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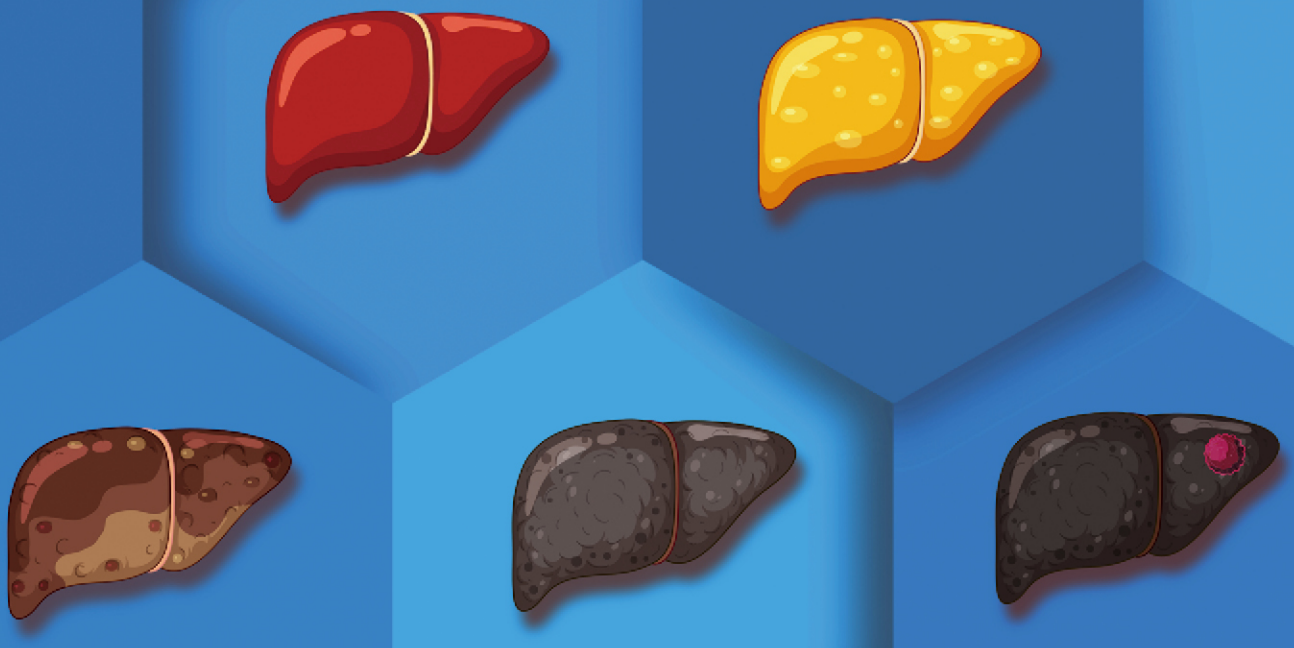

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CLINICAL and MOLECULAR HEPATOLOGY

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Review

# Prediction and prevention of post-procedural bleedings in patients with cirrhosis

Alix Riescher-Tuczkiewicz[1] and Pierre-Emmanuel Rautou[1,2]

[1]Paris City University, Inserm, Inflammatory Research Center, UMR 1149, Paris; [2]AP-HP, Beaujon Hospital, Hepatology Department, DMU DIGEST, Reference Center for Vascular Diseases of the Liver, FILFOIE, ERN RARE-LIVER, Clichy, France

Although post-procedural bleedings are infrequent in patients with cirrhosis, they are associated with significant morbidity and mortality. Therefore, predicting and preventing such bleedings is important. Established predictors of post-procedural bleeding include high-bleeding risk procedure, severe cirrhosis and high body mass index; prognostic value of anemia, acute kidney injury and bacterial infection is more uncertain. While prothrombin time and international normalized ratio do not predict post-procedural bleeding, some evidence suggests that platelet count, whole blood thrombin generation assay and viscoelastic tests may be helpful in this context. Prevention of post-procedural bleeding involves careful management of antithrombotic drugs during the periprocedural period. Patients with cirrhosis present unique challenges due to altered pharmacokinetics and pharmacodynamics of antithrombotic drugs, but there is a lack of dedicated studies specifically focused on this patient population. Guidelines for periprocedural management of antithrombotic drugs developed for patients without liver disease are thus applied to those with cirrhosis. Some technical aspects may decrease the risk of post-procedural bleeding, namely ultrasound-guidance, opting for transjugular route rather than percutaneous route, and the level of expertise of the operator. The effectiveness of platelet transfusions or thrombopoietin-receptor agonists remains uncertain. Transfusion of fresh-frozen plasma, of fibrinogen, and administration of tranexamic acid are not recommended for reducing post-procedural bleeding in patients with cirrhosis. In conclusion, prediction of post-procedural requires a global approach taking into account the patients characteristics, the risk of the procedure, and the platelet count. There is little data to support prophylactic correction of hemostasis, and dedicated studies are needed. **(Clin Mol Hepatol 2025;31(Suppl):S205-S227)**

**Keywords:** Blood coagulation; Liver diseases; Anticoagulants; Antiplatelet; Hemostasis

## INTRODUCTION

Patients with cirrhosis frequently require invasive procedures as part of the management of their liver disease or of their comorbidities. These procedures pose significant challenges in this setting. First, cirrhosis is associated with a fragile hemostatic balance, stemming from disruptions across all three phases of hemostasis. Second, many patients with cirrhosis receive anticoagulants, typically for portal vein thrombosis, or antiplatelet drugs to mitigate cardiovascular risk, especially in those with metabolic dysfunction-associated steatotic liver disease. Lastly, the se-

**Corresponding author :** **Pierre-Emmanuel Rautou**
Service d'hépatologie, Hôpital Beaujon, 100. boulevard du Général Leclerc, 92110 Clichy, France
Tel: +33.1.40.87.52.83, Fax: +33.1.40.87.55.30, E-mail: pierre-emmanuel.rautou@inserm.fr
https://orcid.org/0000-0001-9567-1859

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verity of cirrhosis increases the risk of post-procedural bleeding, further complicating patients' management.[1] Moreover, the occurrence of post-procedural bleeding leads to significant morbidity and mortality, particularly in hospitalized patients with cirrhosis.[1,2] Therefore, predicting and preventing post-procedural bleeding is critical for improving outcome of patients with cirrhosis undergoing invasive procedures.

In this review, we will first discuss features that predict post-procedural bleeding in cirrhosis and then review preventive strategies, including management of anticoagulants and antiplatelet drugs. The method used to identify the articles of interest in this review is reported in the Supplementary Method 1.

## PREDICTION OF POST-PROCEDURAL BLEEDING

Accurately predicting post-procedural bleeding is essential for implementing tailored preventive measures, especially for patients at high risk of bleeding. Three key parameters can be considered when assessing bleeding risk in patients with cirrhosis undergoing invasive procedures: the risk inherent to the procedure, patient-specific characteristics (such as comorbidities), and the results of the laboratory workup, although the predictive value of the latter remains a topic of debate.

### The risk of procedure

Understanding the bleeding risk associated with an invasive procedure is critical for two reasons: (i) the procedural risk itself is one of the most significant predictors of post-procedural bleeding[1,3]; (ii) the bleeding risk of the procedure directly influences the approach to managing peri-procedural antiplatelet and anticoagulant drugs (see the section "Periprocedural management of anticoagulant and antiplatelet drugs").

Outside the liver disease field, numerous scientific societies have developed classifications for assessing bleeding risk associated with invasive procedures or surgery, over the past decade.[4-9] These classifications aimed at standardization of patient care and the harmonization of research studies. As cirrhosis is associated with specific changes in haemostasis, the main scientific societies of hepatology and haemostasis have proposed classifications tailored to patients with cirrhosis in recent years.[10-15] However, these classifications have some limitations. First, procedures were generally categorized as either 'high-risk' or 'low-risk' for bleeding, but definitions of a 'high-risk' procedure varied across guidelines, some defining it as an expected bleeding risk (minor or major) greater than 1.5%,[11,14,15] while others use this threshold but for major bleeding risk only.[10,12]

Second, even when using the same definition, some guidelines did not come up with the same bleeding risk for a single procedure. For example, transjugular liver biopsy was categorized as high-risk in some guidelines[10,14,15] and low-risk in others.[11,12]

To overcome these discrepancies, a broad survey of experts was recently conducted to reach a consensus on the risk of bleeding in patients with cirrhosis.[16] Fifty-two experts in coagulation and liver diseases were asked to classify procedures frequently performed in patients with cirrhosis. A high-risk procedure was defined as any procedure associated with an estimated risk of major bleeding greater than 1.5%, or even minor bleeding that could lead to significant morbidity or death, such as intracranial bleeding. For 52 of the 80 procedures, more than 75% of the experts agreed on the risk of bleeding associated with the procedure. Seventeen procedures, mainly interventional endoscopies, percutaneous organ biopsies, and those involving the central nervous system, were classified as high-risk, while 35 diagnostic procedures were classified as low-risk (Fig. 1). Although based on expert opinion, this study represents a valuable step towards standardizing future research and classification, and will help clinicians in their day-to-day practice.

One aspect that is difficult to capture in the various classifications should be emphasized. The definition of bleed-

**Abbreviations:**

AKI, acute kidney injury; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; EASL, European Association for the Study of the Liver; FFP, fresh frozen plasma; INR, international normalized ratio; MELD, model for end stage liver disease; PT, prothrombin time; ROTEM, rotational thromboelastometry; TEG, thromboelastography; VKA, vitamin K antagonist; TGA, thrombin generation assay; TPO-RA, thrombopoietin receptor agonist


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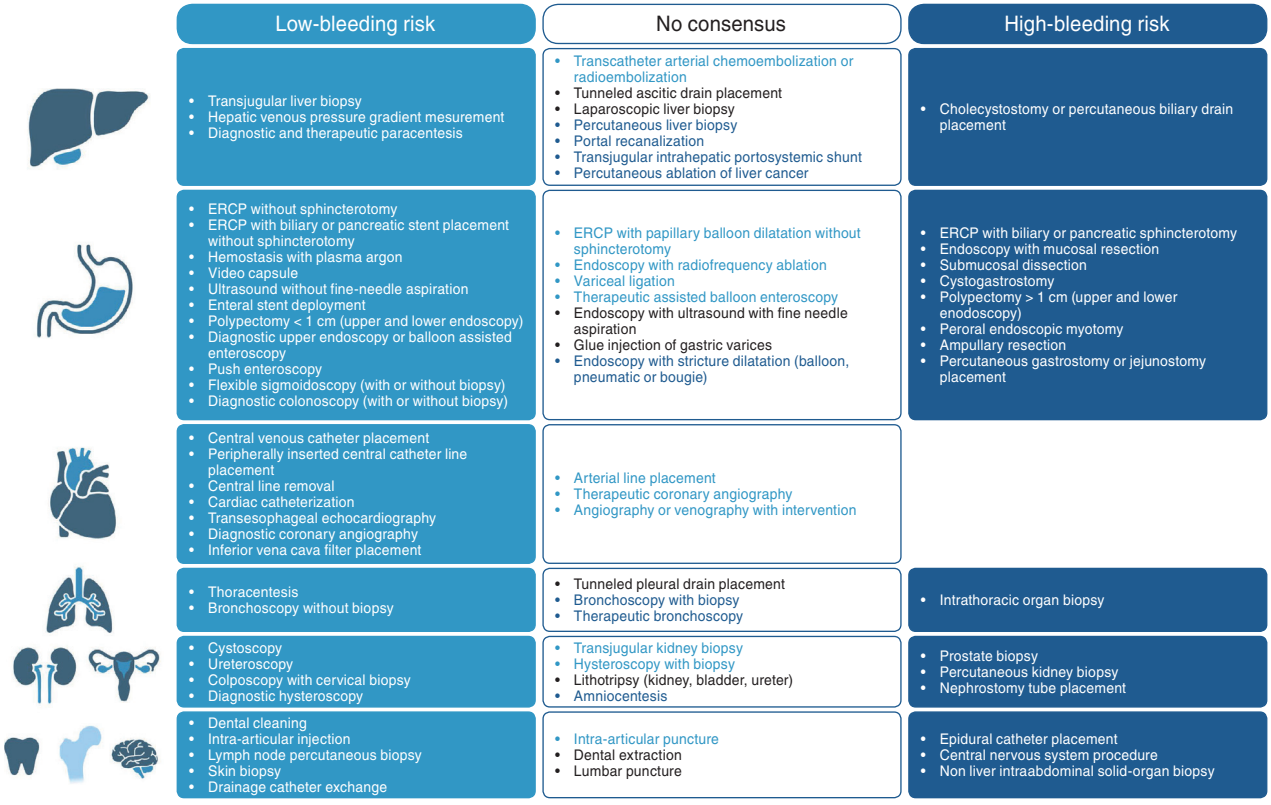


**Figure 1.** Bleeding risk associated with invasive procedures in patients with cirrhosis according to a published expert opinion.[16] In the 'no consensus' column, the light blue color indicates that 60% to 74% of the experts considered the procedure to be low-risk and the dark blue color indicates that 60% to 74% of the experts considered the procedure to be high-risk of bleeding. ERCP, endoscopy retrograde cholangiopancreatography.

ing risk is based on a bleeding rate associated with the procedure, which does not consider the specific population in which the procedure is performed. For instance, liver biopsy can be conducted via transjugular or percutaneous routes, but the transjugular approach is typically recommended for more fragile patients with precarious hemostasis while the percutaneous route is generally used when hemostasis is preserved. Therefore, at equivalent bleeding rates, transjugular biopsy may actually present a lower bleeding risk since it is performed in patients who are otherwise at a higher risk of bleeding.

## Characteristics of patients

### Kidney injury

Acute kidney injury (AKI) in patients with cirrhosis is associated with hemostatic changes summarized in Table 1.[17-20] While some changes are associated with an increased risk of bleeding and others with thrombosis, global coagulation assays, such as thrombin generation assays (TGA), showed no significant abnormalities.[17,20] Interestingly, most of the hemostatic changes resolved following the resolution of AKI.[17] Clinically, one retrospective study including 83 patients with decompensated cirrhosis found that AKI was the only independent predictor of post-paracentesis hemoperitoneum.[21] However, two other studies, including patients across all stages of cirrhosis severity, did not confirm this association.[1,3] Although data are limited, current guidelines and expert opinion recommend addressing AKI in patients with cirrhosis prior to performing invasive procedures.[10,12,13,16]

Chronic kidney injury in patients with cirrhosis has also been identified as a risk factor for bleeding following ERCP and paracentesis.[22-24]

The impact of hemodialysis on procedural bleeding risk remains uncertain. On the one hand, anticoagulation is commonly used during hemodialysis to prevent clotting within the dialysis circuit, and hemodialysis activates platelets inducing transient platelet dysfunction and decreased

**Table 1.** Hemostatic changes associated with acute kidney injury and bacterial infection in patients with cirrhosis

| Clinical condition | Reflect bleeding tendency | Reflect a balance between bleeding and thrombosis tendency | Reflect thrombosis tendency |
|---|---|---|---|
| Acute kidney injury | - Impaired platelet function (reduced platelet aggregation and secretion)[17]<br>- Reduced Factor FXIII[17,18]<br>- Increased tPA, decreased alpha-2 antiplasmin, increased plasmin-antiplasmin level (but might be a response to increased coagulation activation)[17,19] | - Whole-blood TGA[20] and PFP-TGA[17]: no change in ETP | - Higher FVIII, lower protein C and S, antithrombin and plasminogen[17]<br>- Increased TAT level indicating a probably increased coagulation activation[17,19]<br>- Increased TAFI activation[17] |
| Bacterial infection | - Circulating endogenous heparinoids, inducing a "heparin-like" effect[36]<br>- Reduced platelet aggregation and decreased levels of factor VII[37]<br>- TEG®: prolonged R and K times, along with a reduced alpha angle and maximum amplitude[38]<br>- Whole blood TGA: reduced ETP[20] | - PFP-TGA: no change in ETP[37] | - Lower protein C, protein S, and antithrombin[37] |

ETP, endogenous thrombin potential; PFP, platelet free plasma; TAFI, thrombin-activated fibrinolytic inhibitor; TAT, thrombin-antithrombin; TEG, thromboelastography; TGA, thrombin generation assay; tPA, tissue plasminogen activator.

platelet receptor expression, but on the other hand, hemodialysis alleviates uremia-mediated platelet dysfunction associated with chronic kidney disease.[25-27] One study evaluating hemostasis in patients with chronic kidney disease, with or without hemodialysis, reported no significant difference in platelet function nor coagulation parameters measured by rotational thromboelastometry (ROTEM) (e.g., clotting time and maximum clot firmness) and TGA (e.g., endogenous thrombin potential) or clot lysis time between the two groups.[28] Although hemodialysis has been identified as a risk factor for procedural bleeding, it is unclear whether this risk stems directly from hemodialysis or from the underlying chronic or acute kidney injury necessitating dialysis.[29-35] Further research is required to clarify this relationship, especially in the population of patients with chronic liver disease as no data are available at the moment.

### Bacterial infection

Hemostatic changes observed during bacterial infections in patients with cirrhosis are summarized in Table 1.[20,36-38] Notably, two global hemostasis assays—thromboelastography (TEG) and whole-blood TGA—identified a hypocoagulable profile in these patients during bacterial infection.[20,38] However, the link between these changes and post-procedural bleeding remains unclear. While most studies found no significant association between bacterial infection and increased procedural bleeding risk,[1,3,21] one study did report a higher risk of bleeding following variceal band ligation in infected patients.[39] Despite the limited data, current guidelines and expert opinion recommend treating bacterial infections before performing invasive procedures in patients with cirrhosis.[10,12,16]

### Anemia

Red blood cells play a key role in the hemostatic process by (i) promoting platelet adhesion and aggregation and (ii) pushing the platelets near the vessel wall, where they are strategically placed to respond to vascular injury.[40] One study found that lower hemoglobinemia was associated with bleeding following endoscopic variceal ligation and colonoscopic polypectomy,[39] but none of the other studies found such association.[1,41] Guidelines from the European Association for the Study of the Liver (EASL) recommend managing anemia prior to invasive procedures by addressing underlying deficiencies, such as vitamin B12, folate (B9), and iron.[11] Conversely, red blood cell transfusions are not advised solely as they carry significant risks.

### Cirrhosis severity

Severity of cirrhosis must be thoroughly evaluated before undertaking any invasive procedure for two reasons. First, severity of cirrhosis, indicated by a higher model for end


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stage liver disease (MELD)[1,39] or Child-Pugh score,[42-46] or signs of liver failure or portal hypertension[47,48], has been consistently identified as an independent risk factor for both minor and major post-procedural bleeding. Second, although not specifically addressed in the studies, post-procedural bleeding occurring in patients with decompensated cirrhosis, who are already in a fragile state, is more likely to lead to significant morbidity and mortality compared to patients with compensated cirrhosis.[23]

Acute on chronic liver failure (ACLF) is a distinct syndrome observed in patients with acutely decompensated chronic liver disease characterized by an intense systemic inflammatory response, single or multiple organ failure, and high 28-day mortality rates.[49] Hemostatic alterations in ACLF range from a normal to hypocoagulable profile, as demonstrated by TGA or viscoelastic tests, and highly variable fibrinolytic profile, which can span from hypofibrinolysis to hyperfibrinolysis.[50-54] Clinically, neither ACLF *per se,* nor the associated coagulopathy, predict procedural related bleeding, when adjusted for potential confounders such as AKI or sepsis.[1,55]

**Antiplatelet drugs**

Antiplatelet drugs include inhibitor of cyclooxygenase 1, namely aspirin, and $P2Y_{12}$ receptor inhibitors, namely clopidogrel, prasugrel and ticagrelor (Supplementary Table 1).[56,57] In the general population, the procedural bleeding risk associated with aspirin is lower than that of $P2Y_{12}$ receptor inhibitors, used alone or in combination with aspirin.[58-63] In the perioperative setting, aspirin use reduces the risk of cardiac events, including myocardial infarction, in patients with previous cardiovascular events.[64,65] In patients undergoing procedures with a low risk of bleeding, continued use of aspirin appears as a safe option.[60] In patients undergoing procedures with a high risk of bleeding, the decision to continue or discontinue aspirin must balance the risk of bleeding associated with the procedure against the patient's thrombotic risk.[60]

In patients with cirrhosis, the effect of antiplatelet drugs on procedural bleeding risk is not well documented. One study found that antiplatelet drugs use was associated with a higher incidence of bleeding, but these were mainly spontaneous and portal hypertension-related bleedings and not specifically post-procedural bleedings.[66] The large PROC-BLeeD prospective study found that clopidogrel was associated with a higher incidence of post-procedural bleeding by univariable analysis, but the low number of patients involved did not allow for multivariable analysis.[1] Other studies found no significant association between antiplatelet use and post-procedural bleeding, but the infrequent use of these drugs in the studies makes it difficult to draw firm conclusions.[1,39,67] Dedicated trials testing interruption or not of aspirin in patients with cirrhosis would be needed to guide clinical practice, but these will be difficult to conduct given the low frequency of bleeding events.

**Anticoagulants**

Anticoagulants include heparin (both unfractionated and low-molecular weight), vitamin K antagonists (VKAs), and direct oral anticoagulants (DOACs) (Supplementary Table 2).[10,56,57,68] In patients without liver disease, VKAs and DOACs, as well as peri-procedural bridging with low-molecular weight heparin, have been associated with an increased risk of bleeding following various procedures compared to no anticoagulant.[58,59,69-74]

In patients with cirrhosis, the substantial literature on the safety of DOACs and VKAs has focused on bleeding events related to portal hypertension or spontaneous gastrointestinal or intracranial bleeding, rather than on post-procedural bleedings.[75-78] In the specific setting of endoscopic variceal ligation, low-molecular weight heparin was not associated with an increased risk of bleeding.[79] Outside this setting, observational studies reported a significant incidence of bleedings following invasive procedures in patients with chronic liver disease treated with anticoagulant than in patients without anticoagulants;[1,39,80,81] patients with a platelet count below $50\times10^9$/L seem particularly at risk.[75] Therefore, careful management of anticoagulants is needed when planning an invasive procedure in patients with cirrhosis.

**Other characteristics**

Higher body mass index (BMI, 31.2 kg/m$^2$ *vs.* 29.5 kg/m$^2$) has recently been identified as a risk factor for post-procedural bleeding in patients with cirrhosis, independently of ascites, which may confound both procedural bleeding risk and BMI measurements.[1] While this association may seem surprising, given that obesity is typically considered procoagulant, it may be related to technical challenges during procedures, as excess adipose tissue may obscure anatomical landmarks and potentially complicate the proce-

dure, but also to the fact that some confounding factors, such as sarcopenia and edema, were not taken into account.[1,82,83]

A history of bleeding is commonly assessed as part of the pre-anesthesia workup to identify patients at higher risk of bleeding.[84,85] A prospective study including 302 patients, both with and without cirrhosis, undergoing liver biopsy found that questionnaires quantifying history of bleeding had no predictive value for liver biopsy-related bleeding.[41] To date, no data support the use of such questionnaires to predict post-procedural bleeding in cirrhosis.

Overall, future research is needed to better characterize the impact of AKI, bacterial infections, and anemia on post-procedural bleeding, as well as the potential benefits and harms of treating these conditions prior to the procedures. These studies should take into account the increasing bleeding risk associated with cirrhosis progression from the compensated stage to stable decompensation, acute decompensation and acute-on-chronic liver failure.

## Hemostasis tests

### Prothrombin time (PT) and international normalized ratio (INR)

PT and INR are widely used in the management of patients with cirrhosis for prognostic purposes (e.g., calculation of the Child-Pugh and MELD scores). Conversely, it became clear over the recent years that PT and INR are not reliable predictors of post-procedural bleeding, highlighted, for instance, in a systematic review with meta-analysis and in a large recent prospective multicenter study.[1,24] Likewise, a recent survey gathering 52 experts concluded that INR should not be considered when assessing bleeding risk prior to low-risk procedures,[16] in line with recently published guidelines in patients with cirrhosis.[10-12] As for high-risk procedures, experts also agreed not to take INR into account, although the predefined consensus threshold of 75% was not fully reached (71% agreement). Thus, the maximum acceptable INR value for performing high-risk procedures and surgeries was set at 2.[16]

### Platelets

Thrombocytopenia is a common feature in cirrhosis, affecting up to 78% of patients.[86] Moderate thrombocytopenia (platelet count=50–100×$10^9$/L) and severe thrombocytopenia (platelet count <50×$10^9$/L) are observed in approximately 13% and 1% of the patients, respectively, but are dependent on the stage of cirrhosis.[87] The ability of platelet count to predict post-procedural bleeding is highly debated in the literature. Biologically, Tripodi et al.[88] demonstrated, using a TGA, that a platelet count above 56.$10^9$/L was required to maintain adequate coagulation. Clinically, the thresholds of platelet count predictive of post-procedural bleeding vary from one study to another, ranging from 30×$10^9$/L to 75×$10^9$/L.[1,2,89-91] Practically speaking, data concur for stating that above 75×$10^9$/L, the risk of post-procedural bleeding is not increased, which ultimately concerns the vast majority of patients with cirrhosis. If the platelet count is below 75×$10^9$/L, the exact threshold at which the risk of post-procedural bleeding is increased has not been determined. Retrospective studies indicated that profound thrombocytopenia might predict post-procedural bleeding, but the thresholds were inconsistent.[92] Prospective studies showed no correlation between platelet count and post-procedural bleeding risk.[1,92] However, it is important to note that most studies had limitations:(i) patients with very profound thrombocytopenia (e.g., <30×$10^9$/L) were often not included in the studies; (ii) patients with severe thrombocytopenia frequently received pre-procedural platelet infusion; and (iii) major bleeding episodes were not individualized from minor bleeding.

Therefore, no definitive conclusions can be drawn from the available literature on the predictive value of platelet count for post-procedural bleeding risk. Yet, platelets being necessary for clot formation to stop bleeding, a certain level of platelet count is needed to prevent post-procedural bleeding, but this level has not been identified. From a practical standpoint, the above-mentioned recent expert opinion suggested that the lowest acceptable platelet counts for performing a low-risk procedure or a high-risk procedure are 30×$10^9$/L and 50×$10^9$/L, respectively.[16] Further prospective randomized studies are needed to assess in patients with severe thrombocytopenia the procedural bleeding risk and the best management in this context.

### Viscoelastic tests

Compared to conventional hemostasis tests, viscoelastic tests, such as ROTEM and TEG, offer a more comprehensive assessment of hemostasis in patients with cirrhosis as (i) they include the dynamics of clot formation, stabilization


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and lysis, and (ii) they are performed on whole blood, accounting for the contributions of both cells and plasma proteins.[93] Several randomized controlled trials have demonstrated the value of these tests in reducing the need for blood product transfusion in patients with cirrhosis undergoing invasive procedure or liver transplantation.[94-100] However, their predictive value for post-procedural bleeding remains unclear as summarized in Table 2.[41,55,101-106] Some studies identified an association between specific TEG (e.g., K time, maximum amplitude)[103,105] or ROTEM parameters (e.g., clotting time, maximum clot firmness)[102] and post-procedural bleeding, while others did not.[41,101,104] This inconsistency may be attributed to the heterogeneity of the studies in terms of types of procedures performed (ranging from low to high risk of bleeding procedures), type of bleeding (post-procedural vs. portal hypertension-related), and included patients having various severities of cirrhosis. Accordingly, there is insufficient evidence to support the routine use of viscoelastic tests in predicting post-procedural bleeding in cirrhosis. Additionally, the limited availability of viscoelastic tests, currently confined to certain tertiary care centers, and the absence of clearly identified thresholds, restrict their applicability. In this line, current guidelines do not recommend viscoelastic tests to predict post-procedural bleeding in patients with cirrhosis, and encourage further prospective studies to clarify their potential utility.[10-12]

#### TGA

TGA is a global coagulation assay that continuously monitors continuously thrombin generation after triggering coagulation cascade with tissue factor, with or without the addition of phospholipids, at various concentrations.[107,108] TGA takes into account the activity of natural plasma anticoagulants (such as protein C) by adding soluble thrombomodulin, a protein present on the endothelium, which activates protein C.[109] TGA can be performed on platelet free plasma or on whole blood. Three prospective studies consistently showed that TGA performed on platelet free plasma does not predict post-procedural bleeding (Supplementary Table 3).[41,110,111] Conversely, TGA performed on whole blood might be of interest to predict post-procedural bleeding. Indeed, Zanetto et al.[110] observed, in patients with decompensated cirrhosis, that impaired whole blood TGA parameters predicted major post-procedural bleeding. These results must be confirmed by dedicated independent studies.

Overall, laboratory workup seems to have a limited value in predicting post-procedural bleeding, although definitive conclusions cannot be drawn for platelet count. Still, platelet count, hemoglobin level and INR can be useful, particularly before high-risk procedures, as they provide an overview of the baseline hemostatic status and can guide management in case bleeding complications occur. Additionally, platelet count and INR may alert clinicians to coagulopathies unrelated to cirrhosis or signal the need for greater caution or procedure postponement if INR reveals liver function worsening. While TGA on platelet free plasma does not predict post-procedural bleeding, more studies are needed for viscoelastic tests and for TGA on whole blood.

## PREVENTION OF BLEEDING

### Periprocedural management of antiplatelet and anticoagulant drugs

Managing antithrombotic drugs during the periprocedural period requires a patient-specific approach, considering the indication for antithrombotic treatment (primary or secondary prevention), the thrombotic risk of the patient, the indication for the procedure, its bleeding risk and its urgency. In recent years, several societies have issued recommendations for the management of antithrombotic drugs in the periprocedural/surgical setting in the general population. In this section, we first reviewed the guidelines published in the past five years (2019–2024) by various societies of Cardiology, Hepatology, Gastroenterology, Pulmonology, Anesthesiology, Thrombosis and Haemostasis, Hematology and Interventional Radiology.[5,57,85,112-121] Some guidelines focus specifically on procedures,[5,85,112,115,118] others on surgeries[57] and others on both procedures and surgeries[113,114,116,117] which can partly account for the differences in the proposed management. These guidelines are summarized below and in Figure 2 and Supplementary Tables 4, 5. We then highlight areas where adaptation to the cirrhosis setting may be required. Regarding discontinuation of antithrombotic drugs, the number of days mentioned refers to the number of full days before the day of the procedure/surgery in which the patient does not take any dose of antithrombotic drugs. The

**Table 2.** Studies assessing the ability of viscoelastic tests to predict post-procedural bleeding in patients with cirrhosis

| Article | Population | Study design | Test | Type of bleeding | Bleedings | Parameters associated with bleeding |
|---|---|---|---|---|---|---|
| Vieira Da Rocha et al., 2009[101] | 92 patients with cirrhosis<br>All severity stages | Prospective | TEG | Ulcer bleeding after variceal band ligation | 5/92 | None |
| Bedreli et al., 2017[102] | 74 patients with cirrhosis<br>All severity stages | Retrospective | ROTEM | Any type of bleeding (including portal hypertension related, spontaneous and post-procedural) | 22/74 | ↑ CT EXTEM<br>↓ MCF EXTEM<br>↓ MCF FIBTEM |
| Pandey et al., 2017[103] | 90 patients with cirrhosis<br>Child-Pugh B or C | Retrospective | TEG | Post elective central venous catheter insertion-bleeding | 11/90 | K time ≥3.05 min (bleeding)<br>Maximum amplitude ≥48.8 mm (absence of bleeding) |
| Somani et al., 2017[104] | 150 patients with cirrhosis<br>All severity stages | Prospective | TEG | Post procedural and surgical bleeding | 1/150 | None |
| Zanetto et al., 2020[105] | 72 patients with cirrhosis<br>Decompensated cirrhosis | Prospective | TEG | Post-procedural bleeding | 7/72 | ↑ K time<br>↓ α-angle<br>↓ Maximum amplitude<br>Maximum amplitude <30 mm discriminates major bleeding from no major bleeding |
| Campello et al., 2021[55] | 91 patients with cirrhosis<br>AD and ACLF only | Prospective | TEG | Any type of bleeding (including portal hypertension related, spontaneous and post-procedural) | 8/91 | None |
| Bissonnette et al., 2022[41] | 148 patients with advanced fibrosis or cirrhosis<br>All severity stages | Prospective | ROTEM | Post-liver biopsy bleeding | 7/148 | None |
| Janko et al., 2024[106] | 162 patients with cirrhosis<br>All severity stages | Prospective | ROTEM | Any type of bleeding (including portal hypertension related, spontaneous and post-procedural) | 19/162 | ↓ MCF EXTEM |

ACLF, acute on chronic liver failure; AD, acute decompensation; CT, clotting time; MCF, maximum clot firmness; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

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drugs are also not taken on the day of the procedure/surgery.

## In the general population

### Elective procedure

*Antiplatelet drug*

Aspirin is widely used in the general population either for primary prevention in individuals with high atherosclerotic cardiovascular disease risk or for secondary prevention in those with existing cardiovascular disease.[122] Practically speaking, for procedures with a low risk of bleeding, most guidelines concur for continuing aspirin. For procedures with a high risk of bleeding, there is a consensus in favor of considering aspirin interruption, except for most endoscopic procedures (but ampullectomy), where aspirin can be continued.[5,57,85,112-115] The duration of interruption before the procedure/surgery varies from 3 to at least 7 days.[5,57,114] The appropriate time to resume aspirin after surgery/procedure varies from "as soon as possible" to "within 48 hours".[5,57,114]

$P2Y_{12}$ inhibitors are mostly prescribed as part of dual antiplatelet therapy (DAPT) in combination with aspirin (following acute coronary syndrome or percutaneous coronary intervention), but also as monotherapy as part of a de-escalation following DAPT, or due to a recent stroke, peripheral artery disease or aspirin intolerance.[57] In patients with a high thrombotic risk, defined by the European Society of Cardiology as acute coronary syndrome <3 months, percutaneous coronary intervention <1 month or a high risk of stent thrombosis (history of stent thrombosis under antiplatelet therapy, left ventricular ejection fraction <40%, poorly controlled diabetes, severely impaired renal function/hemodialysis, recent complex percutaneous coronary intervention or stent malapposition/residual dissection), discontinuing DAPT significantly increases the risk of ischemic events.[57] It is thus preferable to either maintain DAPT in case of low-bleeding risk procedure or defer the elective procedure/surgery until the completion of the full course of DAPT.[5,57,113,114] In patients with a low thrombotic risk, DAPT can be either continued (only in low-bleeding risk procedure) or $P2Y_{12}$ inhibitors can be interrupted while continuing aspirin.[5,57,112,115] $P2Y_{12}$ inhibitors are interrupted 3–5 days for ticagrelor, 5 days for clopidogrel and 7 days for prasugrel before the procedure/surgery.[57,114,115] It is usually indicated to restart antiplatelet drug within 24–48 hours.[57,112,114]

*Anticoagulant*

Most guidelines agree on the management of VKA in the periprocedural/surgical period. In low bleeding risk procedure/surgery, continuation of VKA is indicated.[5,57,112,114-116] INR should be checked before the procedure/surgery to ensure that it does not exceed therapeutic range or is in the lower level if VKAs are continued.[57,112] In high bleeding risk procedures/surgeries, suspension of VKA is the rule.[5,57,112-116] Warfarin is interrupted 5 days,[5,57,85,112,115,117] phenprocoumon 7 to 12 days[57,113] and acenocoumarol 3 days,[57,116] before the procedure/surgery. Whether or not to do a bridge with heparin in the periprocedural/surgical period depends on the patient's thrombotic risk. Indeed, two randomized trials, namely the BRIDGE and PERIOP-2 trials, found no significant benefit of heparin bridging (in the peri-surgical or post-surgical period) to prevent major thromboembolism while it increased in the BRIDGE trial the risk of major bleeding.[74,123] Consequently, in cases of low thrombosis risk (generally patients taking VKAs for atrial fibrillation without high $CHADS_2VASC_2$ score, venous thromboembolism (VTE) >3 months, and mechanical heart valve with no other risk factor for thrombosis), a heparin bridge is not indicated. Bridging might still be beneficial in a subset of patients at very high risk of thrombosis.[115] In these selected cases, cardiologist's opinion should be sought to determine the best management of periprocedural anticoagulation. INR should be checked to ensure it is below a "safe" threshold (usually INR <1.5) in case of withdrawal.[57,116] VKA can usually be resumed quickly after the procedure/surgery; timing suggested in the different guidelines varies from "evening of the procedure/surgery" to "within 24 hours after the procedure/surgery".[57,85,112-114,116,117] Guidelines recommend checking INR after the procedure/surgery once the VKA has been restarted to ensure adequate anticoagulation.

The management of DOACs in the periprocedural or surgical setting is more consistent across guidelines thanks to the PAUSE trial.[124] This prospective study evaluated a standardized protocol in patients with atrial fibrillation treated with DOACs (including apixaban, dabigatran and rivaroxaban) undergoing procedure/surgery without bridging heparin.[124] This protocol resulted in low rates of both major

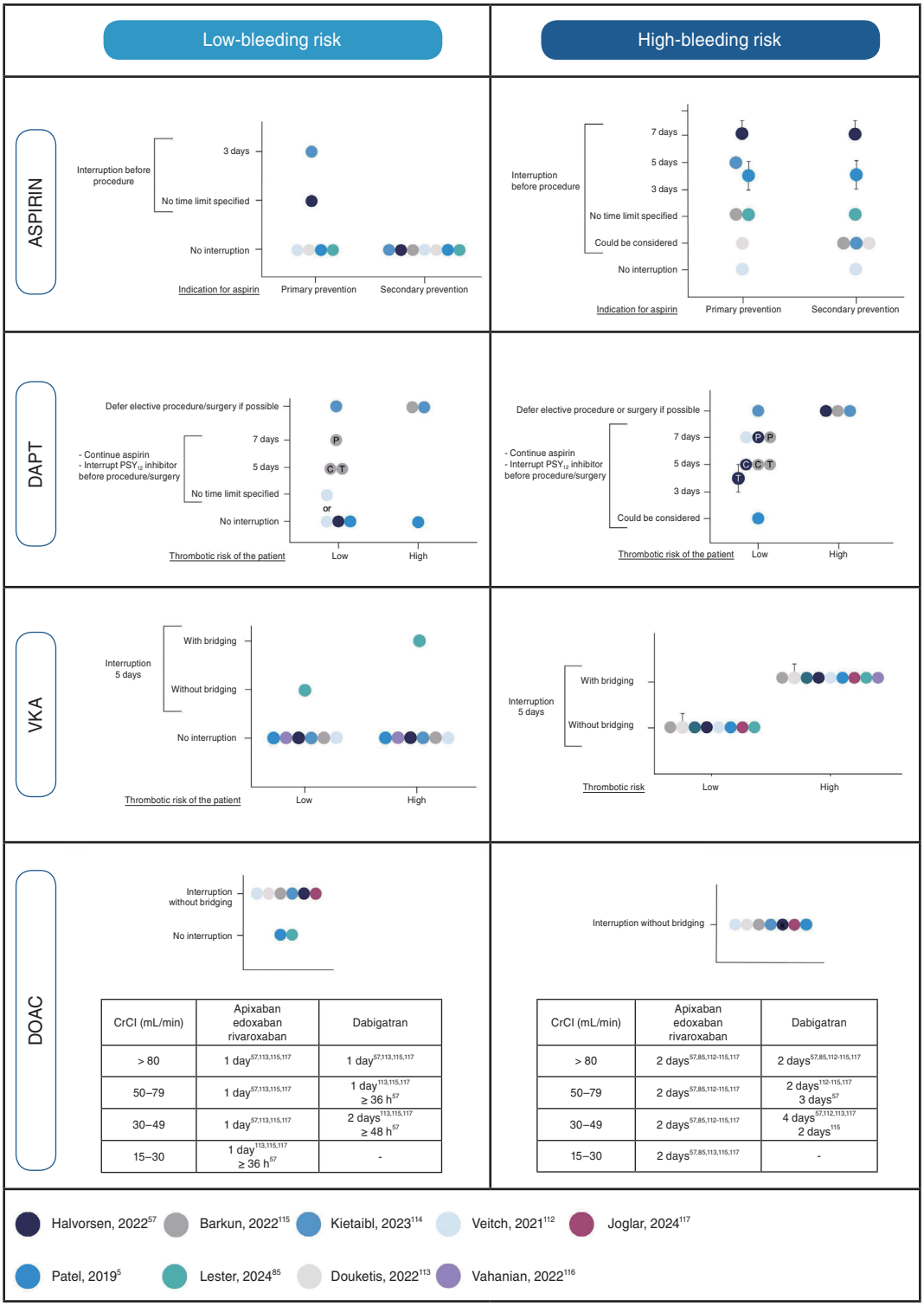


**Figure 2.** Summary of current guidelines on the interruption of antiplatelet and anticoagulant drugs before invasive procedure and surgery. The aim of this figure is to provide a simple summary of the current guidelines on the management of antithrombotic drugs in the periprocedural/surgical period in patients without liver disease. These are also summarised in Supplementary Tables 4 and 5. VKA mentioned in the figure refers to Warfarin. Timing are different for acenocoumarol (3 days) and phenprocoumon (7 to 12 days). CrC, creatinine clearance; C, clopidogrel; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; P, prasugrel; T, ticagrelor; VKA, vitamin K antagonist.


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bleeding (0.9–1.85%) and thrombotic events (<1%). Accordingly, DOAC interruption is recommended before performing both low and high bleeding risk procedure/surgery, without heparin bridging.[57,112-115,117] The number of days to stop and resume DOACs in the periprocedural/surgical period depends on the bleeding risk of the procedure, the type of DOAC and the patient's renal function. For procedures with a low risk of bleeding, DOACs may be discontinued and resumed 1 day before/after the procedure/surgery (excluding the day of surgery),[57,113,115,117] some guidelines even suggest omitting DOAC only on the day of procedure/surgery.[112,114] For procedures with a high risk of bleeding, DOACs can be stopped 2 days before the procedure/surgery and resumed 2 to 3 days after the procedure/surgery. These durations are longer in dabigatran-treated patients with impaired renal function. Deferral of elective surgery should be considered in patients within 3 months of acute VTE, stroke or transient ischaemic attack.[115]

**Specific case of non-elective procedures**

The management of non-elective procedures differs from that of elective procedures as (i) there is often insufficient time to allow antithrombotic drugs to dissipate, necessitating the use of reversal agents in some cases or performance of the procedure while antithrombotic drug is still active, and (ii) patients may require procedures with a high risk of bleeding, but it may not be possible to optimize preoperative conditions to mitigate this risk (e.g., in cases of acute renal failure, bacterial infection, etc.), as the urgency of the procedure outweighs the bleeding risks.

Data on the management of antithrombotic drugs in non-elective procedures remain limited.[5,57,85,114,125,126] The management approach depends (i) on the urgency of the procedure—classified as immediate, urgent, or expedited—based on the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) classification (Supplementary Table 6)[127] and (ii) on whether the procedure can be performed while the patient remains on antithrombotic treatment.

For antiplatelet agents, immediate or urgent procedures (to be performed within hours) typically preclude sufficient time for drug withdrawal (at least three days for aspirin and even longer for $P2Y_{12}$ inhibitors). As a result, involving a multidisciplinary team or discussing with a cardiologist is needed to decide on a case-by-case basis the management of antiplatelet agents, especially in patients taking $P2Y_{12}$ inhibitors.[85,114] One guideline suggests neutralizing antiplatelet agents using platelet transfusion for neurosurgical procedure (intracranial surgery) while maintaining antiplatelet therapy in other procedures.[125] In cases of intra- or postoperative bleeding potentially related to antiplatelet agents, platelet transfusion may be used for neutralization.[114,125] However, this approach may be ineffective, especially in patients taking ticagrelor.

For patients on DOACs, it is important to inquire about the timing of the last dose and perform blood-coagulation tests (e.g., PT, aPTT, anti-Xa, diluted thrombin time) alongside DOAC plasma level testing.[57,113] These assessments can help determine the necessity for active DOAC reversal. If the last dose was taken more than 12 hours previously and there is no renal impairment, the procedure can usually be completed without reversal,[57] but a longer stopping time may also be required for rivaroxaban.[128] Otherwise, reversal may be required, particularly for immediate procedures with a high bleeding risk. Reversal agents include Idarucizumab and Andexanet alfa which are specific for dabigatran and FXa inhibitors, respectively, but also prothrombin complex concentrate (PCC) or activated PCC. PCC, idarucizumab, and Andexanet alfa demonstrated similar effective hemostasis rates and comparable mortality among the three agents, though Andexanet alfa was associated with a significantly higher rate of thrombotic events.[129]

For VKA-treated patients requiring an emergency procedure with moderate-to-high bleeding risk, the patient's INR should be measured upon hospital admission. Rapid reversal of anticoagulation is best achieved using four-factor PCCs, preferred over plasma transfusion, as they provide more reliable and quicker correction.[57,85,114] Vitamin K can also be administered but takes time to be efficient (approximately 6 hours).[85] If reversal proves insufficient or there is a risk of prothrombotic rebound, an interdisciplinary approach is necessary to decide on the timing of anticoagulation resumption.

## In patients with cirrhosis

In patients with cirrhosis receiving antithrombotic drugs, some specificities related to the liver disease should be considered when planning invasive procedures. First, anti-

thrombotic drugs pharmacokinetics might be modified in patients with cirrhosis due to (i) hypoalbuminemia resulting in higher circulating concentration of unbound drug, impacting its clearance and toxicity,[130,131] (ii) delayed hepatic clearance (for instance related to altered cytochrome P450 activity[132]), resulting in higher plasma concentrations of some drugs (apixaban, rivaroxaban),[133] (iii) common impaired renal clearance, further compromising drug excretions.[68] Additionally, pharmacodynamics of anticoagulants in patients with cirrhosis are also altered as evidenced by in vitro studies using TGA showing either increased (dabigatran, low-molecular-weight heparin) or decreased (rivaroxaban, apixaban, edoxaban and fondaparinux) anticoagulant effect of the drugs in this setting.[134-139] Finally, monitoring of VKA before invasive procedure is challenging in patients with severe cirrhosis, as INR is influenced both by liver disease severity and the effect of VKA.[140] Although the above considerations are important, no study has specifically investigated the optimal timing for discontinuing antithrombotic therapy in patients with cirrhosis. Therefore, although it remains unclear whether guidelines designed for patients without liver disease are applicable to patients with cirrhosis, they are still used in this population.[11,12] While awaiting dedicated studies specifically in patients with cirrhosis, we propose an algorithm for managing antithrombotic therapy (Fig. 3), as well as suggestions for the timing of discontinuation and resumption of anticoagulants (Fig. 4), based on the guidelines mentioned above in patients without liver disease.[126] The timing for resuming antithrombotic therapy should always take into account input from the physician who performed the procedure, particularly regarding their assessment of whether adequate hemostasis has been achieved at the end of the procedure.

## OTHER PREVENTIVE MEASURES BEFORE AN INVASIVE PROCEDURE IN PATIENTS WITH CIRRHOSIS

### Technical aspects

The use of ultrasound guidance for procedures such as percutaneous liver biopsy, transjugular intrahepatic portosystemic shunt, paracentesis and central venous catheter

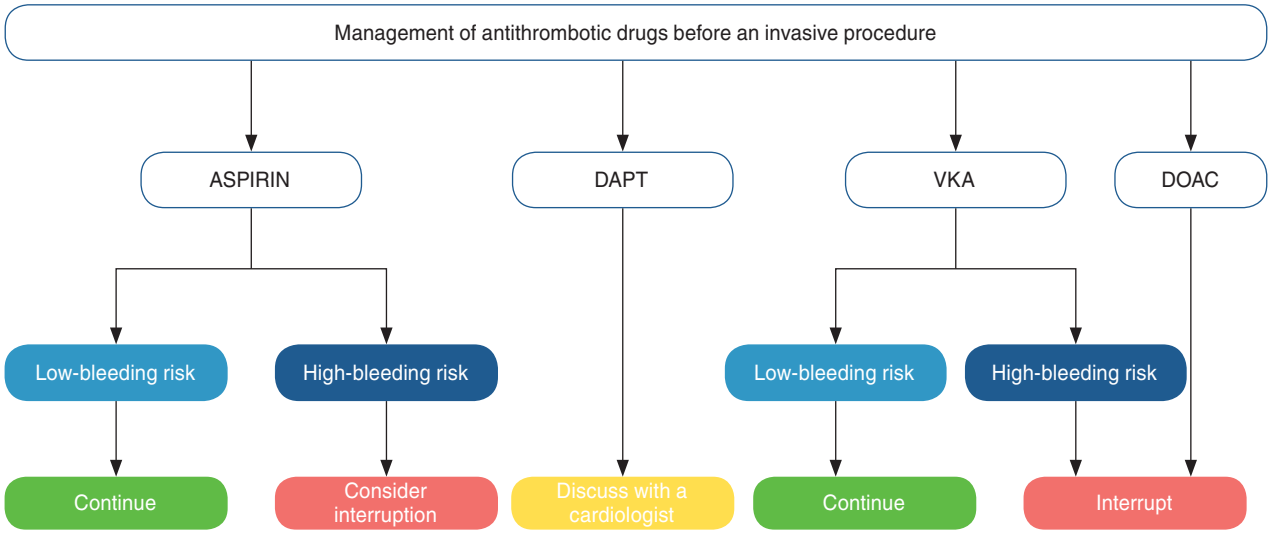


**Figure 3.** Suggested management for antithrombotic drugs in the periprocedural period in patients with cirrhosis derived from those proposed in the general population. For low bleeding risk procedures, aspirin should generally be continued. For procedures with a high risk of bleeding, most endoscopic procedures (except ampullectomy) can still be performed safely with aspirin. For other high-risk procedures, discontinuation of aspirin may be considered, but the decision should balance the risk of bleeding against the risk of thrombosis, with input from a cardiologist being particularly valuable in these cases. Decisions regarding DAPT are more complex, as these drugs are often prescribed following percutaneous coronary intervention or acute coronary syndrome. In such cases, cardiology input is critical to guide management. VKA therapy can usually be continued for low bleeding risk procedures. However, for high bleeding risk procedures, discontinuation is recommended. In patients at very high thrombotic risk, bridging therapy may be considered. For both high and low bleeding risk procedures, interruption of DOACs without bridging is typically advised. DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.


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placement has been associated with a lower incidence of complications, including post-procedural bleeding, compared with no ultrasound guidance, although the populations included in the studies were not always patients with cirrhosis.[141-148]

The impact of operator experience on post-procedural bleeding is unclear. While some studies suggest that experienced operators or high-volume centers reduce bleeding,[43,149] others show no effect,[23,150] and some even indicate an increased risk of bleeding with more experienced operators,[149] both in patients with and without cirrhosis. It is likely that a selection bias is responsible for these results, with patients at higher risk of bleeding or those for whom the procedure appears more complicated being referred to an experienced operator or expert center.

Finally, the route by which the invasive procedure is performed is also important. For instance, the transjugular route for kidney or liver biopsy appears as a safe option in patients with chronic liver disease in whom the percutaneous route is not feasible due to impaired hemostasis.[151-154]

## Measures to modulate hemostasis

Platelet transfusion has been traditionally used before invasive procedures to increase platelet count in patients with chronic liver disease and severe thrombocytopenia. In vitro studies show that infusing one standard adult platelet dose results in only a small increase in platelet count (platelet count, $39\times10^9$/L [16–64] vs. $52\times10^9$/L [19–91]) without normalizing thrombin generation and thromboelastometry tests.[155] Additionally, platelet increase after transfusion is transient and variable from one patient to another and platelet transfusion carries the risk of potential harmful transfusion reactions.[156] Lastly, no study has demonstrated its effectiveness in reducing post-procedural bleeding. Avatrombopag and Lusutrombopag, both thrombopoietin receptor agonists (TPO-RA), stimulate platelet production in the bone marrow. Compared to placebo, these drugs reduce the need for peri-procedural platelet transfusions and are more likely to achieve a platelet count >$50\times10^9$/L before the procedure, without significant differences in thrombotic complications.[157-162] Moreover, their effect lasts up to 2

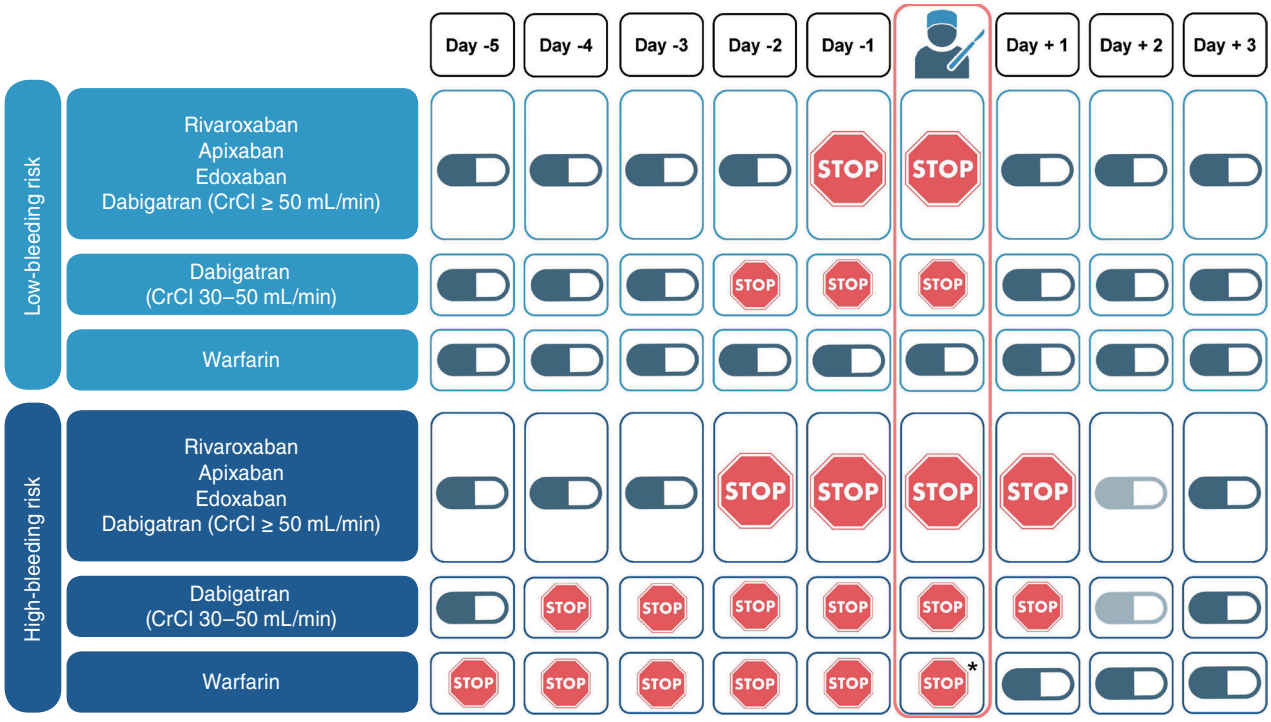


**Figure 4.** Suggested timing of interruption and resumption for anticoagulants in the periprocedural period in patients with cirrhosis. VKA mentioned in the figure refers to Warfarin. The timing is different for acenocoumarol (3 days) and phenprocoumon (7 to 12 days). *VKA can be taken the evening of the procedure. Depending on the procedure and the hemostasis, DOAC can be resumed on the evening of the second day or 2 or the third day after a high-bleeding risk procedure. DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

weeks which may be desirable in patients with delayed post-procedural bleeding. Compared with platelet transfusions, TPO-RA have thus the advantage of enabling a more prolonged increase in platelet count without the side effects associated with transfusions. However, no randomized controlled trial has evaluated their efficacy in reducing post-procedural bleeding and an 8- to 13-day treatment course is required before the procedure, limiting their use to elective settings. Current guidelines do not recommend correcting thrombocytopenia before high-bleeding risk procedures in patients with cirrhosis in case of platelet count ≥50×10$^9$/L.[10-12,14,163] When platelet count is <50×10$^9$/L, recommendations differ from one guideline to another, some suggesting no routine preprocedural correction, while others suggest preprocedural correction in very specific cases associated with a high risk of bleeding (very high-risk procedure, local hemostasis not possible, platelet count <20×10$^9$/L), using platelet transfusion or TPO-RA.[10-12,14] Correction of thrombocytopenia prior to invasive procedure should not aim to normalize their number (i.e., >150×10$^9$/L), but rather to ensure a safe threshold (established depending on the risk of the procedure).

Fibrinogen plays a crucial role in coagulation as it is converted into fibrin, which forms a mesh-like network that stabilizes the clot by trapping platelets and red blood cells. Patients with cirrhosis can have both hypofibrinogenemia (due to decreased liver synthesis) and dysfibrinogenemia, i.e., a functionally abnormal fibrinogen.[164-166] Two studies suggested that addition of fibrinogen concentrate in vitro into the plasma of patients with cirrhosis improves the structural properties of the fibrin clot and decreases clot permeability.[138,167] However, plasma fibrinogen concentration is not a clear predictor of post-procedural bleeding[1,41] and no prospective study evaluated the interest of infusion of cryoprecipitate/fibrinogen concentrates in patients with cirrhosis before invasive procedures. Therefore, current guidelines do not recommend routine correction of fibrinogen prior to invasive procedures in patients with cirrhosis.[10,11,14]

Fresh frozen plasma (FFP) contains both coagulation factors and anticoagulant proteins. Its use to correct INR prior to invasive procedures in patients with cirrhosis is not supported by current guidelines for several reasons.[10-12] First, the biological effect of FFP remains uncertain, with some studies suggesting a pro-thrombotic effect while others showed no effect or even a slight reduction in thrombin generation.[168-170] Second, there is no evidence that FFP reduces the risk of post-procedural bleeding in patients with cirrhosis. Third, its use is associated with significant risks, including complications such as transfusion-related acute lung injury[171,172] and transfusion-associated circulatory overload,[173] as well as an increase in blood volume and consequently in portal pressure which may increase the risk of portal hypertension-related bleeding.[174]

Fibrinolysis is a complex process that is also altered in patients with cirrhosis, who can display features of hypo- or hyperfibrinolysis.[175] Tranexamic acid is a synthetic lysine derivative that exerts antifibrinolytic effects by binding to lysine-binding sites on plasminogen, preventing its (and plasmin's) interaction with fibrin.[176] In upper gastrointestinal bleeding in patients with cirrhosis, tranexamic use has been associated with reduced risk of failure to control bleeding by day 5 and of rebleeding,[177] but at the cost of an increased risk of venous thrombosis and no reduction of death from gastrointestinal bleeding.[178] Currently, no data supports its use to reduce post-procedural bleeding in patients with cirrhosis and current guidelines do not recommend it in this setting.[10-12]

Altogether, correction of coagulation abnormalities prior to invasive procedures should be restricted to severe thrombocytopenia, with so far unclear thresholds (somewhere between 20 and 50×10$^9$/L), despite the wide heterogeneity of practice and the observed lack of compliance to guidelines in real world practice.[179,180] Clinicians must also bear in mind the "expected" time when bleeding usually occurs after the procedure. For example, bleeding following endoscopic variceal ligation occurs mainly between 5 to 15 days after endoscopy, and transfusion of blood products prior to endoscopic ligation is unlikely to prevent this late bleeding.[67,181,182]

When a high-risk procedure is scheduled, particularly in patients at high risk of thrombosis, anticipating the attitude in case bleeding would occur might prove useful to guide the physicians on call who will have to take care of the patients in emergency. Such protocol would mention the procedure the patient underwent and the measures to undertake to stop bleeding, including local treatment and hemostasis correction measures adapted to the hemostasis status of the patient.


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## CONCLUSION

In conclusion, management of invasive procedures in patients with cirrhosis requires first an assessment of the bleeding risk associated with the procedure, taking into account the characteristics of the patient, the procedure or the laboratory work-up. Preventing post-procedural bleeding requires managing antithrombotic therapies and correcting potential risk factors, including AKI and bacterial infections, although the benefits of these have not been formally demonstrated. The interest of drugs and blood products to prevent post-procedural bleeding has not been proven in this context.

### Authors' contributions

A.R.T and P.E.R wrote the manuscrit. P.E.R supervised the manuscript.

### Conflicts of Interest

The authors have no conflicts to disclose.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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