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Liver coagulopathy and treatment of bleeding and thrombosis in patients with liver disease

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Disclosure belangen spreker – Ton Lisman, Karina Meijer	
Nederlands Trombose Congres – 16 mei 2025	
(potentiële) Belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	geen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk:	Ton: geen Karina: speaker fees from Alexion, participation in trial steering committees for Bayer and Astra Zeneca, consulting fees from Therini, participation in data monitoring and endpoint adjudication committee for Octapharma

Ms A

- Liver cirrhosis Child-Pugh B
  - INR 2.1, aPTT 31, fibrinogen 2.5, platelets 90
- Scheduled for radiological punction of suspicious lesion, in workup for liver transplant
- ‘How much Cofact?’

2 Minute Medicine®	Child-Pugh Score		2minutemedicine.com
Factor	**1 point**	**2 points**	**3 points**
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	**Class B**	**Class C**
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

Table I. Child-Pugh score.

How to handle?

1. Comply with radiologist
2. Consider plasma, consider TPO agonist
3. ‘Do as much nothing as possible’

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Importance of the liver in hemostasis

Synthesis of

- Coagulation factors
- Fibrinolytic proteins
- Thrombopoietin

Hemostatic alterations in liver disease

- Thrombocytopenia and platelet function defects
- Low levels of coagulation proteins & inhibitors
- Low levels of fibrinolytic proteins
- High VWF, FVIII, tPA, PAI-1

Hemostatic alterations in liver disease

Consequences for labvalues

- Low platelet count
- Prolonged PT, APTT

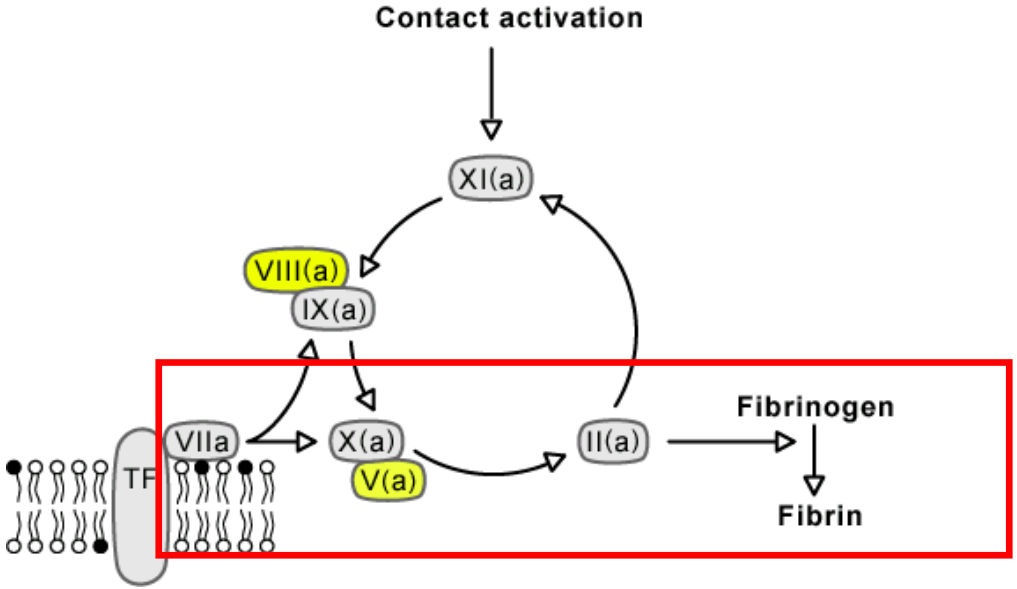
Hemostatic alterations in liver disease

- Low platelet count
- Prolonged PT, APTT

Bleeding?

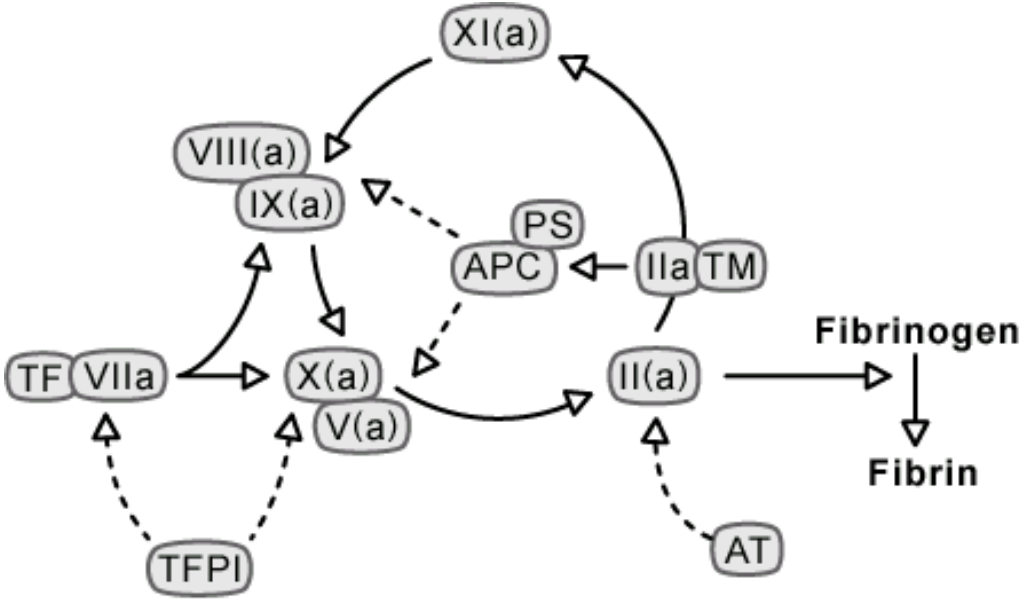
Caveats of routine diagnostic tests of hemostasis

Prothrombin time is only sensitive for VII, X, V, II, fg

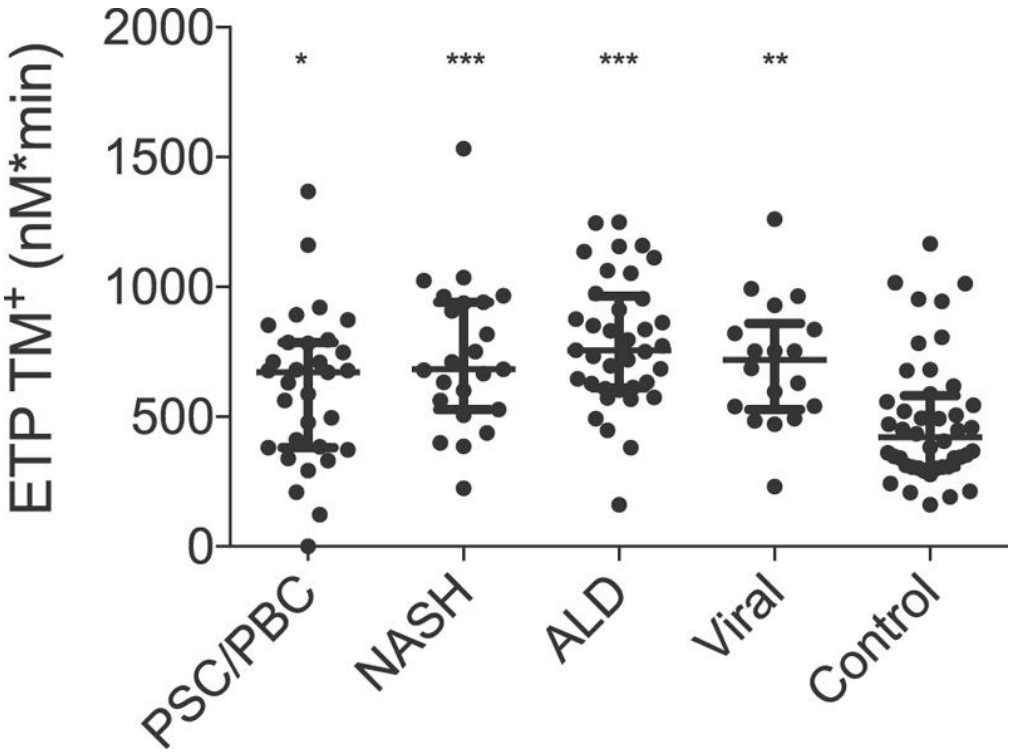


Prothrombin time is insensitive for natural anticoagulants (AT, TFPI, PC/PS)

No protein C activation during TF-induced coagulation in plasma due to absence of thrombomodulin

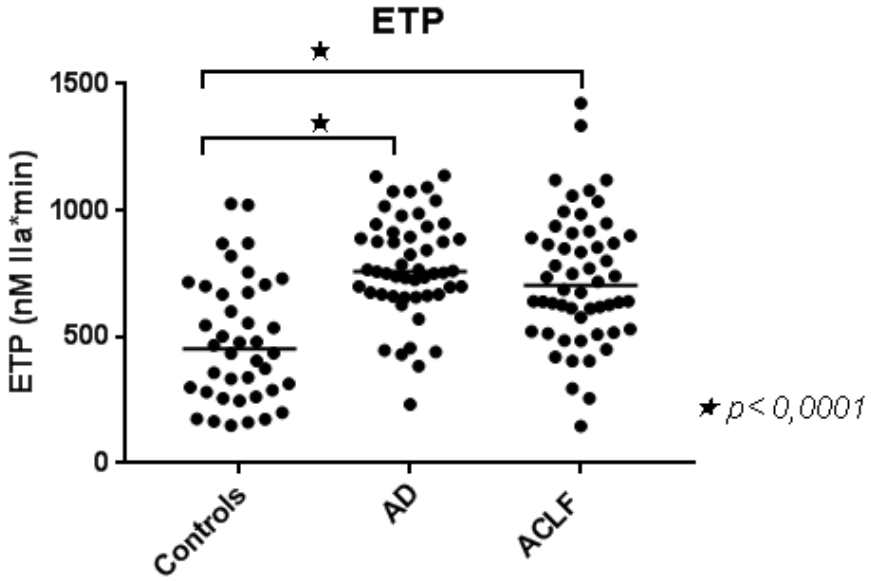


Thrombomodulin-modified thrombin generation testing identifies hypercoagulability in mild cirrhosis



Thromb Haemost 2019;119:246

Critically ill patients with cirrhosis are *hyper*coagulable according to thrombin generation tests



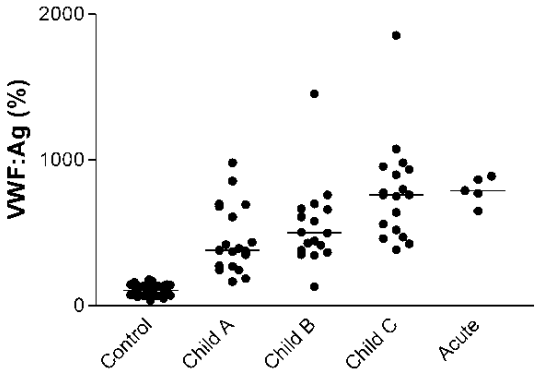
Liver Int. 2022 Feb;42(2):435-443

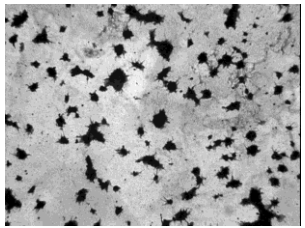
A VWF/ADAMTS13 unbalance in patients with liver disease

- Thrombocytopenia is common

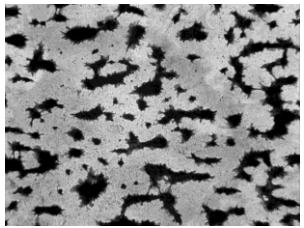
- VWF is substantially elevated and compensates in part for the low platelet count

- ADAMTS13 may be low



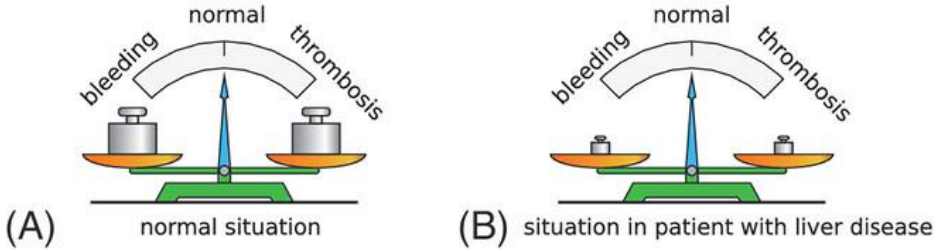


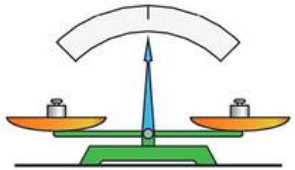
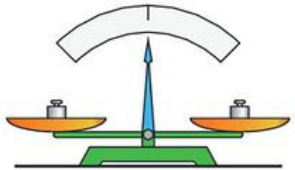
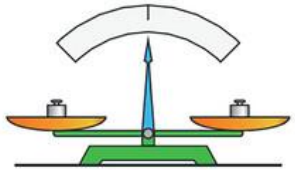
Control



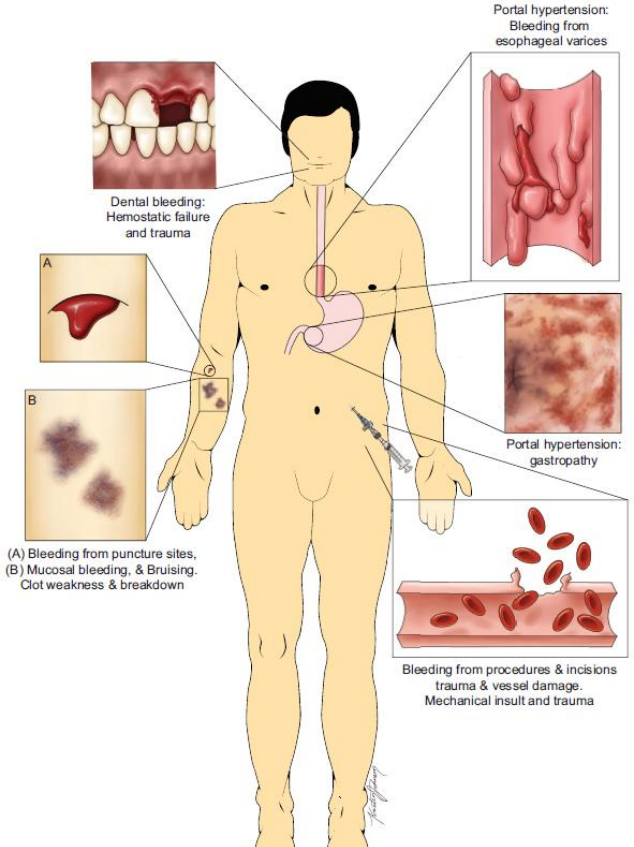
Patient

Hepatology. 2006; 44:53-61



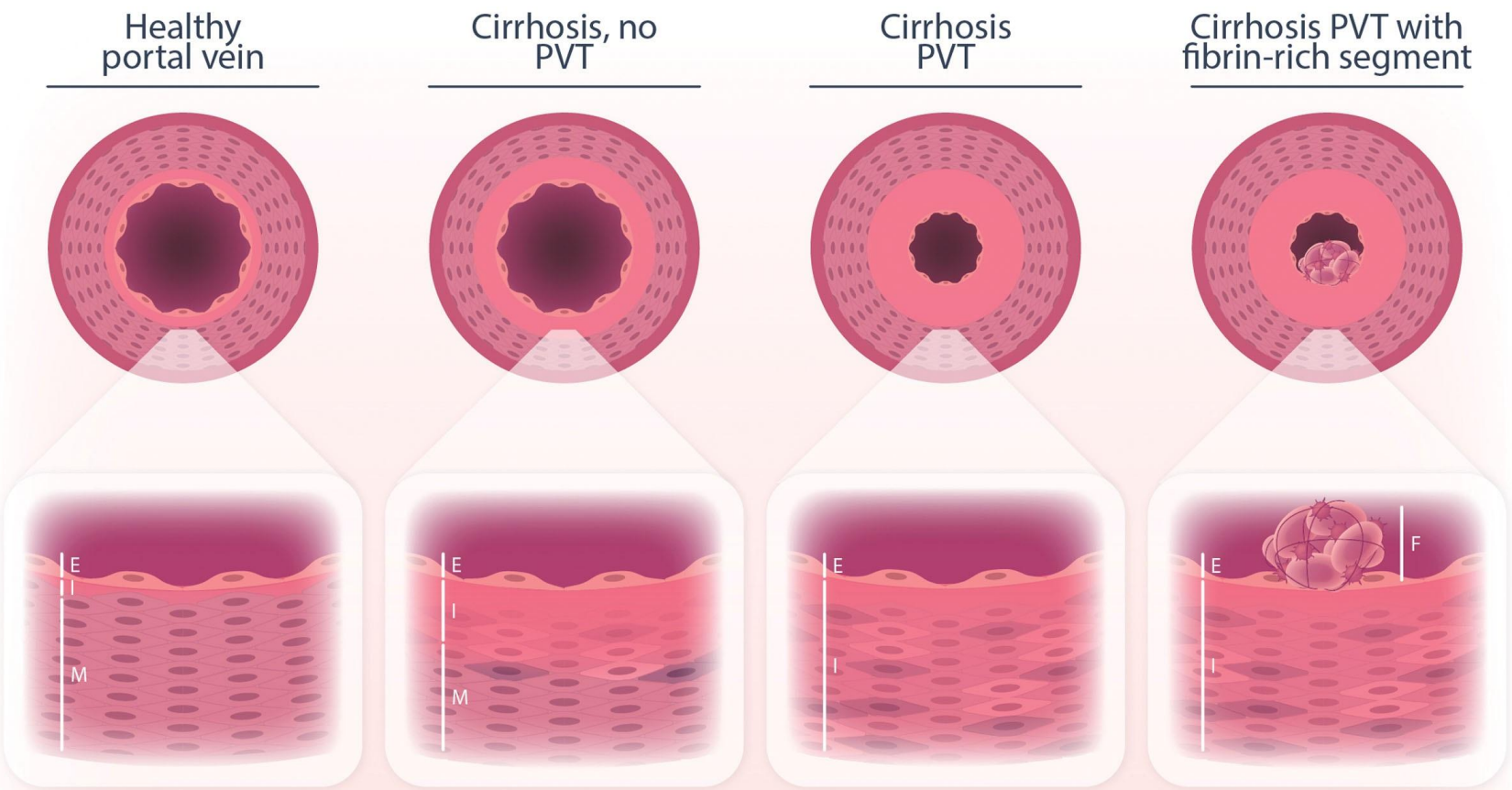
antihaemostatic changes	'rebalance'	prohaemostatic changes
- Thrombocytopaenia - Platelet function defects - Enhanced production of nitric oxide and prostacyclin	 primary haemostasis	- Elevated levels of VWF - Decreased levels of ADAMTS13 - Platelet activation by endotoxaemia
- Decreased levels of coagulation factors II, V, VII, IX, X, XI - Vitamine K deficiciency - Hypo- and dysfibrinogenaemia	 secondary haemostasis	- Elevated levels of factor VIII - Decreased levels of protein C, protein S and antithrombin - Prothrombotic fibrin clot structure
- Decreased levels of α2-antiplasmin, factor XIII and TAFI - Elevated levels of tPA	 fibrinolysis	- Decreased levels of plasminogen - Elevated levels of PAI-1

Bleeding complications in liver disease: often unrelated to hemostatic failure



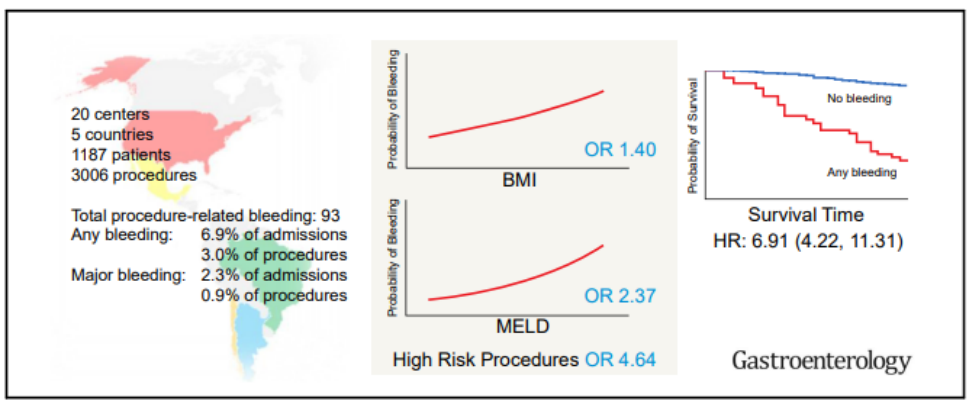
Hepatology. 2021;73(1):366-413.

Thrombotic complications in liver disease: PVT may be unrelated to hemostatic failure

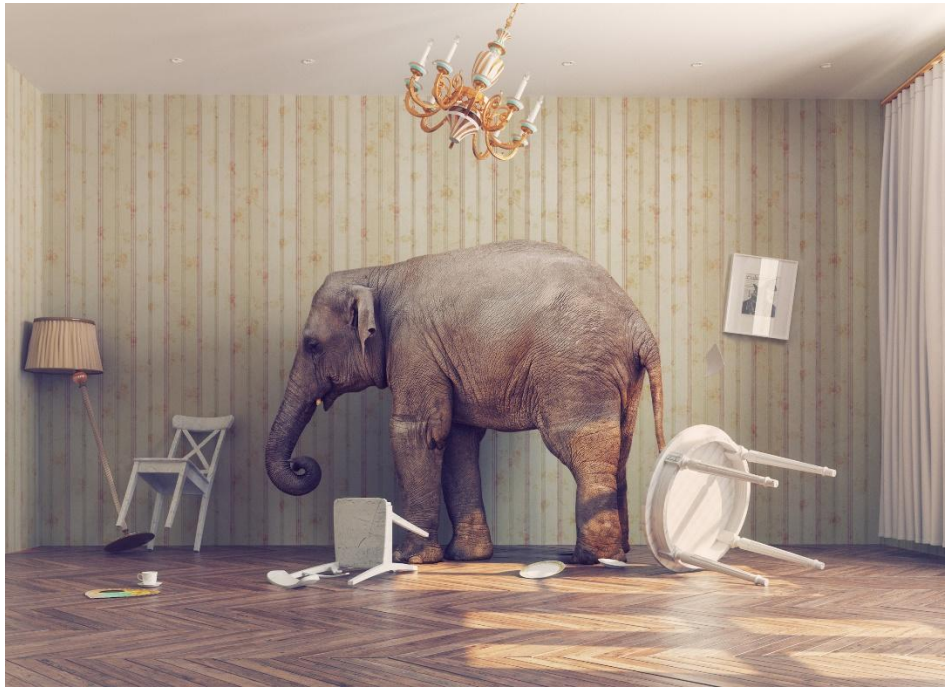


Bleeding is not – strongly - predicted by INR
but risk is higher in sicker patients

- Systematic review, OR for bleeding w ↑INR: 1.52 (0.99-2.33)
  - for ↑INR w bleeding, pooled mean difference 0.05 (-0.03-0.13)
- International cohort:



Intagliata, Gastroenterol 2023; Kovalic Aliment Pharmacol Ther 2020



Guidelines, 1/2

- AASLD
  - ……..it is reasonable to perform both low- and high-risk procedures without prophylactically correcting the platelet count.
  - Measures aimed at reducing the INR are not recommended prior to procedures in patients with cirrhosis who are not taking VKAs.
- Nederlandse richtlijn Bloedtransfusiebeleid
  - Geef geen plasma aan patiënten met coagulopathie veroorzaakt door leverinsufficiëntie/leverfalen met een INR <3,0 die een ingreep ondergaan, onafhankelijk van het bloedingsrisico van die ingreep.

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Hepatology. 2021;73(1):366-413; Richtlijnendatabase.nl

Guidelines, 2/2

- ISTH
  - We suggest PT/INR, APTT, platelet count, and fibrinogen should not be routinely evaluated to predict bleeding risk prior to procedural intervention in patients with cirrhosis, even in those who are critically ill.
  - We recommend against prophylactic correction of abnormal coagulation parameters in the periprocedural setting in the absence of vitamin K antagonist use.
  - We recommend no treatment to increase the platelet count prior to most procedures for patients with cirrhosis.

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J Thromb Haemost 2022 Jan;20(1):39-47


SON-OF-A PREACHER MAN
JUST A LITTLE LOVIN' (EARLY IN THE MORNIN')
PHILIPS
DUSTY SPRINGFIELD

Thromboprophylaxis?

Ms A, readmission

- Symptomatic portal vein thrombosis

- Does she need anticoagulation?
- What drug?
- For how long?

Anticoagulation

- Observational data: improved survival, no increased risk of bleeding, no worse outcome of variceal bleeding
- Guidelines from hepatological societies recommend treatment of acute, symptomatic portal vein thrombosis. Less clear on chronic or non-occlusive disease.
- ISTH guidance: *We recommend anticoagulation for all patients with cirrhosis with symptomatic PVT for a minimum of 6 months.*

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What drug?

- No high-quality data
- LMWH considered gold standard
  - Despite dependency on antithrombin, uncertainty about monitoring
- In Child-Pugh A or B, little data on apixaban and rivaroxaban, but consistent with safe use
- No VKA in patients with baseline ↑INR

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Duration

- No high-quality studies
- Consensus that anticoagulation should be continued in patients who are candidate for transplant
- All others, case by case

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Take to work

- Bleeding and thrombosis in cirrhosis are in part unrelated to hemostatic alterations
- INR is marker for severity of disease, but not for bleeding
- Challenge is to educate interventionalists

- Acute portal vein thrombosis requires anticoagulation, with no indication that aXa agents are inferior to LMWH
- Evidence-poor area with opinionated experts ☺

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