Gnerre Paola

Terapia antiaggregante/anticoagulante nel paziente epatopatico cronico

A growing mole of patients with chronic liver disease will be a candidate for anticoagulant therapy in the forthcoming years.

- ✓A higher prevalence of AF seems to be documented in patients with liver cirrhosis, independently of the cause.
- ✓Data from a retrospective analysis of 1727 patients with liver disease evaluated for liver transplantation, presented by Huang *et al*, revealed an 11.2% prevalence of new-diagnosis AF in patients with cirrhosis and a risk that increased with the severity of liver disease

- ✓A meta-analysis of nine observational studies indicated that individuals with liver disease have a 2.5-fold increased risk of ischemic stroke than those without liver disease
- ✓PVT is the most common thrombotic presentation in individuals with liver damage, according to research, with a frequency of 8% to 18% in patients with liver cirrhosis

- ✓ Chronic hepatitis B
- ✓ Alcoholic liver disease
- ✓ Chronic hepatitis C
- ✓ Nonalcoholic fatty liver disease (NASH) /nonalcoholic steatohepatitis(NAFLD)

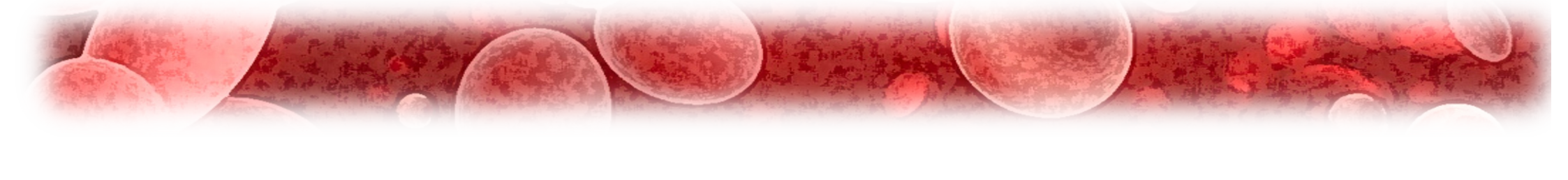
Non-alcoholic fatty liver disease – a procoagulant condition?

Croat Med J. 2021

NASH/NAFLD are independently associated with an increased risk of atrial fibrillation (AF) and unprovoked venous thromboembolism (VTE).

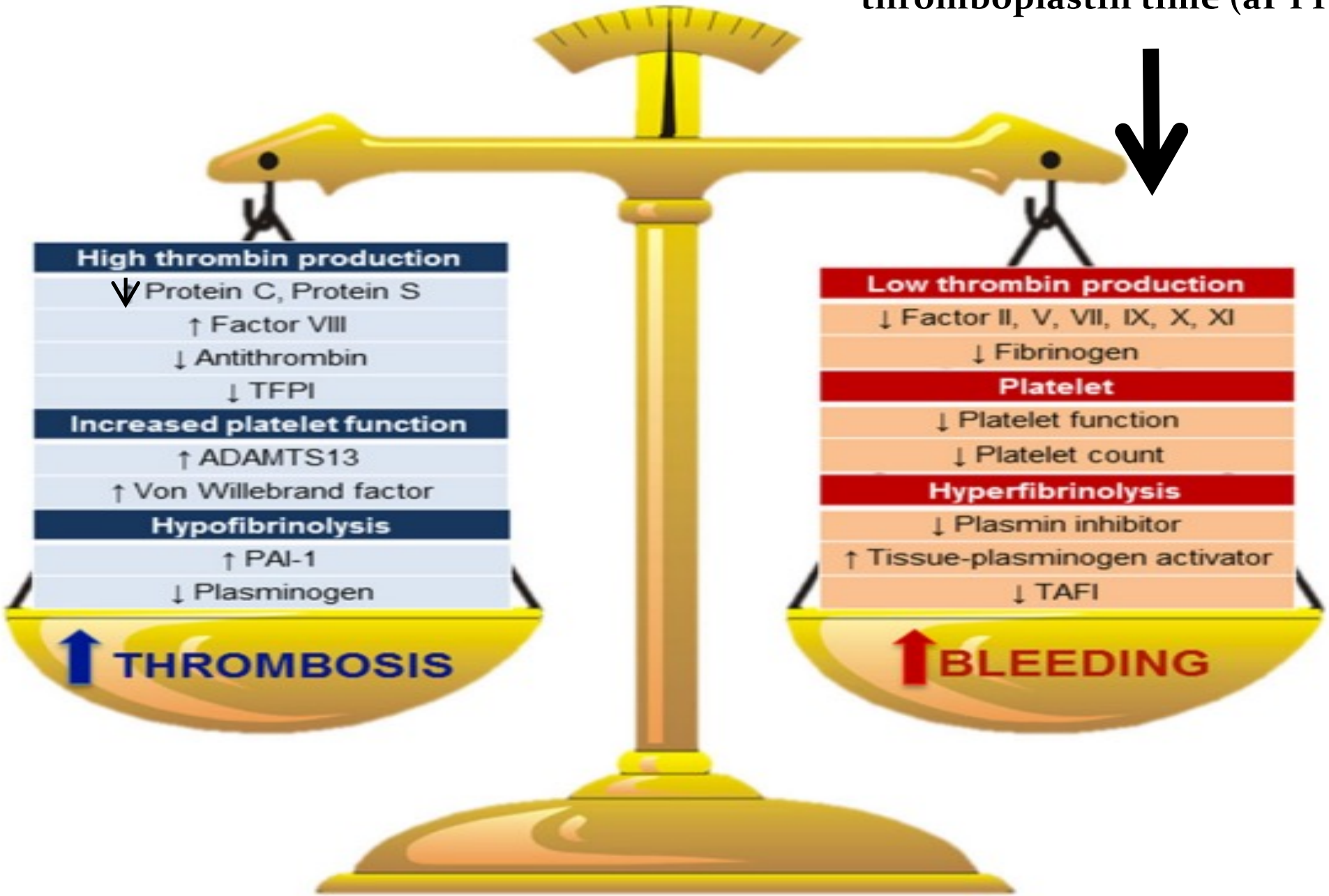
A growing mole of patients with chronic liver disease will be a candidate for anticoagulant therapy in the forthcoming years.

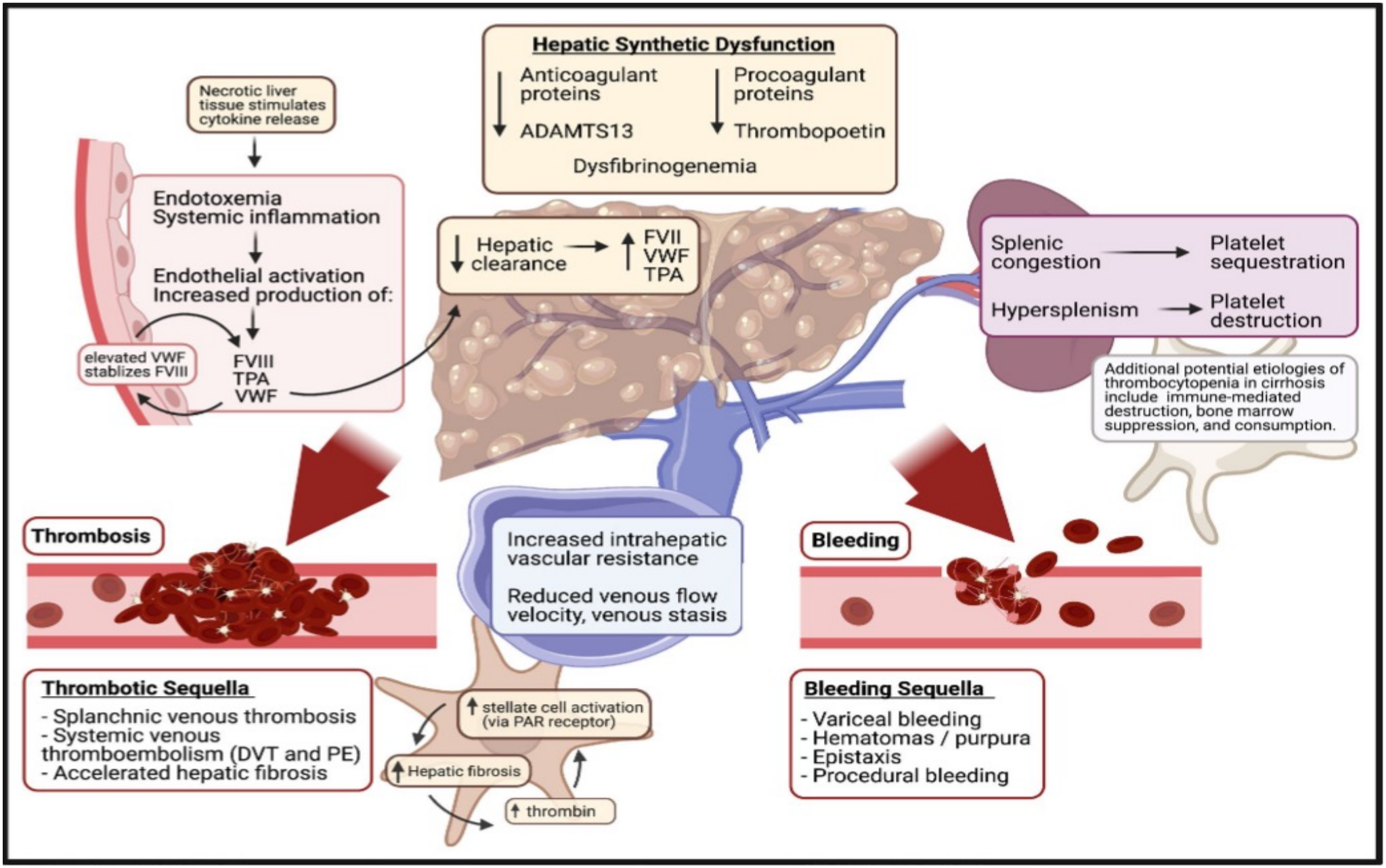
Management of anticoagulated patients with liver disorders is difficult because they are a higher ischemic risk and an increased risk of bleeding (correlated with a reduction in synthetic liver functions in cases of progressive liver disease, varicose lesions, and thrombocytopenia)



There is an imbalance between thrombosis and bleeding

Prolonged PT and activated partial thromboplastin time (aPTT)




Hepatic Synthetic Dysfunction
Anticoagulant proteins
Procoagulant proteins
ADAMTS13
Thrombopoetin
Dysfibrinogenemia
Necrotic liver tissue stimulates cytokine release
Endotoxemia
Systemic inflammation
Endothelial activation
Increased production of:
elevated VWF stablizes FVIII
FVIII
TPA
VWF
Hepatic clearance
FVII
VWF
TPA
Splenic congestion
Platelet sequestration
Hypersplenism
Platelet destruction
Additional potential etiologies of thrombocytopenia in cirrhosis include immune-mediated destruction, bone marrow suppression, and consumption.
Thrombosis
Increased intrahepatic vascular resistance
Reduced venous flow velocity, venous stasis
Bleeding
Thrombotic Sequella
- Splanchnic venous thrombosis
- Systemic venous thromboembolism (DVT and PE)
- Accelerated hepatic fibrosis
stellate cell activation (via PAR receptor)
Hepatic fibrosis
thrombin
Bleeding Sequella
- Variceal bleeding
- Hematomas / purpura
- Epistaxis
- Procedural bleeding

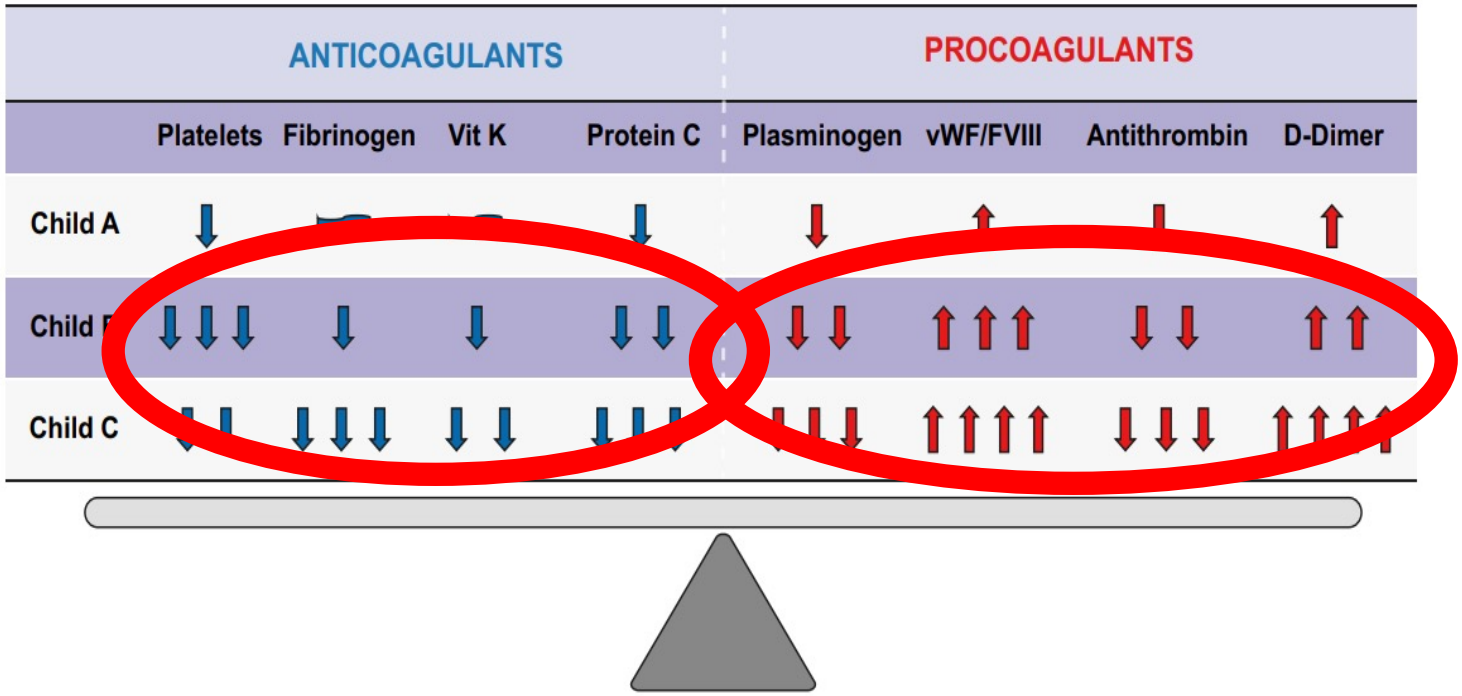
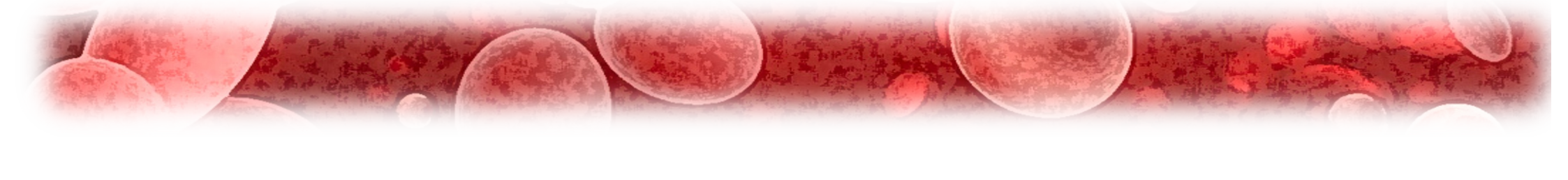


Fig. 1. Haemostatic balance in cirrhotic patients in different Child-Pugh classes. Modifications of pro- and anti-coagulants factors during progression of chronic liver disease.

JHEP Reports 2019

DOACs are currently recommended as a first-line treatment in the management of atrial fibrillation or VTE in the guidelines



Liver disease could influence several aspects of DOAC pharmacokinetics, including systemic elimination, plasma protein binding, cytochrome P450 mediated metabolism, biliary excretion, and also comorbidities such as renal insufficiency

	Hepatic Metabolization (%)	Renal Excretion (%)
Warfarin	100%	0
Apixaban	75%	25%
Rivaroxaban	65%	35%
Edoxaban	50%	50%
Dabigatran	20%	80%

Each DOAC has a different hepatic excretion rate (20 percent for dabigatran, 65 percent for rivaroxaban, 50 percent for edoxaban, and 75 percent for apixaban), but warfarin has a 100 percent hepatic excretion rate, implying more predictable pharmacokinetics for DOACs in liver cirrhosis

- ✓ The administration of DOAC in patients with liver disease is complicated because of the lack of evidence;
- ✓ Unfortunately, patients with liver disease have been systematically excluded from clinical trials.

- ✓In the ROCKET AF trial, for rivaroxaban, the exclusion criteria (indicators) were acute or chronic hepatitis, liver cirrhosis, an ALT > 3x upper limit of normal (ULN), or a level of hemoglobin < 10 g/dL.
- ✓ In the ARISTOTLE trial, for apixaban, the exclusion criteria conditions were AST or ALT 2x ULN or total bilirubin > 1.5x ULN, hemoglobin < 9 g/dL, or thrombocytopenia < 100.000/mm3.
- ✓ In the RE-LY trial, dabigatran was ruled out with persistently high levels of ALT or AST, the presence of hepatitisA, B, or C, anemia (hemoglobin < 10 g/dL), or thrombocytopenia < 100.000/mm3
- ✓In the ENGAGE AF-TIMI 48 trial, when ALT or AST > 2x UL or total bilirubin > 1.5 UL, anemia (hemoglobin under 10 g/dL), or thrombocytopenia (100.000/m3), **precaution is recommended for edoxaban**

Table 1. Oral anticoagulant options related to Child–Pugh classes. Green: no dosage reduction needed, yellow: careful usage, red: contraindication.

	AVKs	DOACs
Child–Pugh A	Warfarin	Dabigatran, Rivaroxaban, Apixaban, Edoxaban, Betrixaban
Child–Pugh B	Warfarin	Dabigatran, Apixaban, Edoxaban
Child–Pugh C	Warfarin	Dabigatran, Rivaroxaban, Apixaban, Edoxaban, Betrixaban

	Warfarin	DOAC	
Study	bleeding/no bleeding	bleeding/no bleeding	OR (95% C.I.)
Goriacko et al.	25/133	10/65	1.22 (0.55, 2.70)
Pastori et al.	11/66	1/51	8.50 (1.06, 68.00)
Serper et al.	83/527	12/189	2.48 (1.32, 4.65)
Summary			2.13 (1.00, 4.54)

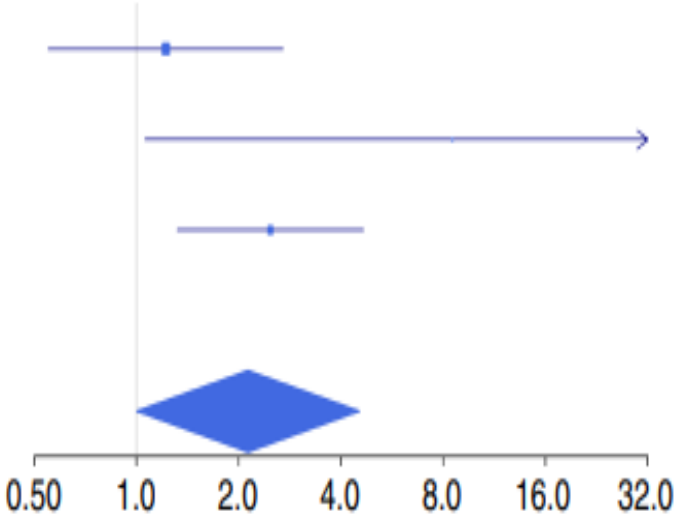


FIGURE 2 Meta-analysis of warfarin versus DOAC for atrial fibrillation

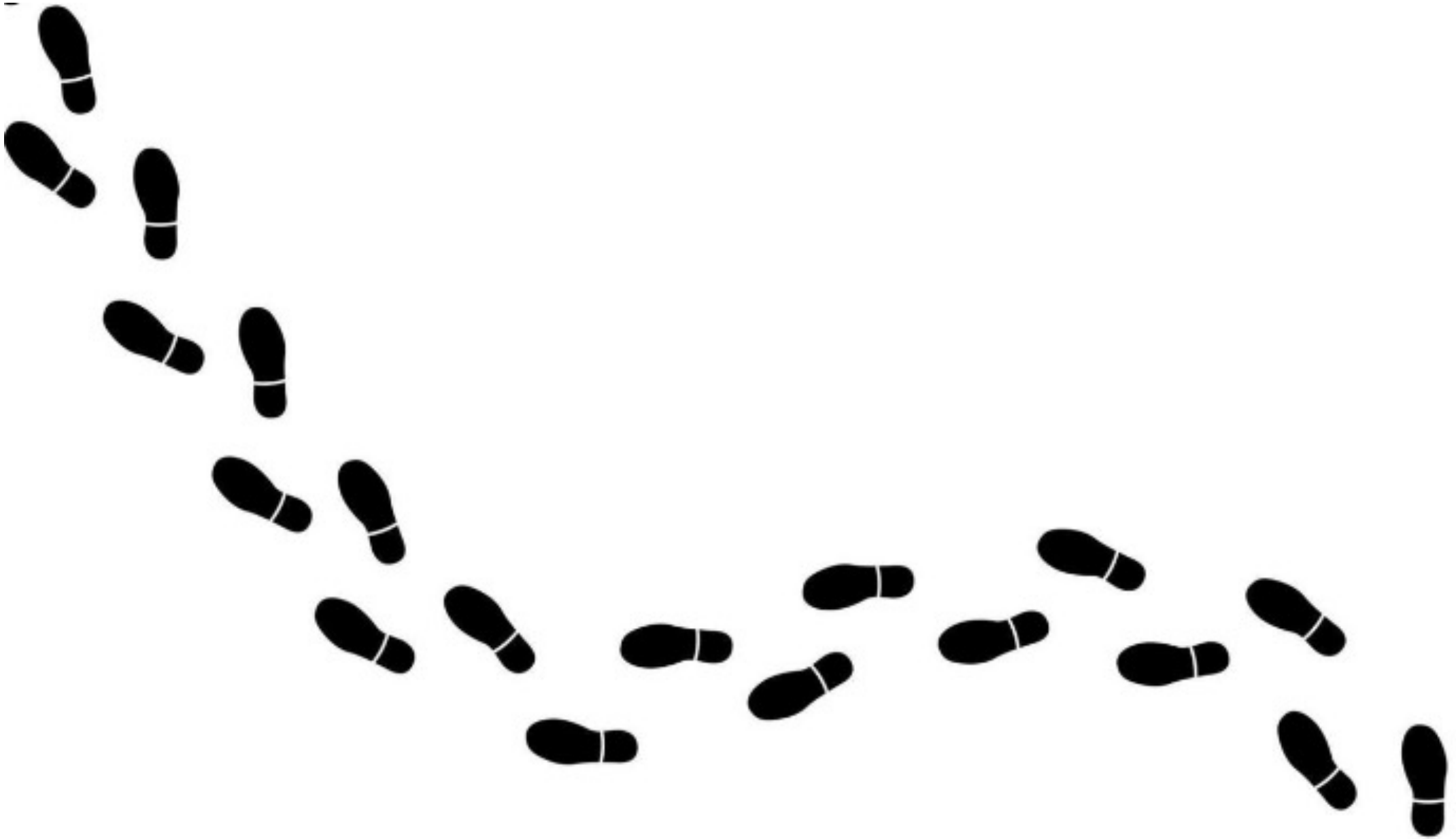
Aliment Pharmacol Ther. 2023

- ✓Accumulating real world data suggest that, compared to warfarin, DOACs have similar efficacy and reduced bleeding complications in cirrhotic patients with AF or VTE
- ✓RCTs evaluating efficacy, safety and possible dose adaptation rules in patients with cirrhosis are needed

Ballestri et al, Adv Ther (2020)

Direct-acting anticoagulants, such as the factor Xa and thrombin inhibitors, are relatively safe and effective in stable cirrhotic patients, but are in need of further study in patients with more advanced liver disease

AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW
Gastroenterology 2019



A Practical Approach to the Prescription of OAC

- ✓Indication to anticoagulation should be based on currently available general guidelines for AF and VTE, given the lack of specific guideline recommendations and evidence from RCTs in cirrhotic patients
- ✓Before starting OACs, all patients with or at risk of liver disease might have their liver function tests, platelet levels, serum creatinine, and coagulation profile evaluated, and the results should be monitored during therapy.
- ✓Before administering OACs, all at-risk patients must be examined for varices and high-risk abnormalities.
- ✓Before starting OAC, all individuals with liver disease should be evaluated for alcohol abuse and, if necessary, they should be provided with cessation therapy

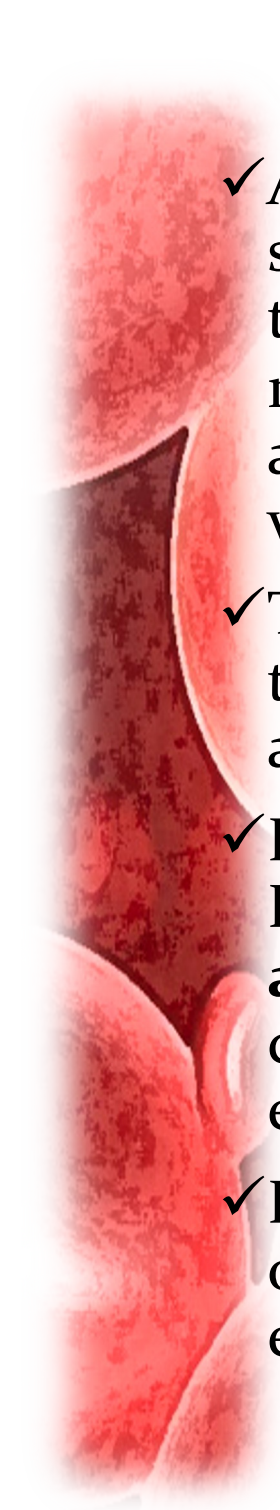
- ✓In the context of significant thrombocytopenia (platelet count levels between 50,000 and 70,000/mm3), anticoagulation medication should be postponed, based on the patient's thrombotic risk
- ✓Patients with a significant recent bleeding event, persistent coagulopathy, or clinically significant hemorrhagic risk (including high-risk esophageal varices) should be given personalized anticoagulant therapy.

- ✓Even though warfarin has generally been the therapeutic option for most patients with hepatic impairment who need OACs
- ✓DOACs (without dosage adjustment) might be a safe option in certain individuals with minimal hepatic impairment (Child–Pugh A).
- ✓In patients with serious hepatic impairment, warfarin seems to be the only OAC that is advised (Child–Pugh C).
- ✓When warfarin is not an option, apixaban, dabigatran, or edoxaban may be cautiously administered in individuals with mild hepatic impairment (Child–Pugh B).

- ✓INR is a less accurate monitoring indicator in hepatic dysfunction due to metabolic alterations in coagulation factors synthesis.
- ✓INR does not appear to be a reliable tool to monitor haemostasis in cirrhotic patients because it only measures the activity of some procoagulants factors (FI, FII, FV, FVII and FX), but not that of anticoagulant proteins C/S .
- ✓Despite being hypercoagulable, cirrhotic individuals have elevated serum INRs, which could lead to a misleading identification of therapeutic warfarin anticoagulation despite sub-therapeutic dosages

Specific clotting tests (e.g. thromboelastography) may overcome the diagnostic limits of INR but lack validated target levels and are not routinely used

Treatment of PVT?



- ✓Although recanalization of the portal axis has been observed to occur spontaneously in some patients with cirrhosis who develop PVT, there are studies that show anticoagulation improves the recanalization rate (42% of patients with anticoagulation therapy alone and 13% of patients who did not receive anticoagulation or vascular intervention).
- ✓The AGA suggests using anticoagulation over no anticoagulation for the treatment of PVT, citing a lack of data supporting one anticoagulant over another
- ✓In clinical practice, the European Association for the Study of the Liver (EASL) guidelines recommend **LMWH treatment at weight-adjusted dose for the treatment of acute PVT** in patients with cirrhosis. LMWH is preferred over unfractionated heparin (UFH), except in patients with severe renal impairment
- ✓Long-term anticoagulation therapy with VKAs should be proposed only after a careful evaluation of risks and benefits, and should be re-evaluated at regular time intervals

Treatment of PVT

- ✓DOACs have a similar or better bleeding profiles compared to VKA, although they should not be used in severe hepatic impairment

- ✓There are limited data on DOACs for treatment of PVT in patients with cirrhosis.
- ✓Case reports and small retrospective studies suggest that DOACs are safe in patients with mild or moderate cirrhosis.
- ✓Recently Hanafy et al. reported a clinical trial comparing low doses of rivaroxaban (10 mg twice daily) vs. warfarin in 80 patients with cirrhosis (Child-Pugh class A or B) who had developed acute PVT.
- ✓Recanalization of the portal vein was obtained in 85% of patients treated with rivaroxaban, and only 45% of patients treated with warfarin.
- ✓No bleeding complications were observed in the rivaroxaban group.

Screening for PVT?

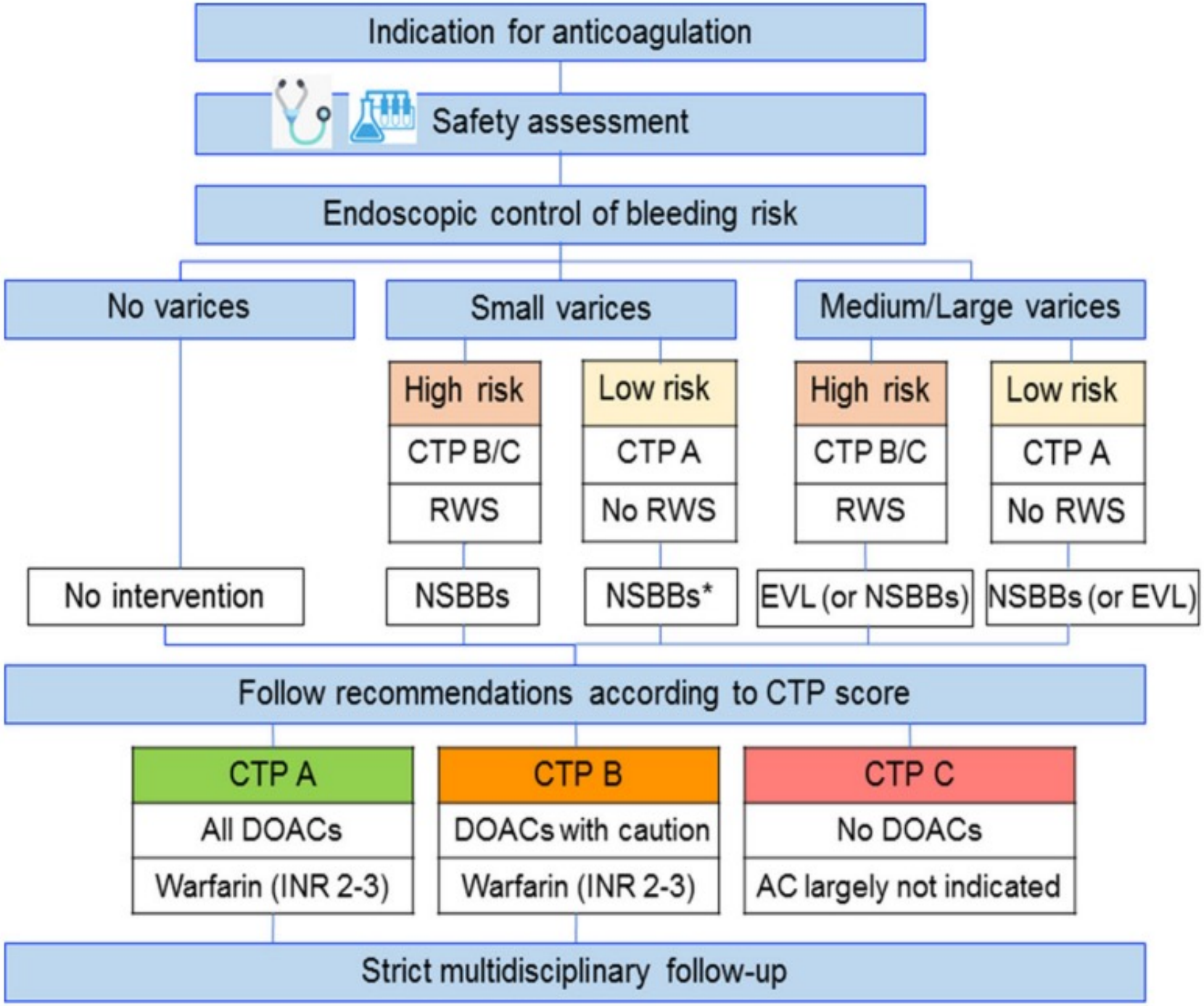
The American Gastroenterological Association Institute (AGA) suggests against PVT routine screening in cirrhotic patients, except for candidates for liver transplantation

And prophylaxis?

AGA suggests standard anticoagulation prophylaxis in patients with cirrhosis and who otherwise meet standard guidelines for the use of VTE prophylaxis over no anticoagulation .

- ✓Anticoagulant therapy should not be used in patients with Child–Pugh Class C, which has a 1-year survival rate of less than 50% without a liver transplant.
- ✓Patients with portal hypertension, esophageal varices, portal-hypertensive gastropathy, thrombocytopenia, coagulopathy, bleeding risk, decreased drug metabolism, and reduced glomerular filtration rate should be investigated

A


Indication for anticoagulation
Safety assessment
Endoscopic control of bleeding risk
No varices
Small varices
Medium/Large varices
High risk
CTP B/C
RWS
Low risk
CTP A
No RWS
High risk
CTP B/C
RWS
Low risk
CTP A
No RWS
No intervention
NSBBs
NSBBs*
EVL (or NSBBs)
NSBBs (or EVL)
Follow recommendations according to CTP score
CTP A
All DOACs
Warfarin (INR 2-3)
CTP B
DOACs with caution
Warfarin (INR 2-3)
CTP C
No DOACs
AC largely not indicated
Strict multidisciplinary follow-up

Antiaggregant therapy

- ✓Limited data is available on aspirin, but it is likely safe to use in mild and moderate hepatic impairment. Weigh risks and benefits in patients with severe hepatic impairment.
- ✓Consider AP agents on a case-by-case basis in patients with severe thrombocytopenia with platelet counts of < 50000.
- ✓For P2Y12 antagonists, all are likely safe to use in patients with mild and moderate hepatic impairment, although data are limited. These agents should be avoided in severe hepatic impairment

Aliment Pharmacol Ther. 2023

Dual antiplatelet therapy in patients with cirrhosis and acute myocardial infarction – A 13-year nationwide cohort study

- A total of 150,887 patients with AMI retrieved. After exclusion criteria and propensity scorematching, 914 cirrhotic and 3,656 non-cirrhotic patients with AMI on DAPT were studied
- During 1-year follow-up, there was significantly increased mortality in cirrhotic patients compared to non-cirrhotic patients
- There was significantly decreased recurrent MI in cirrhotic patients compared to non-cirrhotic patients.
- However, non-significantly increased major bleeding and significantly increased gastrointestinal bleeding
- In cirrhotic patients with AMI, DAPT offers benefit with decreased recurrent MI at the expense of increased gastrointestinal bleeding

Chien-Chia Wu,*Plos One 2019*

- ✓This is the largest study to date to directly compare the clinical outcomes of DAPT in cirrhotic patients with AMI and non-cirrhotic patients with AMI, which showed DAPT had significant benefit in preventing recurrent MI in cirrhotic patients with AMI compared to non-cirrhotic patient with AMI
- ✓ This is the first study to compare the clinical outcomes DAPT and SAPT in cirrhotic patients with AMI, which showed similar protection of DAPT and SAPT in recurrent MI, major bleeding, and gastrointestinal bleeding in physician directed treatment

Antiplatelets May Prevent Hepatic Fibrosis in Patients at Risk for Chronic Liver Disease

Results showed that among patients at risk for chronic liver disease, the likelihood of hepatic fibrosis was reduced by 32% in patients who received antiplatelet agents


*Take
home message

- ✓Anticoagulation should be interrupted/reduced in the presence of severe thrombocytopenia (platelet count \50 x 10^9 /L to \ 70 x 10^9 /L) depending on the thrombotic risk of the patient.
- ✓ INR 1.8 and/or platelet count 50 x 10^9 /L has been defined as significant coagulopathy in cirrhotic
- ✓The target **INR is usually maintained at 2-3**
- ✓Upper endoscopy should be performed in all cirrhotic patients to screen for oesophageal varices in order to reduce the bleeding risk before starting any type of anticoagulant