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Cirrhosis & Coagulation: Bleeding Risk From Invasive Procedures

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MVF

MALADIES VASCULAIRES DU FOIE

RÉSEAU D'EXPERTISE

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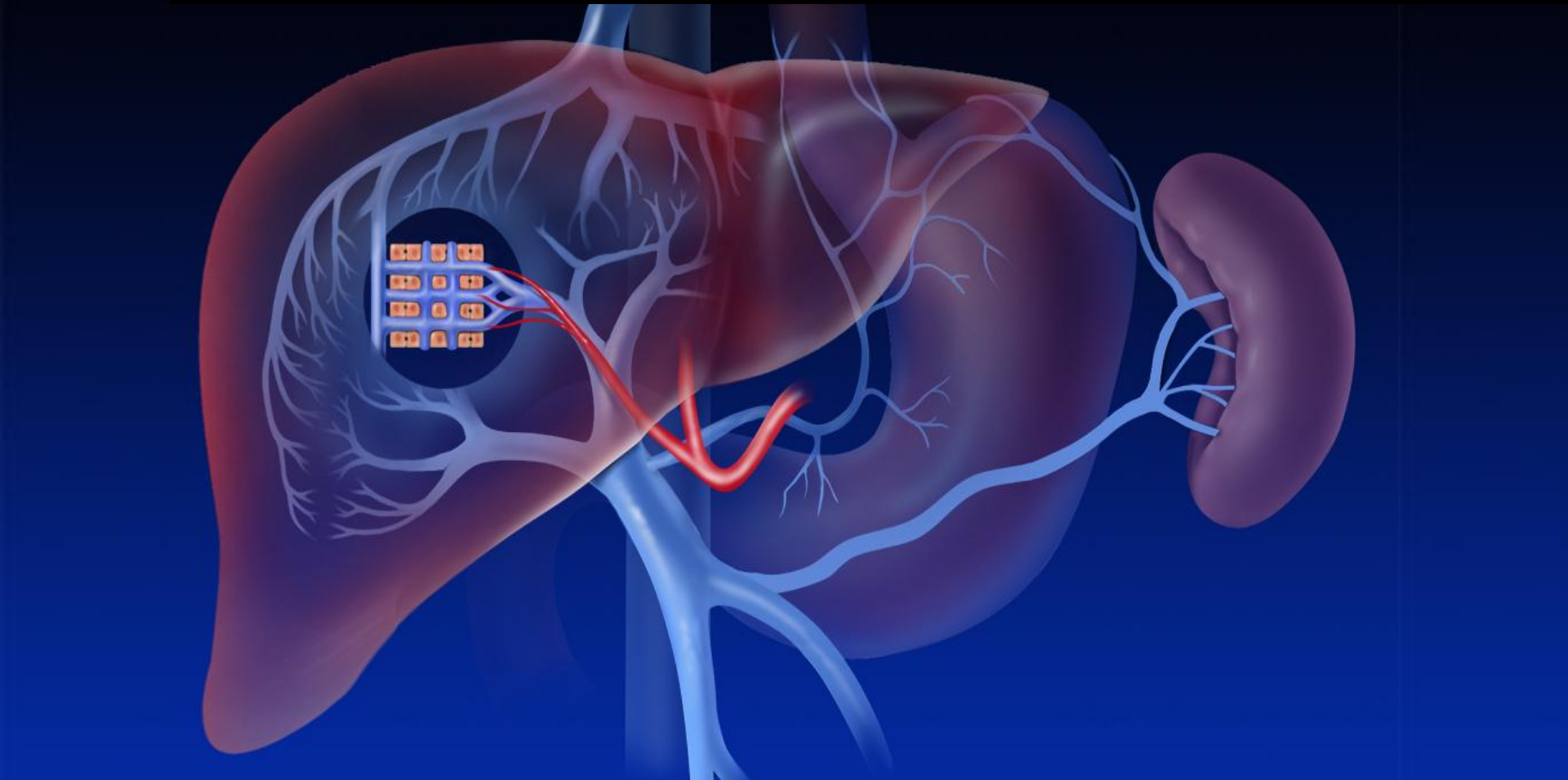
CRI

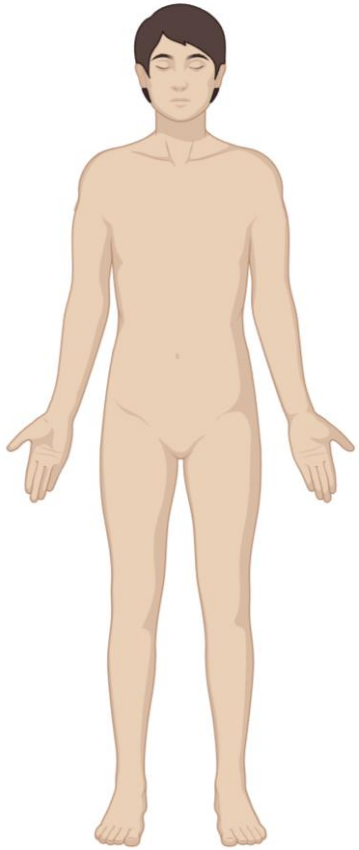
CENTRE DE RECHERCHE SUR L'INFLAMMATION

La vascularisation hépatique

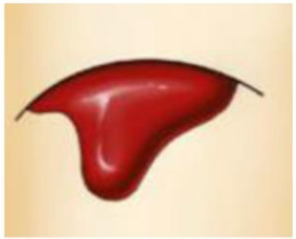


Bleeding in patients with cirrhosis

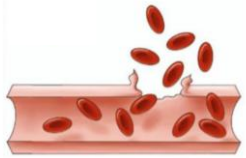
Portal hypertension



Haemostasis related



Post-procedure



Northup, Hepatology, 2021

Invasive procedures in patients with cirrhosis

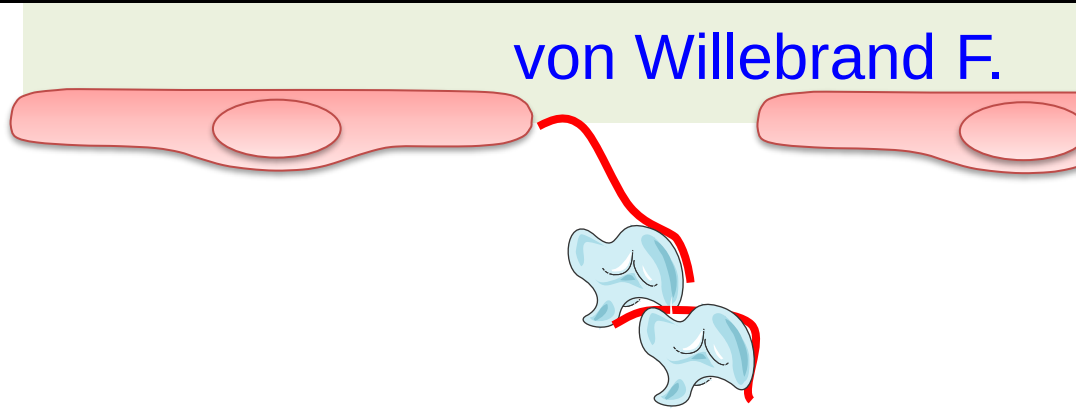
- Coagulation changes in patients with cirrhosis
- Management of invasive procedures in cirrhosis
- Management of anticoagulants and antiplatelet agents
- Current indications for anticoagulants in cirrhosis

Coagulation in cirrhosis

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

Coagulation in cirrhosis

Primary hemostasis:
platelet aggregation



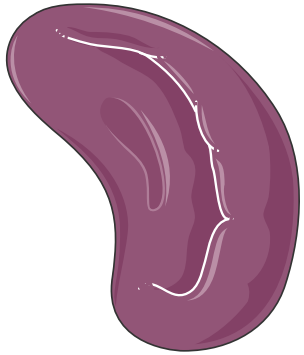
Thrombocytopenia

↑ von Willebrand F.
↑ Multimer size

Favors bleeding

Favors thrombosis

Thrombocytopenia and cirrhosis

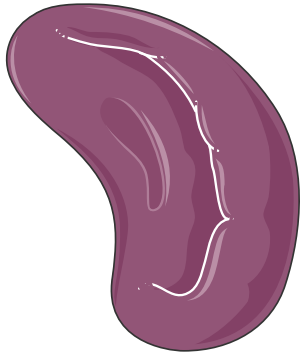


Hypersplenism

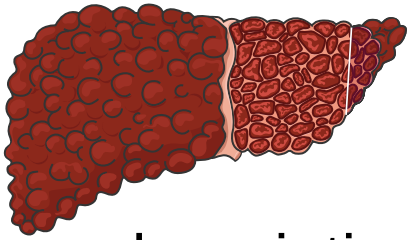
↘

Thrombocytopenia

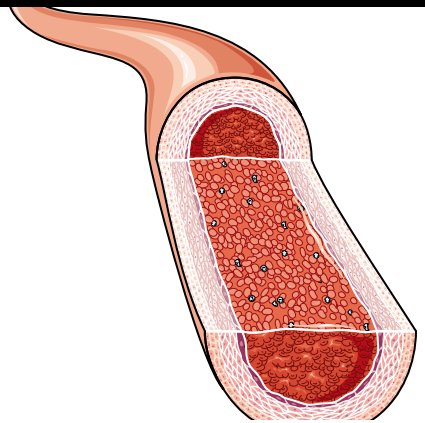
Thrombocytopenia and cirrhosis



Hypersplenism



↓ thrombopoietin



- Coagulation activation
- Anti platelet Ab

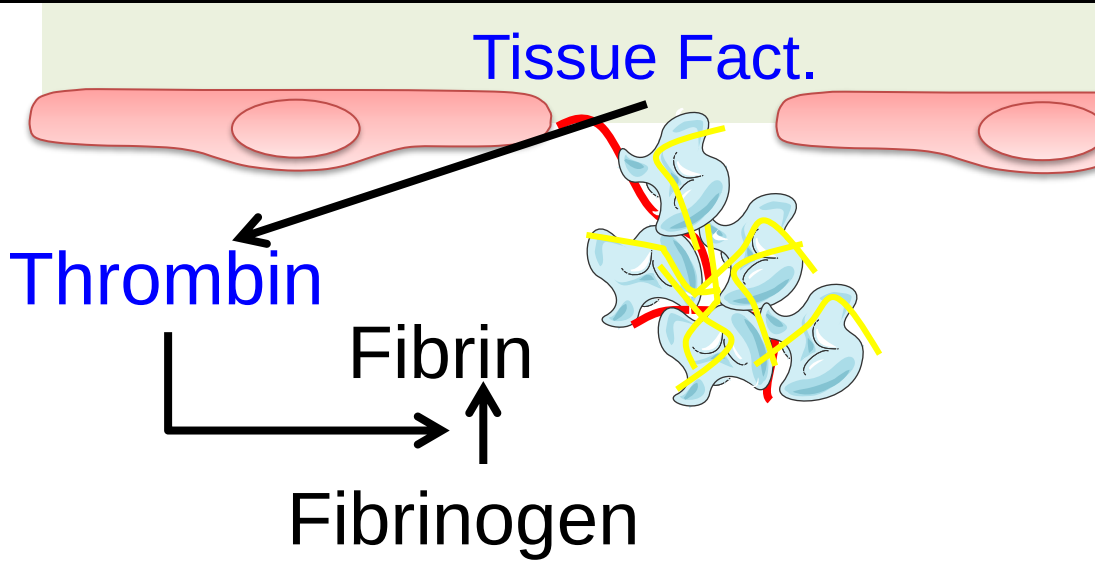
Thrombocytopenia

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

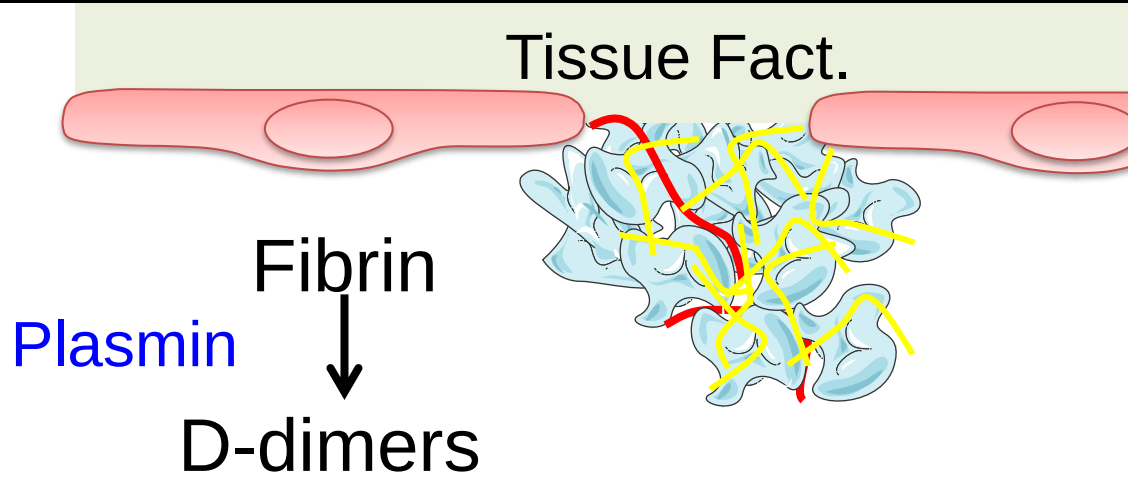
Favors thrombosis

Coagulation in cirrhosis

Primary hemostasis:
platelet aggregation

Coagulation:
fibrin formation

Fibrinolysis:
fibrin lysis



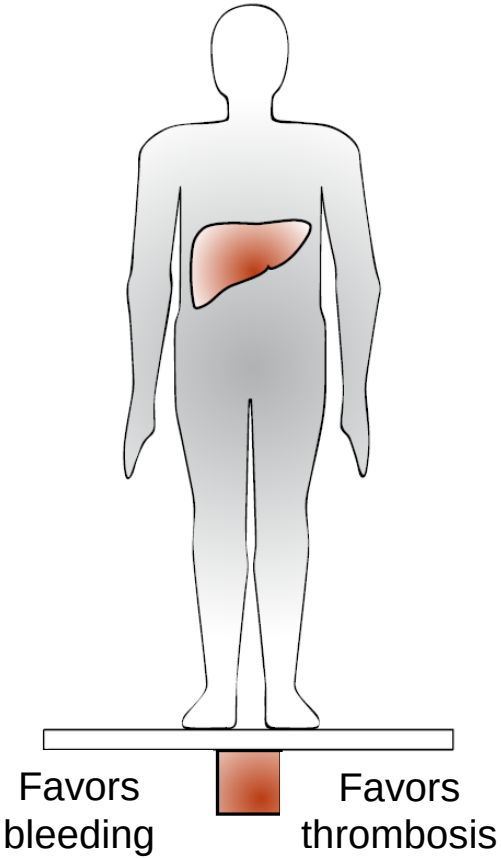
↑ tPA

↓ plasminogen, α2 antiplasmin, ↑ PAI-1

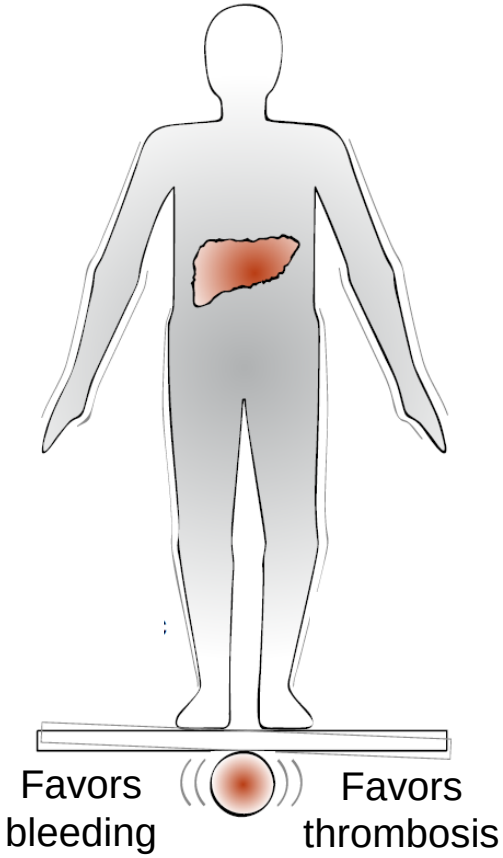
Favors bleeding

Favors thrombosis

Coagulation in cirrhosis



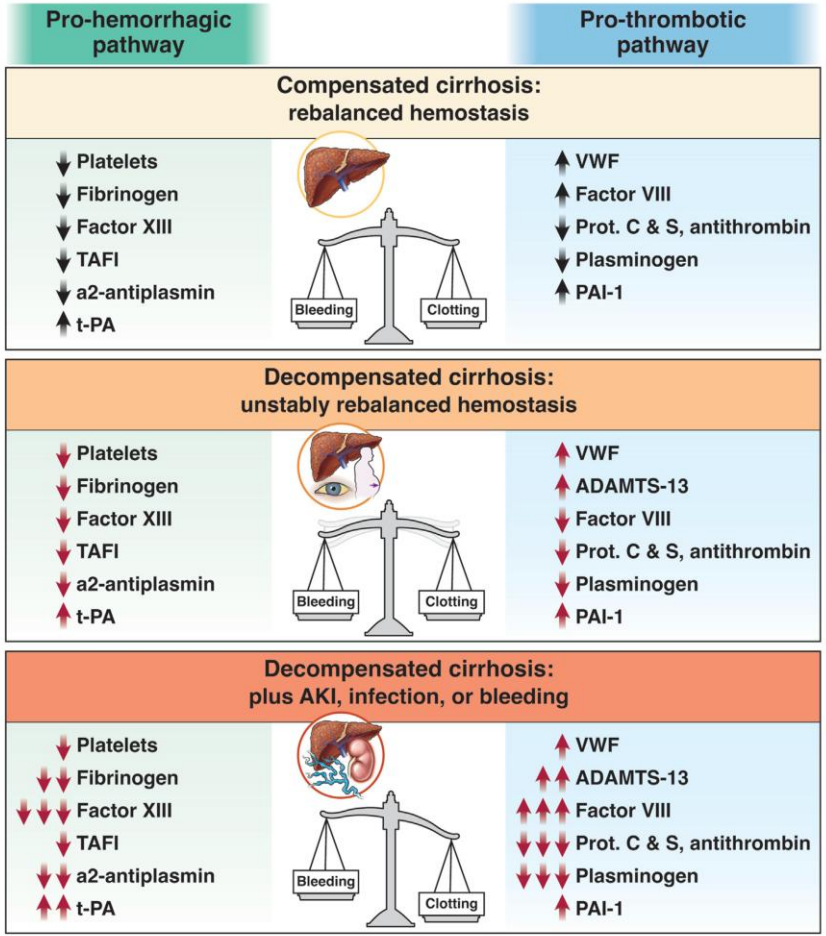
Normal



Cirrhosis

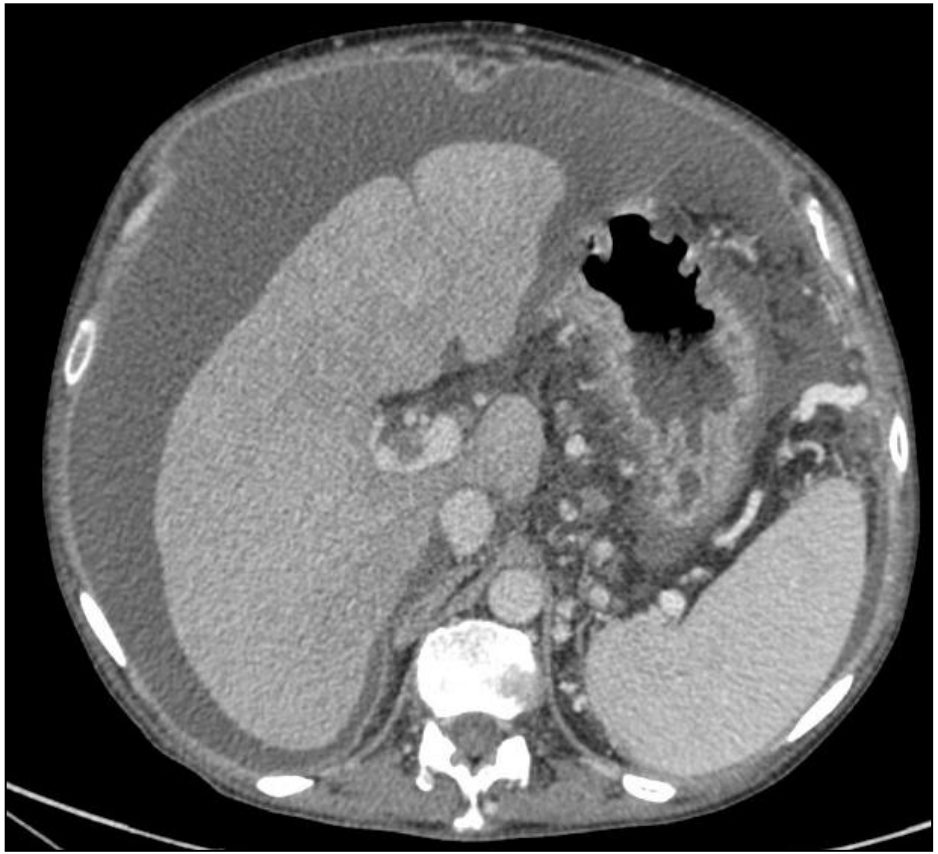
Lisman, J Hepatol 2013

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
- Management of anticoagulants and antiplatelet agents
- Current indications for anticoagulants in cirrhosis

Invasive procedures in patients with cirrhosis

- The patient
- The procedure
- The laboratory

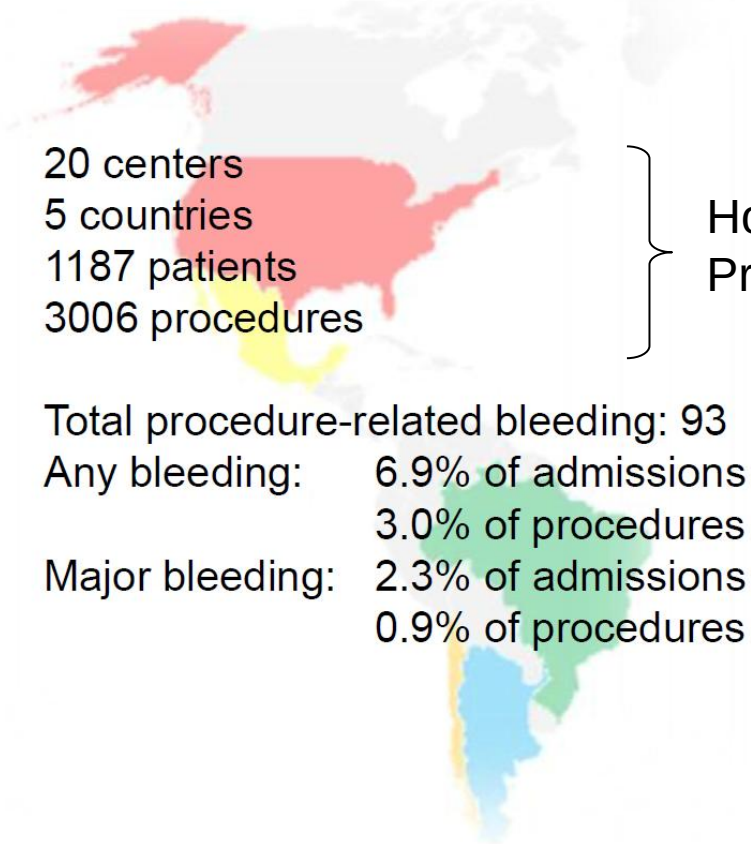
Prediction: the patient

When the procedure is scheduled

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

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

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

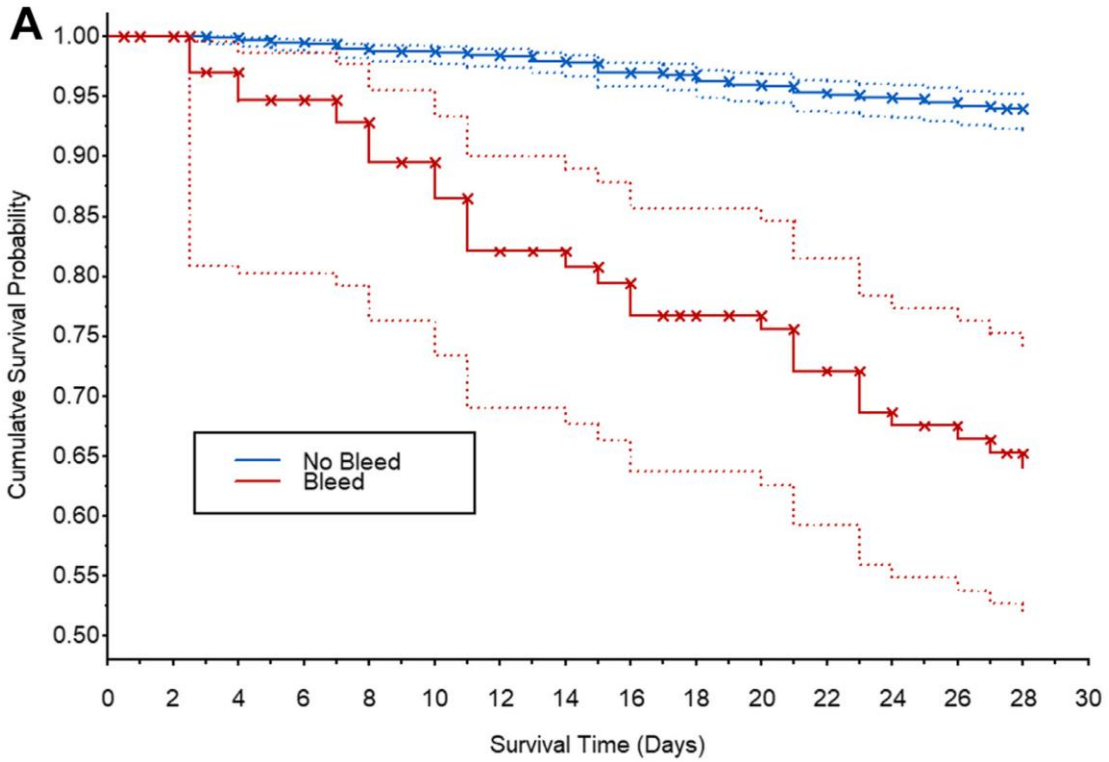
Any bleeding:	6.9% of admissions
	3.0% of procedures
Major bleeding:	2.3% of admissions
	0.9% of procedures

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

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

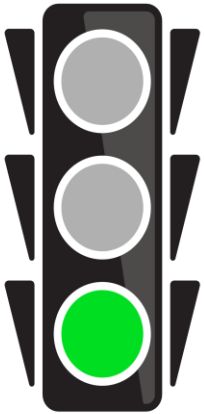
80 invasive procedures

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	



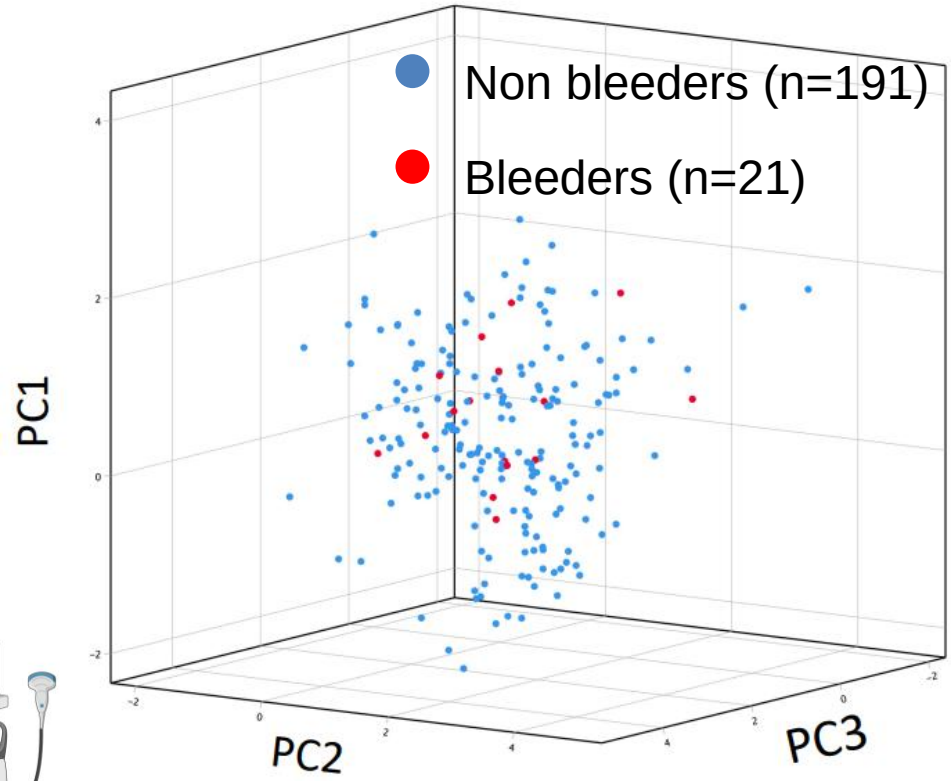
Riescher *et al.*, JHEP Rep 2023

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

302 patients undergoing liver biopsy

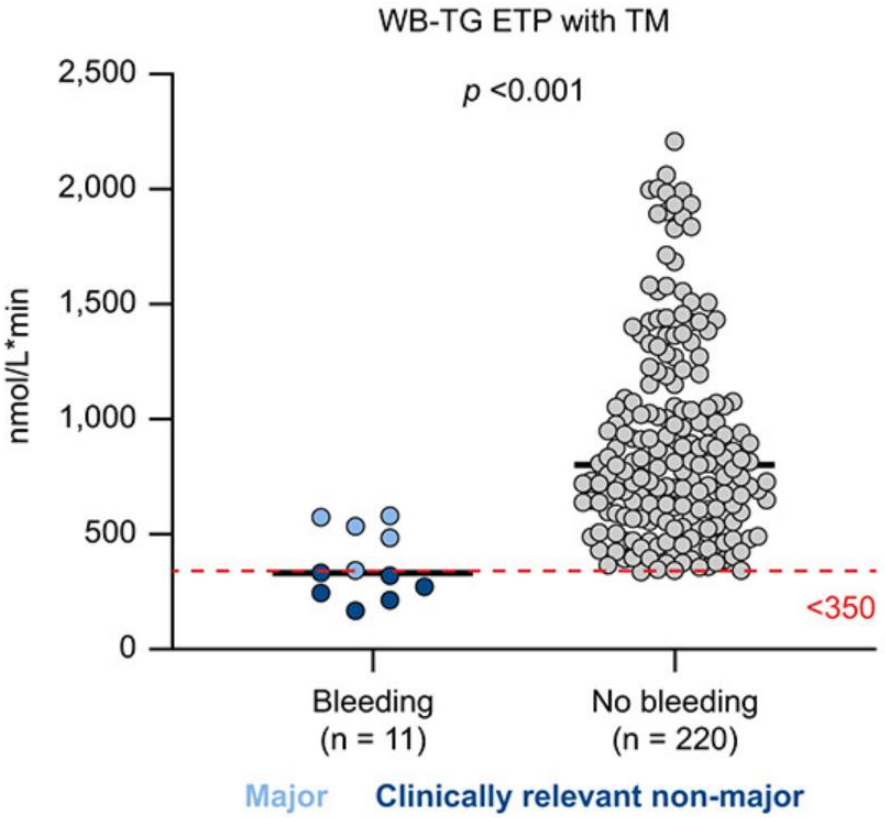
- PT, aPTT, platelet, coag factors
- PFA-100
- Thromboelastography
- Thrombin generation assays
- Plasma clot lysis time
- Clinical questionnaire

Endpoint: liver hematoma or ↓ Hb



Bissonnette*, Riescher* et al, JTH 2022

Whole blood thrombin generation assay: some potential?



Zanetto, *et al.* J Hepatol 2025

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

Invasive procedures in patients with cirrhosis

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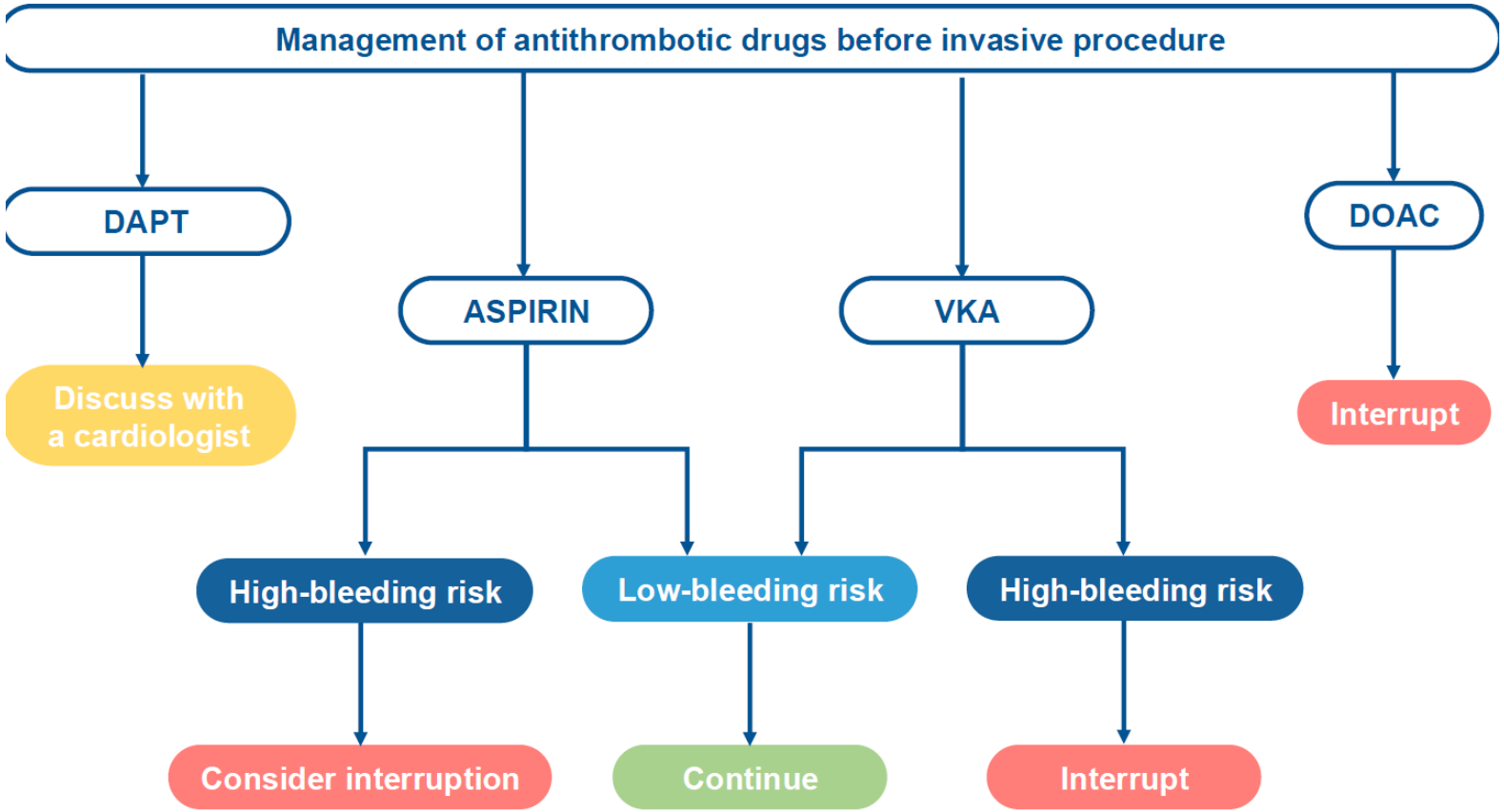
Management of anticoagulants and antiplatelet agents



Riescher-Tuczkiewicz A, Rautou PE. Clin Mol Hepatol. 2025

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*

Invasive procedures in patients with cirrhosis

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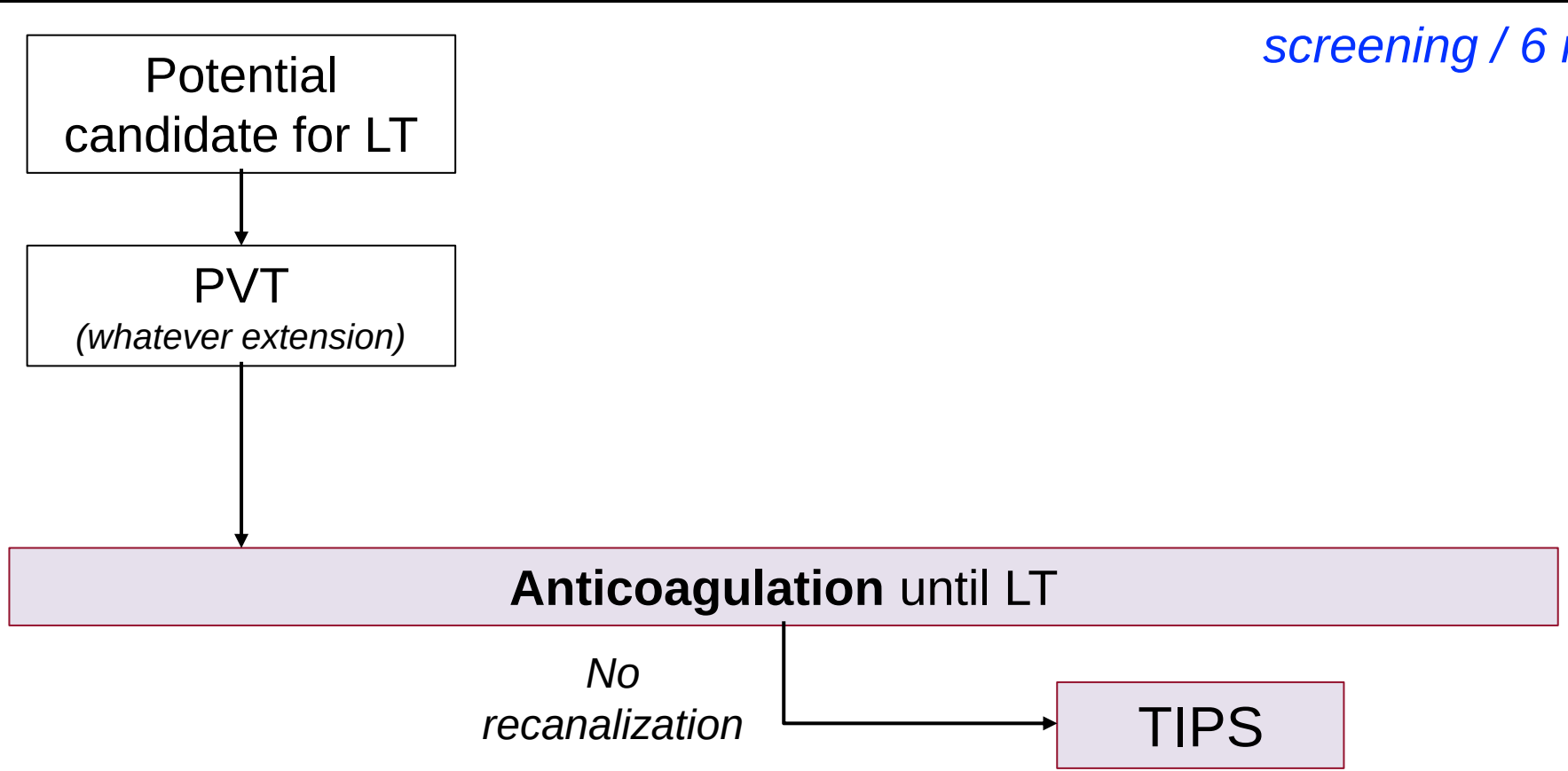
Indications for anticoagulants in patients with PVT and cirrhosis



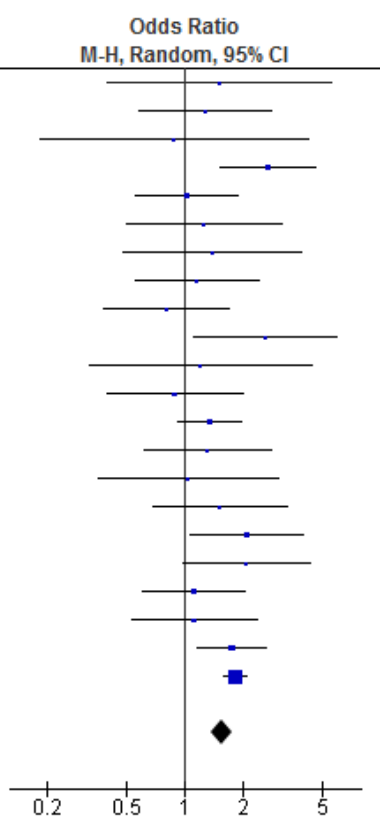
LT, liver transplantation; PVT, portal vein thrombosis

De Franchis et al, J Hepatol 2022

PVT is associated with worse post-LT outcome

Goal of anticoagulation:
facilitate adequate portal anastomosis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Gayowski 1996	4	23	8	65	0.9%	1.50 [0.41, 5.55]	1996
Lerut 1997	10	38	63	288	2.5%	1.28 [0.59, 2.77]	1997
Figueras 1997	2	14	19	119	0.6%	0.88 [0.18, 4.24]	1997
Yerdel 2000	21	63	123	779	4.6%	2.67 [1.53, 4.66]	2000
Molmenti 2002	13	85	232	1546	4.0%	1.02 [0.56, 1.88]	2002
Dumortier 2002	6	38	61	468	1.8%	1.25 [0.50, 3.12]	2002
Shi L 2003	5	19	89	433	1.4%	1.38 [0.48, 3.93]	2003
Gimeno 2005	20	83	18	83	2.8%	1.15 [0.56, 2.37]	2005
Bertelli 2005	9	64	111	657	2.8%	0.80 [0.39, 1.68]	2005
Lendoire 2007	10	26	55	281	2.1%	2.57 [1.11, 5.97]	2007
Wu 2009	3	24	18	170	0.9%	1.21 [0.33, 4.45]	2009
Tao 2009	9	42	52	221	2.3%	0.89 [0.40, 1.97]	2009
Pan 2009	34	253	261	2508	9.0%	1.34 [0.91, 1.96]	2009
Gao 2009	11	46	51	262	2.7%	1.30 [0.62, 2.73]	2009
Doenecke 2010	5	24	34	169	1.4%	1.04 [0.36, 3.00]	2010
Englesbe 2010	10	30	143	574	2.4%	1.51 [0.69, 3.30]	2010
Suarez 2010	14	48	94	569	3.4%	2.08 [1.07, 4.03]	2010
Shi 2010	11	48	45	356	2.7%	2.05 [0.98, 4.32]	2010
Ravaioli 2011	14	91	112	798	4.0%	1.11 [0.61, 2.04]	2011
D'Amico 2013	10	51	71	396	2.7%	1.12 [0.53, 2.33]	2013
Hlbi 2014	36	174	157	1205	8.3%	1.74 [1.16, 2.61]	2014
Ghabril 2015	282	3321	2217	45249	36.7%	1.80 [1.58, 2.05]	2015
Total (95% CI)		**4605**		**57196**	**100.0%**	**1.55 [1.37, 1.75]**	
Total events	539		4034				



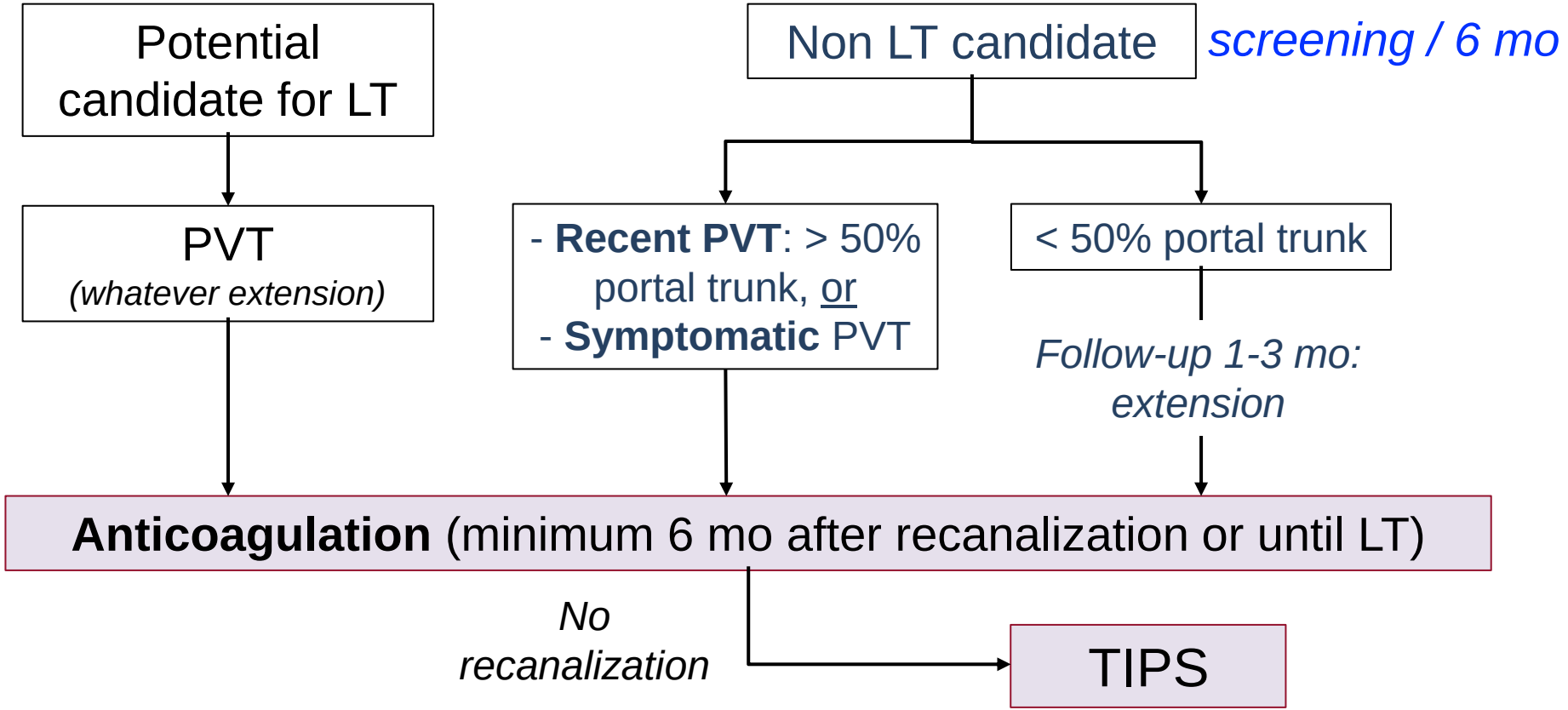
1 year mortality

No PVT PVT

De Franchis et al, J Hepatol 2022

Zanetto et al. Transpl Int 2018

Indications for anticoagulants in patients with PVT and cirrhosis



LT, liver transplantation; PVT, portal vein thrombosis

De Franchis et al, J Hepatol 2022

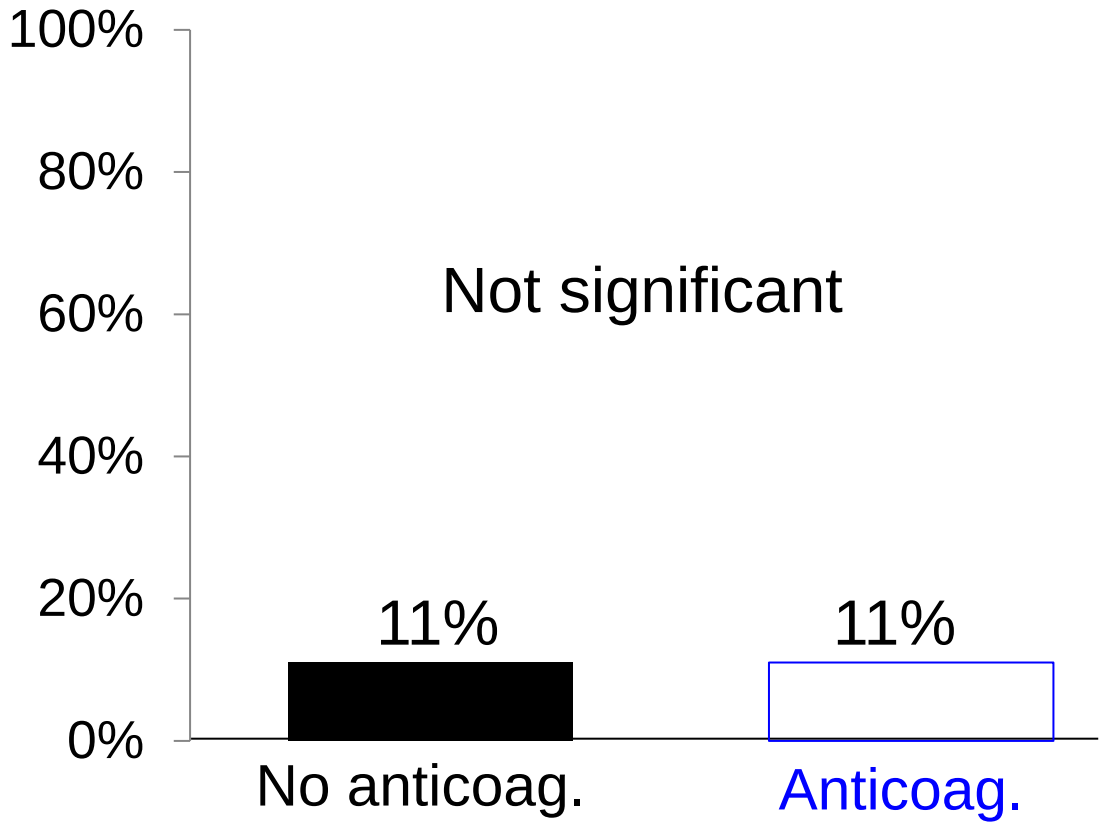
Current indications for anticoagulants in cirrhosis

Baveno VII
Consensus Workshop
&
Pediatric Research Workshop

"Anticoagulation should not be discouraged in patients with cirrhosis and an approved indication for anticoagulation, since anticoagulation may reduce liver-related outcomes in patients with and without portal vein thrombosis and may improve overall survival."

De Franchis et al, J Hepatol 2022

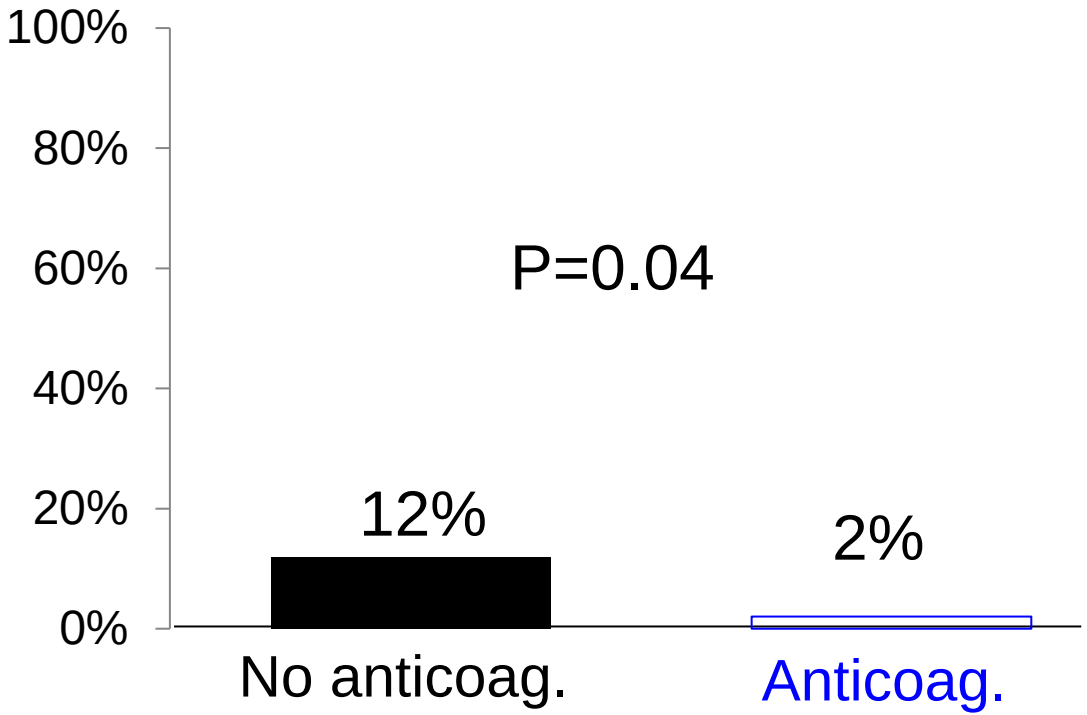
Major or minor bleedings



6 studies; 257 patients

Loffredo, Gastroenterology 2017

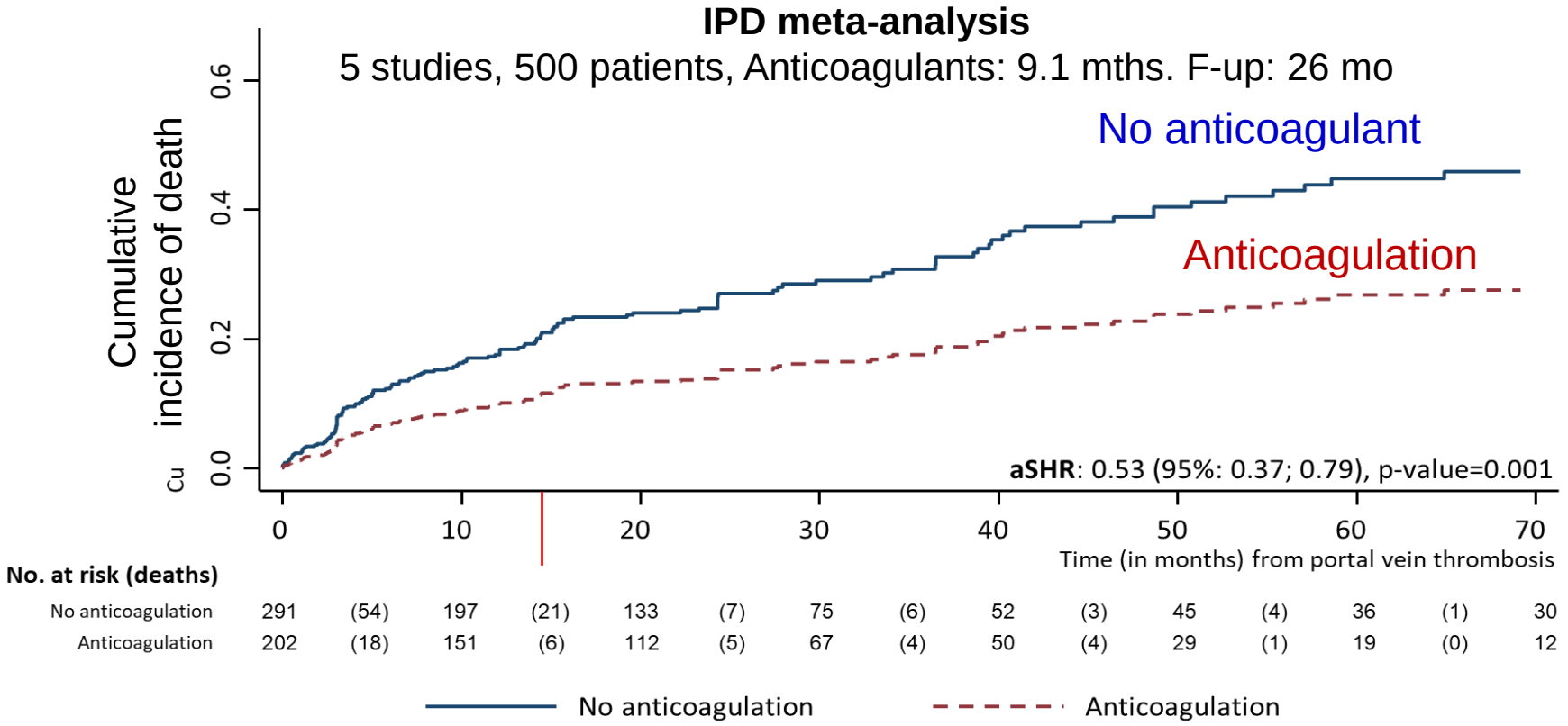
Portal hypertension related bleeding



4 studies; 158 patients

Loffredo, Gastroenterology 2017

Anticoagulants in cirrhosis improve outcome



Sub-hazard ratio adjusted (**aSHR**) by age at diagnosis, etiology, Child, thrombosis extension and localization and variceal prophylaxis

Competing risk model with LT

A Guerrero et al. J Hepatol 2023

Hémorragies non liés à l'HTP

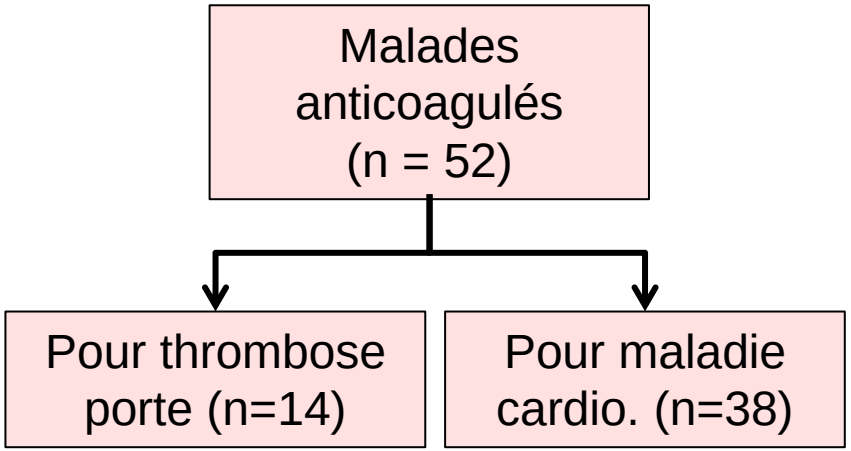
5 patients (10%)

Hémorragie	5
• Vaginale	1
• Incisionelle	1
• Extraction dentaire	1
• Digestive basse	2

Plaquettes <50.000 seul facteur indépendemment associé aux hémorragies (p=0.018)

Seijo, Clin Gastroenterol Hepatol 2012

Impact de l'anticoagulation sur les hémorragies digestives de la cirrhose



Malades non-anticoagulés (n = 104)

Pairés sur:
- severité de la cirrhose
- age
- sexe
- source du saignement
- SOFA

Cerini, Hepatology 2015

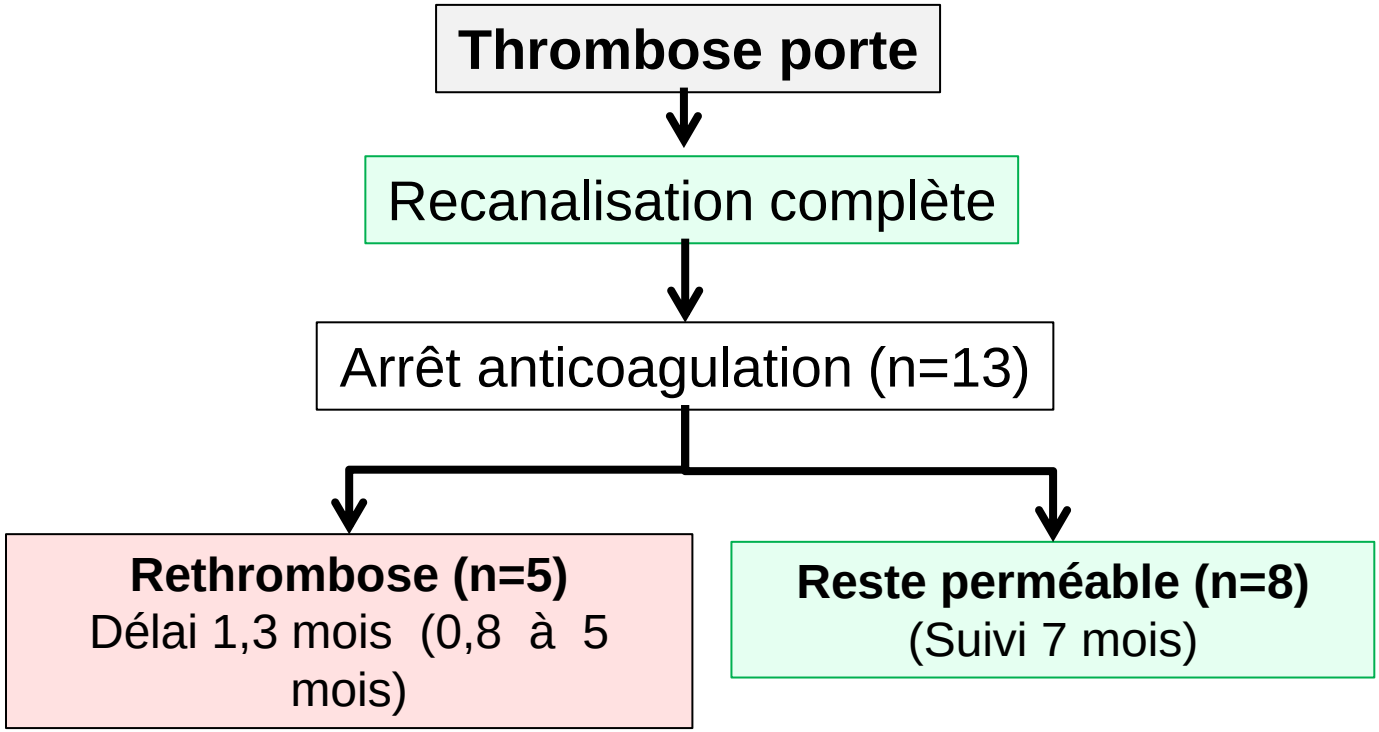
Impact de l'anticoagulation sur les hémorragies digestives de la cirrhose

Mortalité à 6 sem dans la cohorte totale (n = 156)

Variable	Analyse Univariée		Analyse Multivariée	
	OR	***P* Value**	**OR**	***P***
Anticoagulation	2.5	0.076		
Raison de anticoag:		0.085		0.07
Pour thromb porte	0.9		1.08	
Pour maladie cardio	3.2		**3.9**	
Bilirubine	1.2	<0.01		
Score de Child	1.5	0.009		
MELD XI	1.2	0.002		
MELD	1.2	0.001		
SOFA score	1.5	<0.001	**1.7**	<0.001
Charlson Comorbidity Index	1.3	0.026	**1.5**	0.012

Cerini, Hepatology 2015

Récidive à l'arrêt



Faire une échographie à 1 mois, à 3 mois et à 6 mois

Delgado, Clin Gastroenterol Hepatol. 2012

What kind of anticoagulants in cirrhosis?

Baveno VII
Consensus Workshop
&
Pediatric Research Workshop

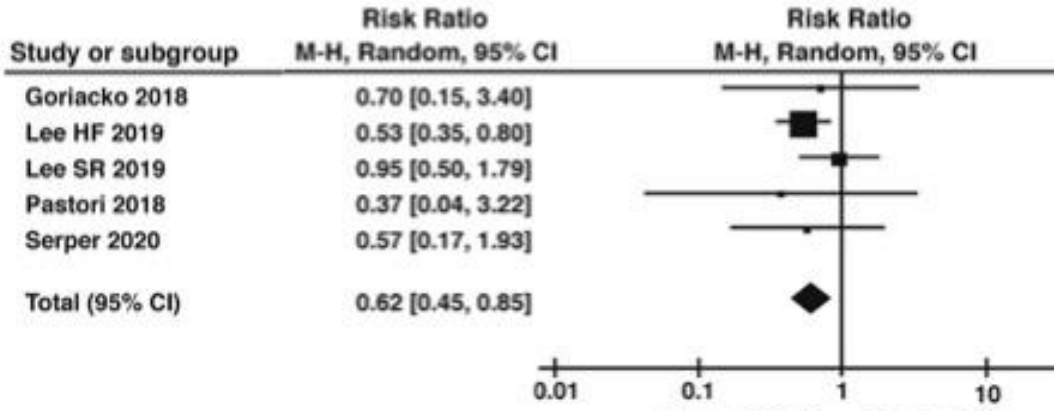
Start using LMWH

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

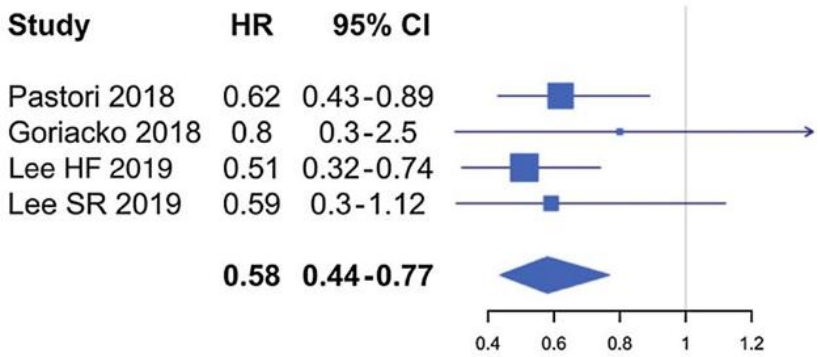
De Franchis et al, J Hepatol 2022

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

- Indications for anticoagulation in cirrhosis and PVT:
  - ✓ liver transplant candidates
  - ✓ recent PVT > 50% or extending

- 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

Networks for vascular liver diseases

European Reference Network | Hepatological Diseases (ERN RARE-LIVER)

VALDIG

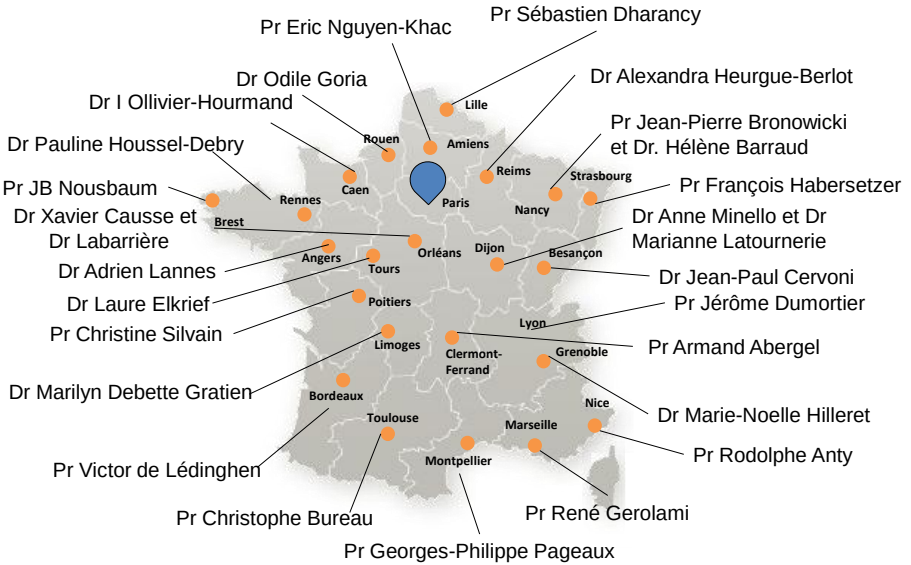
VASCULAR LIVER DISEASE GROUP

French network for vascular liver diseases

MVF
CENTRE DE RÉFÉRENCE
MALADIES VASCULAIRES
DU FOIE

FILFOIE
FILIÈRE DE SANTÉ MALADIES RARES DU FOIE DE L'ADULTE ET DE L'ENFANT

Centre de compétence maladies vasculaires du foie



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European vascular liver diseases network

EURO-VALDI-NET

Start Date: 01/11/2024

End Date: 01/11/2028

Instituts thématiques

Inserm
Institut national
de la santé et de la recherche médicale

Université Paris Cité

CRI
CENTRE DE RECHERCHE SUR L'INFLAMMATION

Hepatology unit, Beaujon Hospital
Reference center for vascular liver diseases

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