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Management of invasive procedures in patients with cirrhosis

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MVF CENTRE DE RÉFÉRENCE MALADIES VASCULAIRES DU FOIE

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CRI CENTRE de RECHERCHE sur l'INFLAMMATION

Conflicts of interest

- I do not have a financial relationship relevant to that presentation
- I am not discussing off-label investigative use of a drug/device/product

Invasive procedures in patients with cirrhosis

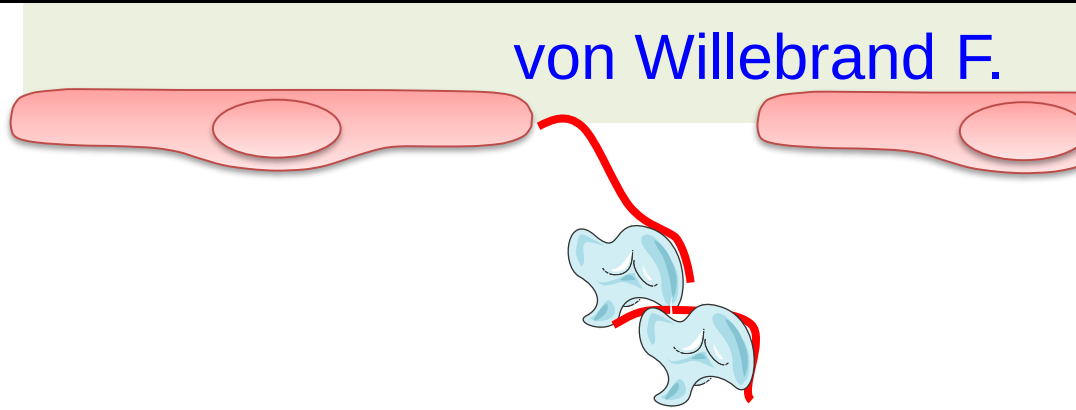
- Coagulation changes in patients with cirrhosis
- Management of invasive procedures in cirrhosis
- Anticoagulants in cirrhosis

Coagulation in cirrhosis

Primary hemostasis: platelet aggregation
Coagulation: fibrin formation
Fibrinolysis: fibrin lysis

Coagulation in cirrhosis

Primary hemostasis:
platelet aggregation



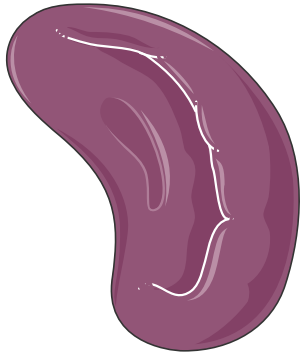
Thrombocytopenia

↑ von Willebrand F.
↑ Multimer size

Favors bleeding

Favors thrombosis

Thrombocytopenia and cirrhosis

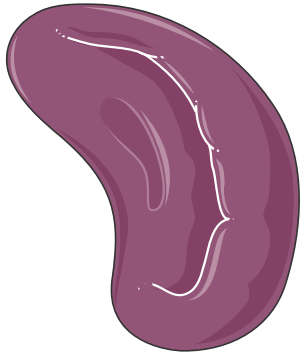


Hypersplenism

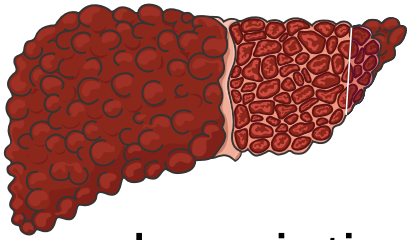
↘

Thrombocytopenia

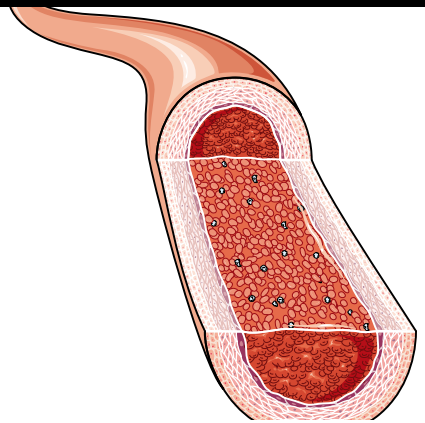
Thrombocytopenia and cirrhosis



Hypersplenism



↓ thrombopoietin



- Coagulation activation
- Anti platelet Ab

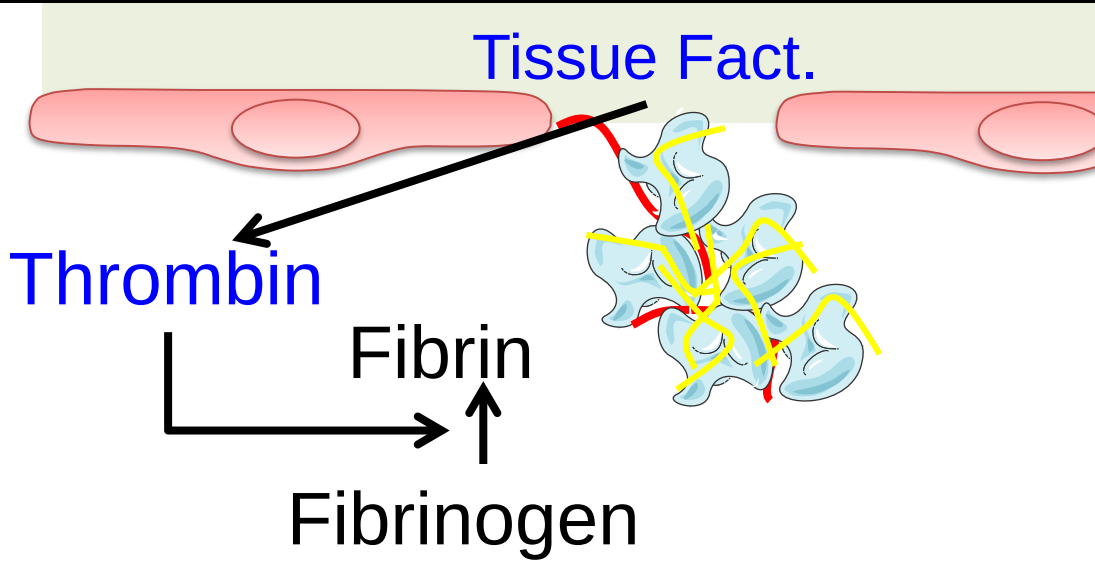
Thrombocytopenia

Alcohol and HCV toxicity

Coagulation in cirrhosis

Primary hemostasis:
platelet aggregation

Coagulation:
fibrin formation



↓ fact II, V, VII, IX, X and Fg

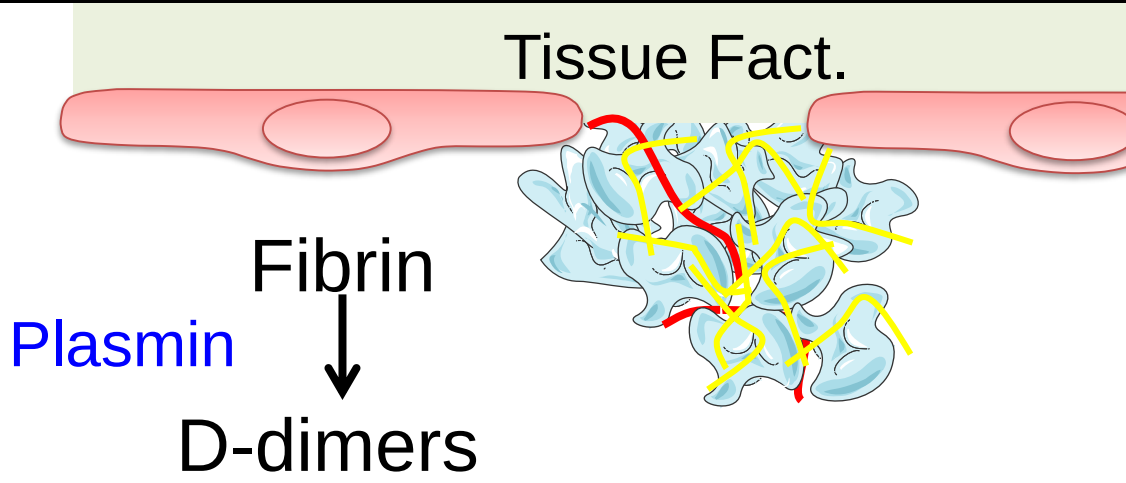
↓ AT, prot C, S,
↓ ↑ factor VIII

Favors bleeding

Favors thrombosis

Coagulation in cirrhosis

Primary hemostasis: platelet aggregation
Coagulation: fibrin formation
Fibrinolysis: fibrin lysis



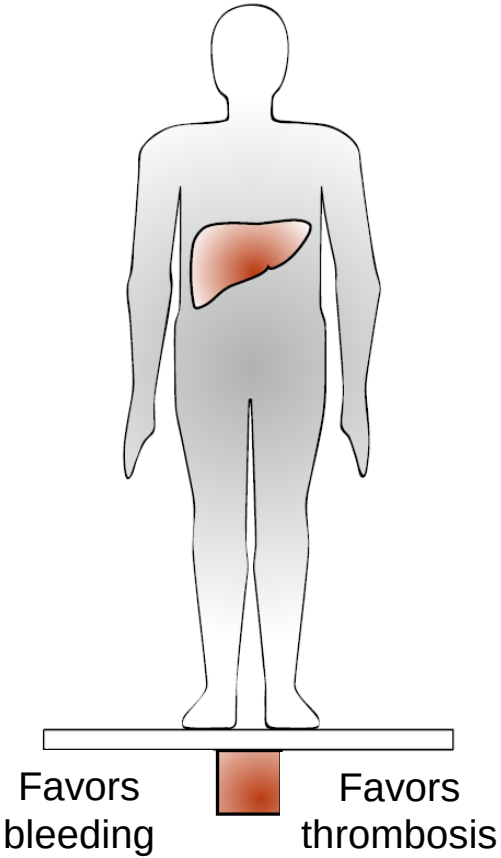
↑ tPA

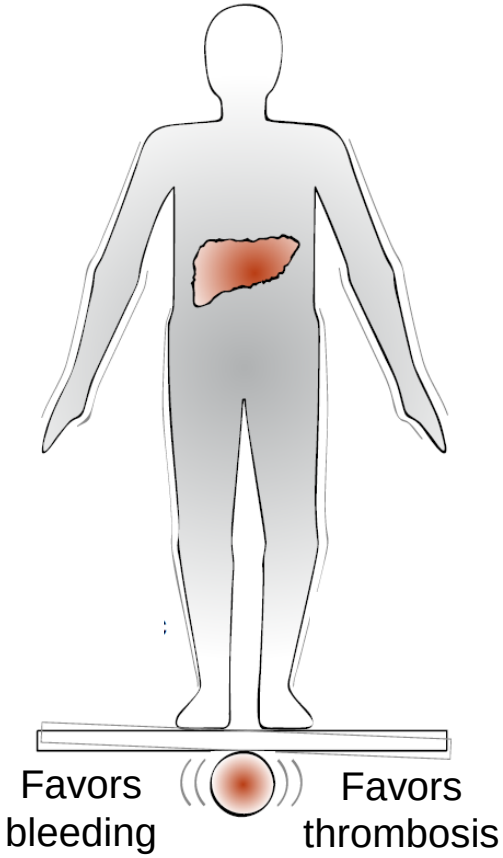
↓ plasminogen, α2 antiplasmin, ↑ PAI-1

Favors bleeding

Favors thrombosis

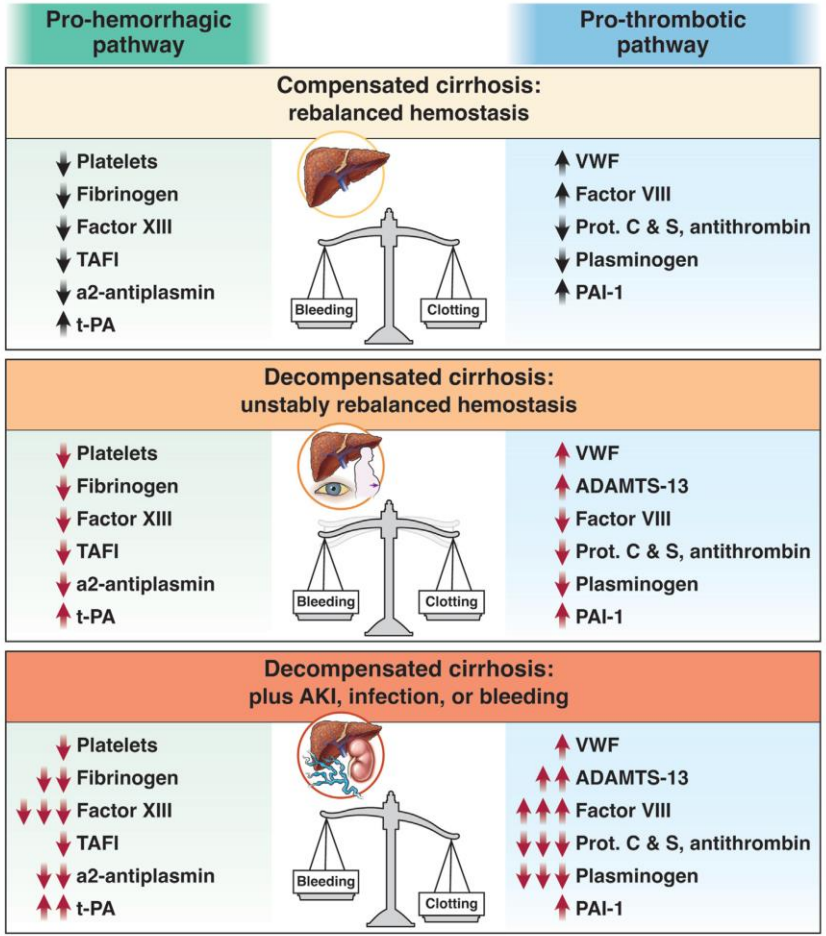
Coagulation in cirrhosis





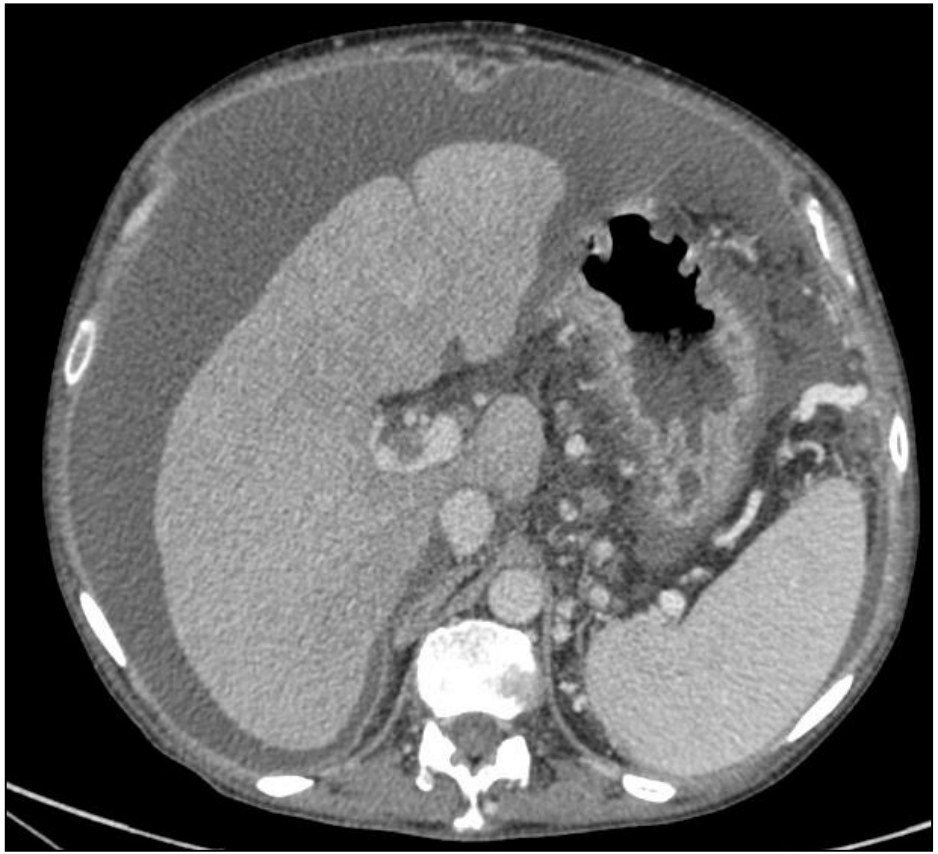
Lisman, J Hepatol 2013

Coagulation changes with cirrhosis progression



Rautou, Caldwell, Villa, CGH *2023*

Coagulation in cirrhosis



Invasive procedures in patients with cirrhosis

- Coagulation changes in patients with cirrhosis
- Management of invasive procedures in cirrhosis
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Invasive procedures in patients with cirrhosis

- The patient
- The procedure
- The laboratory

Prediction: the patient

When the procedure is scheduled

- Personal or familial history of bleeding
- Anticoagulants / antiplatelet agents

Rodeghiero, JTH 2010; Tosetto JTH, 2010; SFAR 2012

No more VKA-LMWH bridging
(for low thrombosis risk)

Randomized controlled study:
1884 patients with atrial fibrillation

	VKA-LMWH bridging n=934	**VKA-placebo bridging** n=950	**P=**
Arterial events	0.3%	0.4%	NS
Major bleeding	3.2%	1.3%	0.005

Douketis , NEJM 2015

Prediction: the procedure

Guidelines	Percutaneous liver biopsy	Transjugular liver biopsy
EASL 2022	Low	Low
ISTH 2021	High	Low
AASLD 2021	High	High

Based on same definition: threshold > 1.5%

52 experts

80 invasive procedures

Consensus for 52 procedures

High risk:
- ✓ interventional endoscopy
- ✓ percutaneous biopsies
- ✓ central nervous system

Low risk:

“Can you put the finger?”

Riescher *et al.*, JHEP Rep 2023

Prediction: the laboratory

	BSG 2020	ACG 2020	AASLD 2021	AGA 2021	ISTH 2021	EASL 2022
Platelet ≥ 50 × 10^9/L	Do not correct					
PT/INR	If INR > 1.4, transvenous	Do not correct				
aPTT	Not mentioned or do not evaluate					
Fibrinogen	No recommendation / Do not correct / Do not evaluate					
Viscoelastic tests	No specific recommendation / May be useful/ Do not use routinely					

➔ Do not correct most coagulation abnormalities

Rautou & Caldwell & Villa, CGH 2023

Prediction: the laboratory

	BSG 2020	ACG 2020	AASLD 2021	AGA 2021	ISTH 2021	EASL 2022
Platelet < 50× 10^9/L	Trans-venous	Platelet infusions or TPO rec. agonists	No correction	severe thrombo-cytopenia and high-risk procedure	very high-risk surgery and <30-50 x 10^9/L: correct	< 50 × 10^9/L + local hemostasis not possible: correction possible

➔ **Platelet < 50× 10^9/L should raise attention**

Rautou & Caldwell & Villa, CGH 2023

52 experts

80 invasive procedures

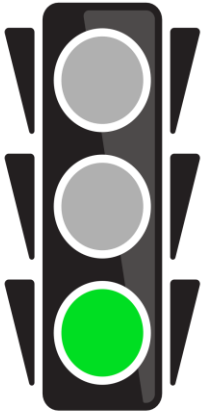
Consensus for 52 procedures

35 at low risk of bleeding

17 at high risk of bleeding

Suggested thresholds

	Low-risk procedure	High-risk procedure or surgery
Platelet count	> $30x10^9$/L	> $50x10^9$/L
INR	Do not measure	< 2 *
aPTT	Do not measure	

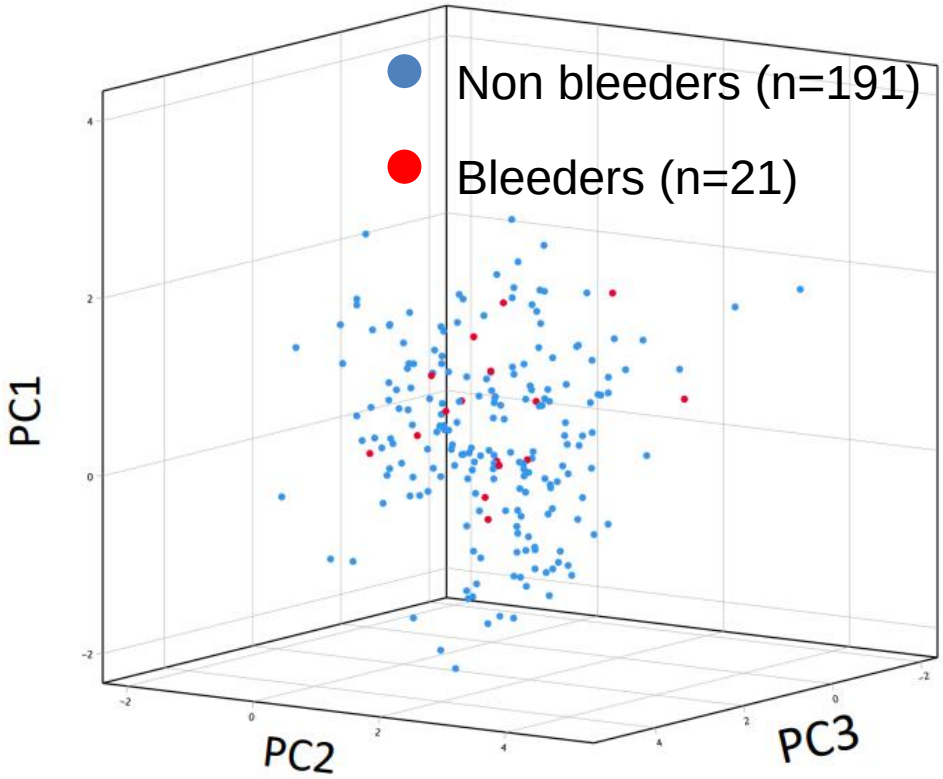


Riescher *et al.*, JHEP Rep 2023

A comprehensive work-up for hemostasis changes does not improve prediction of liver biopsy related bleeding

302 patients undergoing liver biopsy

- PT, aPTT, platelet
- Coag factors: II, V, VII, VIII
- PFA-100
- Thromboelastography (INTEM, FIBTEM)
- Thrombin generation assays
- Plasma clot lysis time



Bissonnette*, Riescher* et al, JTH 2022

Going beyond the limits: interest of thromboelastography?

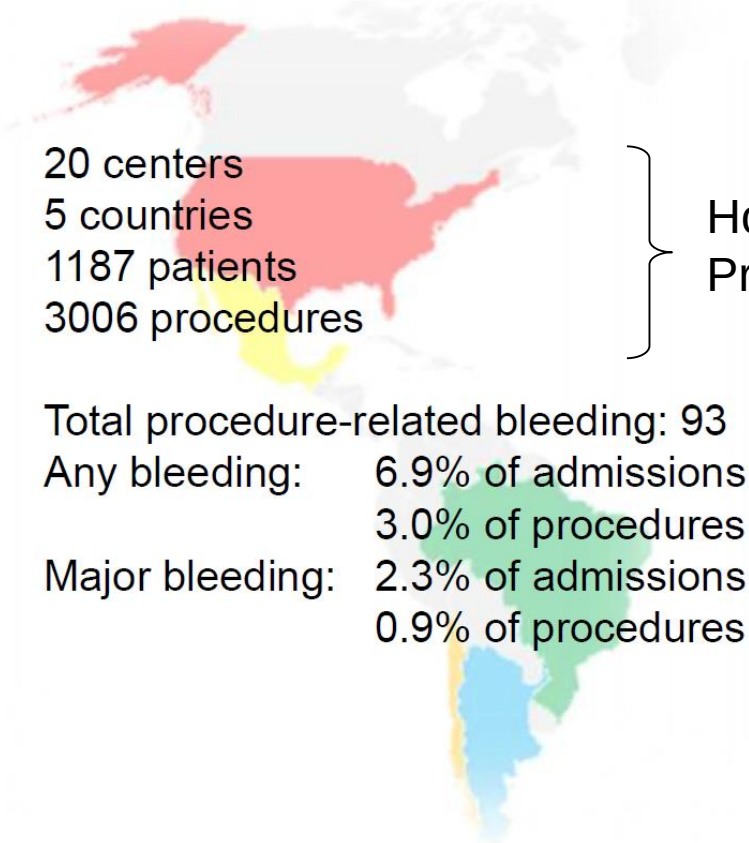
Cirrhosis; INR > 1.8 or PLT < 50’000 /mm^3

	SOC (n=30)	TEG guided (n=30)
PLT transfusion	46%	17%
FFP transfusion	66%	10%
Bleeding	3%	0%
Allergic reaction	3%	0%

SOC, standard of care

Pietri, Hepatology 2016

Predictors of bleeding in hospitalized patients with cirrhosis



20 centers
5 countries
1187 patients
3006 procedures

Hospitalized patients with cirrhosis
Prospectively enrolled

Total procedure-related bleeding: 93

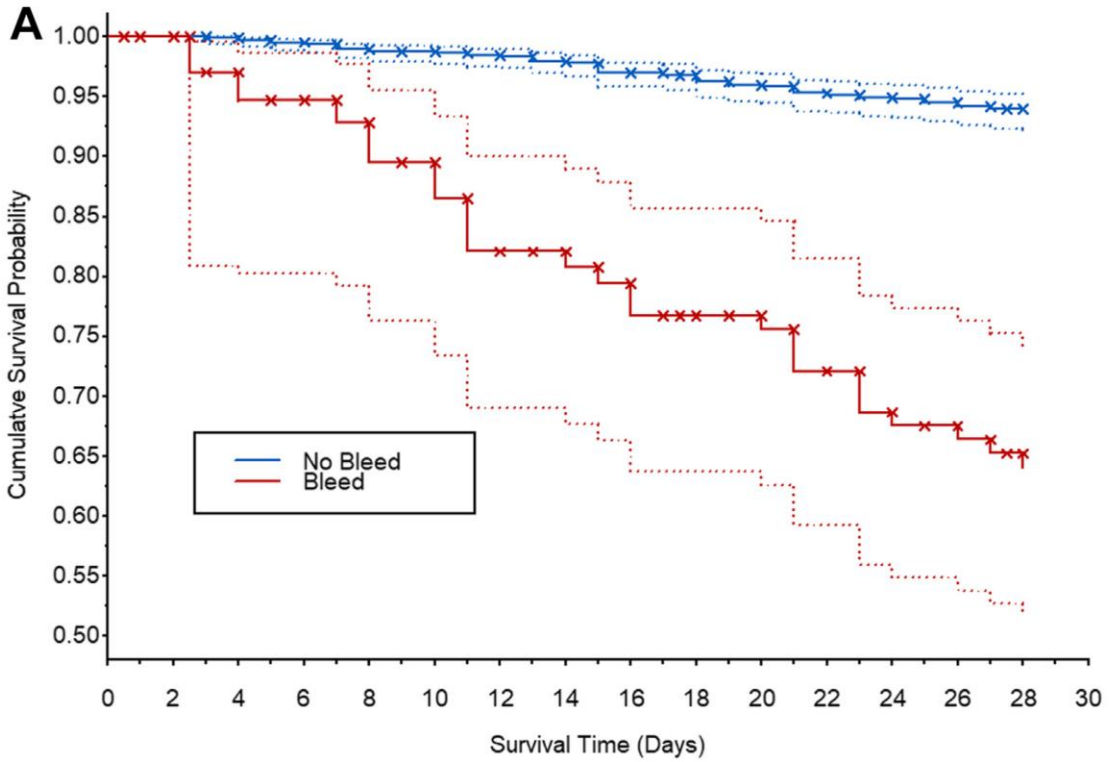
Any bleeding:	6.9% of admissions
	3.0% of procedures
Major bleeding:	2.3% of admissions
	0.9% of procedures

Intagliata, *et al.* Gastroenterology 2023

Predictors of bleeding in hospitalized patients with cirrhosis

Independent predictors of procedure related bleeding	aOR	*P* value
Procedure risk	**4.64**	**<.001**
MELD score at admission	**2.37**	**<.001**
BMI	**1.40**	**.007**
Ascites	1.31	.062
Trainee	1.56	.177
AKI present at admission	0.72	.223
INR prior to procedure	1.22	.294
Infection at admission	1.26	.337
Antithrombotic prior to procedure	1.34	.394
Platelet level prior to procedure	0.93	.635
Number of prior procedures	1.02	.657
ACLF present at admission	1.04	.776
VTE prophylaxis at admission	1.01	.972

Bleeding in hospitalized patients with cirrhosis: a poorer survival



Intagliata, *et al.* Gastroenterology 2023

Treatment of post-procedure bleeding

Local treatment +++

Treatment	Indication
Platelet transfusion	Platelet < 50’000/mm^3; Thrombopathy Antiplatelet
TPO receptor agonists	Not for acute setting
Fibrinogen concentrates	If Fg < 100 or 120 mg/dL
Fresh frozen plasma	If hemorrhagic shock
Prothrombin complex conc.	If hemorrhagic shock
Tranexamic acid	If hyperfibrinolysis
Desmopressin	No
Recombinant FVIIa	No

Rautou, Caldwell, Villa, CGH *2023*

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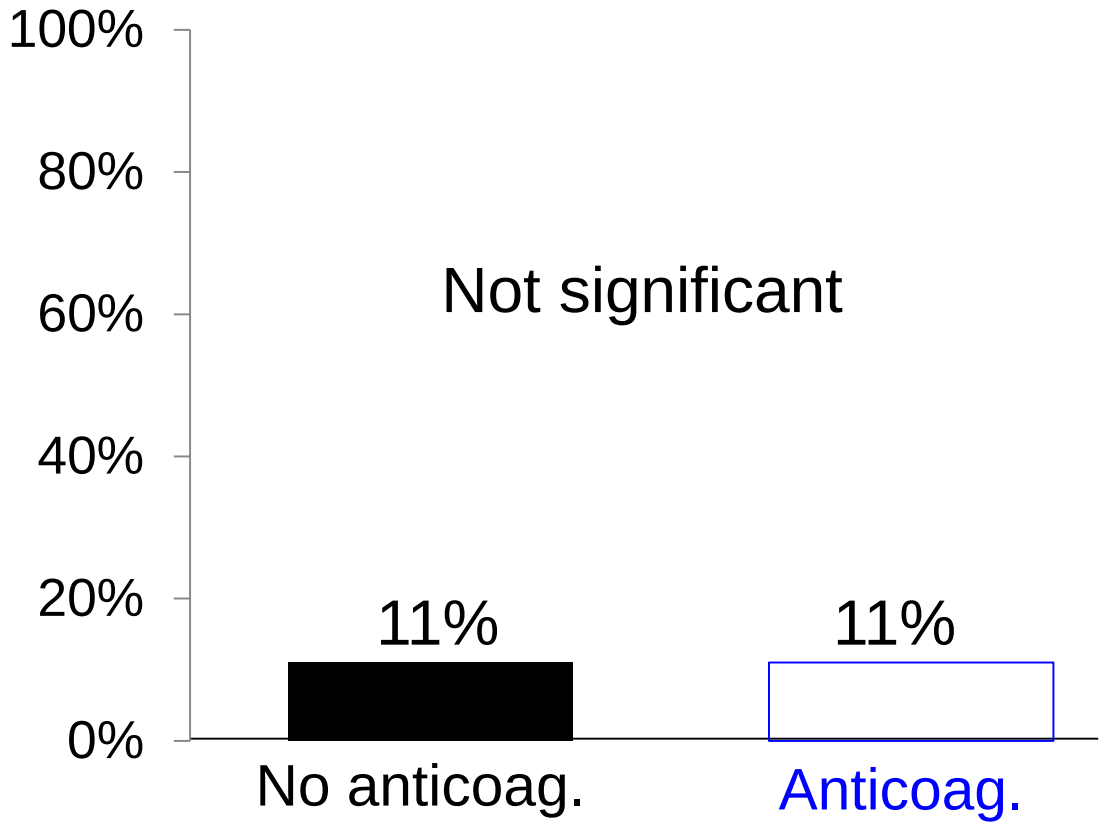
Safety of anticoagulants in cirrhosis

	LMWH/VKA	No anticoagulant
Francoz, 2005	**19**	**10**
Garcovich, 2011	15	15
Senzolo, 2012	**35**	**21**
Cai, 2013	5	6
Chung, 2014	14	14
Risso, 2014	50	20
Chen, 2015	30	36
Wang, 2016	**31**	**33**
TOTAL	**199**	**155**

Loffredo, Gastroenterology 2017

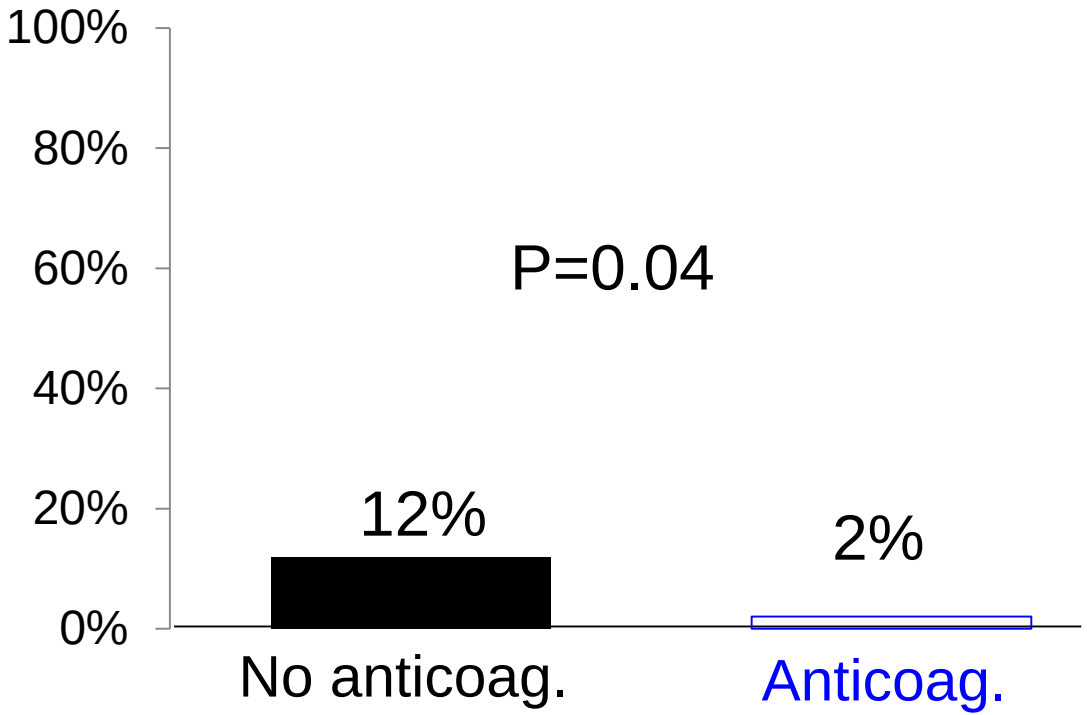
Major or minor bleedings



6 studies; 257 patients

Loffredo, Gastroenterology 2017

Portal hypertension related bleeding



4 studies; 158 patients

Loffredo, Gastroenterology 2017

What kind of anticoagulants in cirrhosis?

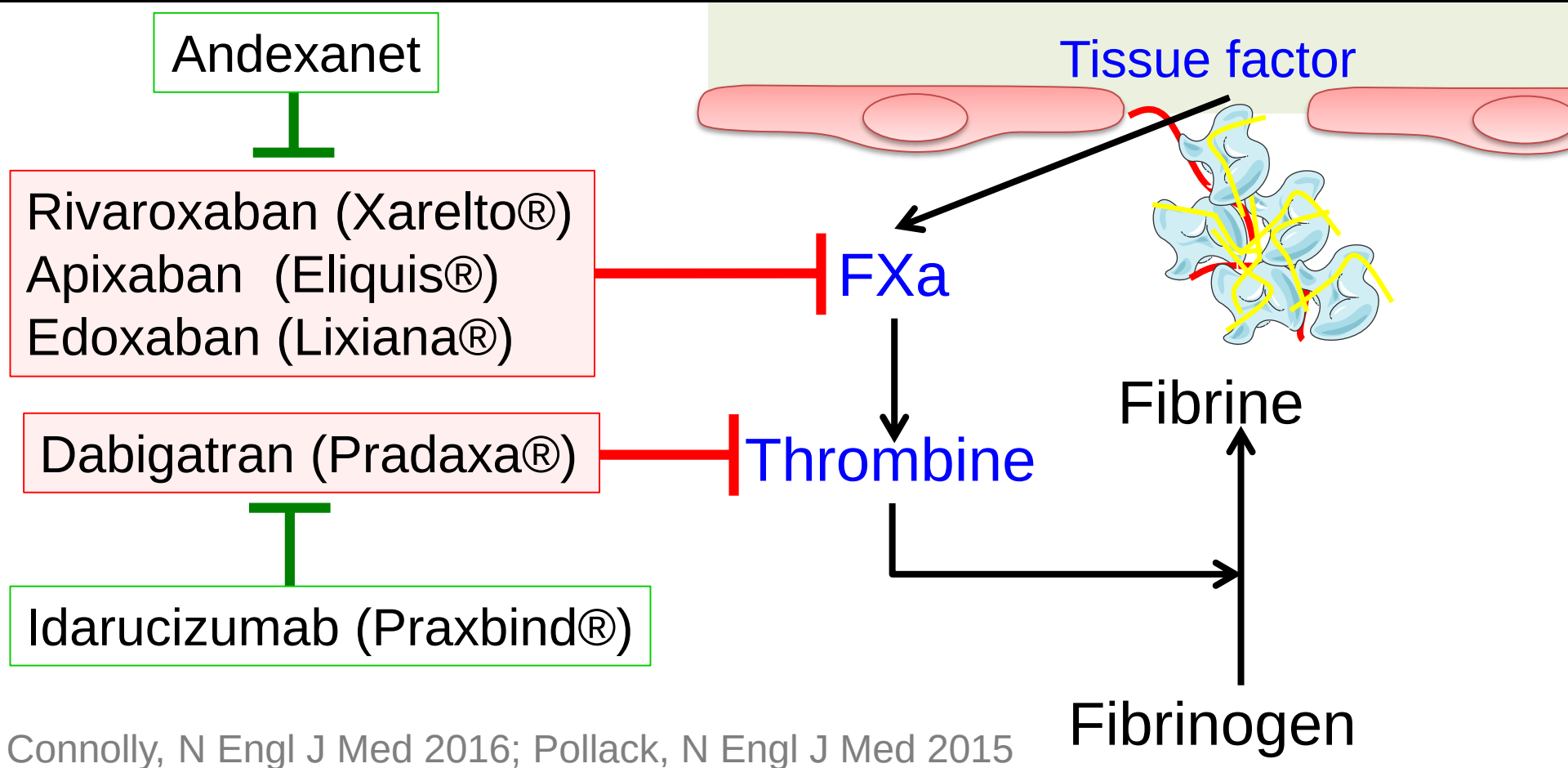
Baveno VII
Consensus Workshop
&
Pediatric Research Workshop

Start using LMWH

- LMWH — Solid data
- VKA — Challenging monitoring if INR ↑
- DOACs

De Franchis et al, J Hepatol 2022

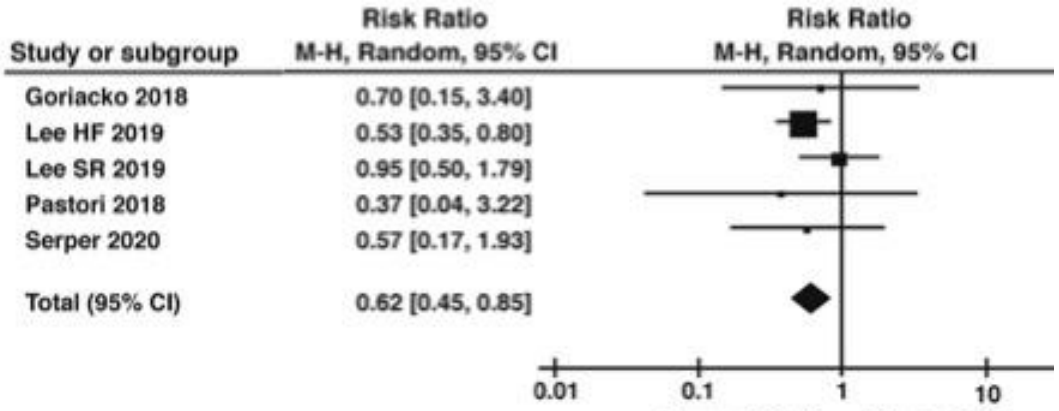
Direct oral anticoagulants (DOACs)



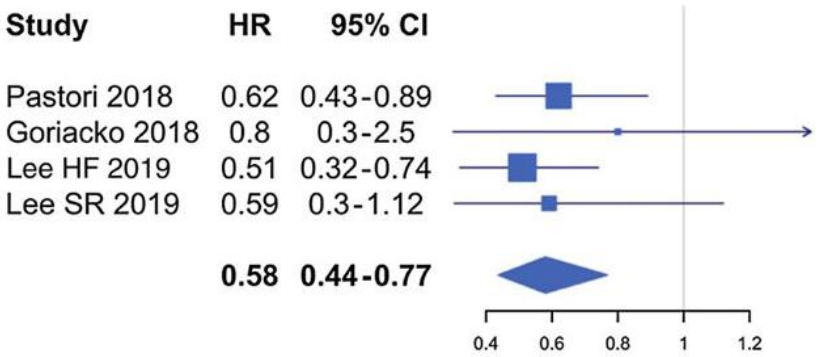
Connolly, N Engl J Med 2016; Pollack, N Engl J Med 2015

VKA *vs.* DOACs in patients with cirrhosis and **atrial fibrillation**

Major bleeding events



Favors DOACs Favors VKA



Favors DOACs

Intagliata, Gastroenterology, 2021

Violi, Hepatol Comm. 2020

VKA *vs* DOACs in patients with cirrhosis and **PVT**

References	Number of patients	Bleeding risk
Koh *et al.* 2022	N=551	DOAC = VKA
Chen *et al.*	N= 3479	DOAC = VKA
Ng *et al.* Hepatology Int 2021	N=527	DOAC = VKA
Mohan *et al*. Ann Gastr 2020	N=648	DOAC = VKA
Valeriani *et al.* Thromb H. 2021	N=1475	

Rautou & Caldwell & Villa, CGH 2023

Safety of DOACs according to cirrhosis severity

- Child A: no concern
- Child B or creatinine clearance < 30 ml/min: used with caution
- Child C: do not use

De Franchis et al, J Hepatol 2022; EASL CPG guidelines 2022 on bleeding & coagulation

Child–Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use

Steffel, Eur Heart J 2018

Conclusion #1

- **Cirrhosis:** fragile balance of haemostasis
- **Predict: be careful if**
  - ✓ platelets < 50’000/mm^3
  - ✓ “we can not put the finger”

Conclusion #2

- DOAC have a good efficacy and can be:
  - ✓ used in Child-Pugh A
  - ✓ used with caution in Child-Pugh B
  - ✓ not used in Child-Pugh C

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Team "*vessels in liver diseases*"

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