4th DECISION GA Meeting

Madrid, 18-21 Oct 2022

Keynote

Overview of the effects of LMWH in cirrhosis

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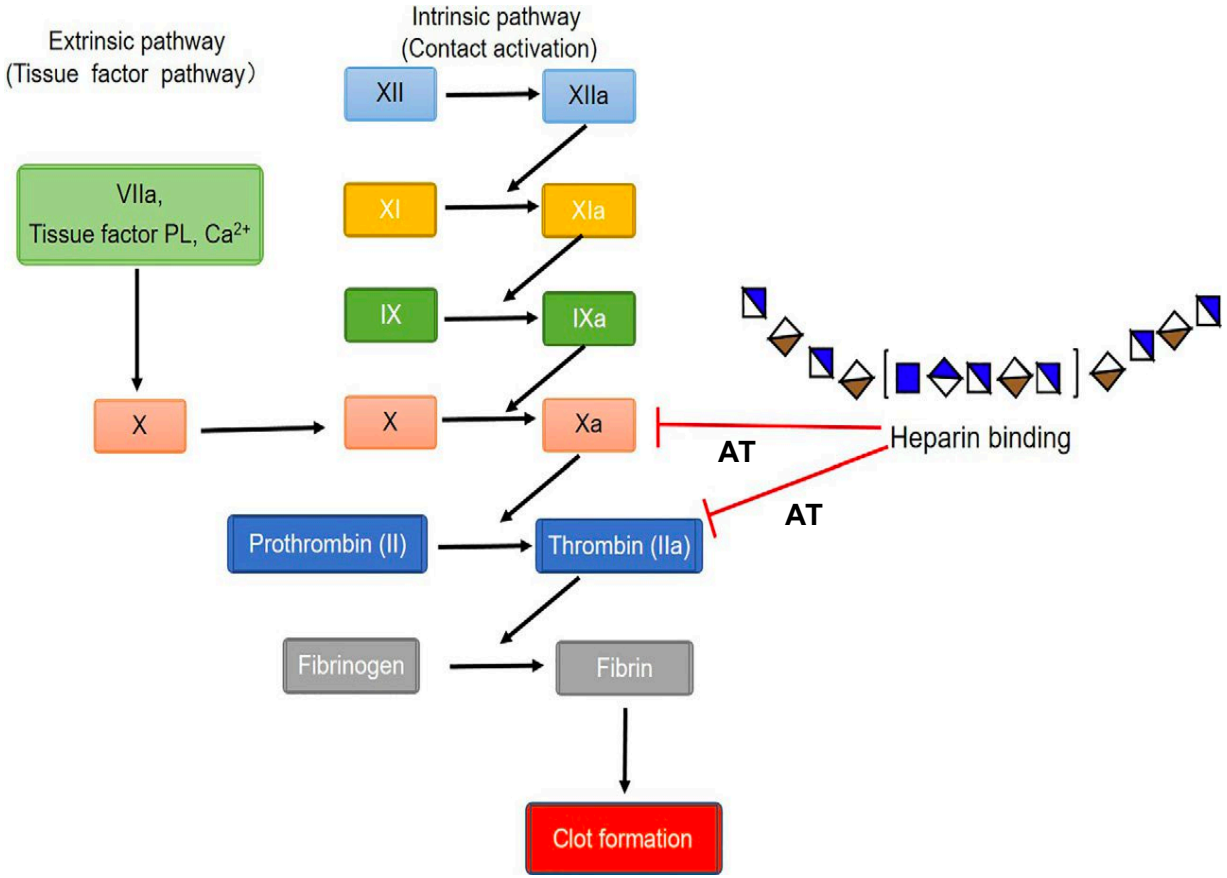
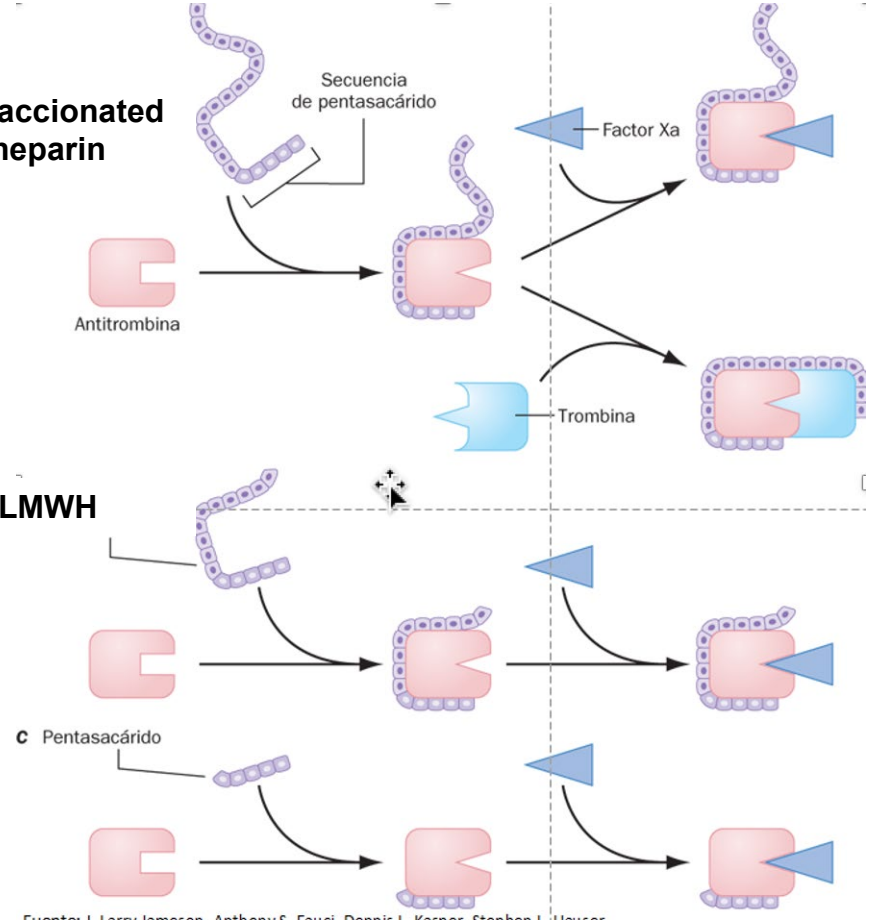
Madrid

Agenda

- Mechanism of action of anticoagulants
- Pathophysiological basis for long-term AG in cirrhosis
- Anticoagulation in portal vein thrombosis
- Anticoagulation improves survival in cirrhosis?

Mechanism of action of heparin





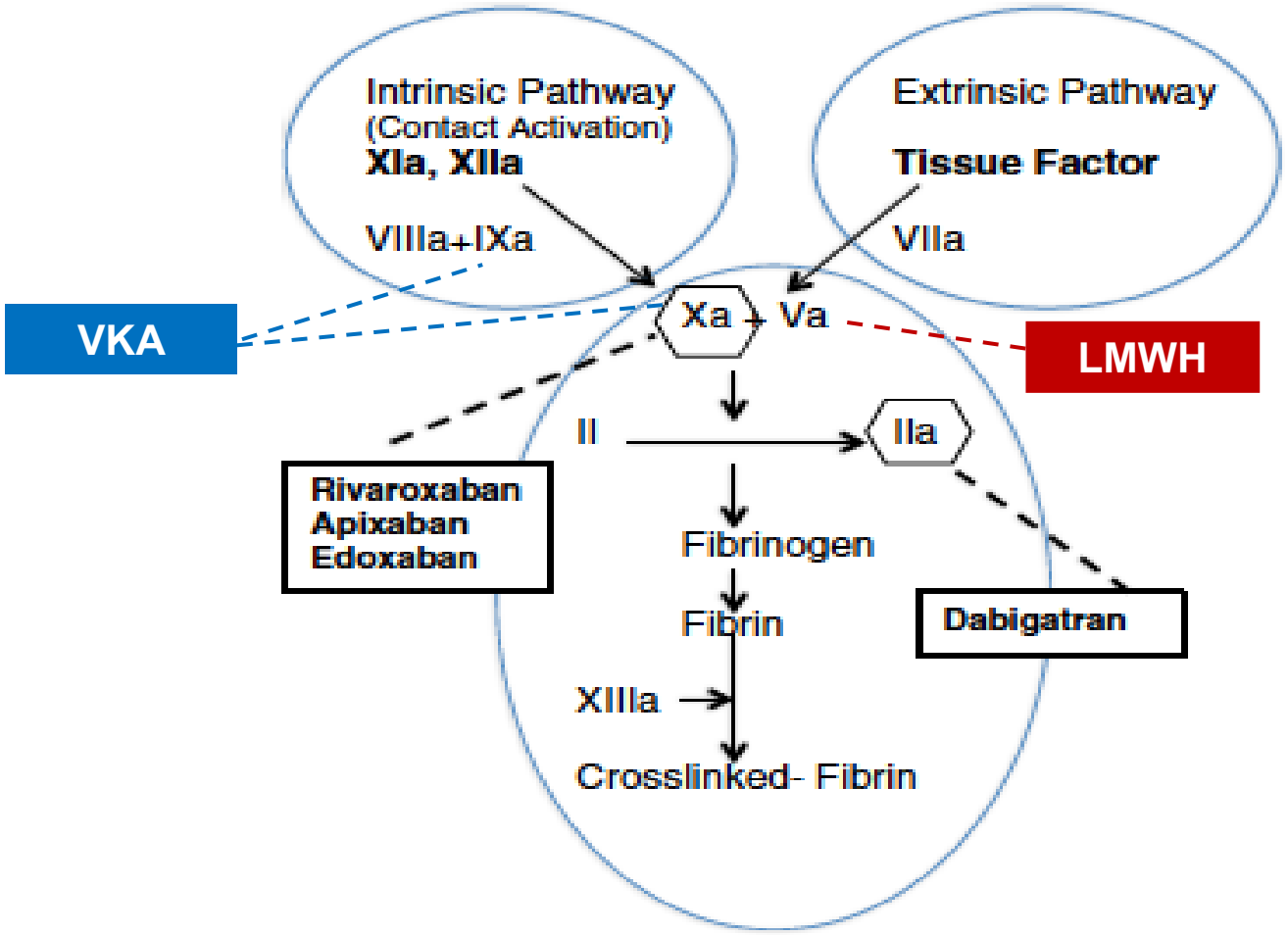
Harrison's, 2021

Role of heparin and related binding proteins

Coagulation pathway	Factors IIa (thrombin), IXa, and Xa
	Antithrombin (AT)
	Protein C inhibitor
Inflammation	Platelet growth factor 4, PGF4
	Interleukin 8, IL-8
	Stromal-derived factor 1a
	Neutrophil elastase
	P-selectin, L-selectin
	CD11b/CD18 (MAC1, macrophage 1)
	Platelet factor 4
	ECP, eosinophil cationic protein; MBP, major basic protein
Growth factor binding and signaling	Fibroblast growth factors (FGFs)
	Endothelial growth factors (EGFs)
	Platelet derived growth factors (PDGFs)
Angiogenesis	VEGF-A
	Angiopoietins/angiogenin
	Midkine/pleiotrophin
	Platelet-derived growth factor (PDGF)
	Heparin-binding EGF-like growth factor (HB-EGF)
	Angiomodulin (AGM/TAF/mac25)

C Hao et al. Progress Mol Biol 2019

Mechanism of action of anticoagulants



Inflammation, microthrombosis and cirrhosis progression

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Cirrhosis

Endothelial liver damage
Inflammation

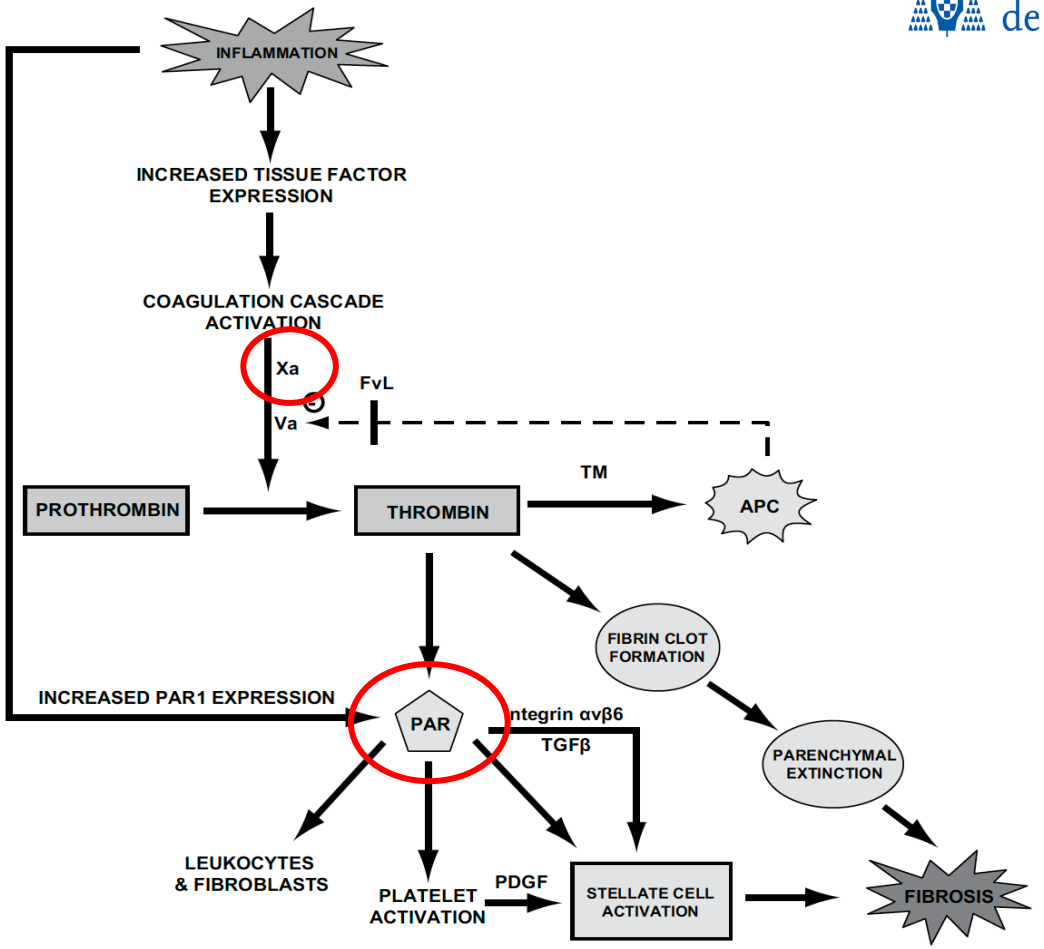
Factor X activation
↑ thrombin generation in cirrhosis

HSC activation

Microthrombosis

Parenchyma extinction

Fibrosis progression



* Protease activated receptors (PAR)

IR Wanless et al. Hepatology 1995
Q Anstee et al. Clin Liver Dis 2009

Chronic enoxaparin in rats with cirrhosis

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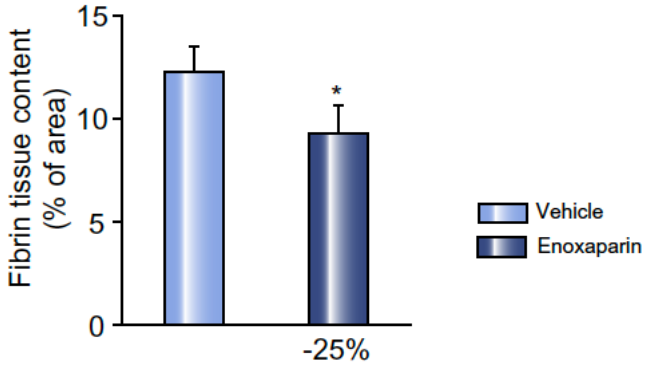
CCl_4-cirrhotic rats

Enoxaparin 1.8 mg/kg.d sc, 2 wk

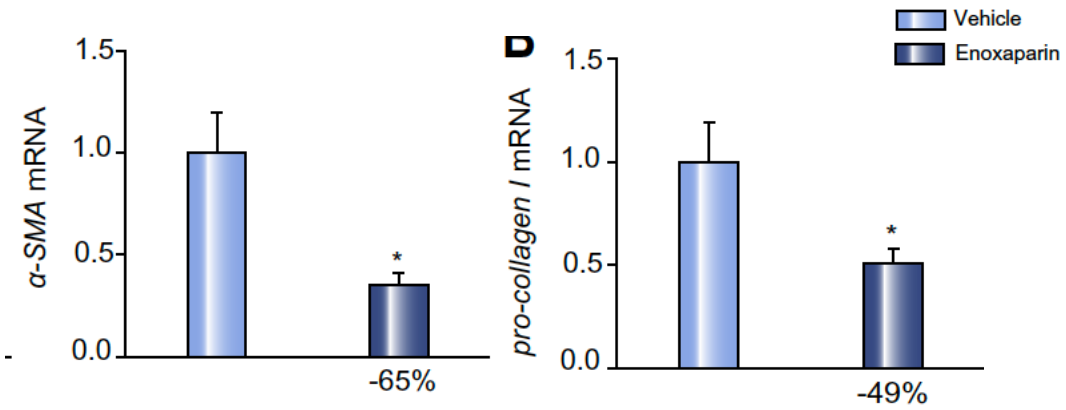
Splanchnic hemodynamics

Variable	Vehicle n = 7	Enoxaparin n = 5	*p* value
PP (mmHg)	12.1 ± 1.8	10.2 ± 0.5	0.04
MAP (mmHg)	105 ± 15	110 ± 31	0.7
PBF (ml/min)	11.9 ± 2.9	16.9 ± 4.7	0.04
HVR (mmHg/ml/min^{-1})	1.1 ± 0.3	0.6 ± 0.2	0.02
HR (beats/min)	347 ± 40	394 ± 54	0.11

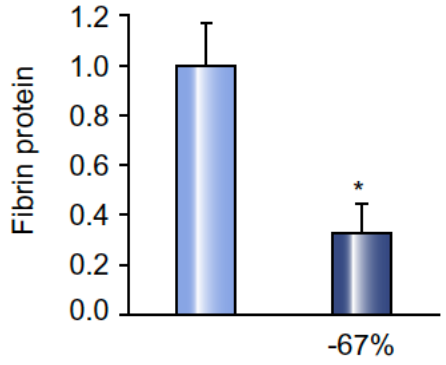
Liver fibrosis Sirius red



HSC activation



Fibrin



Similar results in **TAA-cirrhotic rats**

F Cerini et al. JHEP 2016

Chronic rivaroxaban in rats with cirrhosis

CCl_4-cirrhotic rats
Rivaroxaban 20 mg/kg.d, 2 wks

- ↓ **portal pressure** -16%, ↓ hepatic vascular resistance
- ↓ **hydroxyproline content** and collagen protein expression
  Unchanged liver fibrosis
- **Deactivation of HSC** (↓ SMA, ↓ pro-collagen-I expression)
- ↓ **fibrin** deposition

Similar results in TAA-cirrhotic rats

M Vilaseca et al. Hepatology 2018

Sinusoidal thrombosis and mechanical forces drive hepatic fibrogenesis in chronic passive hepatic congestion

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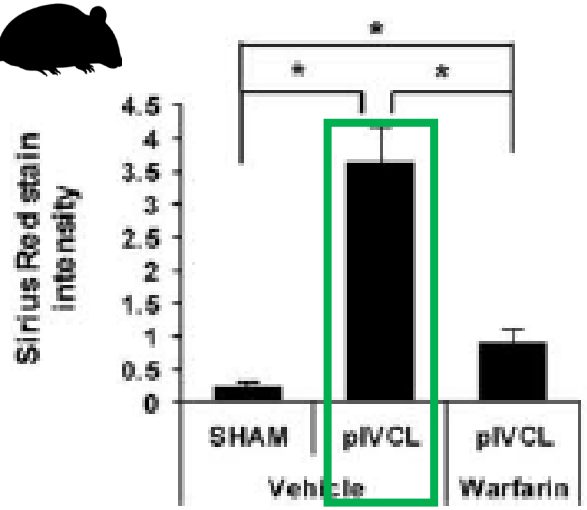
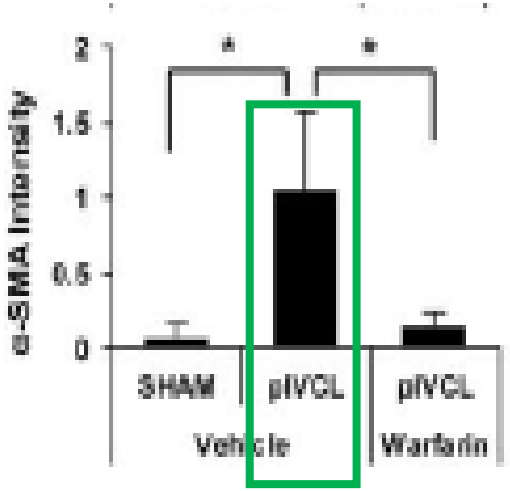
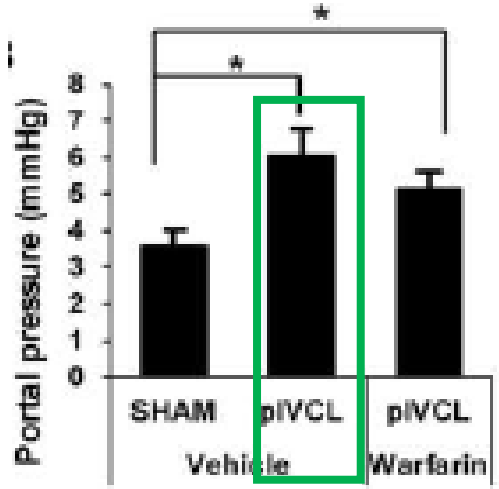
Sirius red stain

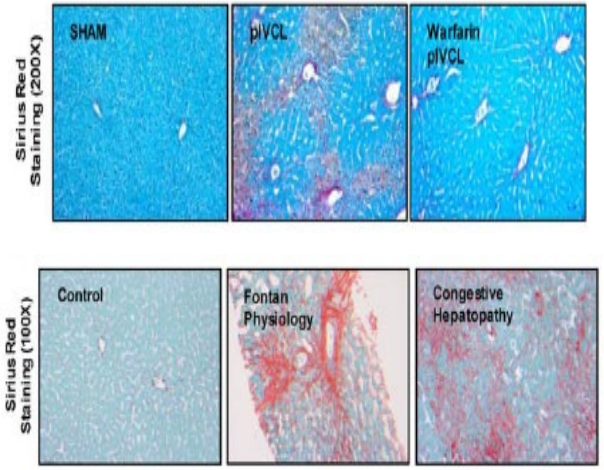


α-SMA

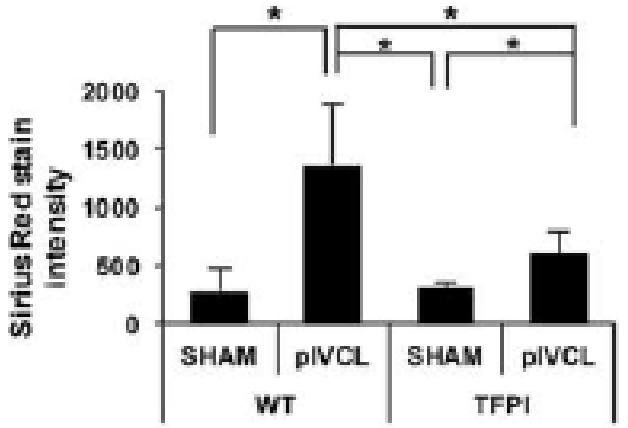


Portal pressure





Sirius red stain



DA Simonetto et al. Hepatology 2015

Sinusoidal thrombosis and mechanical forces drive hepatic fibrogenesis in chronic passive hepatic congestion

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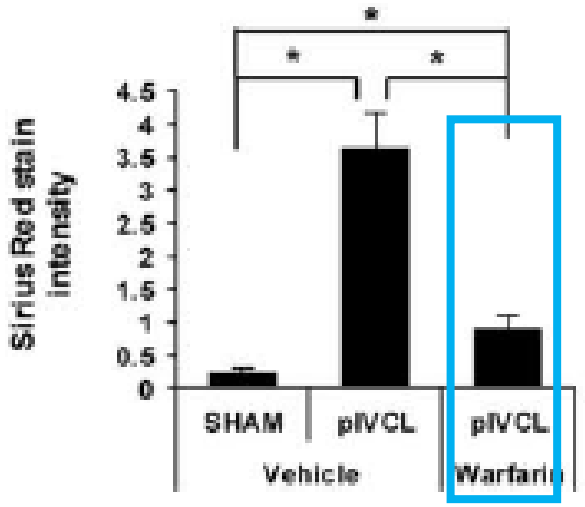
Sirius red stain



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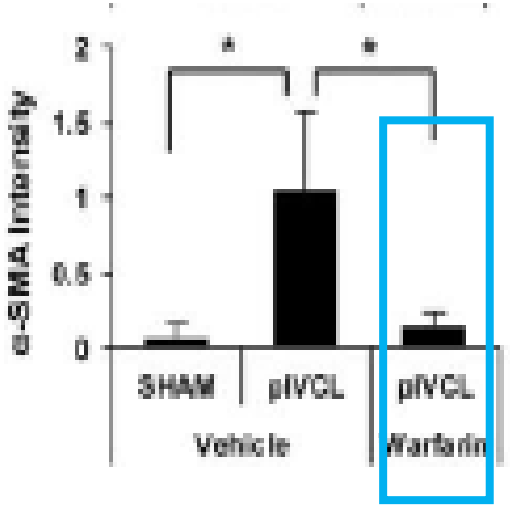
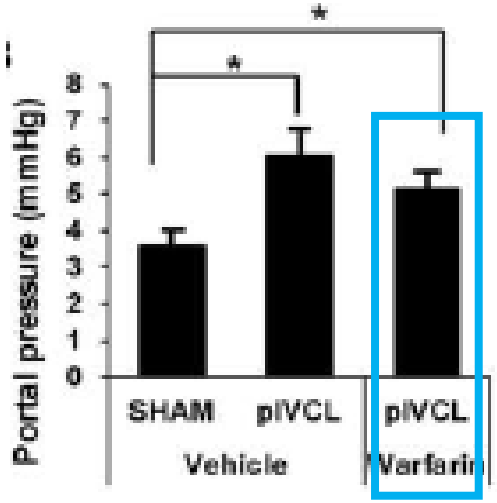
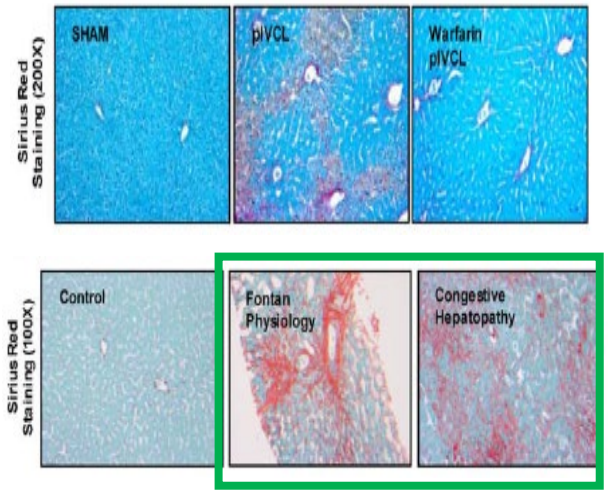


Portal pressure





DA Simonetto et al. Hepatology 2015

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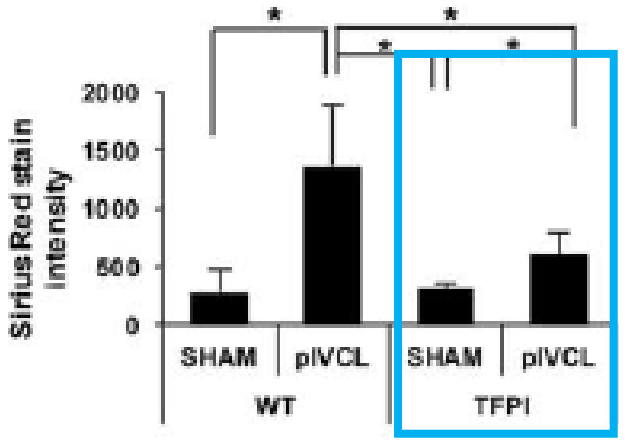

Agenda

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- **Anticoagulation in portal vein thrombosis**
- Anticoagulation improves survival in cirrhosis?

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Questions

Question 1

Should all patients with cirrhosis and recent (<6 m) complete or >50% PVT receive anticoagulation?

Question 2

Is anticoagulation a life commitment in patients with cirrhosis and PVT independently of achieving recanalization?

Anticoagulation of portal vein thrombosis in cirrhosis

CONS

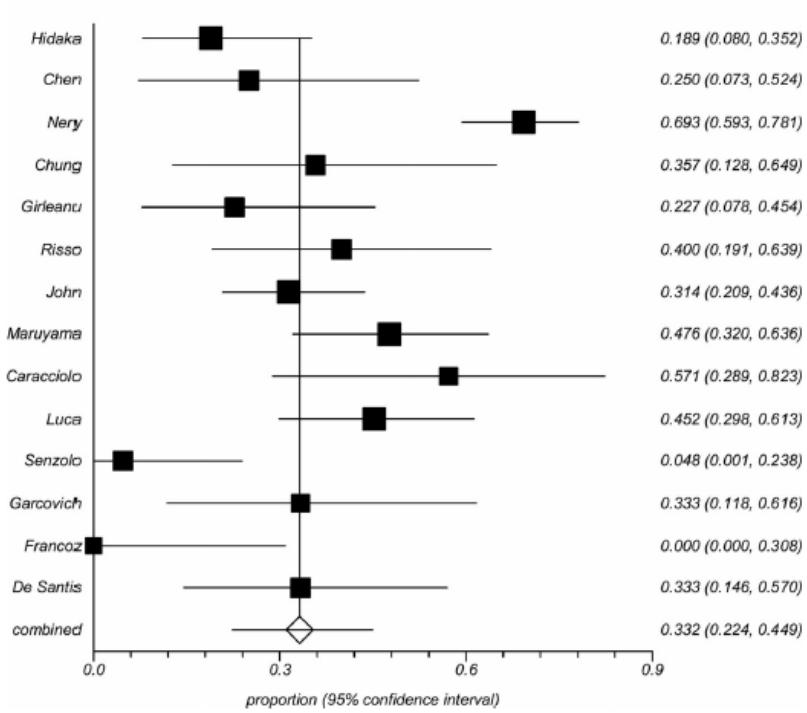
- PVT <50%: mostly transient
- Hepatic decompensation and death: independent of PVT
- Risks of AG

PROS

- Benefit of AG in recanalization and progression
- Benefit of AG in outcomes and survival?
- Low risks of AG

“Transient” portal vein thrombosis in cirrhosis

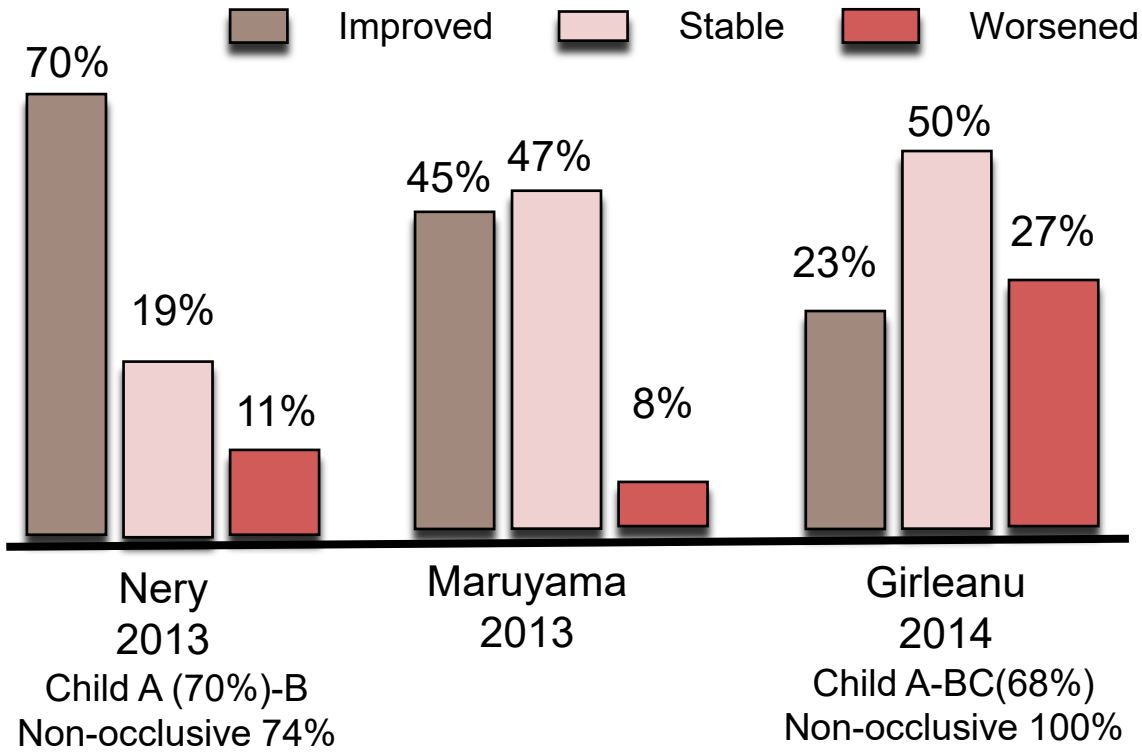
Meta-analysis, 14 cohort studies
Heterogeneity, I^2=84.2%



39.8% (95%CI 35-44)

X Qi et al. BMC Medicine 2018

~70% of PVT are non-occlusive



Trends for spontaneous recanalization:

- Degree of venous occlusion (non-occlusive <50%)
- Severity of cirrhosis (Child A)

Weak evidence

Impact of portal vein thrombosis in cirrhosis progression and survival

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Hepatic decompensation

Longitudinal prospective, 1243 pts, US q. 6 mths
86% non-occlusive, Child A-B

	Univariate Models Unadjusted Estimates			Multivariate Models Adjusted for the Baseline Prognostic Variables*		
Models		HR	95% CI	P	HR	95% CI
Liver disease progression						
- Partial PVT	1.58	1.02-2.45	0.04	1.51	0.73-3.14	0.27
- Partial or Complete PVT	1.48	0.97-2.26	0.067	1.32	0.68-2.55	0.41
Decompensation						
- Partial PVT	1.77	1.07-2.92	0.027	1.60	0.69-3.74	0.28
- Partial or Complete PVT	1.61	0.98-2.62	0.058	1.37	0.62-3.03	0.44

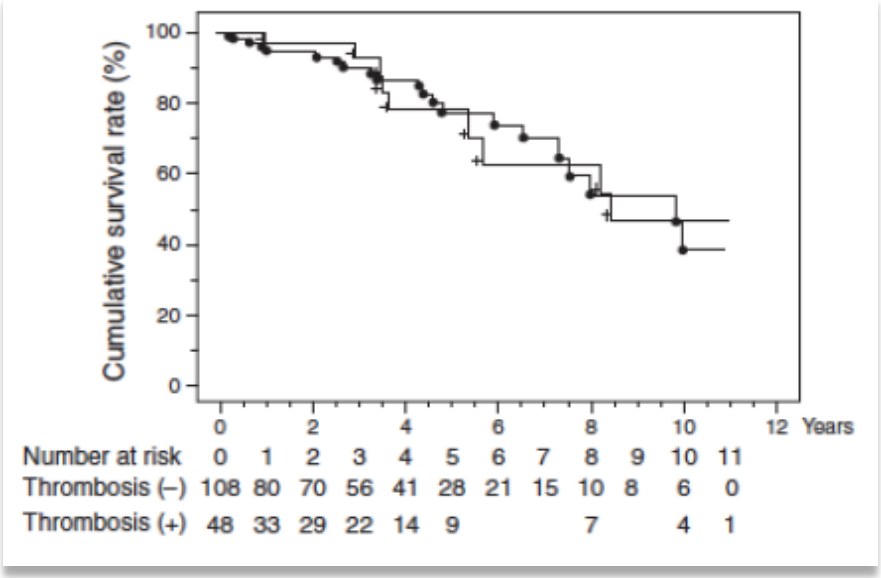
F Nery et al. Hepatology. 2014

Hepatic decompensation and death are **independent** of PVT in prospective observational studies

- US based study, 12-month f-up (2000-2006) (Nery et al.)
- US based study, 29-month f-up (2014-2019) (C Noronha et al. Liv Int 2019)
- CT based study, 24-month f-up (2014-2019) (A Luca et al. Radiology 2012)

Survival

Retrospective, 150 pts viral cirrhosis
72% non-occlusive, Child A-B-C, F-up 11 yr



H Maruyama et al. AJG 2013

Series of anticoagulation for portal vein thrombosis in cirrhosis

Author	Study type	Patients	Anticoagulation	Duration (months)	Recanalization (months)
Francoz, 2005	Prospective	19	LMWH→VKA	**8**	CR 42%
Delgado, 2012	Retrospective	55	LMWH, LMWH→VKA, VKA	**7**	CR/PR 60%
Senzolo, 2012	Prospectivo	35	HBPM	6	CR 36%, PR 27%
Chen, 2016	Retrospective	30	VKA	**8**	CR/PR 68%
Wang, 2916	Prospective	31	VKA	**12**	CR/PR 100%
Hanafy, 2018	Prospective	80	VKA, rivaroxaban	**6**	CR/PR 45, 85%
Artaza, 2018	Retrospective	32	LMWH, VKA	**13**	CR 53%, PR 19%
Pettinari, 2018	Retrospective	81	LMWH, VKA	**12**	CR/PR 57%
Scheiner, 2018	Retrospective	22	LMWH→VKA	**12**	-
Ferreira, 2019	Retrospective	37	LMWH, VKA	**25**	CR/PR 58%
Naymagon, 2020	Retrospective	60	LMWH, VKA, DOAC	**19**	CR 38, 58, 55%
Florescu, 2021	Retro- prospective	54	LMWH, LMWH→VKA	-	CR/PR 55%

Anticoagulation for portal vein thrombosis in cirrhosis

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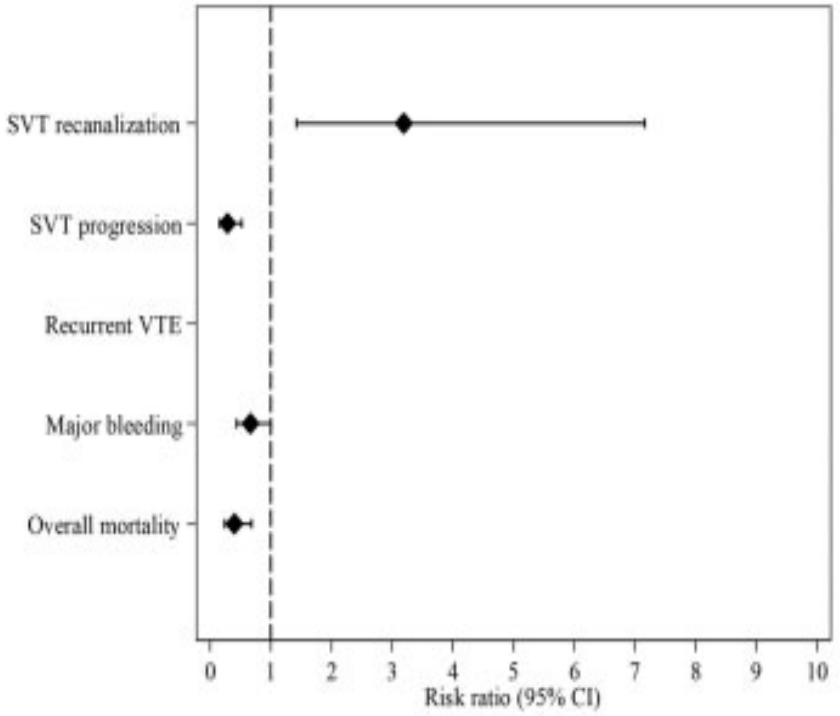
Meta-analysis, 26 studies, 1475 patients, -2019



Outcome	Anticoagulated: events (n/N, %)	Untreated: events (n/N, %)	Studies (n)	I^2 (%)	RR (95% CI)
SVT recanalization	195/305 (63.9%)	79/282 (28.0%)	9	80	3.19 (1.42-7.17)
SVT progression	16/224 (7.1%)	44/181 (24.3%)	8	0	0.28 (0.15-0.52)
Recurrent VTE	8/92 (8.7%)	10/57 (17.5%)	1	-	-
Major bleeding	14/218 (6.4%)	20/179 (11.2%)	6	0	0.52 (0.28-0.97)
Overall mortality	21/230 (9.1%)	39/186 (21.0%)	6	0	0.42 (0.24-0.73)

E Valeriani et al. Throm Haemost 2021

Anticoagulation for portal vein thrombosis in cirrhosis

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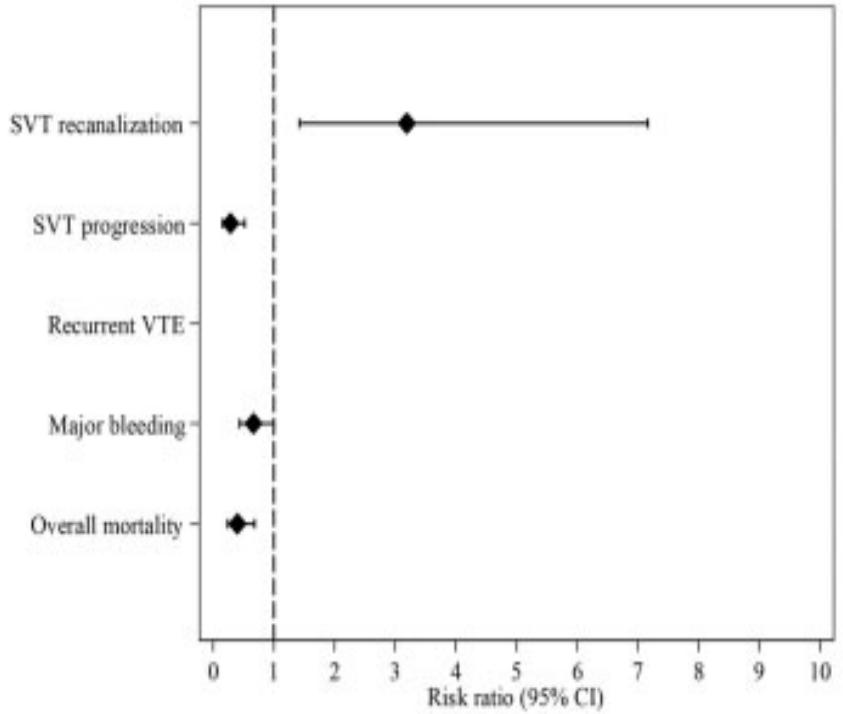

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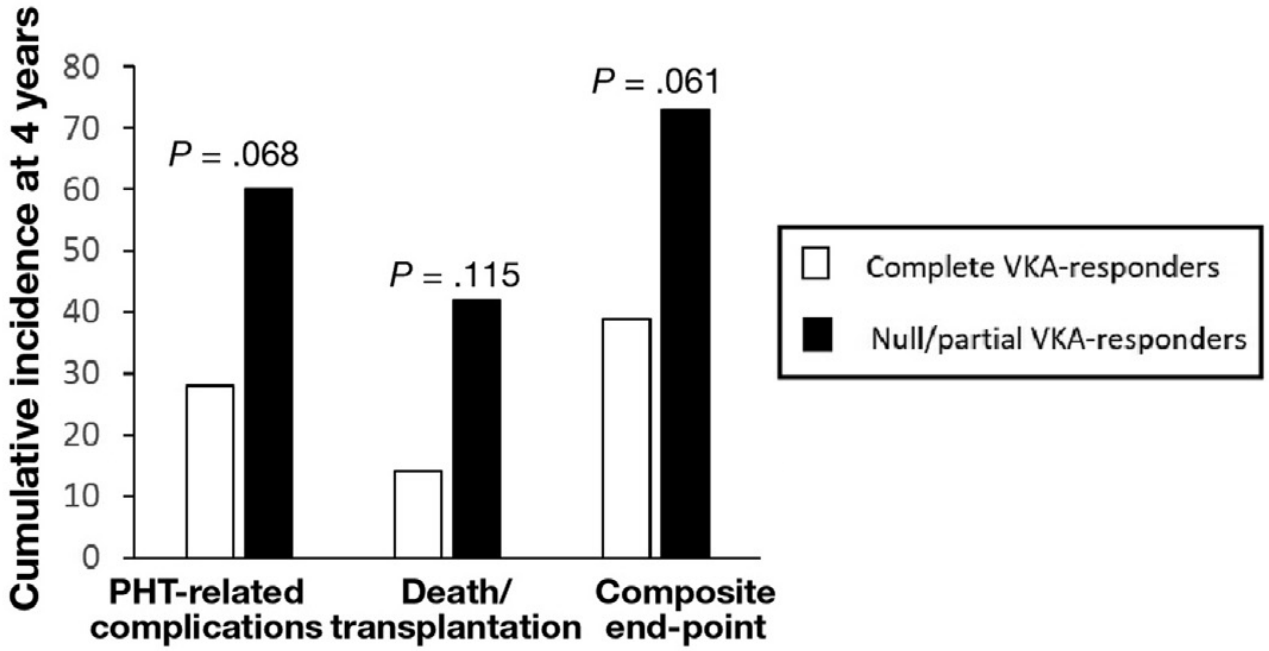
E Valeriani et al. Throm Haemost 2021

Anticoagulation for portal vein thrombosis in cirrhosis
Relationship between complete recanalization and outcomes

Multicentre, Italy
2003-2015, n=63 PVT
LMWH → VKA (ptl >30k/µl)



V La Mura et al. CGH 2018

Recurrence of portal vein thombosis after stopping anticoagulation

Recurrence of PVT after recanalization and stopping anticoagulation:

Meta-analysis of 9 studies

Pooled rate **46.7%** (95% CI 37.7–69.3%)

I2 = 36%; P = 0.1306

Le Wang et al. Adv Ther 2021

Author	Number of patients*	Recurrence (%)	Mean time (months)
Delgado, CGH 2018	13	5 **18%**	1.3
Pettinary, AJG 2018	46	7 **36%**	-
Naymagon, DDS 2020	24	7 **29%**	9.2

* AC&recanalization → AC discontinued

Overall survival in patients anticoagulated for portal vein thrombosis in cirrhosis

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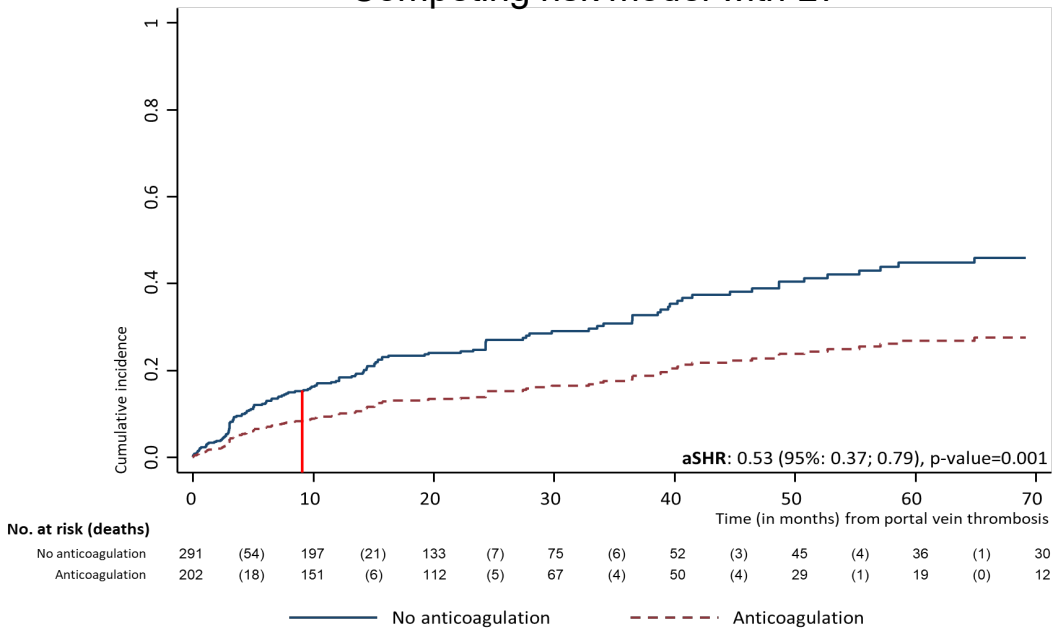
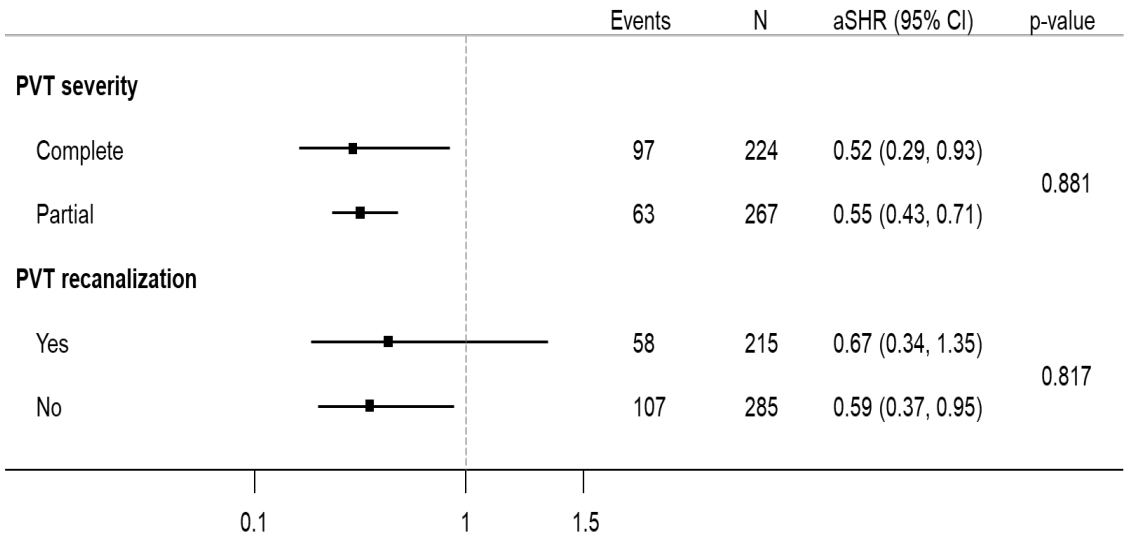
IPD meta-analysis
5 studies, 500 patients, JUN-2020
AC: 9.1 mths. F-up: 26 mths

Overall survival

Competing risk model with LT





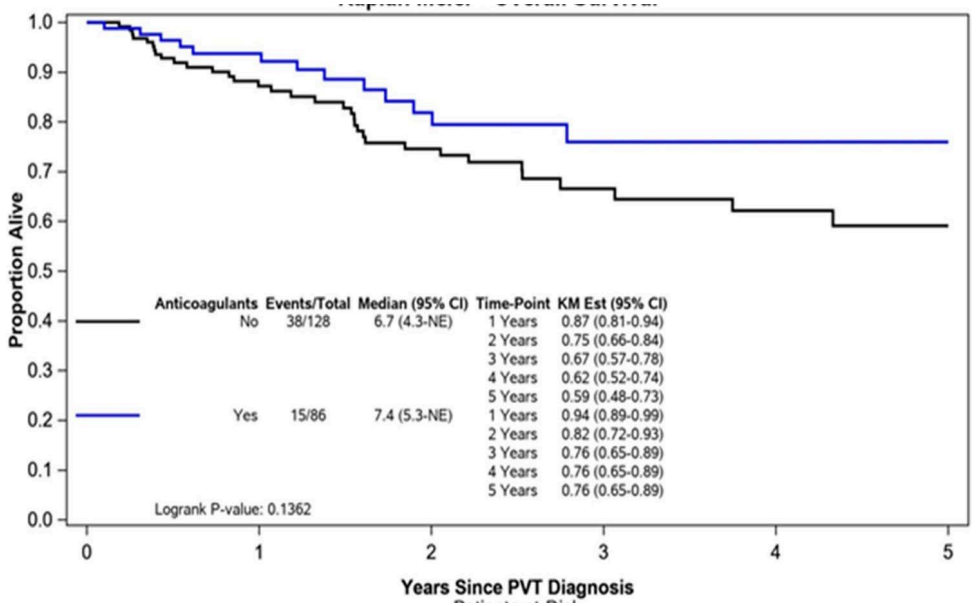
Sub-hazard ratio adjusted (**aSHR**) by age at diagnosis, etiology, Child, thrombosis extension and localization and variceal prophylaxis

A Guerrero et al. Submitted

Overall survival in patients anticoagulated for portal vein thrombosis in cirrhosis

Single center study, 214 patients, **86 AC**/128 no-AC
Non-occlusive 70%. AC: 18.8 mths
F-up: 27 mths

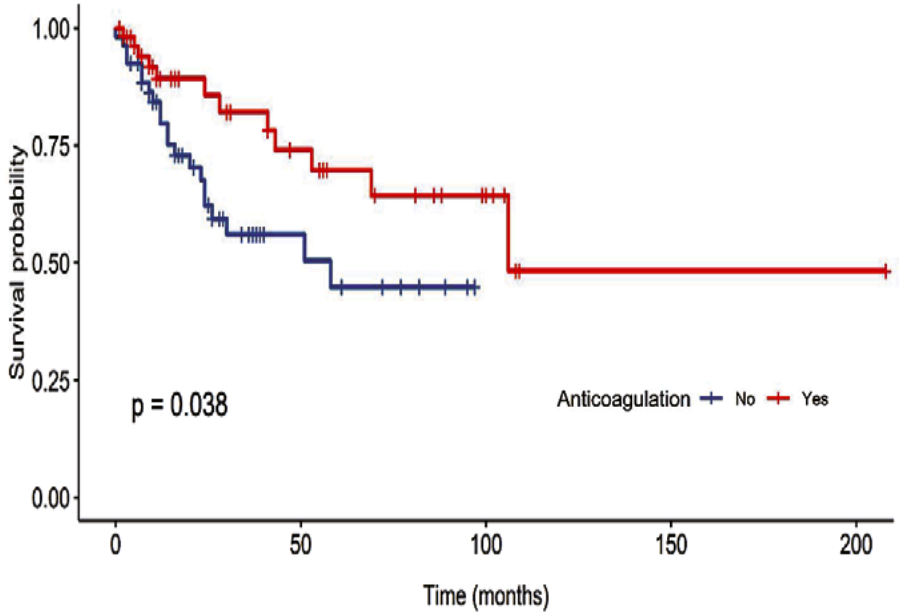
Overall survival



L Naymagon et al. DDS 2020

Single center study, 107 patients, **54 AC**/53 no-AC
Non-occlusive 83%. AC until death or LT
F-up: 32 mths

Overall survival



M Florescu et al. JGLD 2021

Risks of anticoagulation in portal vein thrombosis in cirrhosis

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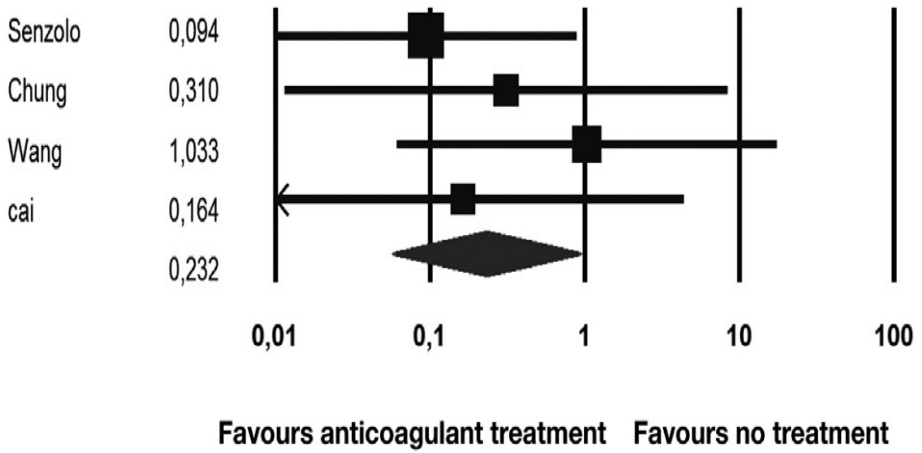
Variceal bleeding
(4 studies, 158 patients)



OR 0.23 (0.05, 0.93)
Treated vs untreated
2 vs. 12%

Any bleeding
(6 studies, 257 patients)

Treated vs untreated
11 vs. 11%

	Variceal Bleeding		
Study-Level Factors	Pooled OR Over Subgroup	95% CI	*P*
Duration of anticoagulation (*per mo*)	1.264	0.986–1.620	.206
Type of anticoagulation			
LMWH (vs untreated)	0.103	0.040–0.264	.041
Warfarin (vs untreated)	0.713	0.318–1.600	.499
Warfarin (vs LMWH)	6.925	2.002–23.952	.0024
Warfarin (vs LMWH), adjusted by study design Study design	4.368	0.158–119.78	.545
R (vs P)	6.476	1.284–32.661	.152

L Loffredo et al. Gastroenterology 2019

Efficacy and safely of DOACs in portal vein thrombosis in cirrhosis

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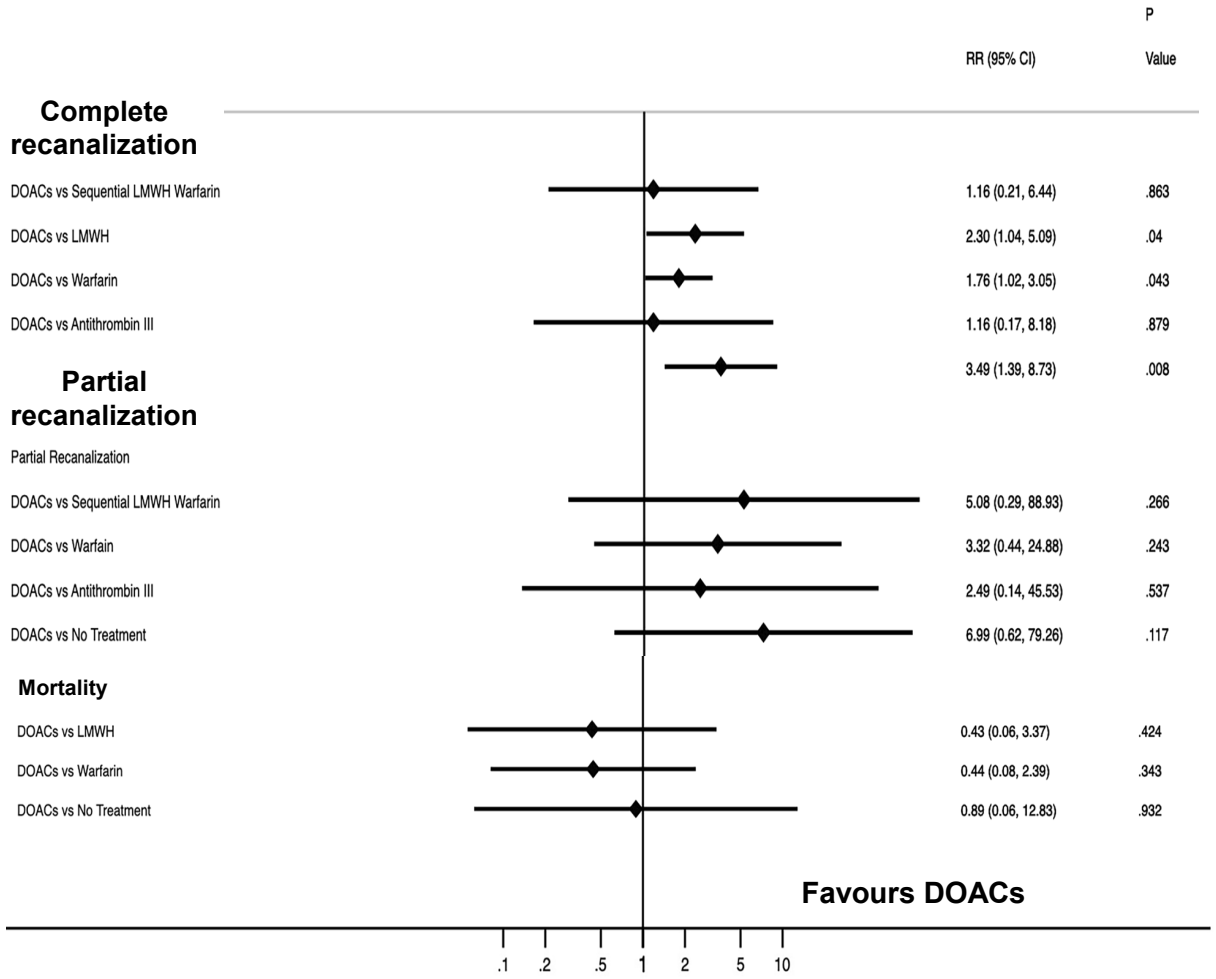
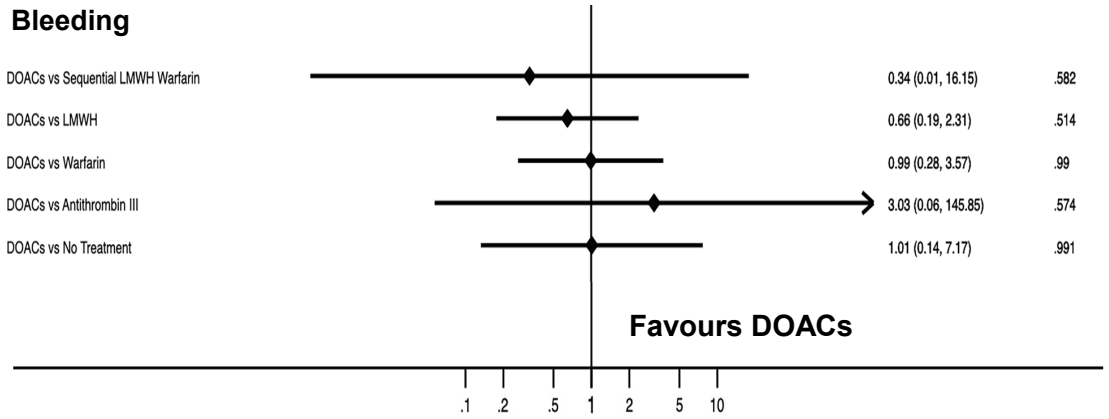
Network meta-analysis
10 studies, 527 patients, JUN-2020





CH Ng et al. Hepatol Int 2021

Safety of DOACs in patients with “advanced” liver disease
(significant fibrosis and cirrhosis)

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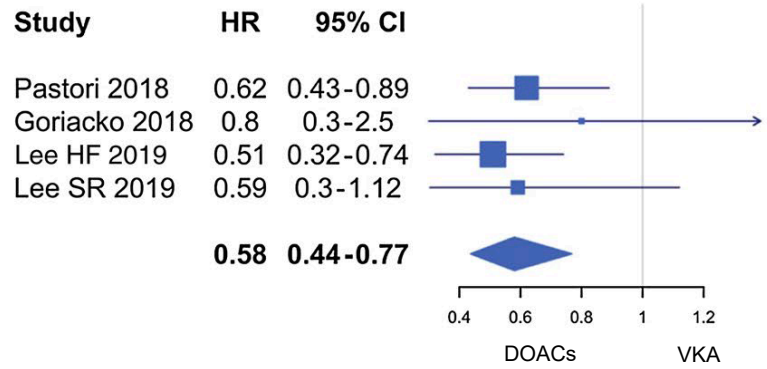
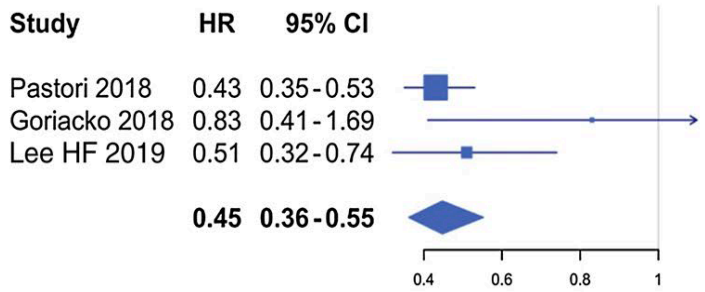
Meta-analysis, 4 studies,
3843 patients, AF and advanced liver disease
1547 VKA, 1936 DOACs

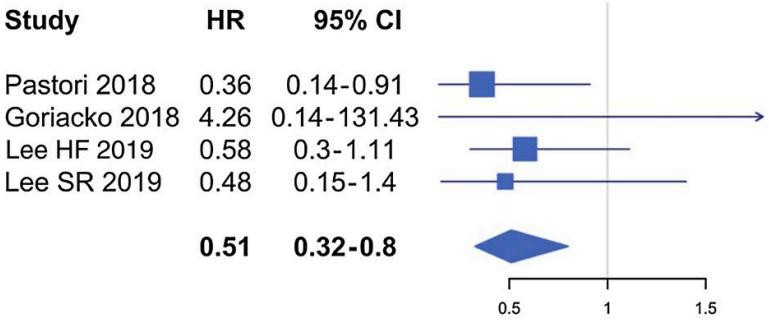
Major bleeding



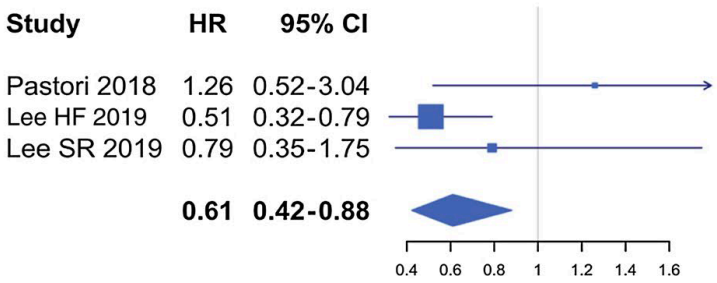
All bleeding



Intracraneal hemorrhage



GI bleeding



F Violi et al. Hepatol Commun 2020

Questions and recommendations

Question 1
Should all patients with cirrhosis and recent (<6 m) complete or >50% PVT receive anticoagulation?

Recommendation
Anticoagulation recommended in patients with cirrhosis and recent PVT trombosis that compromises at least 50% PV lumen

Question 2
Is anticoagulation a life commitment in patients with cirrhosis and PVT independently of achieving recanalization?

Recommendation
In non-LT candidates, individualize prolonging anticoagulation beyond recanalization, considering risk of recurrence and potential survival beneft

Agenda

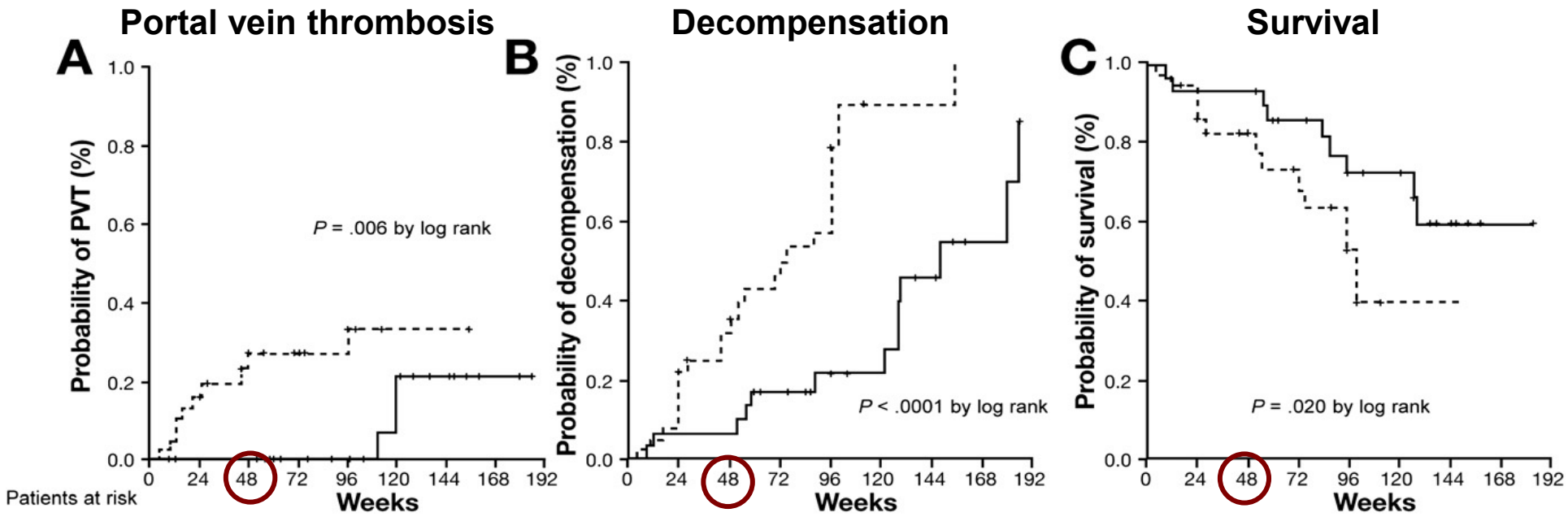
- Mechanism of action of anticoagulants
- Pathophysiological basis for long-term AG in cirrhosis
- Anticoagulation in portal vein thrombosis
- **Anticoagulation improves survival in cirrhosis?**

Enoxaparin prevents portal vein thrombosis and liver decompensation in advanced cirrhosis

DIGESTIVO RAMON Y CAJAL MADRID

Universidad de Alcalá

70 patients with Child B7-C10 cirrhosis
Enoxaparin 4000 U (**40 mg**)/24 h sc for 48 wks *vs*. **No treatment**



Independent risk factors (HR, Cox) of …

… ↓ portal vein thrombosis (HR)	
Enoxaparin treatment	0.009
Protein C levels	0.98

… ↓ decompensation	
Enoxaparin treatment	0.33
Baseline bilirubin	1.47
Portal vein diameter	1.21
Encephalopathy	3.19

… Survival	
Enoxaparin treatment	0.36
Portal vein diameter	1.34

E Villa et al. Gastroenterology 2012

Overall survival in patients anticoagulated for portal vein thrombosis in cirrhosis

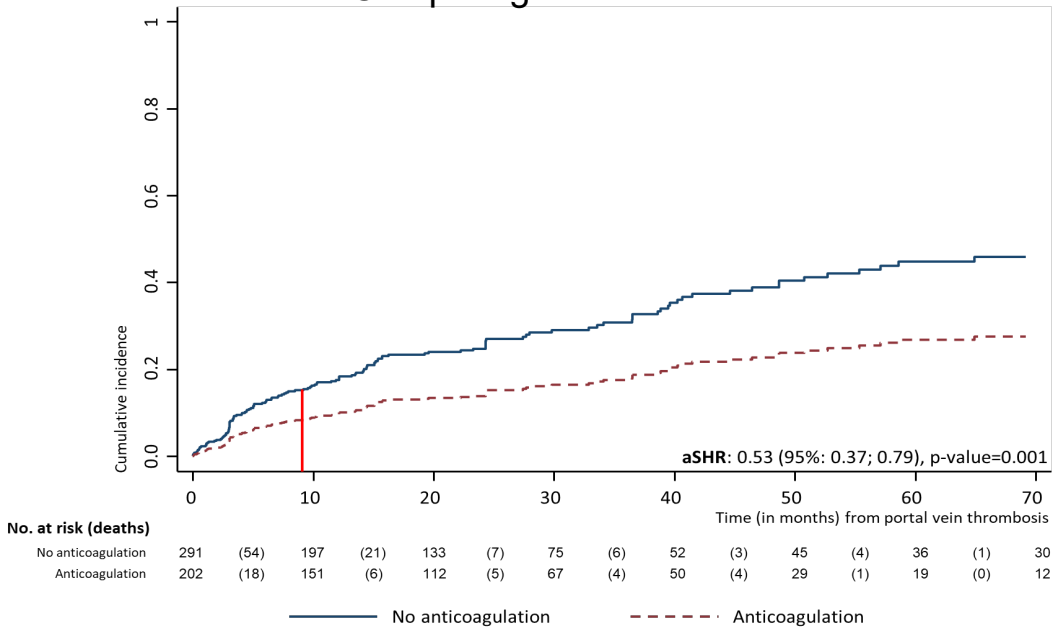
DIGESTIVO RAMON Y CAJAL MADRID

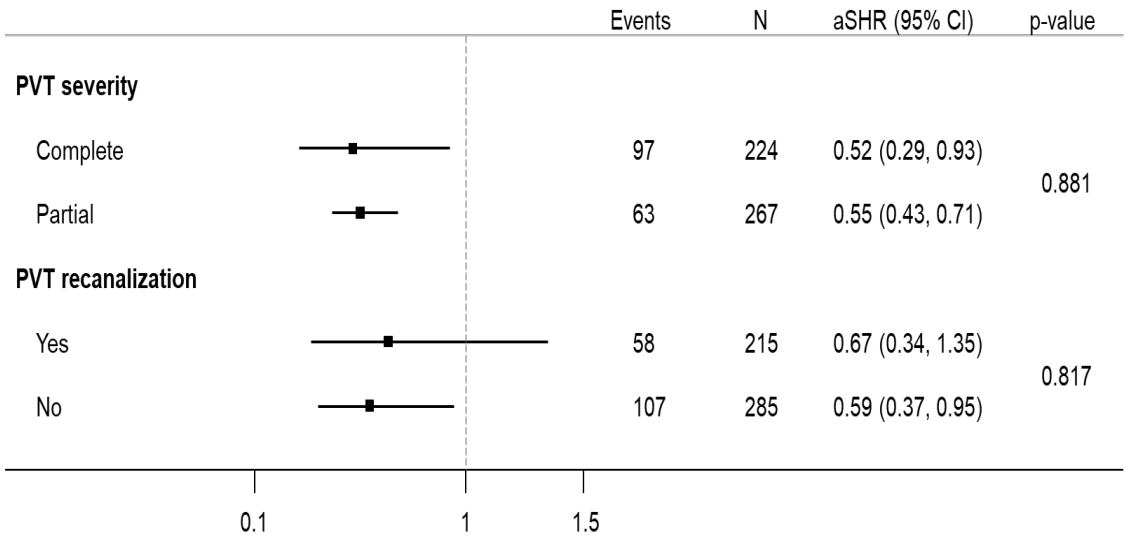
Universidad de Alcalá

IPD meta-analysis
5 studies, 500 patients, JUN-2020
AC: 9.1 mths. F-up: 26 mths

Overall survival

Competing risk model with LT





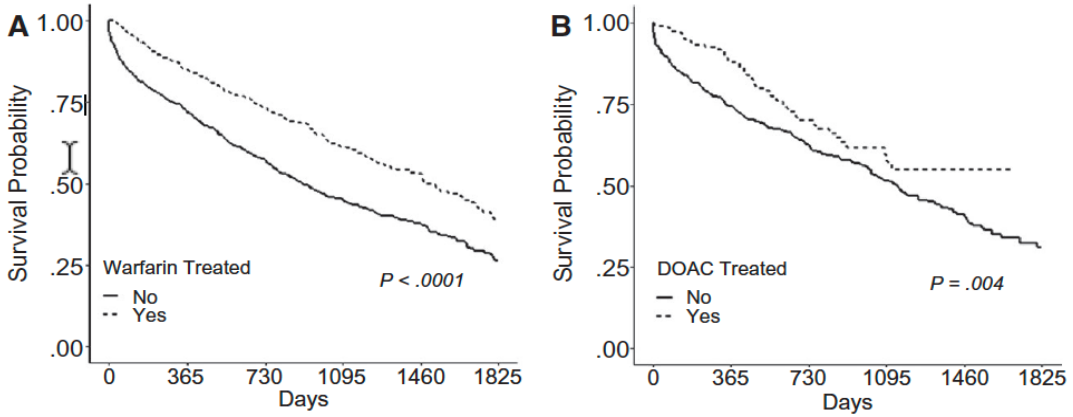
Sub-hazard ratio adjusted (**aSHR**) by age at diagnosis, etiology, Child, thrombosis extension and localization and variceal prophylaxis

A Guerrero et al. Submitted

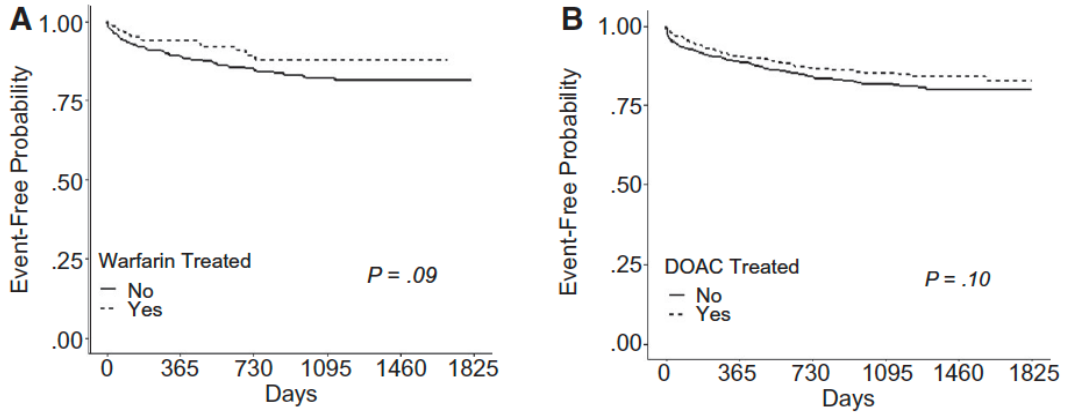
Safety of DOACs in patients with Child A/B cirrhosis

Prophylaxis of atrial fibrillation
1694 controls, 614 warfarin, 704 DOAC
Child A/B, **warfarin** 70/30%, **DOAC** 92/8%
4.6 yr f-up

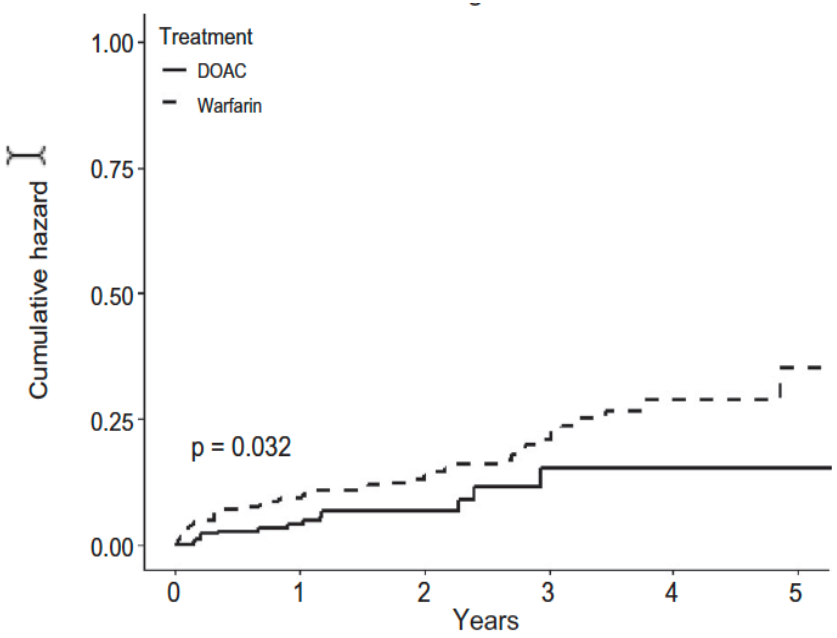
All-cause mortality



Hepatic decompensation



Cumulative risk of bleeding



M Serper et al. Hepatology 2021

Conclusions

- Micro-thrombosis of the cirrhotic liver might contribute to cirrhosis progression

- Potential benefit of long-term anticoagulation on hepatic decompensation and survival in cirrhosis

Anticoagulant of choice

- **LMWH:**
  - activates AT to inhibit factor Xa
  - half-life ~4h, dose-independent elimination
  - renal excretion
  - *but* injection, 90% biodisponibility

- **VKA:**
  - oral administration
  - unreliability of INR in cirrhosis

- **DOACS**
  - oral administration
  - greater efficacy and safety than VKA
  - *but* contraindicated in advanced cirrhosis