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Coagulopathy and anticoagulation in chronic liver disease

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MVF CENTRE DE RÉFÉRENCE MALADIES VASCULAIRES DU FOIE

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

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

Objectives

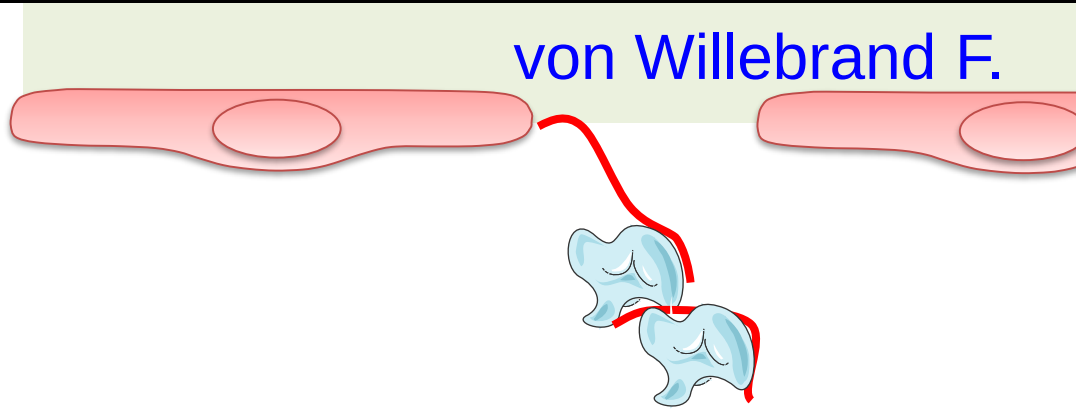
- Coagulation changes in patients with cirrhosis
- Management of invasive procedures in cirrhosis
- Anticoagulants in cirrhosis

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

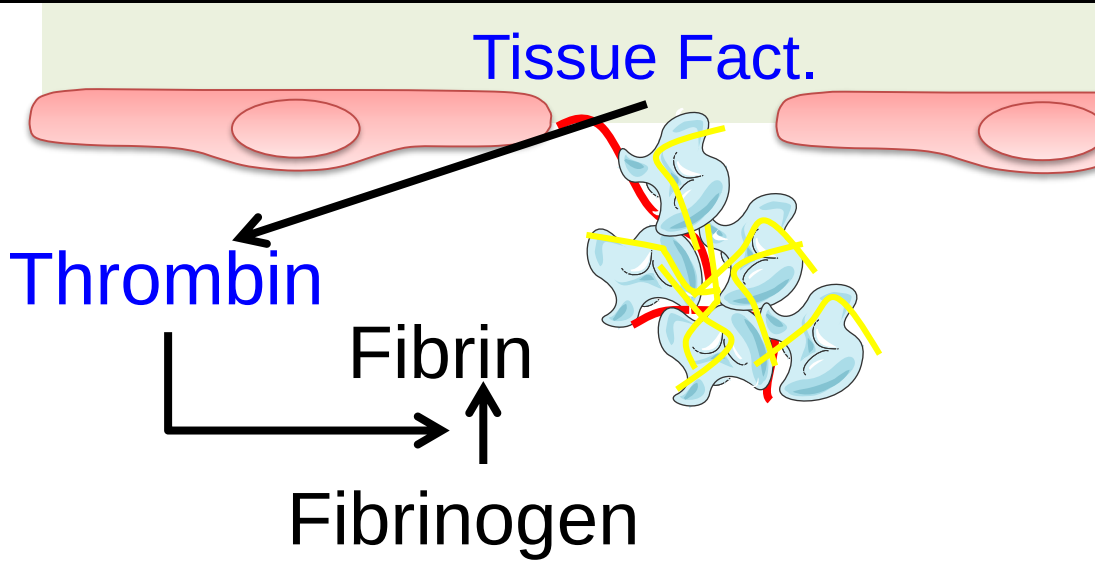
Favors bleeding

Favors thrombosis

Coagulation in cirrhosis

Primary hemostasis:
platelet aggregation

Coagulation:
fibrin formation



↓ fact II, V, VII, IX, X and Fg

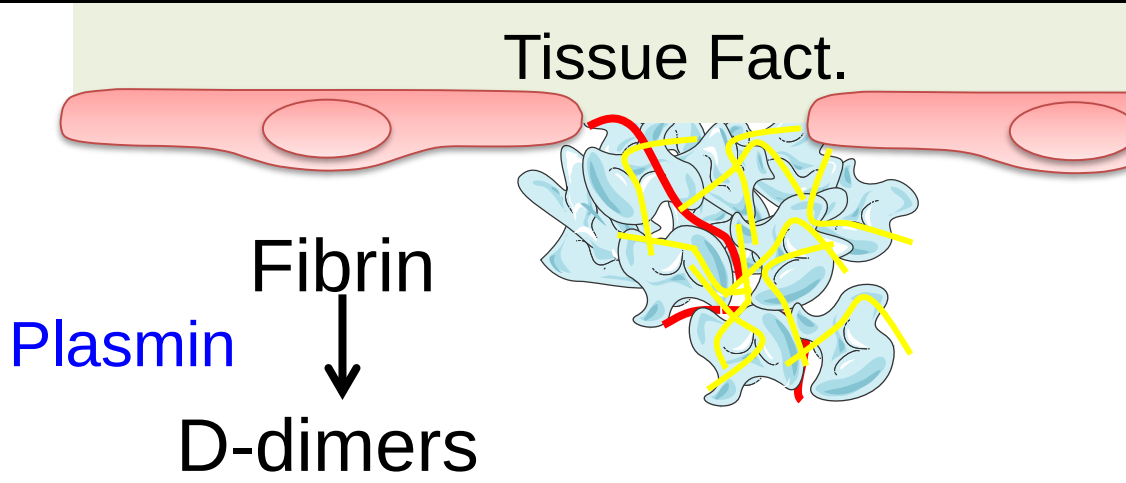
↓ AT, prot C, S,
↓ ↑ factor VIII

Favors bleeding

Favors thrombosis

Coagulation in cirrhosis

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



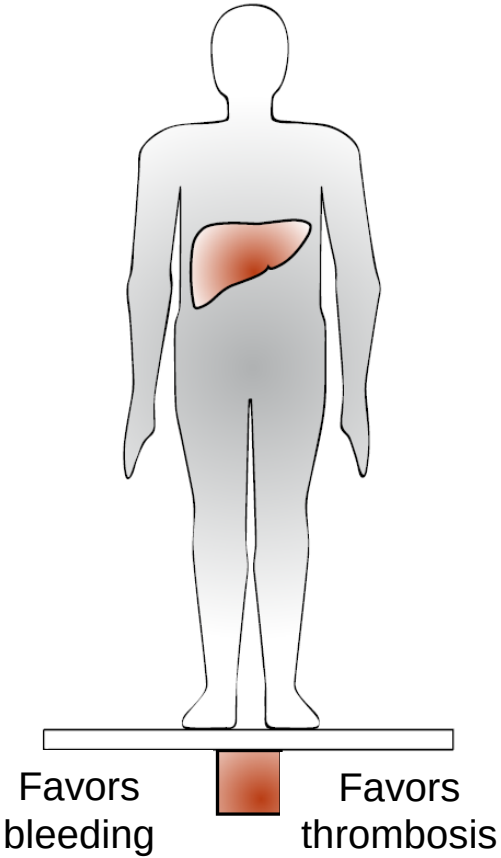
↑ tPA

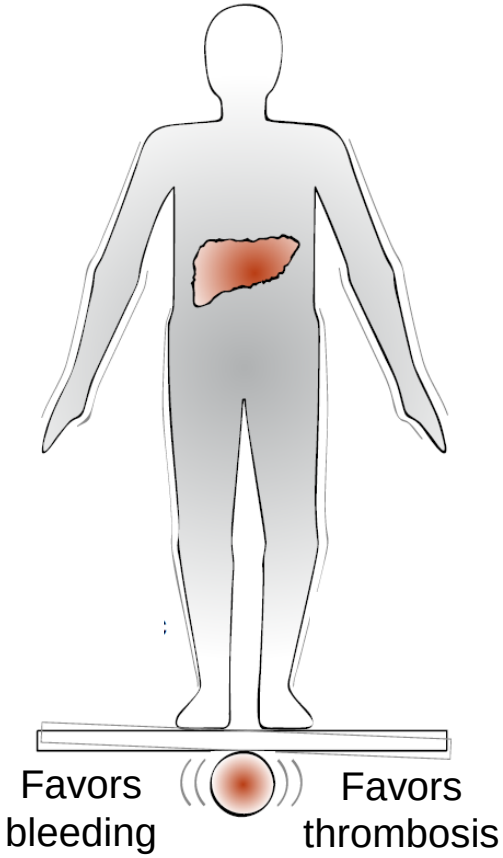
↓ plasminogen, α2 antiplasmin, ↑ PAI-1

Favors bleeding

Favors thrombosis

Coagulation in cirrhosis





Lisman, J Hepatol 2013

Coagulation changes with cirrhosis progression

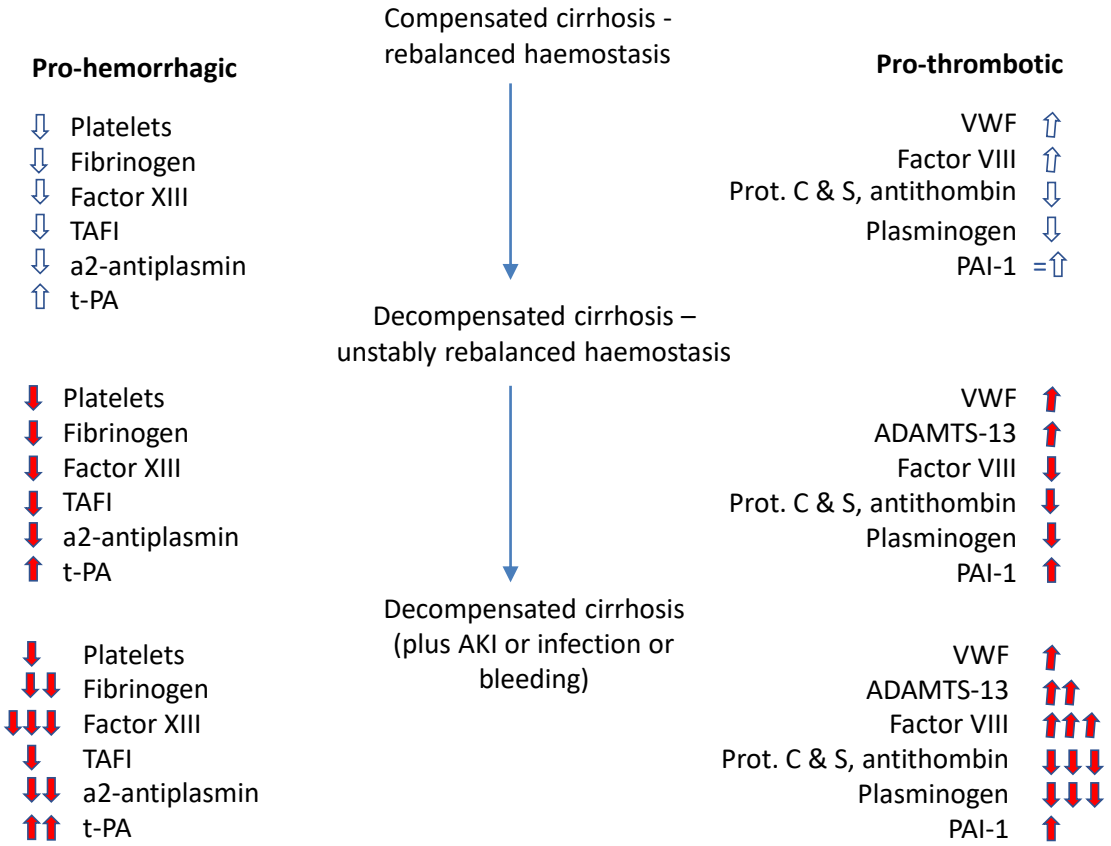
Compensated cirrhosis -

Decompensated cirrhosis –

Decompensated cirrhosis

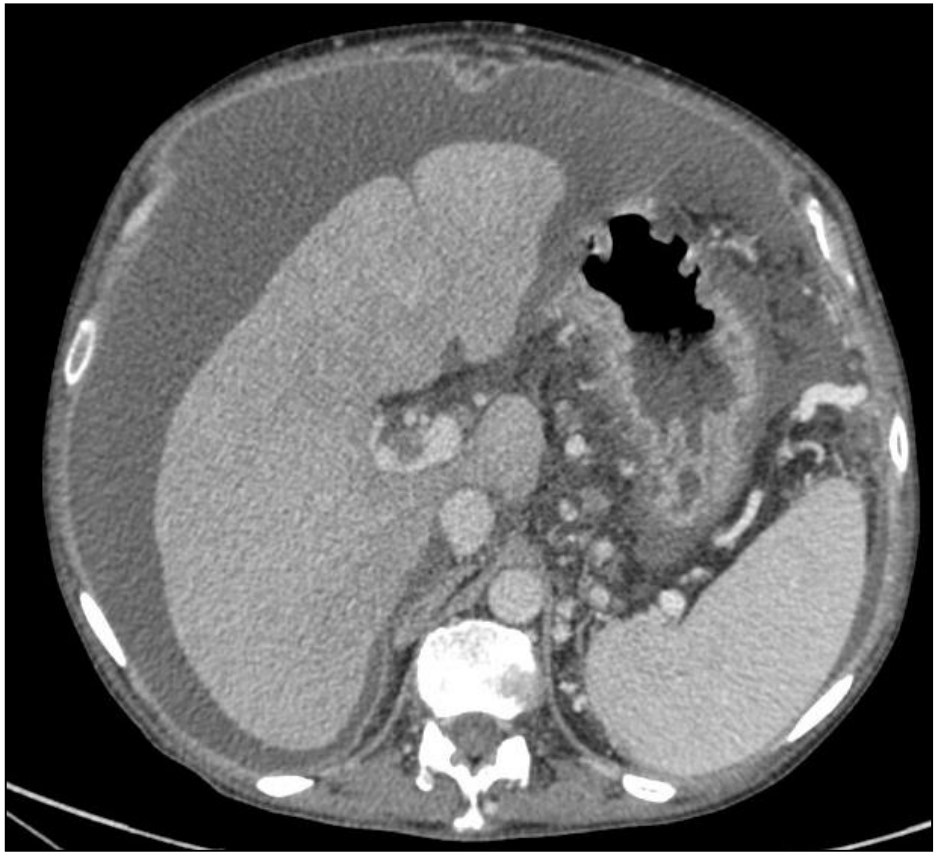
Rautou, Caldwell, Villa, CGH *In Press*

Coagulation changes with cirrhosis progression



Rautou, Caldwell, Villa, CGH *In Press*

Coagulation in cirrhosis



Objectives

- Coagulation changes in patients with cirrhosis
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- Anticoagulants in cirrhosis

Invasive procedures in patients with cirrhosis

- The patient
- The procedure
- The laboratory

Prediction: the patient

When the procedure is scheduled

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

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

Prediction: the procedure

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

"Can you put the finger?"

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 *In Press*

Prediction: the laboratory

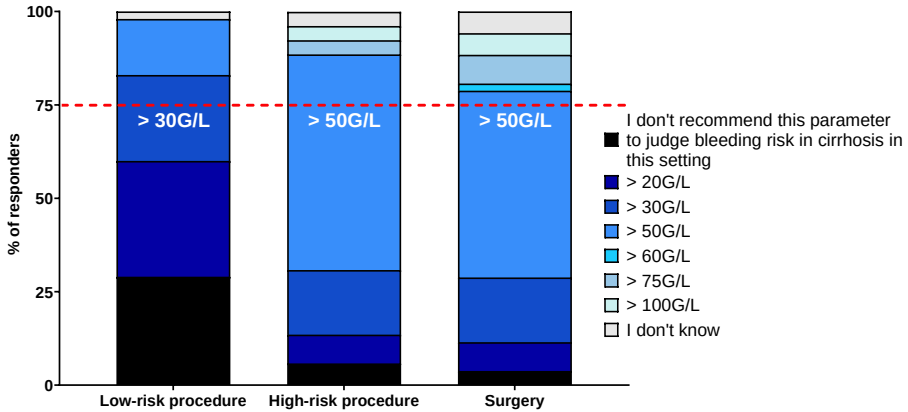
	BSG 2020	ACG 2020	AASLD 2021	AGA 2021	ISTH 2021	EASL 2022
Platelet < 50× 10^9/L	Trans-venous	Platelet infusions or TPO rec. agonists	No correction	severe thrombocytopenia and high-risk procedure	very high-risk surgery and <30-50 x 10^9/L: correct	< 50 × 10^9/L + local hemostasis not possible: correction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

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

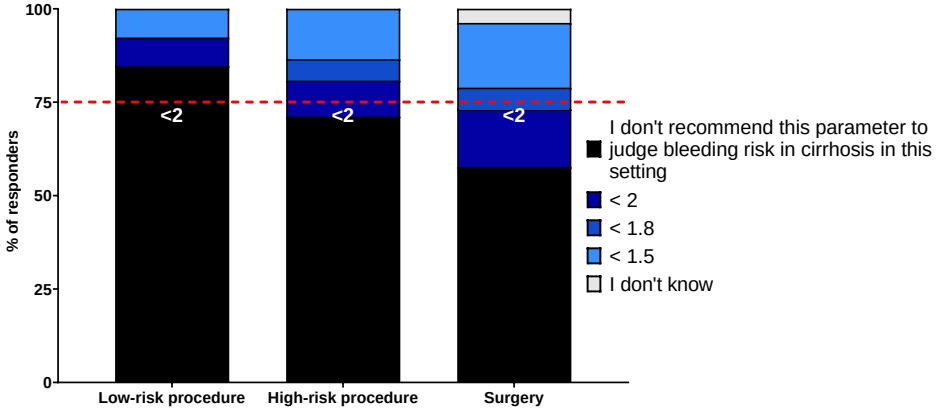
Rautou & Caldwell & Villa, CGH *In Press*

Prediction: the laboratory

Platelet count



INR

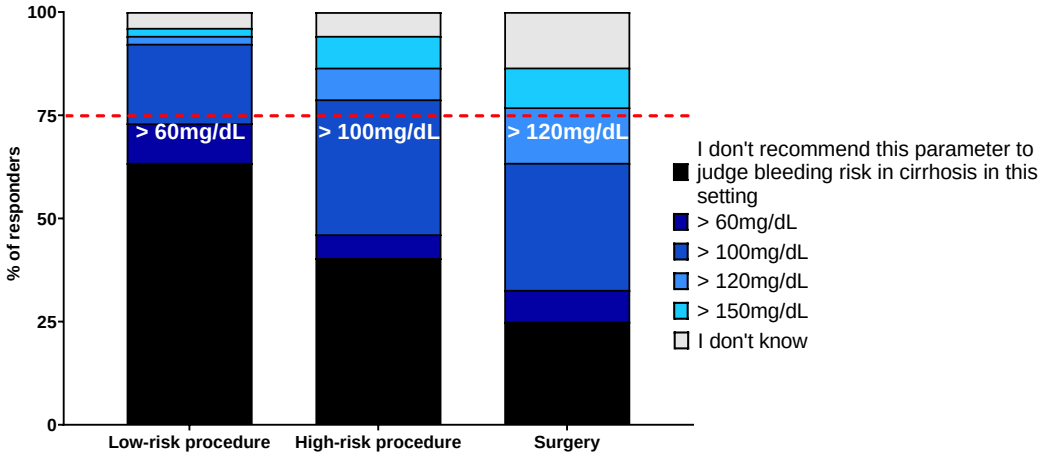


Survey; 52 international experts

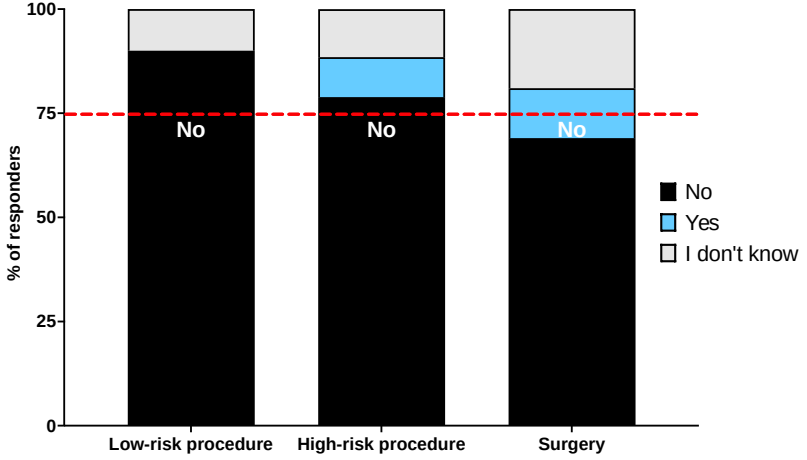
Riescher, Caldwell, Kamath, Villa, Rautou; manuscript in preparation

Prediction: the laboratory

Fibrinogen



aPTT



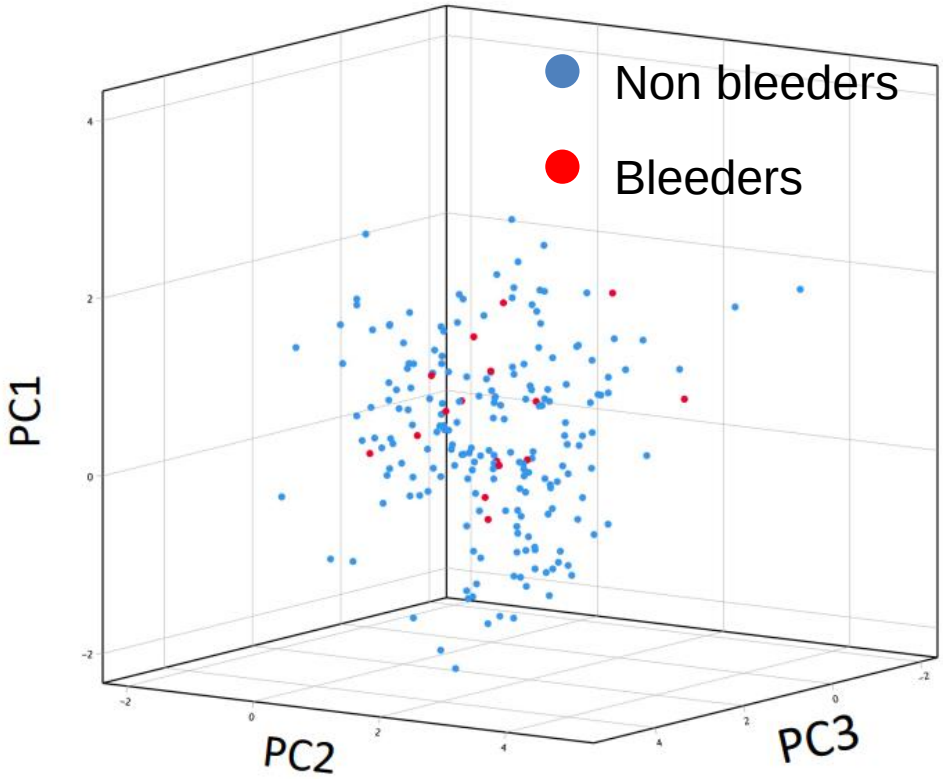
Survey; 52 international experts

Riescher, Caldwell, Kamath, Villa, Rautou; manuscript in preparation

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

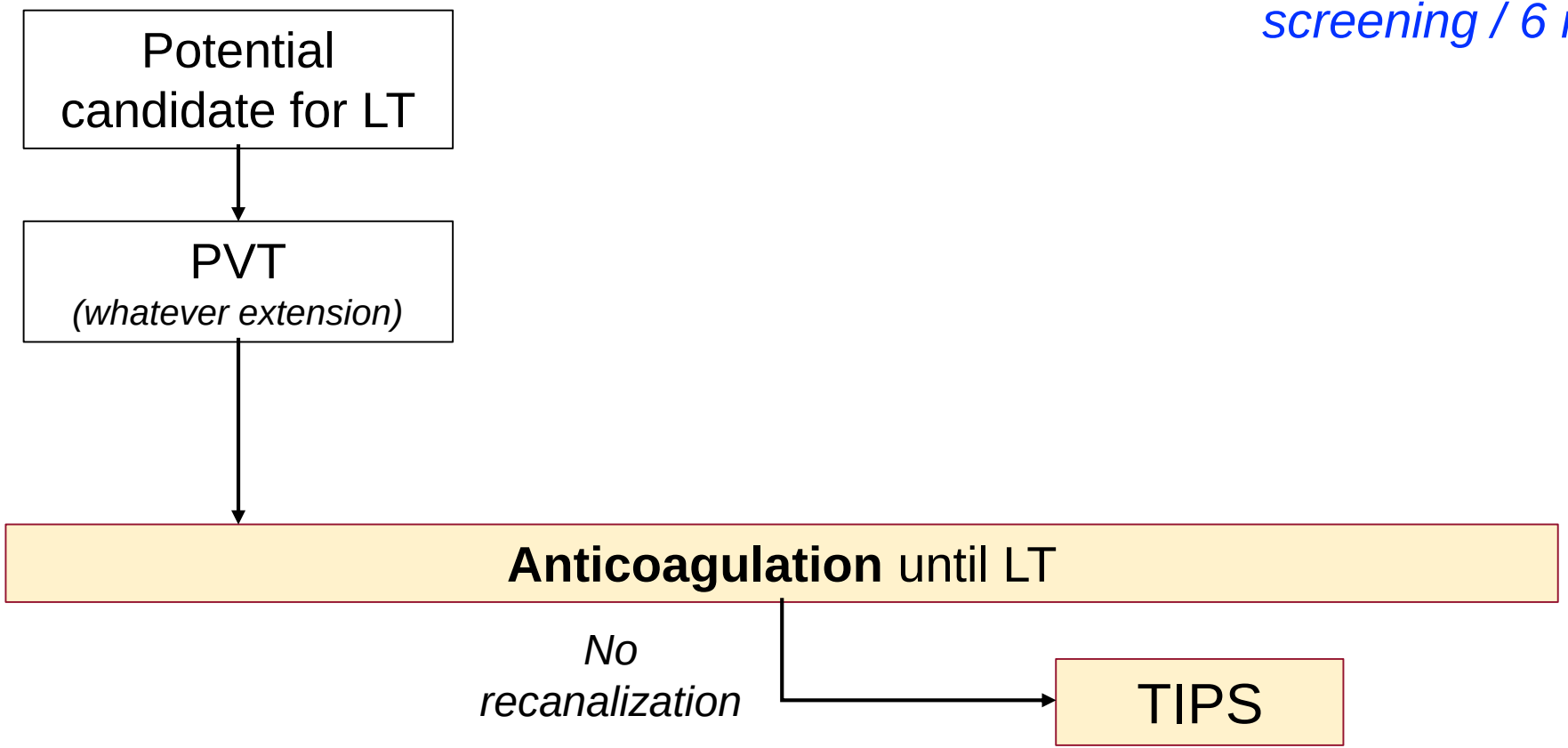


Bissonnette*, Riescher* et al, JTH 2022

Coagulopathy and anticoagulation in cirrhosis

- Coagulation changes in patients with cirrhosis
- Management of invasive procedures in cirrhosis
- Anticoagulants in cirrhosis
  - ✓ Current indications for anticoagulants in cirrhosis
  - ✓ What kind of anticoagulants in cirrhosis?

Current indications for anticoagulants in cirrhosis



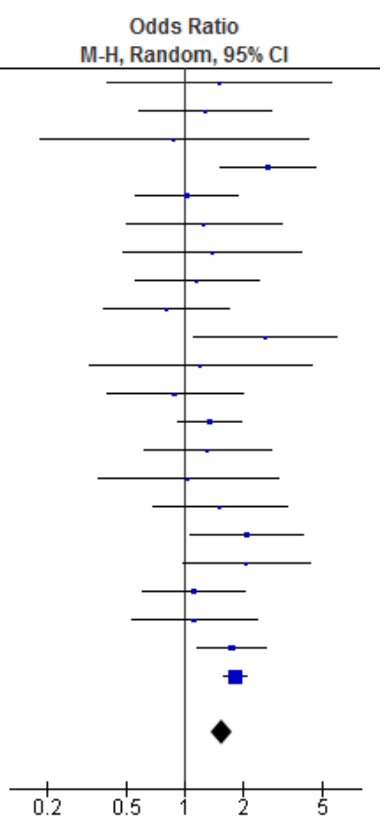
LT, liver transplantation; PVT, portal vein thrombosis

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				



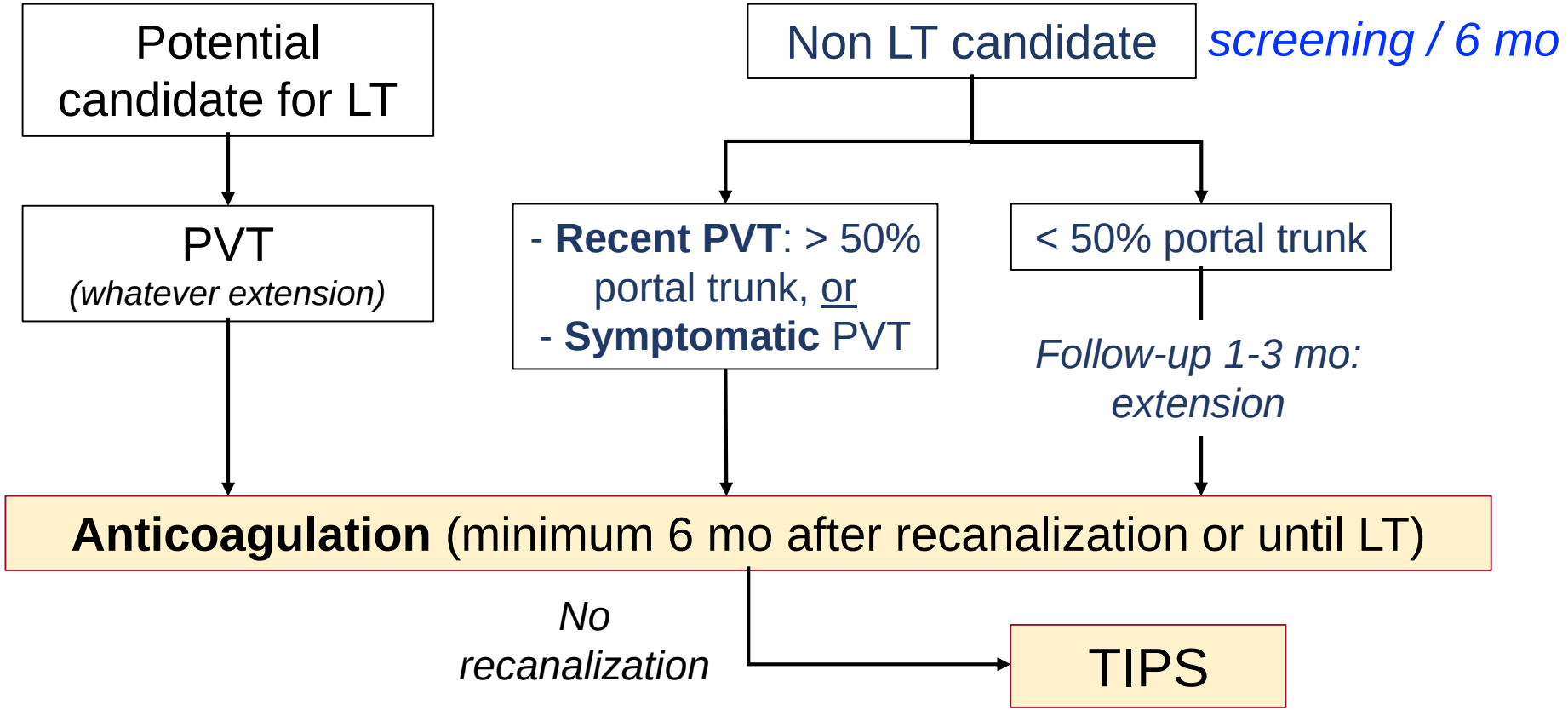
1 year mortality

No PVT PVT

De Franchis et al, J Hepatol 2022

Zanetto et al. Transpl Int 2018

Current indications for anticoagulants in 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."

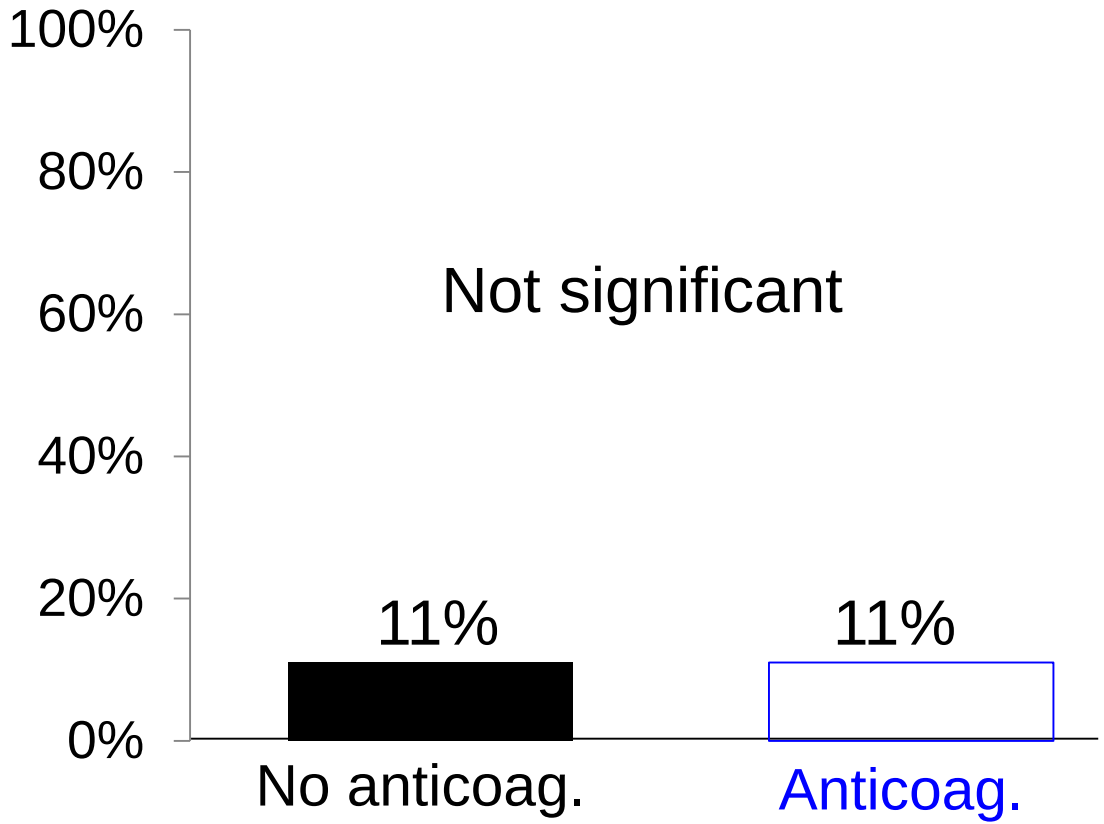
De Franchis et al, J Hepatol 2022

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

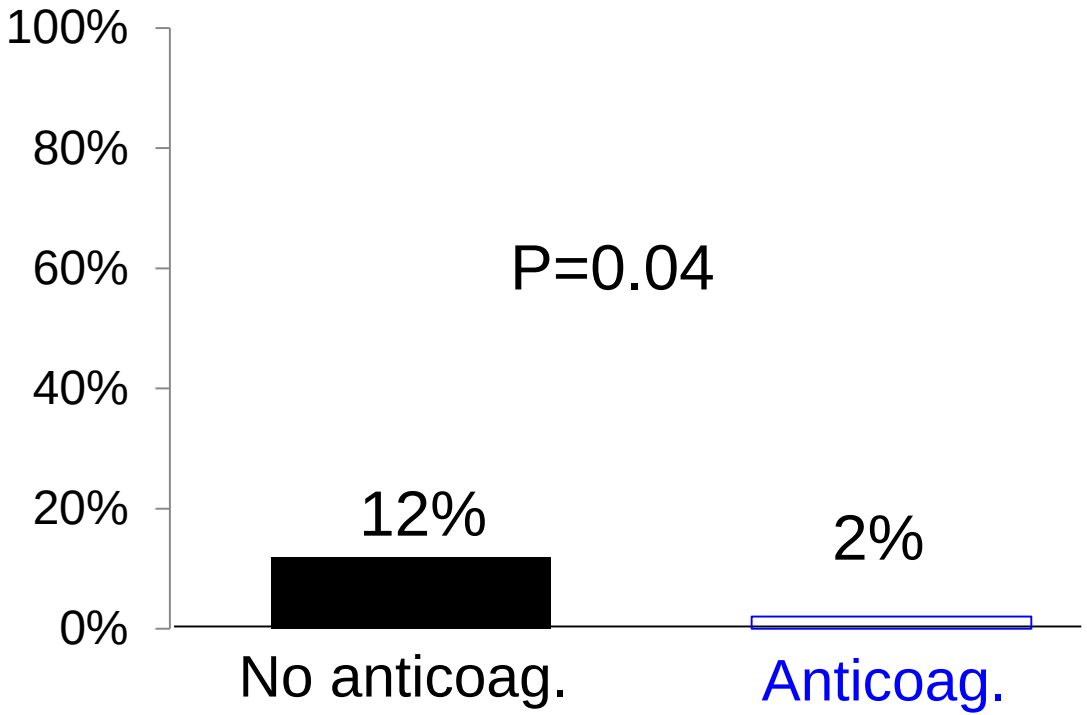
Major or minor bleedings



6 studies; 257 patients

Loffredo, Gastroenterology 2017

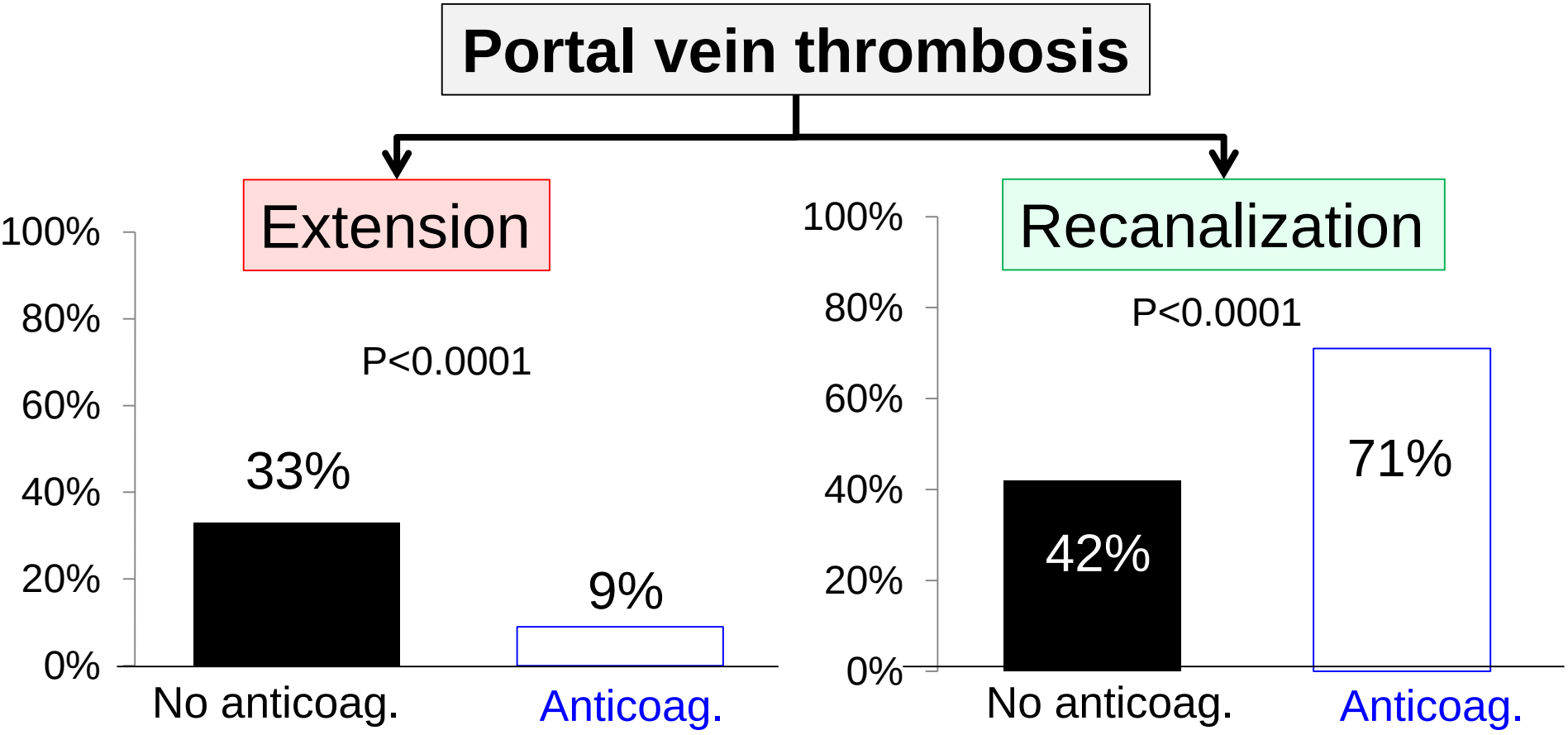
Portal hypertension related bleeding



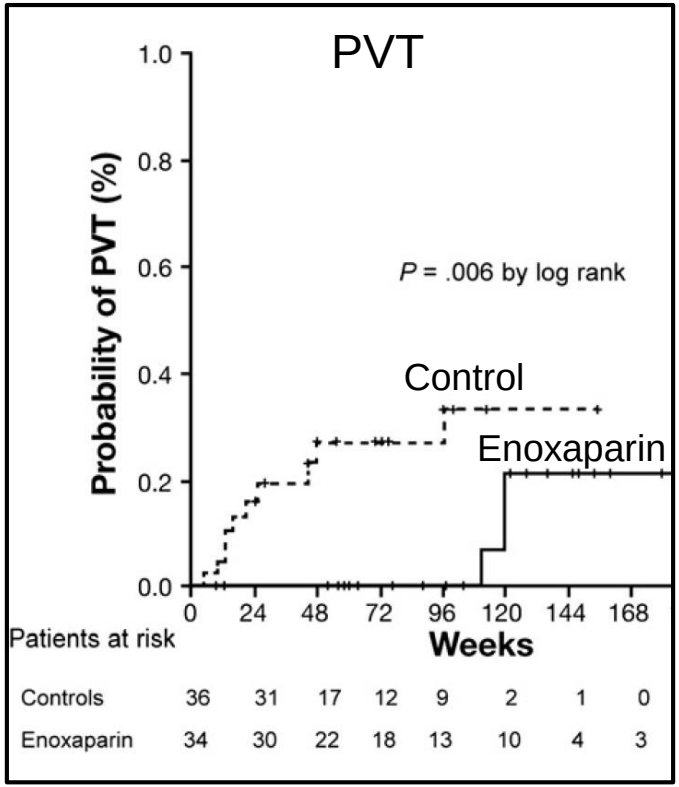
4 studies; 158 patients

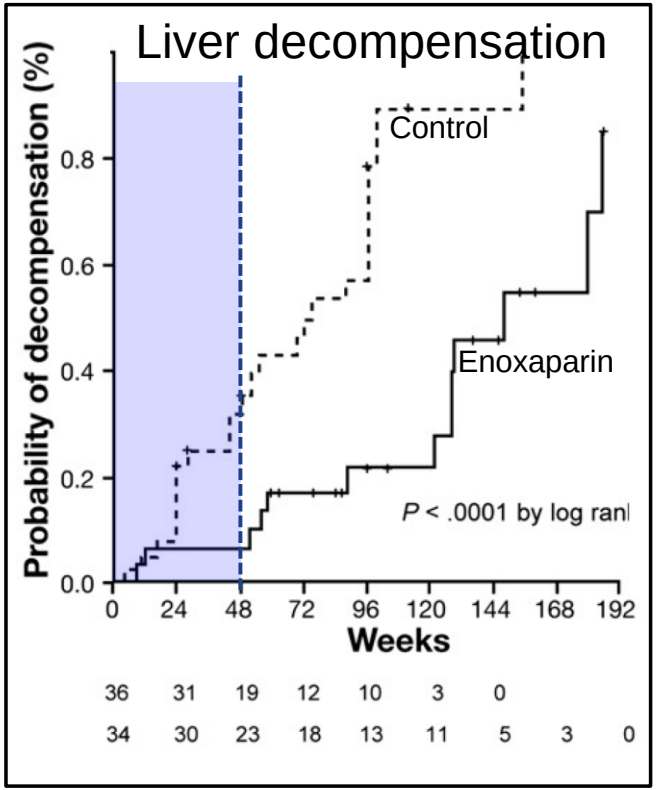
Loffredo, Gastroenterology 2017

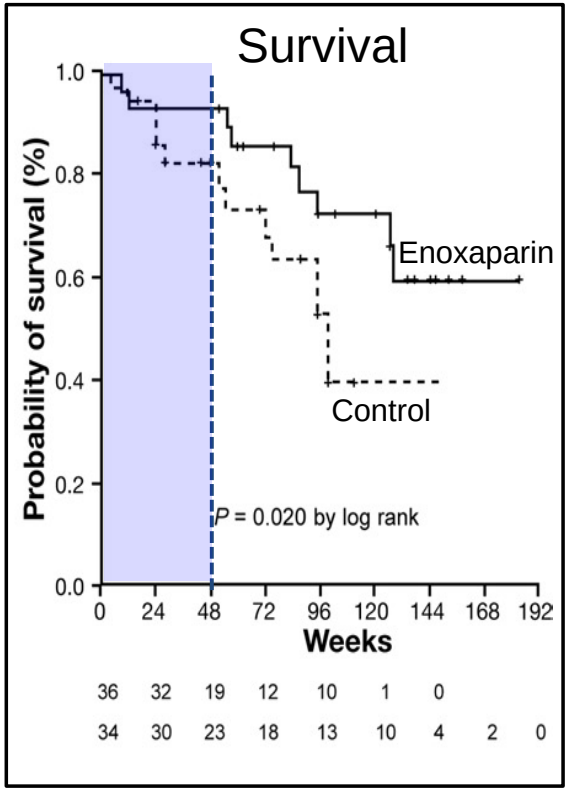
Efficacy of anticoagulation



Anticoagulants in cirrhosis improve outcome

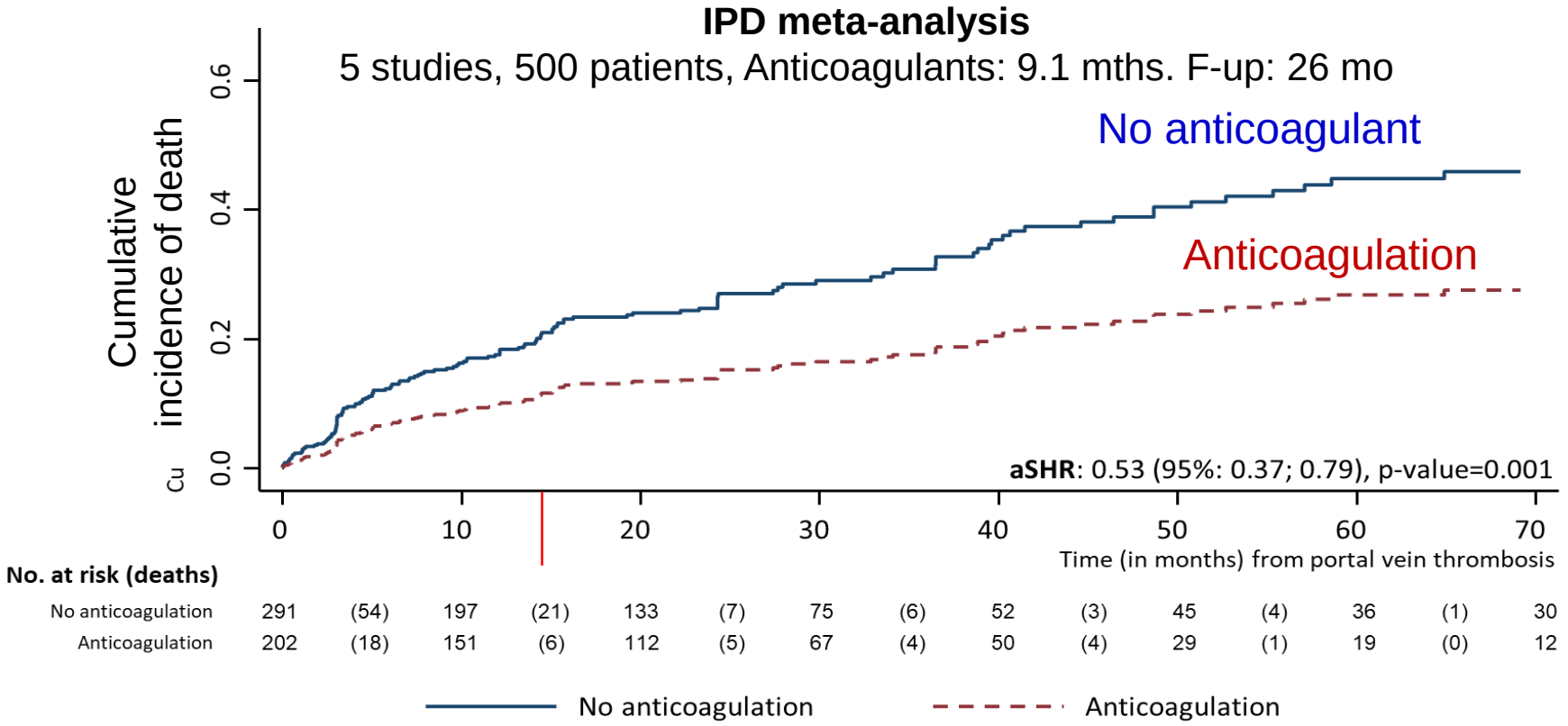






Villa et al. Gastroenterology 2012. Enoxaparin 4.000 UI/d, for 12 mo.

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

Coagulopathy and anticoagulation in cirrhosis

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What kind of anticoagulants in cirrhosis?

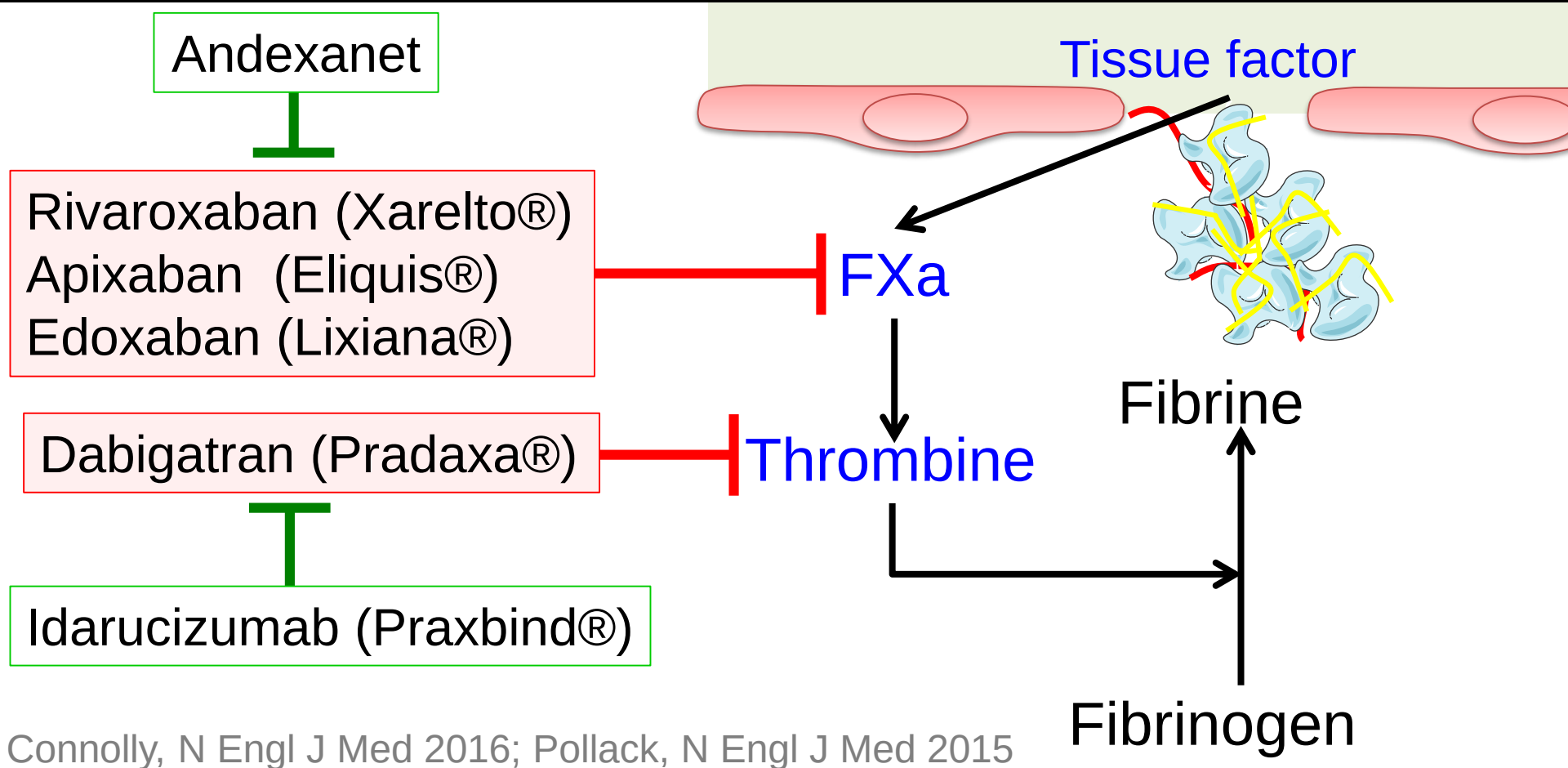
Baveno VII
Consensus Workshop
&
Pediatric Research Workshop

Start using LMWH

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

De Franchis et al, J Hepatol 2022

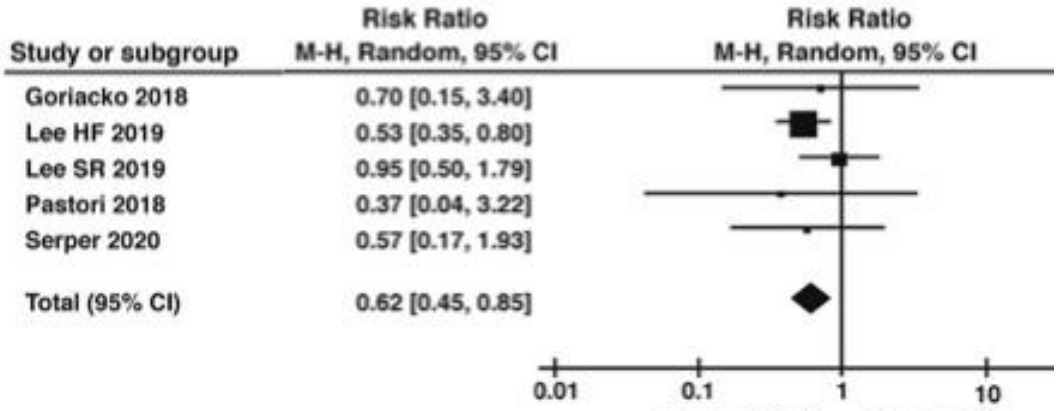
Direct oral anticoagulants (DOACs)



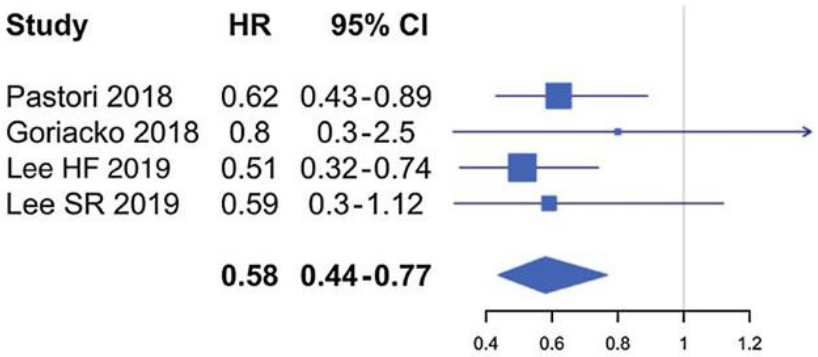
Connolly, N Engl J Med 2016; Pollack, N Engl J Med 2015

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 *In Press*

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

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MALADIES VASCULAIRES
DU FOIE

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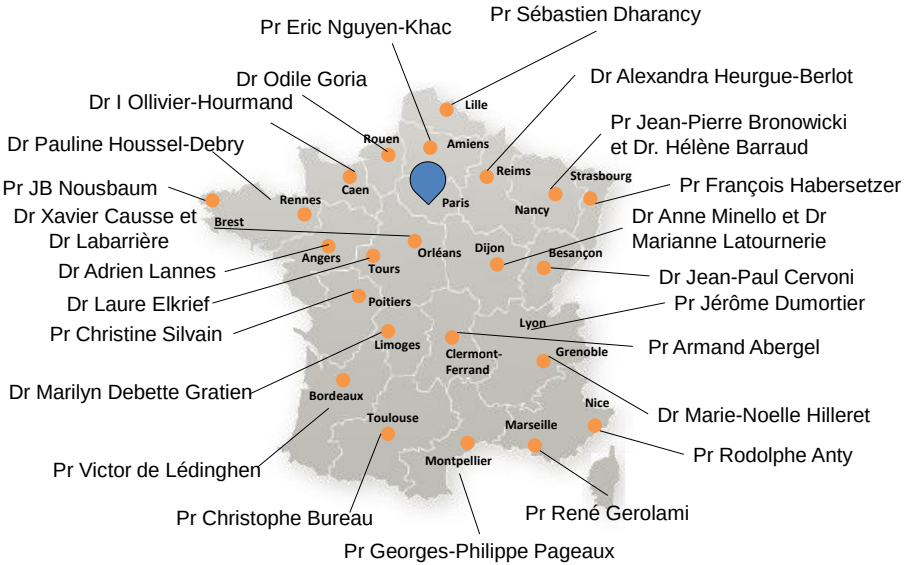
FILIÈRE DE SANTÉ MALADIES RARES DU FOIE DE L'ADULTE ET DE L'ENFANT

Centre de compétence maladies vasculaires du foie



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Instituts thématiques

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Institut national
de la santé et de la recherche médicale

Université Paris Cité

CRI
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Hepatology unit, Beaujon Hospital
Reference center for vascular liver diseases

Inserm U1149 – ATIP AVENIR, www.rautoulab.com/
Team "*vessels in liver diseases*"

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SNFGE

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Les Programmes Hospitaliers de Recherche Clinique (PHRC)

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HORIZON 2020

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