Anticoagulation Trials in Cirrhosis: Lessons Learned

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International Congress on Coagulopathy in Liver Disease

Hemostasis and Thrombosis in Liver Disease: from Bench to Bedside

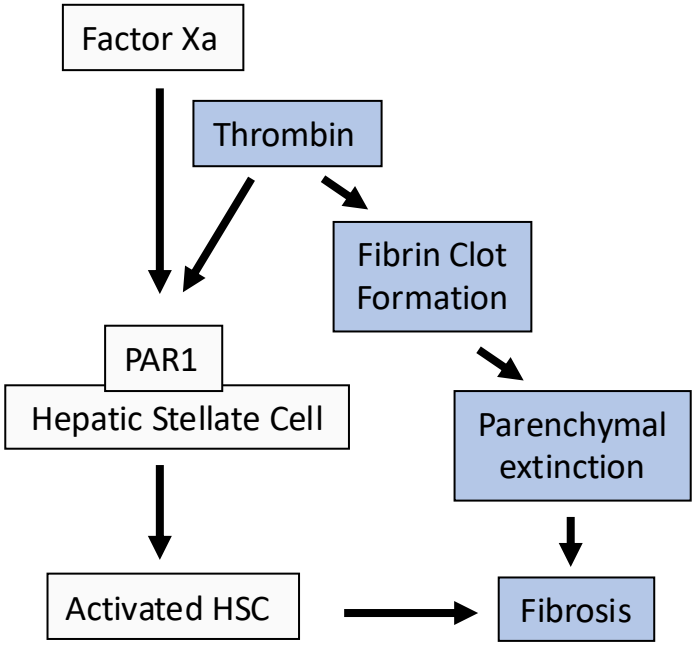
Castellana Grotte (BA)
8-10 April, 2026

- Anticoagulation in Cirrhosis to treat Thrombosis.
  - Clinically relevant efficacy
  - Favorable safety-benefit balance

- Is there a potential role of Anticoagulation as Disease Modifying Therapy in Cirrhosis?

The pre-clinical rationale

In Cirrhosis, there is an Increase in Procoagulants and in Thrombin Generation



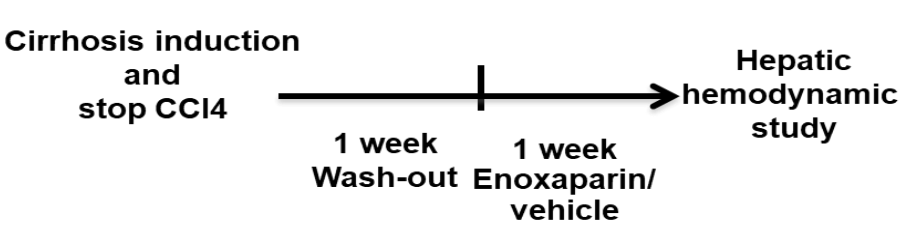
Microthrombi of portal and hepatic vein

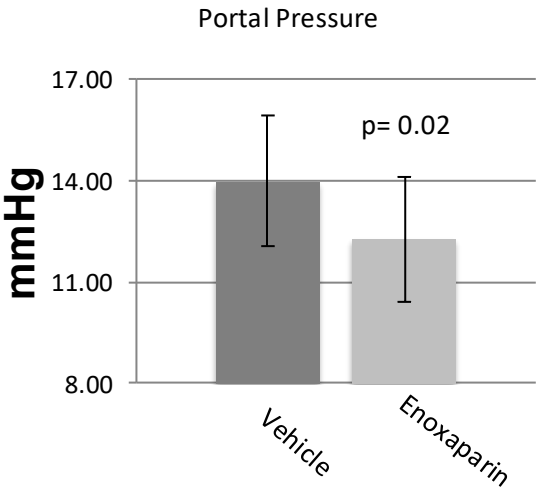
Tissue ischemia, cell death, fibrosis, parenchymal extinction accelerated disease progression

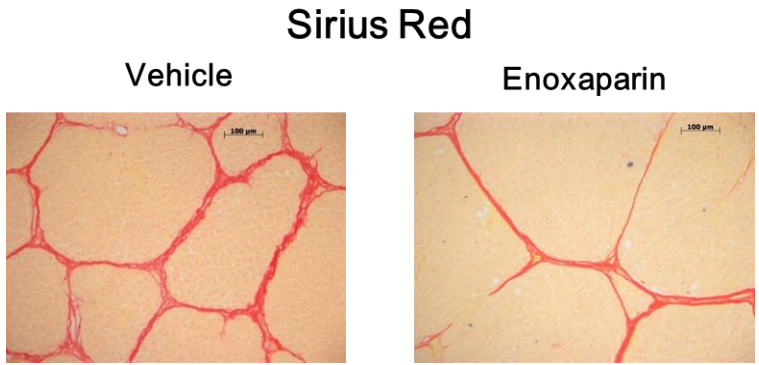
Thrombin and activated Factor X

Increased fibrosis mediated by activation of hepatic stellate cell receptor PAR1

Experimental Studies

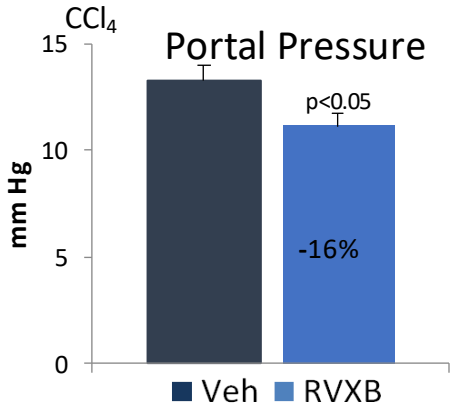


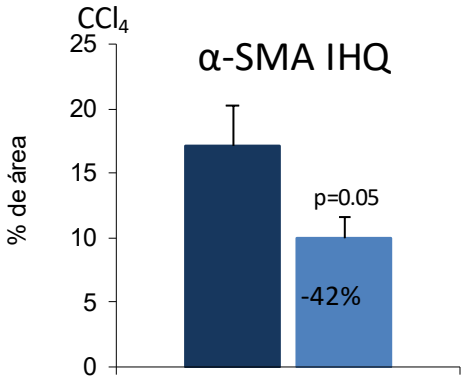


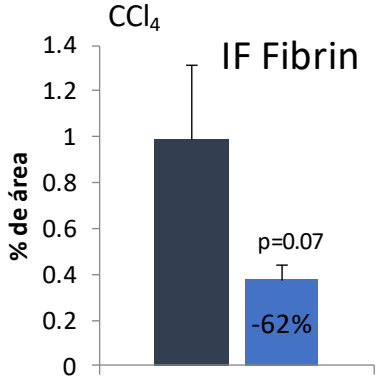


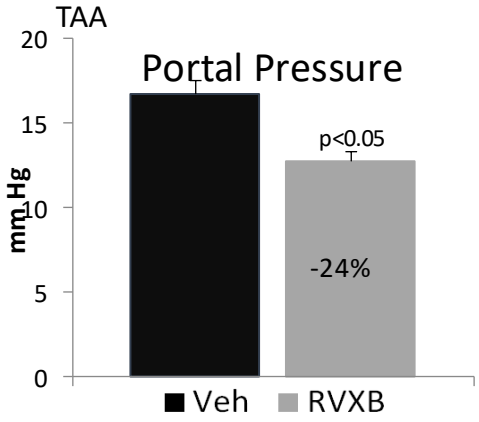
Cerini et Al, J Hepatol 2015

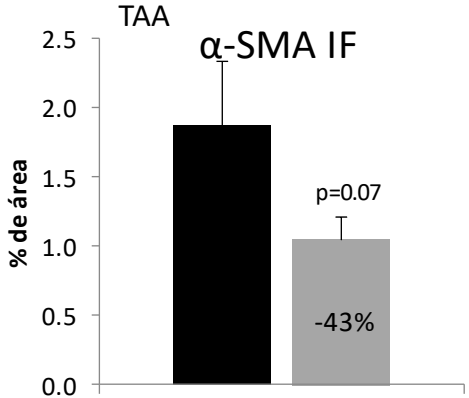
Rivaroxaban reduces PP, deactivates HSCs and reduces hepatic microthrombi in two different advanced experimental models of cirrhosis

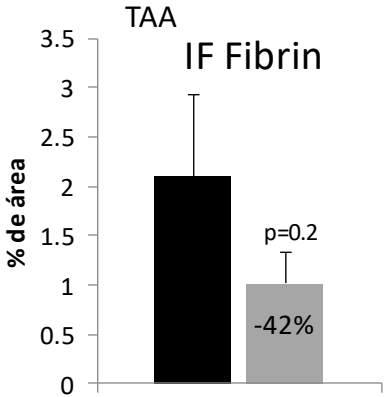












Vilaseca et al, Hepatology 2017

The Clinical rationale

2,694 cirrhotic veterans with AF

- 2 cohorts using PS Matching

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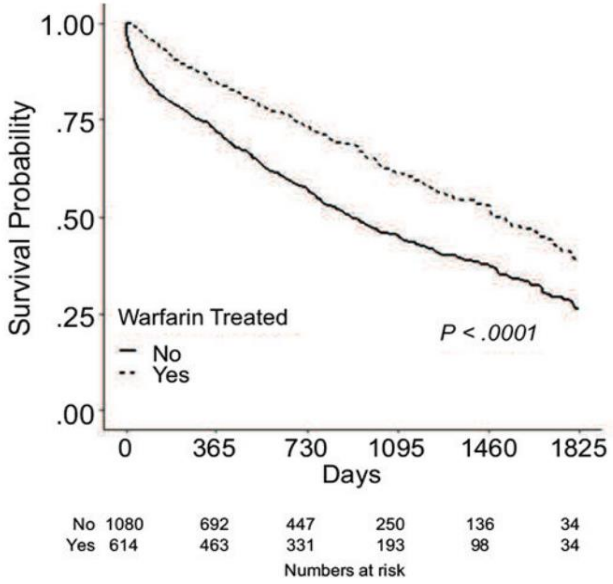
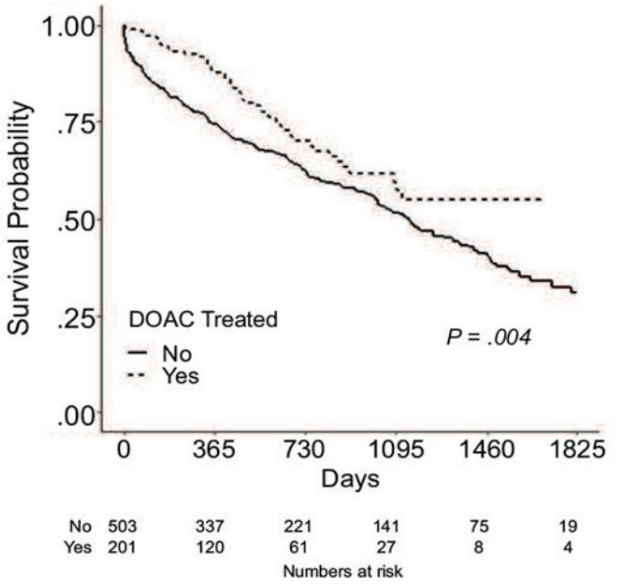
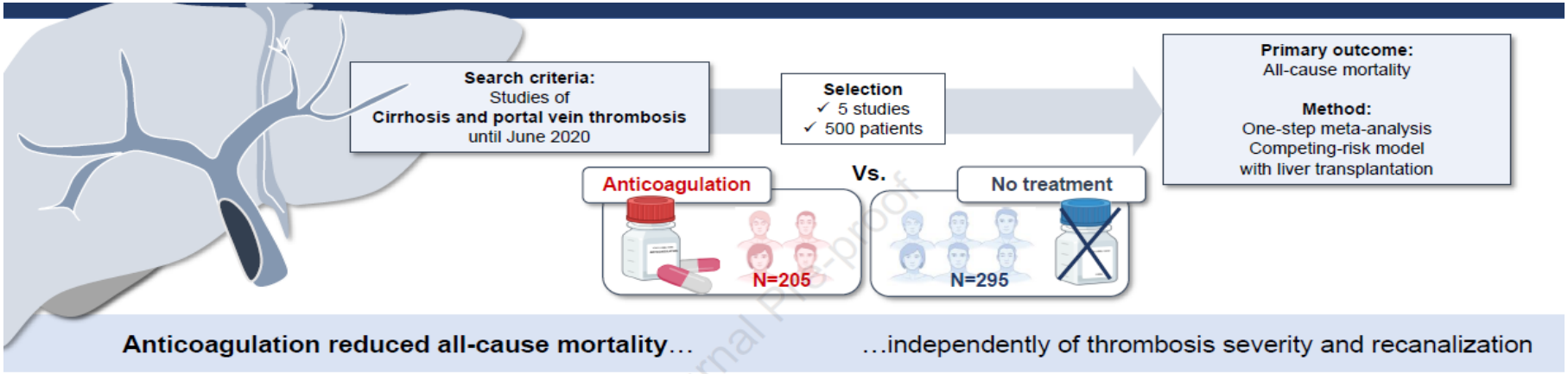




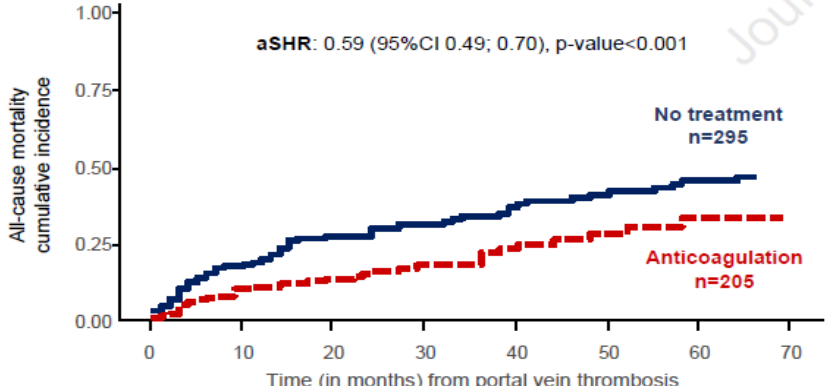
Warfarin and DOACs were associated with reduced all-cause mortality and a marked trend for less hepatic decompensation (especially ascites). Less bleeding (mainly gastrointestinal) with DOACS than with warfarin

Serper et al, Hepatology 2020

The Importal competing-risk IPD meta-analysis

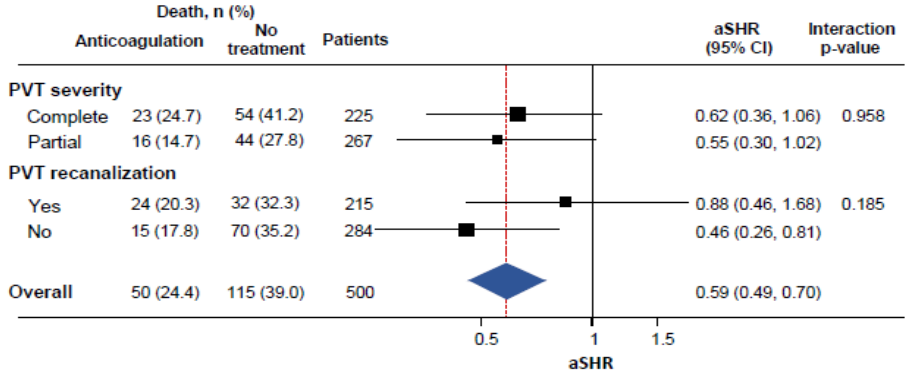


Anticoagulation reduced all-cause mortality…



No. at risk[1] (events)															
No treatment	291	(54)	197	(21)	133	(7)	75	(6)	52	(3)	45	(4)	36	(1)	30
Anticoagulation treatment	202	(18)	151	(6)	112	(5)	67	(4)	50	(4)	29	(1)	19	(0)	12

…independently of thrombosis severity and recanalization



Guerrero et a. J Hep 2023

The Importal competing-risk IPD meta-analysis

	Anticoagulant treatment (n=205)	No treatment (n=295)	P
Total bleeding events, N (%)	39 (19.0)	46 (15.6)	0.315
Portal hypertension related bleedings, N (%)	19 (9.3)	41 (13.9)	0.120
Non-portal hypertension related bleedings, N (%)	20 (9.7%)	5 (1.7%)	<0.001
Intracraneal hemorrhage	1		
Gastrointestinal bleeding	6		
Epistaxis, gingivorrhagia	5	5	
Abdominal hematoma for injection	3		
Others *	5		

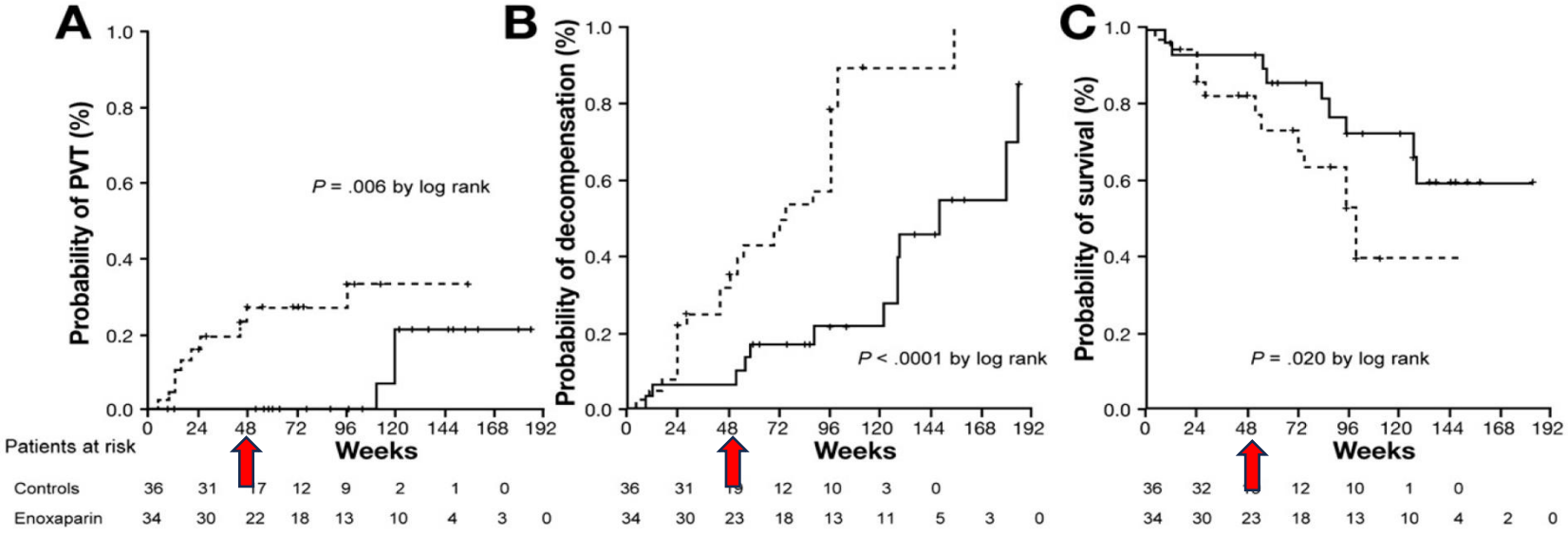
* Hemoptysis (1), post-surgical hemorrhage (1), purpura (1), unspecified (2)

⇦ Significant in the agregated meta-analysis by Intagliata et al. Gastroenterology 2021

Guerrero et a. J Hep 2023

The RCTs

- Nonblinded, single-center study. Including 70 pts with cirrhosis (Child B7-C10) randomized
  - Enoxaparin 4000UI/day (prophylactic dose) (n=34) for 48w: Mean follow-up: 89+57w.
  - No treatment (n=36) for 48w. Mean Follow-up: 58±37w.
  - Primary end point: 2-year prevention of PVT



Villa et al. Gastroenterology 2012

The RCTs (CIRROXABAN Study)

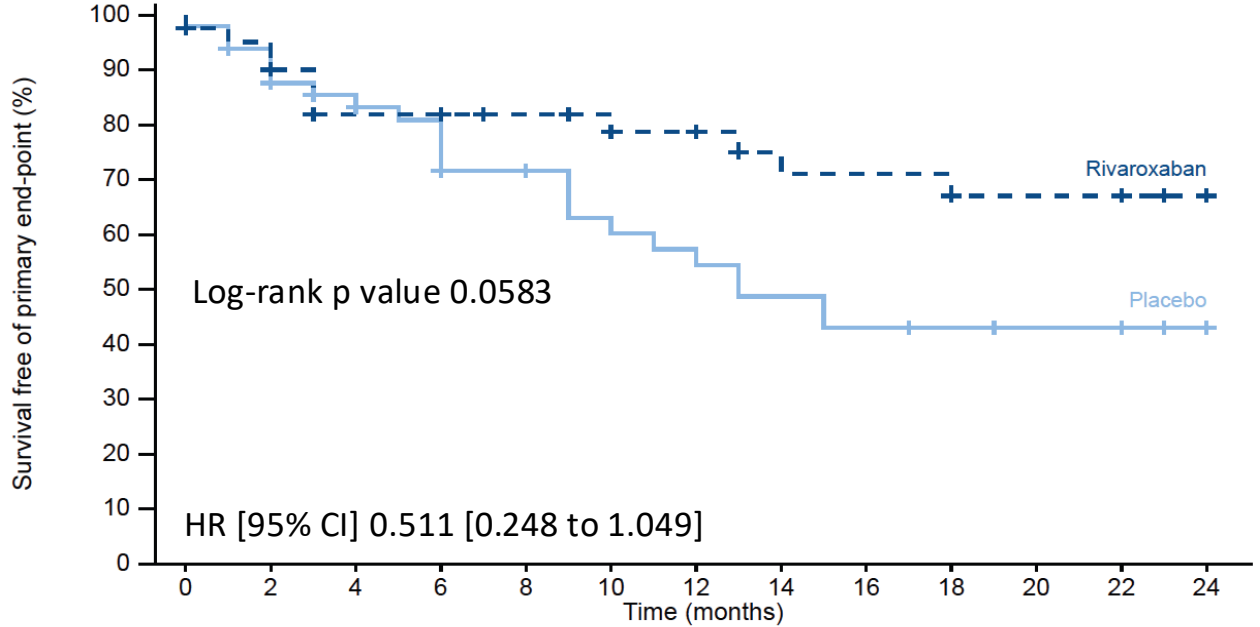
- Doubleblind, placebo-controlled, multicenter randomized trial.
- Rivaroxaban 10 mg/day vs Placebo for 2 years.
- Primary composite endpoint: Development at 2 years of PHT-related complication or death or liver transplantation)
- Secondary: PVT, Each of the PHT complications, death, bleeding.
- Calculated sample size: 160 patients (80 per group) Child-Pugh score between B7 and C10

Low recruitment rate (competing studies) after 50 months, 90 patients included Stop the study

41 in the rivaroxaban group and 49 in the placebo group.

Puente et al. J Hepatol 2025

Survival free of the primary composite endpoint: liver decompensation or death/liver transplant

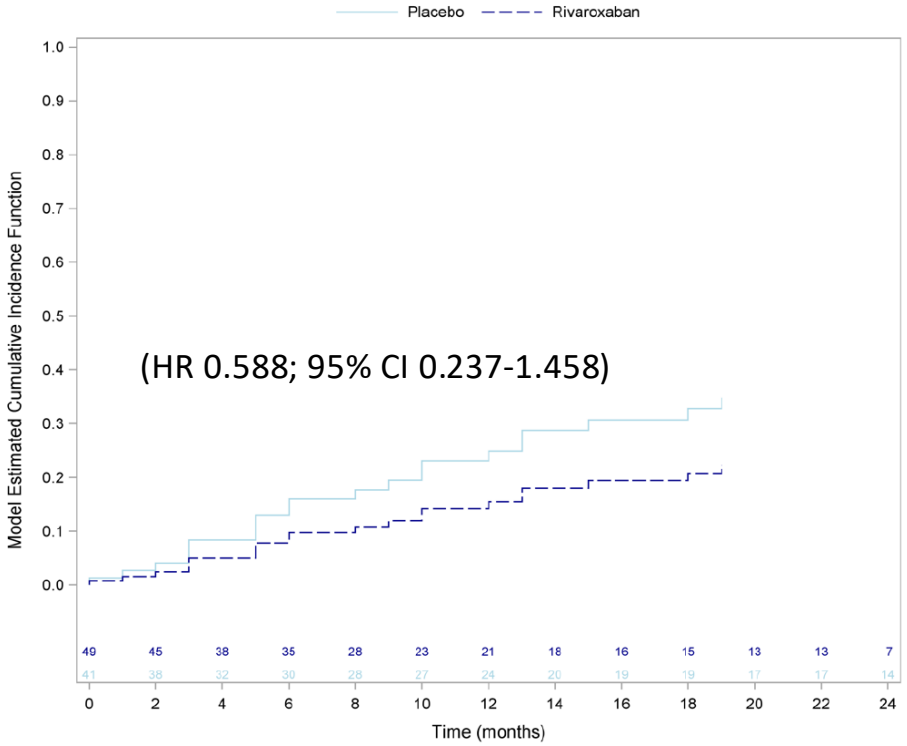


N° at risk													
Placebo	49	45	38	35	26	22	20	17	15	14	13	13	7
Rivaroxaban	41	38	29	29	27	26	23	19	18	18	16	16	13

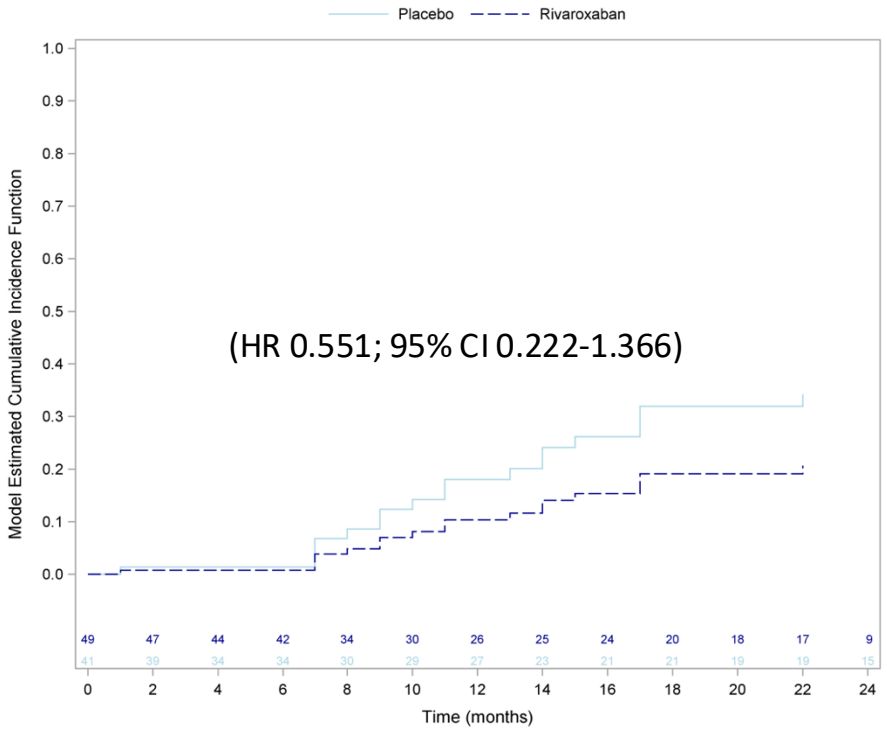
Intention-to-treat (ITT) approach, including all patients who were randomized and had received at least one dose of medical product.

Puente et al. J Hepatol 2025

Ascites with Transplant and death as competing events



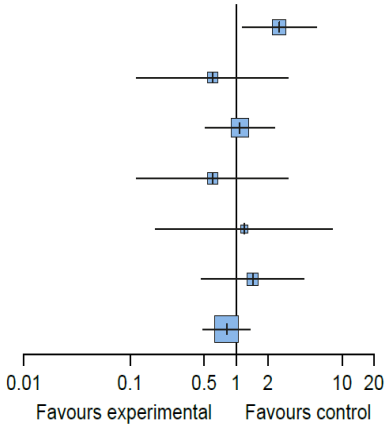
Death with trasplant as a competing event



Puente et al. J Hepatol 2025

Safety. Cirroxaban Study

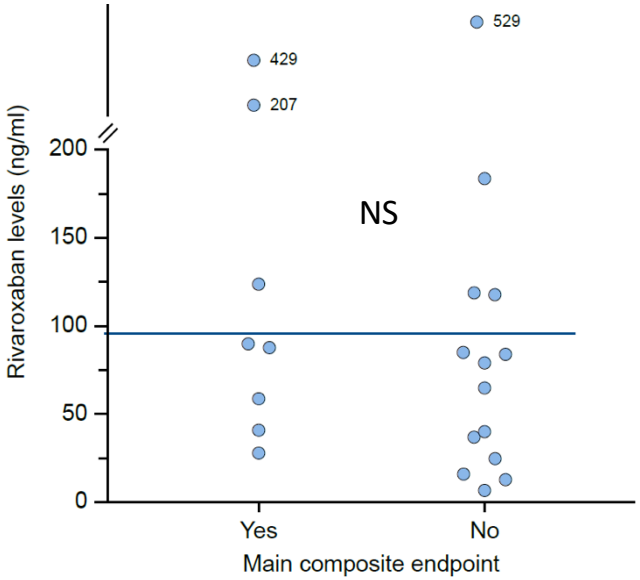
Adverse events	Rivaroxaban events	Rivaroxaban total	Placebo events	Placebo total	Risk	RR	[95% CI]	Weight (%)
Bleeding	15	41	7	49		2.56	[1.16; 5.67]	19.2
Hepatotoxicity	2	41	4	49		0.60	[0.12; 3.10]	6.2
Infection	10	41	11	49		1.09	[0.51; 2.30]	20.7
Neoplasm	2	41	4	49		0.60	[0.12; 3.10]	6.2
AKI	2	41	2	49		1.20	[0.18; 8.12]	4.7
Pain	6	41	5	49		1.43	[0.47; 4.36]	11.9
Others	15	41	22	49		0.81	[0.49; 1.35]	31.2

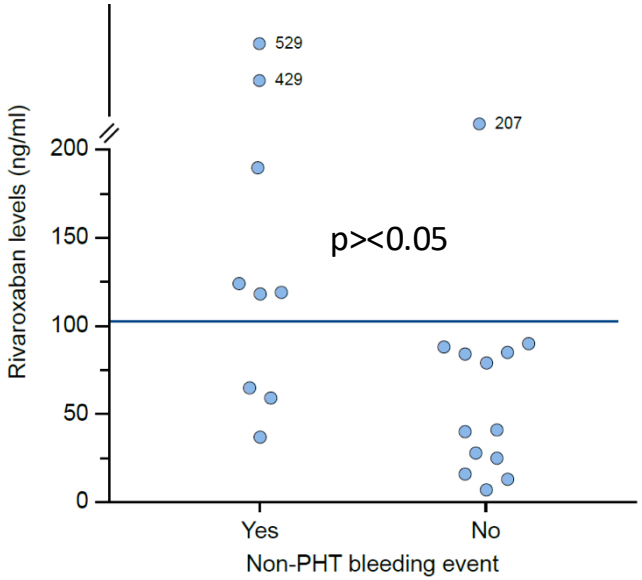


Non-PH related bleedings were more frequent in patients treated with Rivaroxaban

Puente et al. J Hepatol 2025

Rivaroxaban levels after 15 days of Rx and Clinical events (primary outcome and non-PH bleeding) (n=22)





Rivaroxaban levels above 100 ng/ml did not offer more benefit but were associated with a higher risk of developing non-PHT-related bleeding events.

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Lessons Learned – Still Learning !

- There is a strong biological rationale supporting a potential benefit of anticoagulant therapy in preventing cirrhosis progression
- Anticoagulation well tolerated. No fears!. Probably the same risk of non-PH bleeding than in non-cirrhotics
- Currently, DOACs better than Vitamin K antagonists, Apixaban better than Rivaroxaban (less influenced by liver function, less bleeding)
- Anticoagulation is highly likely to be effective, but there is limited industry interest. Recruitment for studies competes with other pharmacological alternatives that have greater industry appeal.

Anticoagulation for Development of Further Decompensation and Survival in Advanced Cirrhosis After Transjugular Intrahepatic Portosystemic Shunt: a Multicenter Randomized Controlled Study

- Rivaroxaban 10mg/day 2 years vs no intervention.
- IP: Guohong Han, (Xina). First version 2016. Status unknown

Impact on Morbidity and Mortality of Prophylactic Dosing of Low Molecular Heparin in Child-Pugh B Cirrhotic Patients (Childbenox)

- Enoxaparin 4.000 units 2 years vs no intervention.
- IP: Armelle Poujol-Robert. Assistance Publique - Hôpitaux de Paris. First version 2014. Premature discontinuation of inclusions by the sponsor for low inclusion (2018: 16 recruited. Estimated 138)

Apixaban to Prevent dEcompensation of eArly liver CirrHosis (APEACH)

- Apixaban 2.5mg/12h vs placebo.
- Estimated sample size: 1.100 patients with compensated cirrhosis
- IP: Prof. Alastair O'Brien. University College London. Start date June 2025.

Baveno VIII. March 2026. Anticoagulation in cirrhosis

3.22. There is insufficient evidence to recommend statins or **anticoagulation** to prevent decompensation (LoE 3) but they should used or maintained if there are approved indications. (LoE 2; SoR: strong; Agreement: 99%)

9.21. Anticoagulation is recommended in patients with cirrhosis and (i) any PVT in potential candidates for liver transplantation, (ii) recent completely or partially occlusive (>50%) thrombosis (iii) symptomatic PVT, independently of the extension, (iv) PVT and HCC , especially those with indication for local regional therapy (LoE3, strong) (Changed)

Barcelona Portal Hypertension/Vascular Liver Group

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A Alvarez JC Reverter
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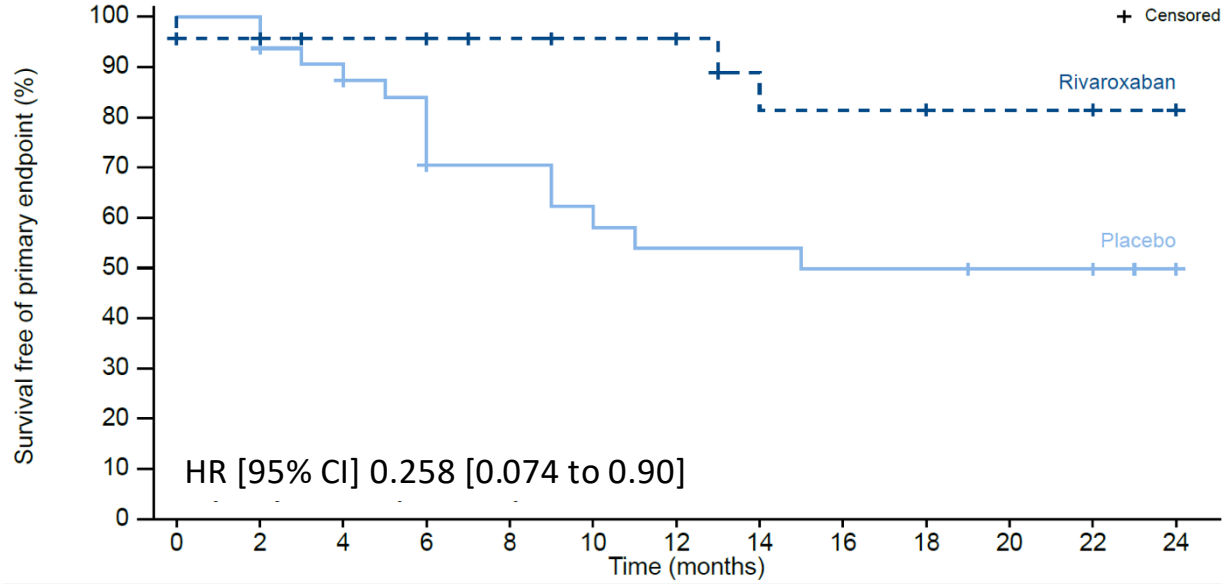
M Torrente

Survival free of the primary composite endpoint. First or further liver decompensation, death or LT (ITT) in Child Score 7 (55/90:62%)



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Puente et al. J Hepatol 2025

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2,694 cirrhotic veterans with AF

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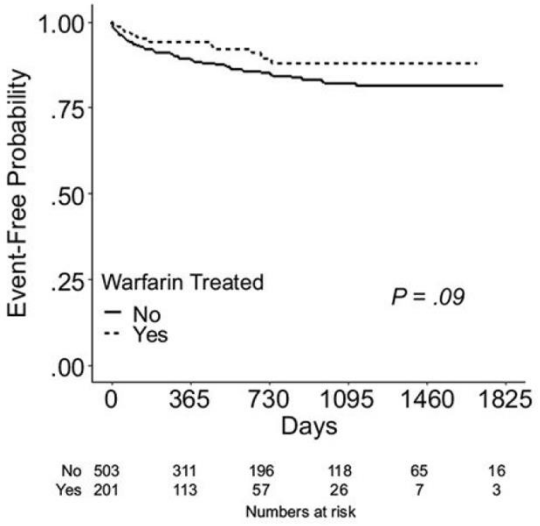

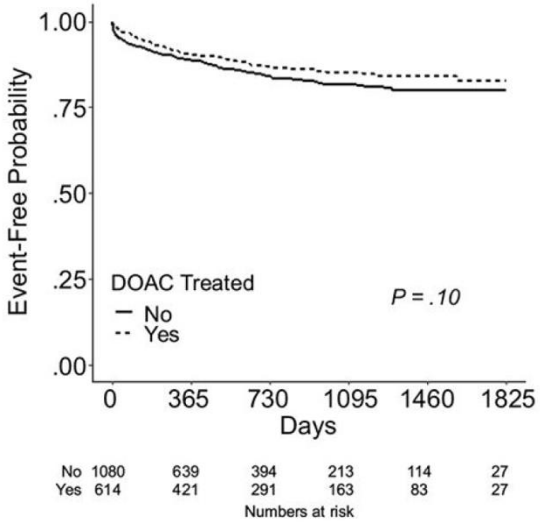

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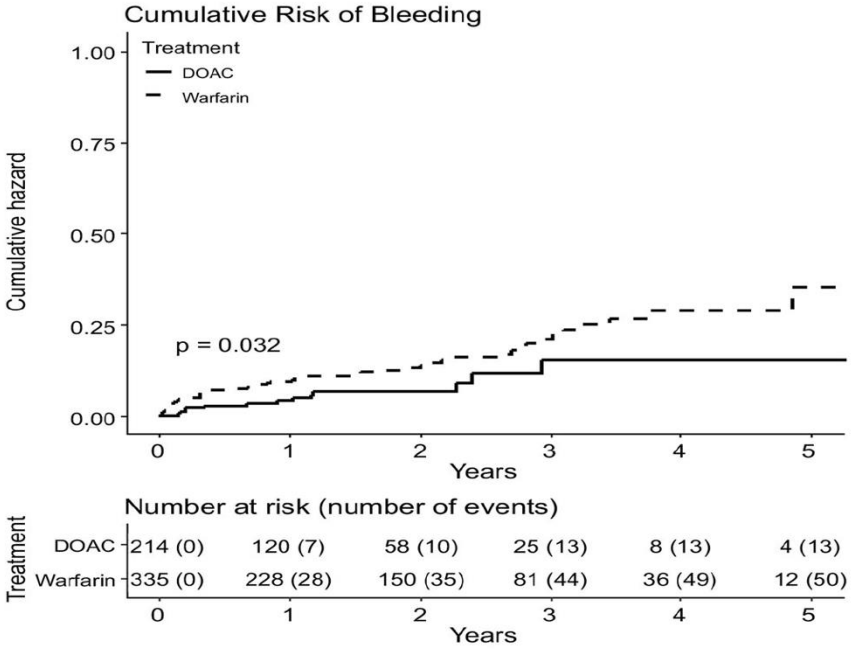

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