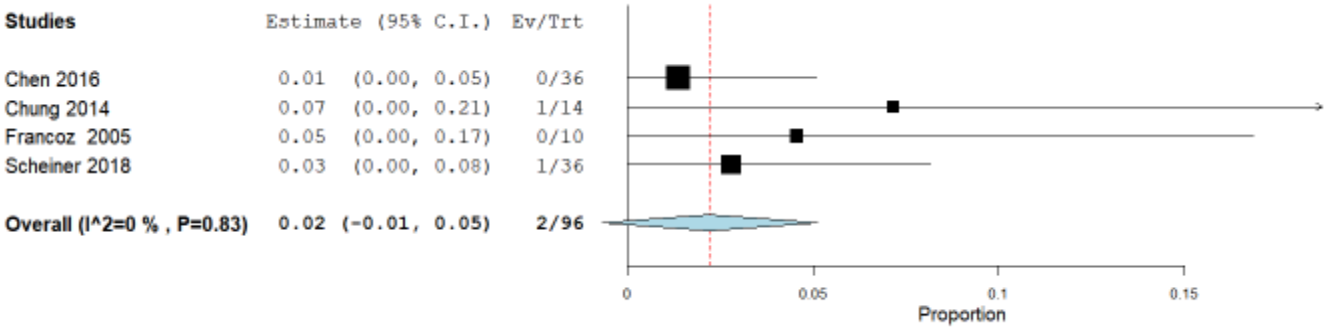

Figure S-21: All bleeds (major and minor) when using anticoagulation for PVT (single arm analysis)

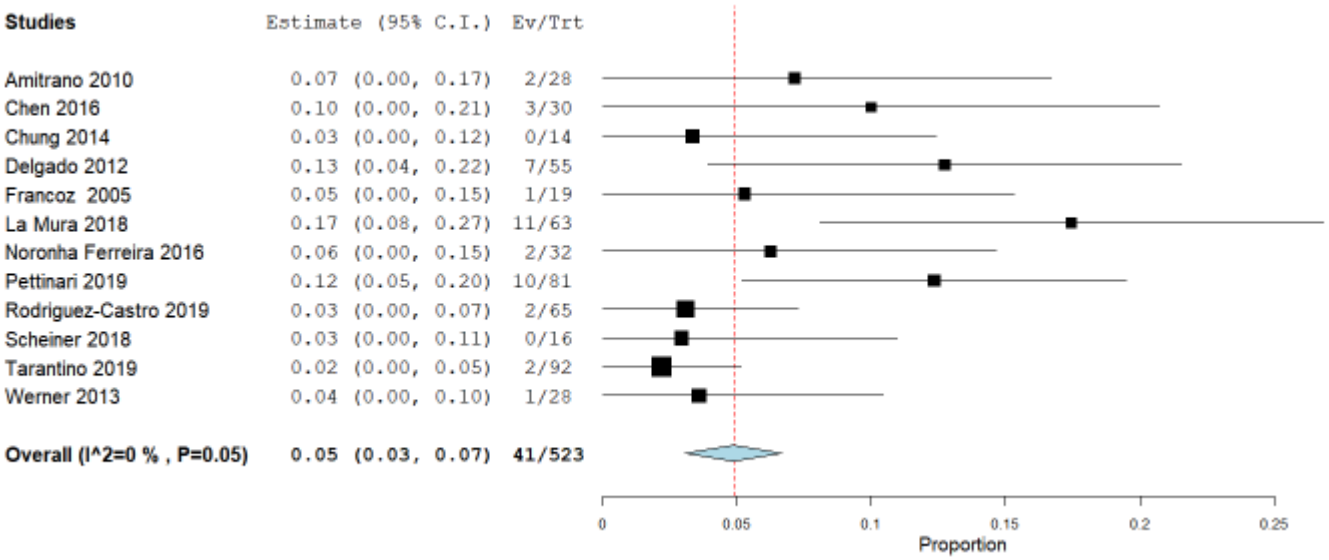

Figure S-22: All bleeding (major and minor) when no treatment prescribed for PVT (single arm analysis)

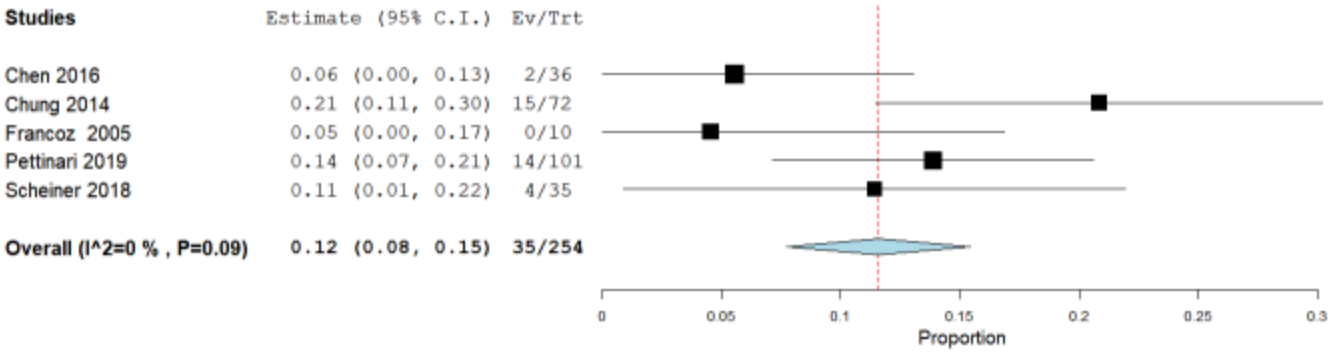

Figure S-23: VKA major bleeding incidence for atrial fibrillation

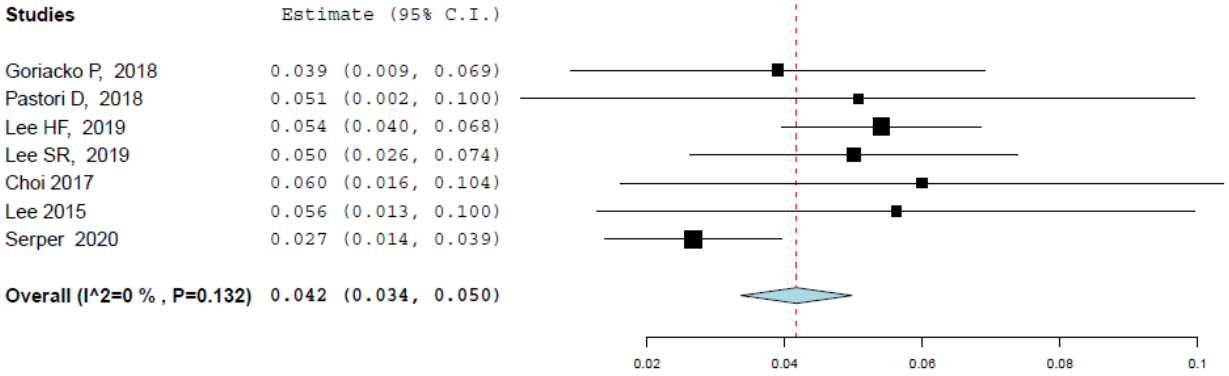

Figure S-24: Major bleeding incidence for no treatment of atrial fibrillation

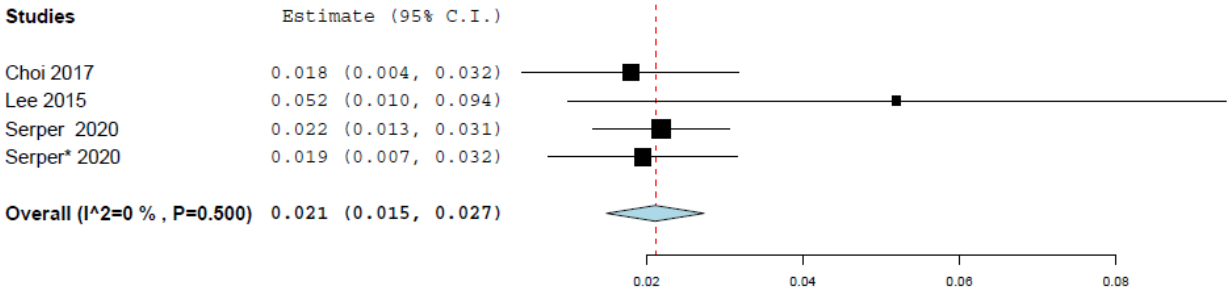

Figure S-25: DOAC major bleeding incidence for atrial fibrillation

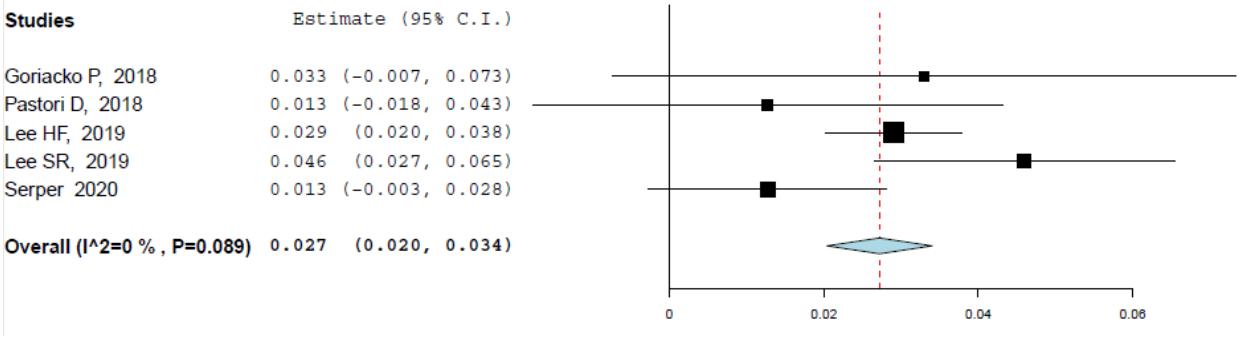

Figure S-26: VKA ICH incidence in patients with atrial fibrillation

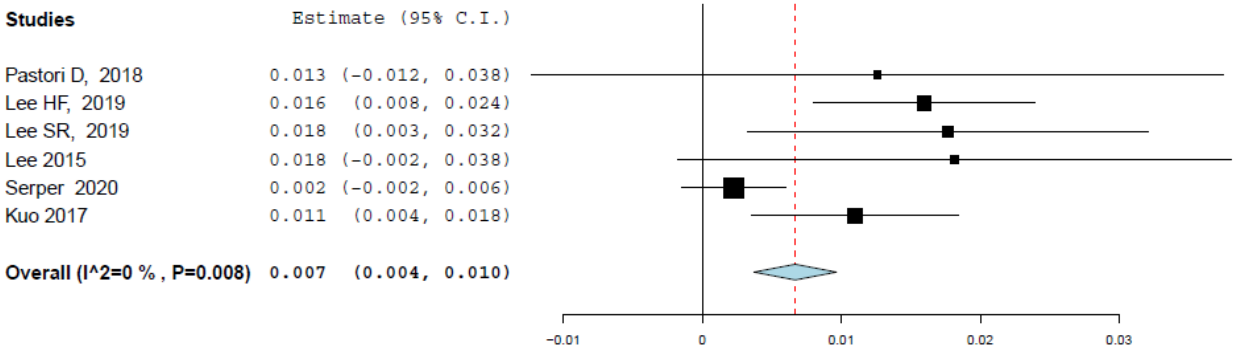

Figure S-27: ICH incidence in patients with atrial fibrillation on no anticoagulation treatment

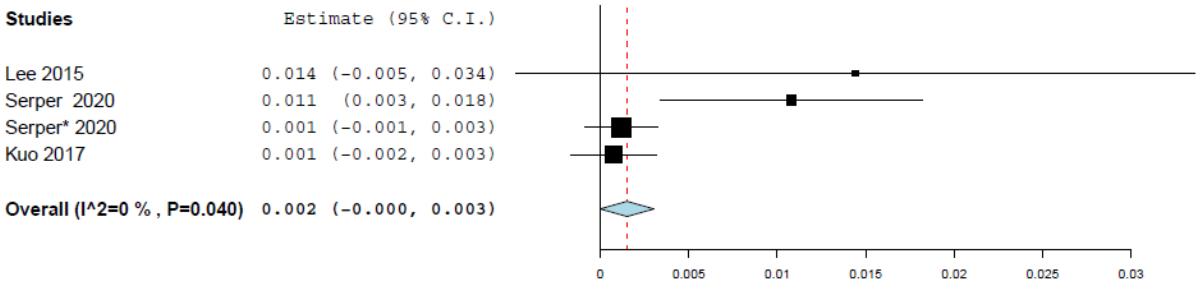

Figure S-28: DOAC ICH incidence in patients with atrial fibrillation

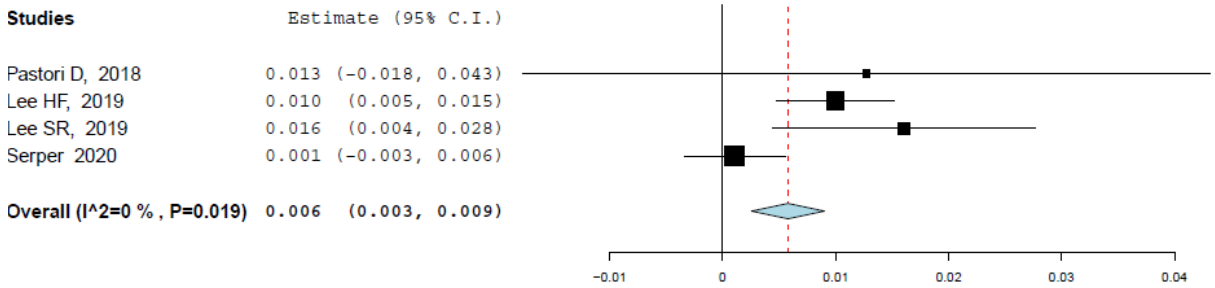

Table 1
PICO questions

Q	Informal Question	PICO Question			
	Diagnosis/Risk assessment	**Population**	**Intervention(s)**	**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 Viscoelastic test (thromboelastography or rotational thromboelastometry)	Usual care	Post-procedural bleeding Mortality Failure to control bleeding Failure to prevent rebleeding Blood product transfusion
2	Does pre-procedure prophylaxis to correct coagulation parameters and/or platelet level reduce the risk of bleeding in patients with cirrhosis?	Patients with cirrhosis undergoing invasive procedures (e.g. 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 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: Transplant candidates, listed patients, non-transplant candidates	Imaging	No screening	Incident PVT
5	What are the data on specific anticoagulation therapies for PVT in patients with cirrhosis?	Patients with cirrhosis and PVT	LMWH, direct-acting oral anticoagulants, warfarin	No intervention	Recanalization of portal vein thrombosis Progression of PVT Bleeding events
6	In patients with atrial fibrillation and cirrhosis is anticoagulation safe and effective?	Patients with cirrhosis and atrial fibrillation	Anticoagulation	No intervention	Mortality Stroke Bleeding ICH

ICH=intracerebral hemorrhage; INR=international normalized ratio; LMWH=low-molecular weight heparin; PVT=portal vein thrombosis; TPO: thrombopoietin; VTE=venous thromboembolism

Table 2
Evidence profile for PICO 1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	SOC	Relative (95% CI)	Absolute (95% CI)		
Post-procedure bleeding												
3	randomized trials	not serious	not serious	not serious	very serious [a]	none	0/78 (0.0%)	1/78 (1.3%)	**RR 0.33** (0.01 to 7.87)	**9 fewer per 1,000** (from 13 fewer to 88 more)	⊕⊕◯◯ LOW	CRITICAL
Proportion with FFP or platelet transfusion received pre-procedure												
3	randomized trials	not serious	serious [b]	serious [c]	serious [d]	none	26/78 (33.3%)	72/78 (92.3%)	**RR 0.37** (0.12 to 1.18)	**582 fewer per 1,000** (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%)	**RR 1.05** (0.45 to 2.44)	**7 more per 1,000** (from 75 fewer to 195 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failure to control bleeding at 5 days												
2	randomized trials	not serious	not serious	serious [c]	serious [d]	none	12/79 (15.2%)	18/77 (23.4%)	**RR 0.64** (0.34 to 1.23)	**84 fewer per 1,000** (from 154 fewer to 54 more)	⊕⊕◯◯ LOW	CRITICAL
Failure to prevent rebleeding after day 5 (Day 6-42)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TEG	SOC	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	not serious	not serious	serious [g]	serious [d]	none	22/62 (35.5%)	19/49 (38.8%)	**RR 0.98** (0.63 to 1.51)	**8 fewer per 1,000** (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%)	**RR 0.58** (0.48 to 0.71)	**420 fewer per 1,000** (from 520 fewer to 290 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Mortality after bleeding (42 days)												
2	randomized trials	not serious	not serious	very serious [h]	serious [d]	none	31/79 (39.2%)	39/77 (50.6%)	**RR 0.77** (0.56 to 1.06)	**116 fewer per 1,000** (from 223 fewer to 30 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

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 a 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. Re-bleeding 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

Table 3

Evidence profile for PICO 3

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulation	no anticoagulation	Relative (95% CI)	Absolute (95% CI)		
Major bleeding												
2	observational studies	serious [a]	not serious	not serious	very serious [b]	none	4/154 (2.6%)	6/200 (3.0%)	**RR 1.07** (0.37 to 3.06)	**2 more per 1,000** (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%)	**RR 1.57** (0.73 to 3.37)	**35 more per 1,000** (from 17 fewer to 146 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Symptomatic DVT*												
4	randomized trials	not serious	not serious	serious [d]	serious [c]	none	13/2805 (0.5%)	40/2870 (1.4%)	**RR 0.47** (0.22 to 1.00)	**7 fewer per 1,000** (from 11 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL
Nonfatal PE*												
6	randomized trials	not serious	not serious	serious [d]	serious [c]	none	7/9993 (0.1%)	21/10163 (0.2%)	**RR 0.61** (0.23 to 1.67)	**1 fewer per 1,000** (from 2 fewer to 1 more)	⊕⊕◯◯ LOW	CRITICAL

a. No detailed reports of other confounders such as comorbidities or antiplatelet therapies in cases versus controls that may impact the risk of bleeding independent from prophylactic anticoagulation and may have impacted patient selection
b. Only 10 events total
c. Less than 300 events total
*d. The studies were not designed specifically for patients with cirrhosis (Kahn SR, Lim W, Dunn AS, *et al*. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e195S-e226)

Table 4
Evidence profile for PICO 5

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LWMH / Warfarin and DOAC	no therapy	Relative (95% CI)	Absolute (95% CI)	
Complete/ partial re-canalization 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%)	**RR 2.27** (1.73 to 2.98)	**309 more per 1,000** (from 179 more to 485 more)	⨁◯◯◯ VERY LOW
Non- responders/ Progression of PVT											
6	observational studies	not serious [a]	not serious	serious [b]	serious [c]	none	78/183 (42.6%)	158/209 (75.6%)	**RR 0.57** (0.47 to 0.68)	**325 fewer per 1,000** (from 401 fewer to 242 fewer)	⨁◯◯◯ VERY LOW
Major bleed not related to Portal hypertension bleed											
4	observational studies	serious [e]	not serious	not serious	very serious [d]	none	1/79 (1.3%)	2/96 (2.1%)	**RR 0.74** (0.12 to 4.48)	**5 fewer per 1,000** (from 18 fewer to 73 more)	⨁◯◯◯ VERY LOW
All bleeds including portal hypertension bleeding											
5	observational studies	serious [e]	not serious	not serious	very serious [d]	none	14/160 (8.8%)	35/254 (13.8%)	**RR 0.86** (0.45 to 1.63)	**19 fewer per 1,000** (from 74 fewer to 87 more)	⨁◯◯◯ VERY LOW
Esophageal variceal bleed											
5	observational studies	serious [e]	not serious	not serious	very serious [d]	none	6/160 (3.8%)	36/255 (14.1%)	**RR 0.34** (0.15 to 0.75)	**93 fewer per 1,000** (from 120 fewer to 35 fewer)	⨁◯◯◯ VERY LOW
Mortality/ Decompensation in cirrhosis											
No evidence was indentified that reported on mortality and or decompensation in cirrhosis											

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 (e.g., mortality, decompensation in cirrhosis)
c. Based on sparse data and low event rate
d. Based on very sparse data just few events
e. 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

Table 5
Evidence profile for PICO 6 (VKA vs. no treatment in atrial fibrillation and cirrhosis)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA	no therapy	Relative (95% CI)	Absolute (95% CI)		
Death*												
6	RCT	not serious	not serious	serious [a]	not serious	none	103/1425 (7.2%)	136/1425 (9.5%)	RR 0.72 (0.55 to 0.94)	**27 fewer per 1,000** (from 43 fewer to 6 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Non-fatal stroke*												
6	RCT	not serious	not serious	serious [a]	not serious	none	36/1425 (2.5%)	CHA2DS2-VASC 0-1 2.2%	RR 0.34 (0.23 to 0.49)	**15 fewer per 1,000** (from 17 fewer to 11 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
								CHA2DS2-VASC 2 4.5%		**30 fewer per 1,000** (from 35 fewer to 23 fewer)		
								CHA2DS2-VASC >2 9.6%		**63 fewer per 1,000** (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%)	Rate Ratio **1.91** (1.85 to 2.26)	**38 more per 1,000** (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%)	Rate Ratio **3.5** (3.3 to 4)	**53 more per 1,000** (from 48 more to 63 more)	⊕◯◯◯ VERY LOW	CRITICAL

*a. Data from VKA compared to no therapy for VTE prevention in patient with AF and no cirrhosis was used (Lip GYH, Banerjee A, Boriani G, *et al*. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest 2018;154:1121-1201)
b. No comparison group single arm studies were analyzed separately
c. Low number of events <200
d. High rates are probably due to hemorrhagic transformation of underlying cerebrovascular attack

Table 6
Evidence profile for PICO 6 (DOAC vs. VKA in AF and cirrhosis)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOAC	VKA	Relative (95% CI)	Absolute (95% CI)		
Non-fatal stroke*												
4	RCT	serious [a]	not serious	serious [b]	not serious	none	911/29312 (3.1%)	1107/29229 (3.8%)	RR 0.81 (0.73 to 0.91)	**6 fewer per 1,000** (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%)	RR 0.62 (0.45 to 0.85)	**15 fewer per 1,000** (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%)	RR 0.70 (0.58 to 0.84)	**6 fewer per 1,000** (from 9 fewer to 3 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

a. Issues with allocation concealment and blinding of participants and personnel
*b. VKA compared to no therapy for VTE prevention in patient with AF and no cirrhosis (Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest 2018;154:1121-1201)
c. selection bias
d. < 200 events
e. High rates are probably due to hemorrhagic transformation of underlying cerebrovascular attack

Figure 1

Cartoon illustration of coagulation in cirrhosis

Figure 2

Viscoelastic testing and pre-procedural blood product transfusion

	TEG		Standard of care			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
De Pietri 2016	5	30	30	30	31.6%	0.18 [0.08, 0.39]
Rocha 2019	13	19	14	19	35.0%	0.93 [0.62, 1.39]
Vuyyuru 2019	8	29	28	29	33.4%	0.29 [0.16, 0.52]
Total (95% CI)		**78**		**78**	**100.0%**	**0.37 [0.12, 1.18]**
Total events	26		72			

Heterogeneity: Tau² = 0.94; Chi² = 24.16, df = 2 (P < 0.00001); I² = 92%

Test for overall effect: Z = 1.68 (P = 0.09)

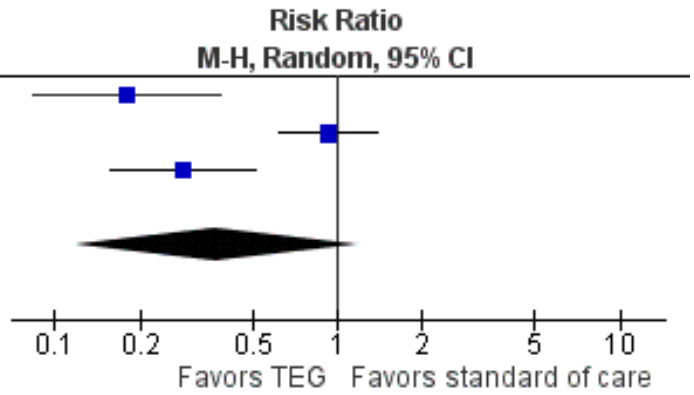

Figure 3

VTE prophylaxis and all bleeding events

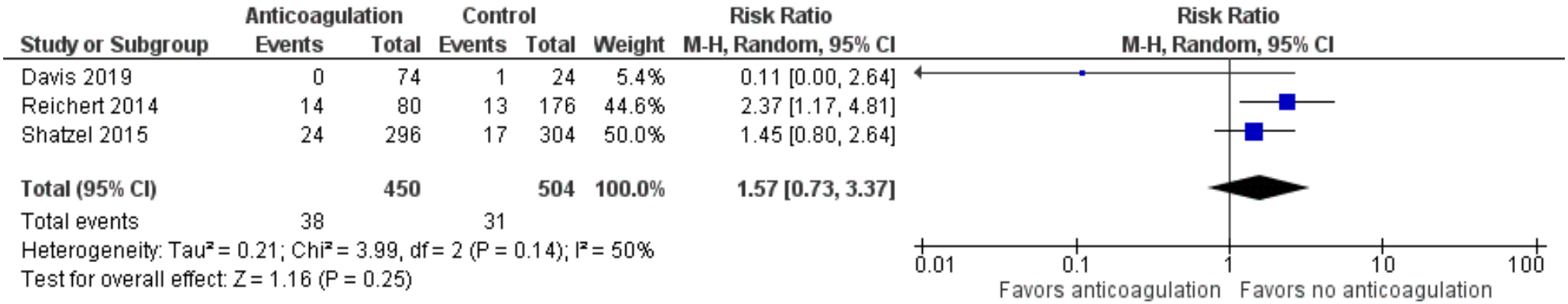

Figure 4

Complete or partial portal vein recanalization, Comparative Anticoagulation vs no treatment

	Anticoagulation		No treatment			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Chen 2016	12	22	4	16	8.6%	2.18 [0.86, 5.53]
Chung 2014	11	14	5	14	13.0%	2.20 [1.03, 4.68]
Francoz 2005	8	19	0	10	1.0%	9.35 [0.59, 147.09]
Noronha Ferreira 2016	18	35	6	32	11.9%	2.74 [1.25, 6.04]
Pettinari 2019	46	81	26	101	50.8%	2.21 [1.51, 3.23]
Scheiner 2018	7	12	10	35	14.7%	2.04 [1.00, 4.15]
Total (95% CI)		**183**		**208**	**100.0%**	**2.27 [1.73, 2.98]**
Total events	102		51			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.44$, df = 5 (P = 0.92); $I^2 = 0\%$

Test for overall effect: Z = 5.89 (P < 0.00001)

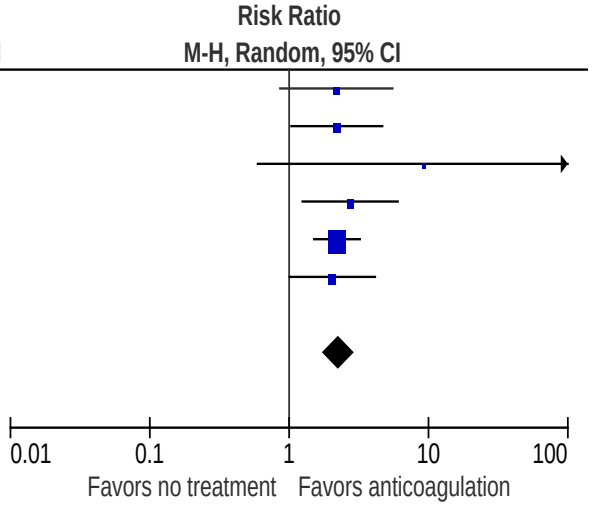

Figure 5

All bleeding events, Comparative Anticoagulation vs. No treatment

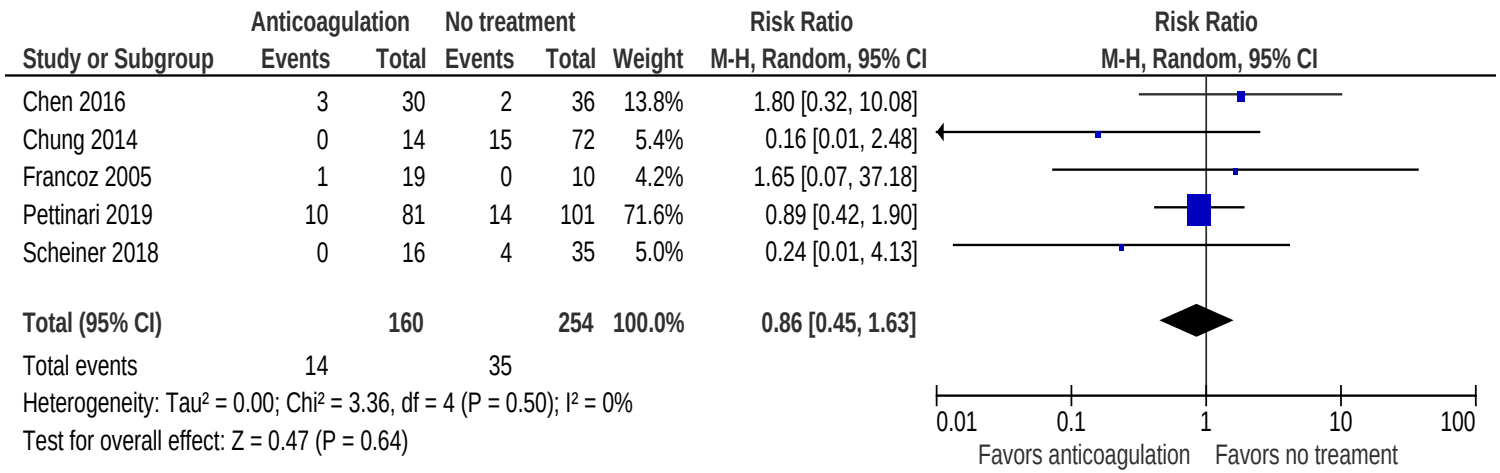

Figure 6

Esophageal variceal bleeding events, Comparative Anticoagulation vs. No treatment

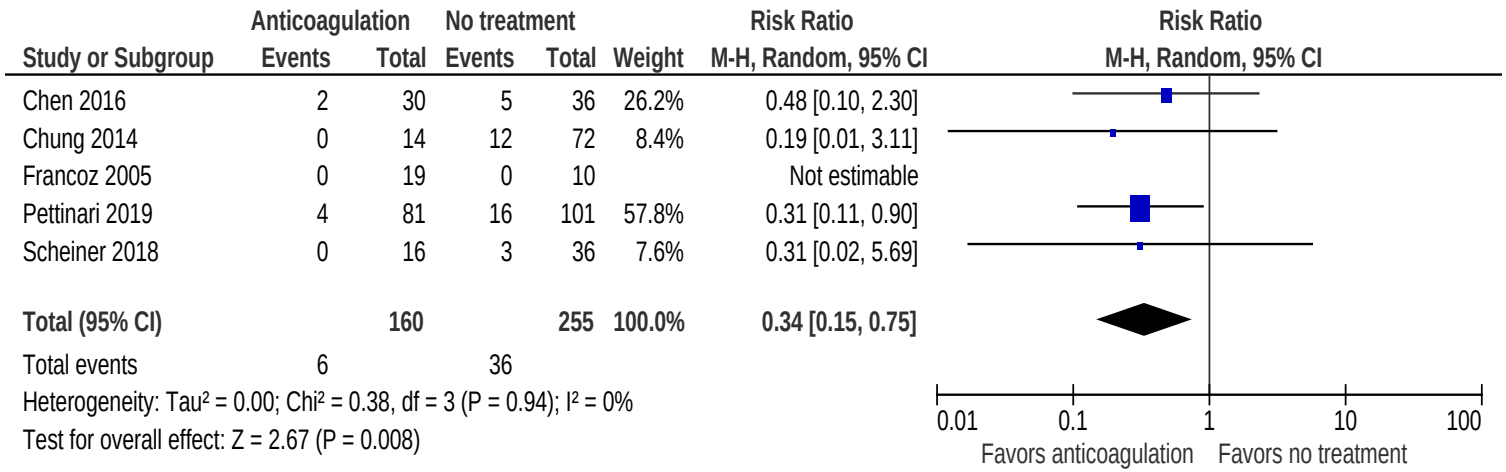

Figure 7

Major bleeding events, VKA vs. DOAC

Study or Subgroup	DOAC Events	DOAC Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
Goriacko 2018	2	75	6	158	4.1%	0.70 [0.15, 3.40]
Lee HF 2019	40	1397	51	946	61.7%	0.53 [0.35, 0.80]
Lee SR 2019	21	446	16	322	25.2%	0.95 [0.50, 1.79]
Pastori 2018	1	52	4	77	2.2%	0.37 [0.04, 3.22]
Serper 2020	3	201	16	610	6.8%	0.57 [0.17, 1.93]
Total (95% CI)		**2171**		**2113**	**100.0%**	**0.62 [0.45, 0.85]**
Total events	67		93			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.54$, df = 4 (P = 0.64); $I^2 = 0\%$

Test for overall effect: Z = 2.94 (P = 0.003)