MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Problemas clínicos y controversias en hepatología

““Anticoagulación en la cirrosis””

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DIGESTIVO RAMON Y CAJAL MADRID

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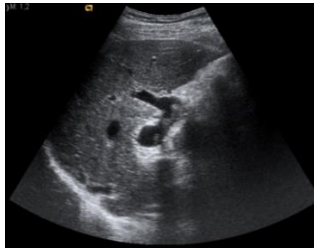
“Trombosis venosa portal y anticoagulación en la cirrosis”

Clinical report

54 yr
Acute alcoholic hepatitis 4 yr before
Compensated cirrhosis
No complications of portal hypertension
Large esophageal varices → propranolol

Bilirubin 0.96 mg/dl, INR 1.15, Albumin 3.7 g/dl
Platelets 59 000/µl, Creatinine 0.74 mg/dl

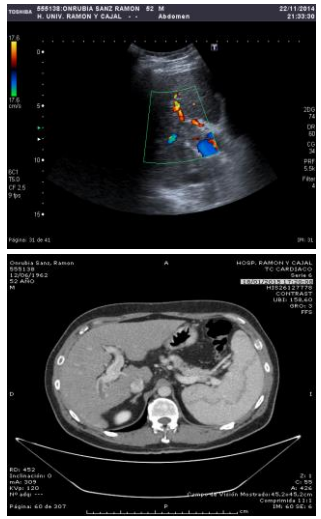
Child A-6, MELD 12



US Doppler
Non-occlusive (<20%) thrombosis of PV trunk

Close f-up

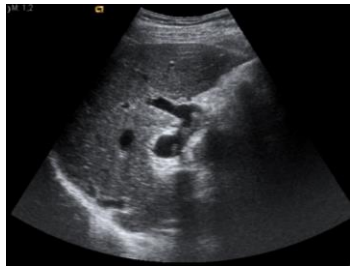
+ 3 months



US Doppler / TAC
Occlusive (>50%) thrombosis of PV trunk and RPV

Enoxaparin

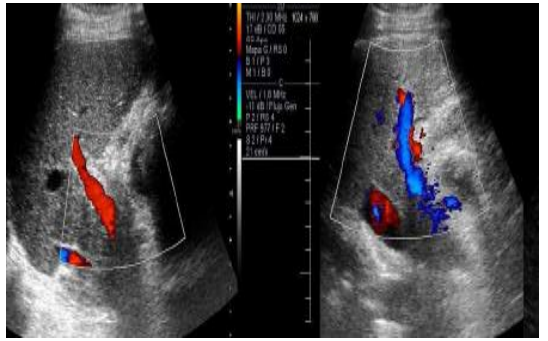
+ 6 months



US Doppler
Laminar thrombosis of PV trunk. No thrombosis of RPV branch

Warfarin

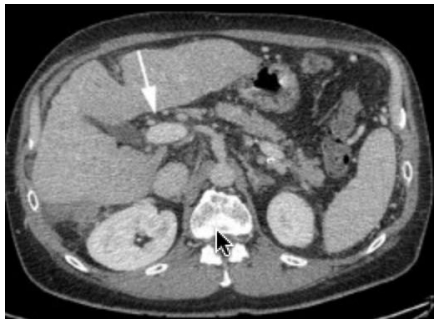
+ 12 months



US Doppler
Complete permeability of main PV and branches

Warfarin withdrawal

+ 15 months



CT
Thrombosis of the right branch of the portal vein

Reinitiate enoxaparin

Anticoagulation to treat portal vein thrombosis in cirrhosis

CONS

- PVT <50%: mostly transient
- Hepatic decompensation and death: independent of PVT
- Definitive risks of AC

PROS

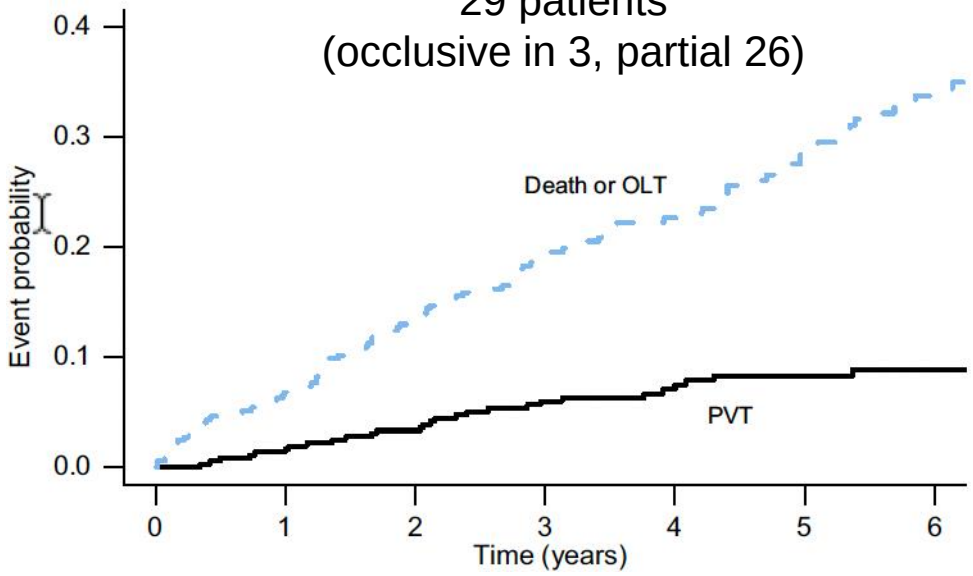
- Benefit of AC in recanalization and progression
- Benefit of AC in outcomes and survival?
- Low risks of AC?

Incidence and risk factors of portal vein thrombosis in cirrhosis

369 cirrhotic patients w/o PVT
Prospective f-up 48 ± 27 months

Portal vein thrombosis

29 patients
(occlusive in 3, partial 26)



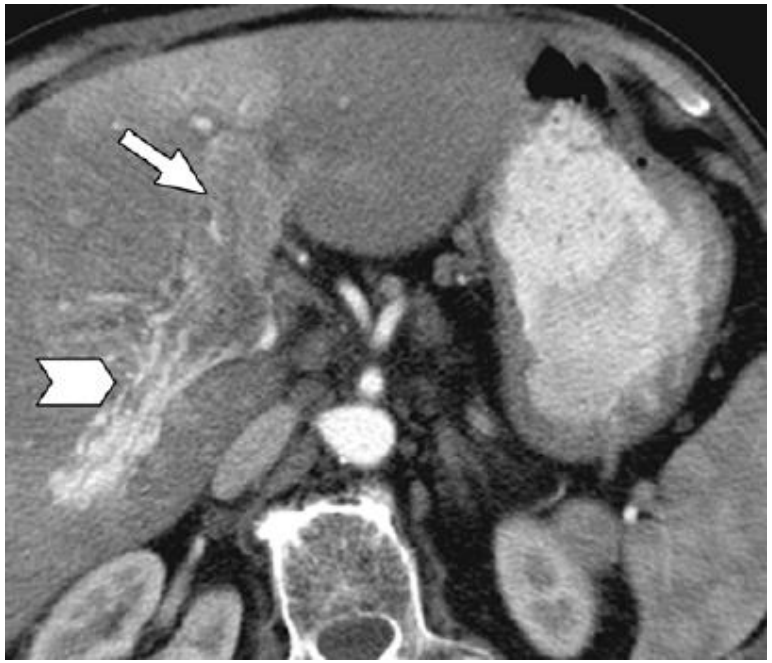
Incidence of **1.6%** at 1 yr, **6%** at 3 yr and **8.4%** at 5 yr

Independent risk factors for portal vein thrombosis

Platelet count	0.98 (0.97-0.99)	**0.002**
PBFV <15 cm/sec	2.28 (0.99-5.26)	**0.05**
Variceal bleeding	2.52 (1.06-5.99)	**0.036**

F Turon et al. JHEP 2021

Hepatocellular carcinoma and portal vein thrombosis in cirrhosis: Prevalence



Diagnostic clues:
- endovascular obstruction adjacent to the tumor
- vessel enlargement by endovascular material
- enhancement of intravascular material at arterial phase

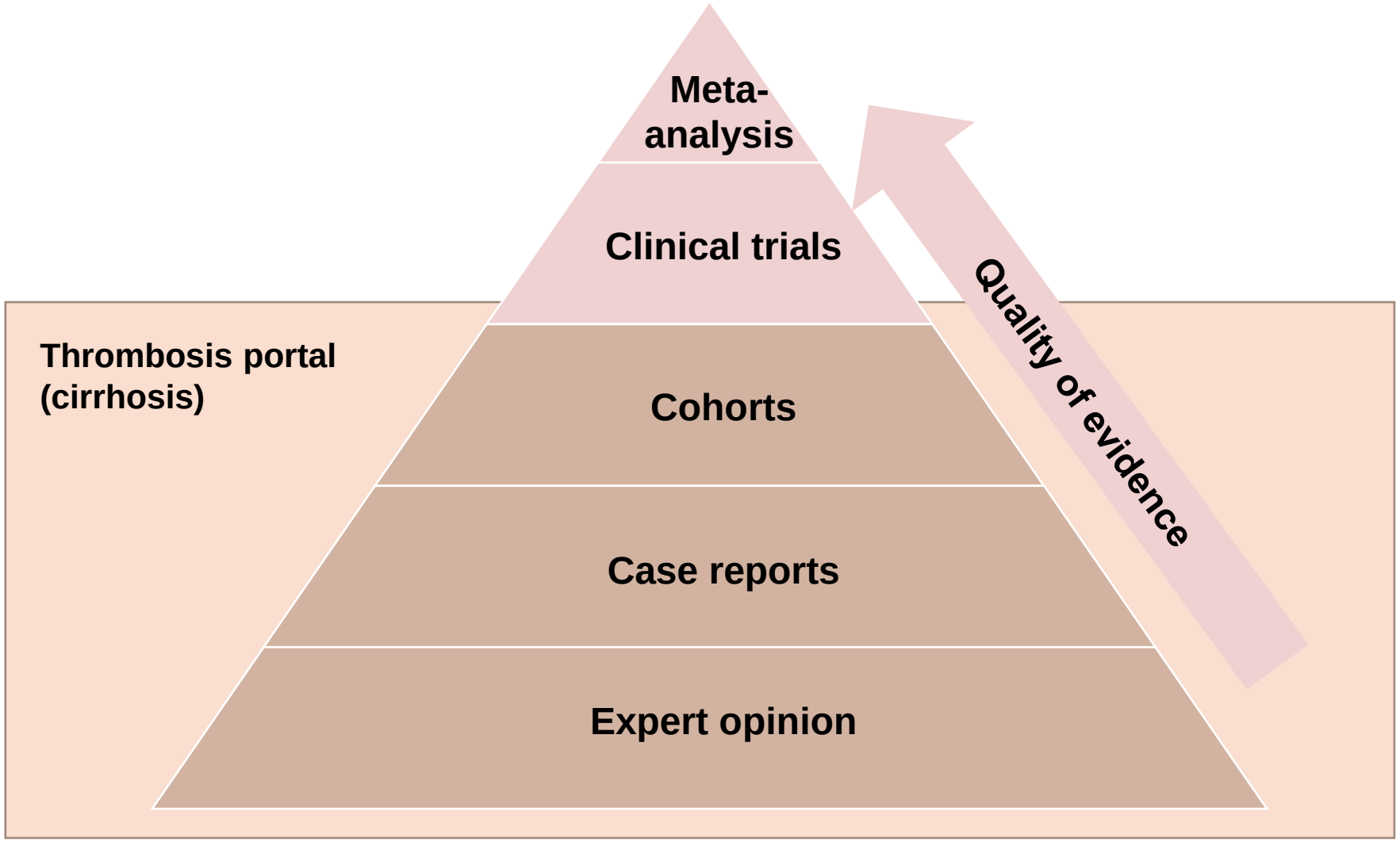
PVT and HCC:
- Neoplastic invasion?
- Neoplasic thrombofilia?

~20-50%

Nonami Hepatology 1992
Pirisi JCRO 1998
Rabe WJG 2001

Series	Neoplasic PVT
Piscaglia, Liver Transp 2010	**27.2%**
Connolli, Thromb Res 2008	**41.6%**

Quality of evidence in portal vein thrombosis in cirrhosis



Courtesy of L Téllez

Agenda

- Does portal vein thrombosis (PVT) influence meaningful outcomes (decompensation, LTx, death) in cirrhosis?
- Does anticoagulation reverse PVT more often than no treatment? Does anticoagulation modify the natural history of cirrhosis?
- Is anticoagulation safe?

Impact of portal vein thrombosis on cirrhosis progression and survival

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

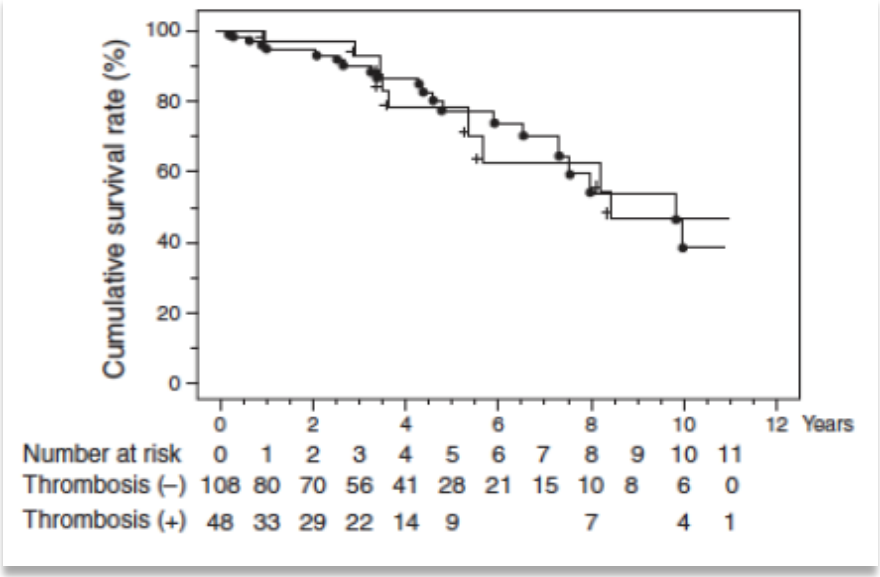
F Nery et al. Hepatology 2014

Hepatic decompensation and death are **independent** of PVT in <u>prospective</u> 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

Impact of portal vein thrombosis on acute variceal bleeding

Variable	No PVT	PVT	OR (95% CI)
5-day failure	15%	25 %	**3.1** (1.39-6.68)
Hypoxic hepatitis	5.9%	15.5%	2.9 (0.88-9.79)
6-week mortality	13%	36%	**3.5** (1.02-11.9)

G D'Amico et al. Hepatology 2003
L Amitrano et al. JCG 2012
S Augustin et al. AJG 2011

Clinical presentation of portal vein thrombosis in cirrhosis

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701 patients admitted

79 patients with PVT (11.9%)

34 asymptomatic (57%)

31 variceal bleeding (39%)

14 **abdominal pain (17.7%)**

Correlation between the extension of PVT and clinical presentation

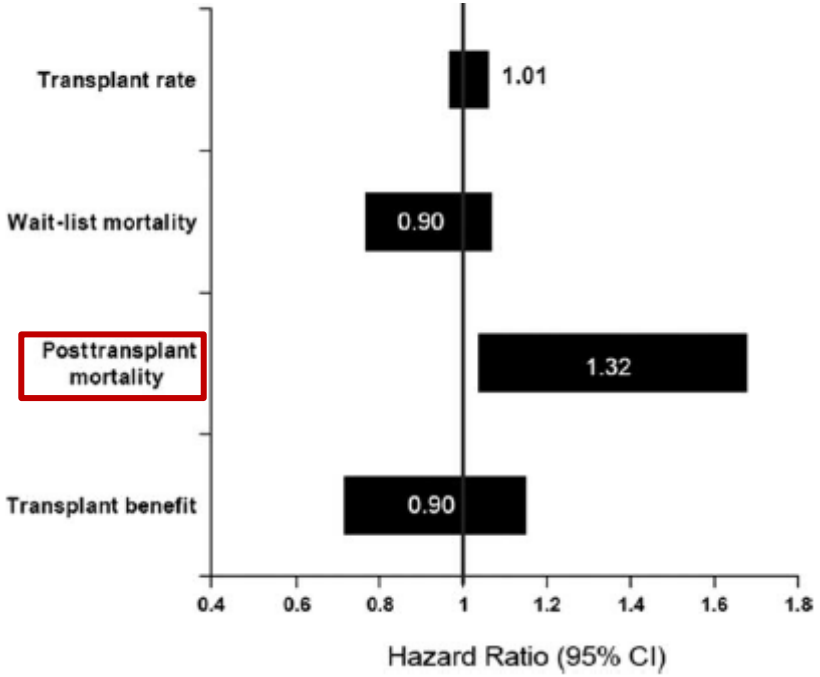
PVT presentation	Asymptomatic	Ischemic	Haemorrhagic	*P* value
Thrombosis				
Portal trunk				
Absent	5 (15.6)	2 (13.3)	4 (12.5)	0.51
Occlusive	12 (37.5)	9 (60)	11 (34.4)	
Partial	15 (46.9)	4 (26.7)	17 (53.1)	
Right branches				
Absent	18 (56.3)	12 (80)	23 (71.9)	0.51
Occlusive	8 (25)	2 (13.3)	6 (18.8)	
Partial	6 (18.8)	1 (6.7)	3 (9.4)	
Left branches				
Absent	23 (71.9)	12 (80)	26 (81.3)	0.87
Occlusive	7 (21.4)	3 (20)	5 (15.6)	
Partial	2 (6.3)	0 (0)	1 (3.1)	
Mesenteric				
Absent	25 (78.1)	4 (26.7)	24 (75)	0.0001
Occlusive	0 (0)	11 (73.3)	0 (0)	
Partial	7 (21.9)	0 (0)	8 (25)	
Splenic				
Absent	27 (84.4)	12 (80)	29 (90.6)	0.25
Occlusive	2 (6.3)	3 (20)	1 (3.1)	
Partial	3 (9.4)	0 (0)	2 (6.3)	

L Amitrano et al. JHEP 2004

Impact of portal vein thrombosis on liver transplantation

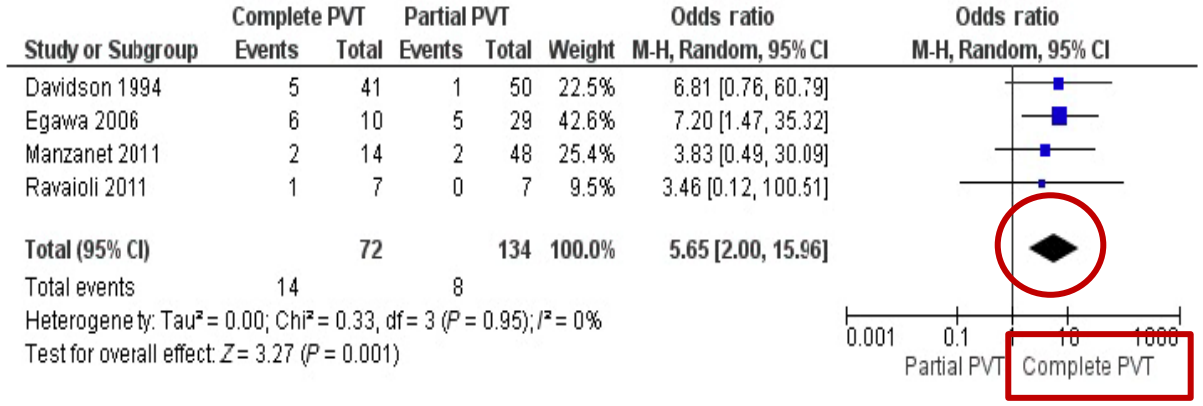
SRTR 22291 receptors

PVT 4.02%

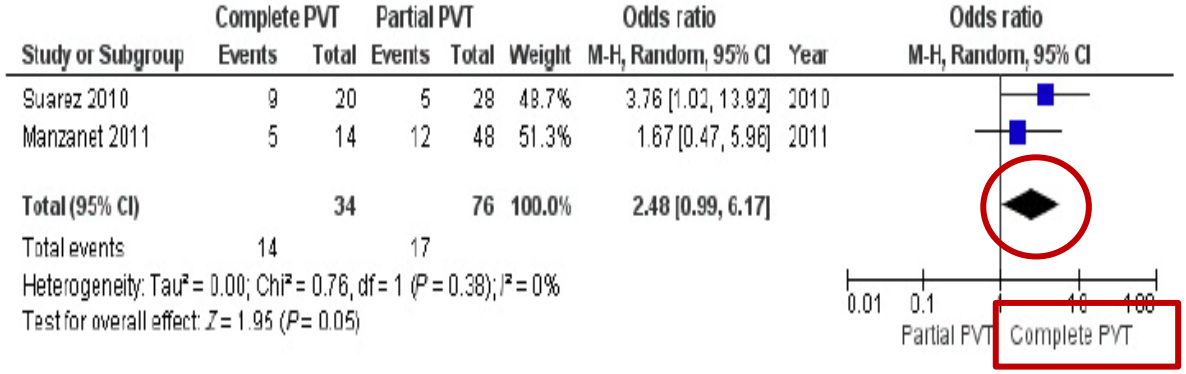


MJ Englesbe et al. Liver Transpl 2010

30-day post-transplantation survival



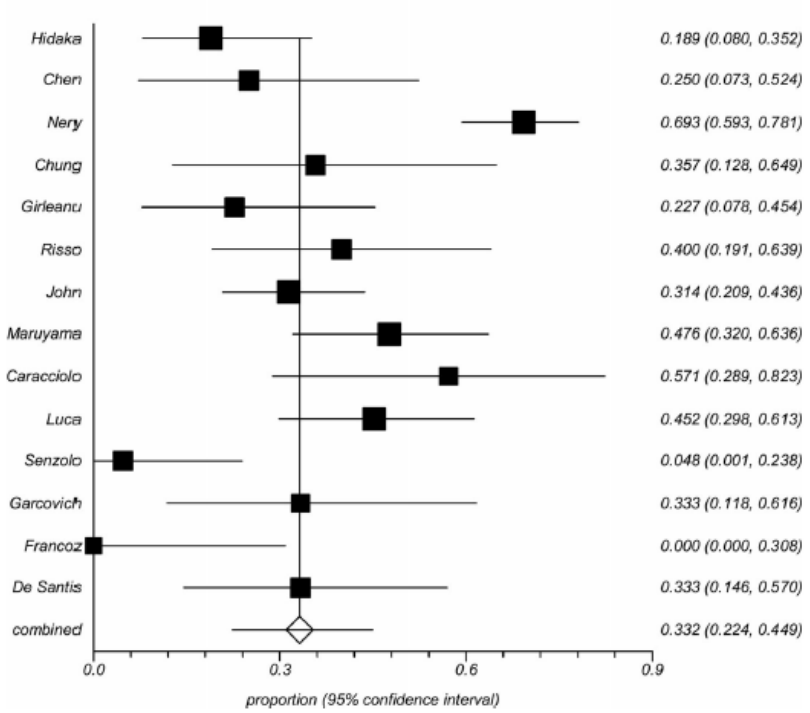
1-year post-transplantation survival



Zanetto A et al. Transplant Int 2018

“Transient” portal vein thrombosis in cirrhosis

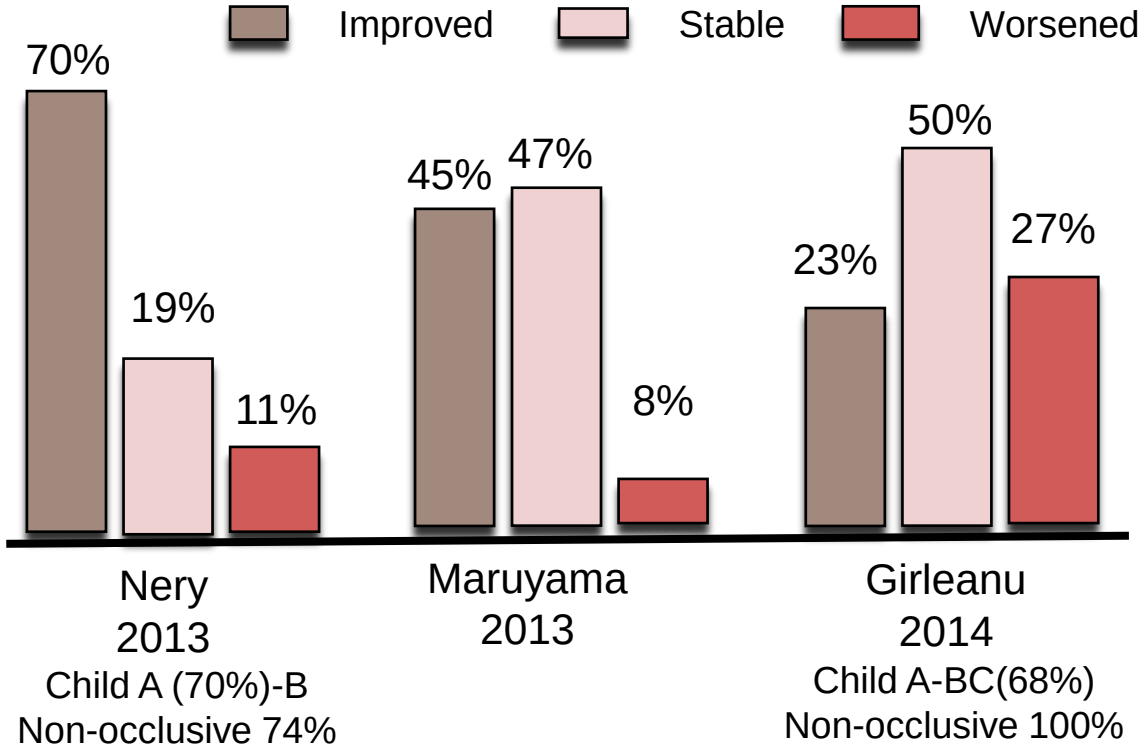
Meta-analysis, 14 cohort studies
Heterogeneity, I^2=84.2%



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

Anticoagulation to treat portal vein thrombosis in cirrhosis

- Does portal vein thrombosis (PVT) influence meaningful outcomes (decompensation, LTx, death) in cirrhosis?
- **Does anticoagulation reverse PVT more often than no treatment?**

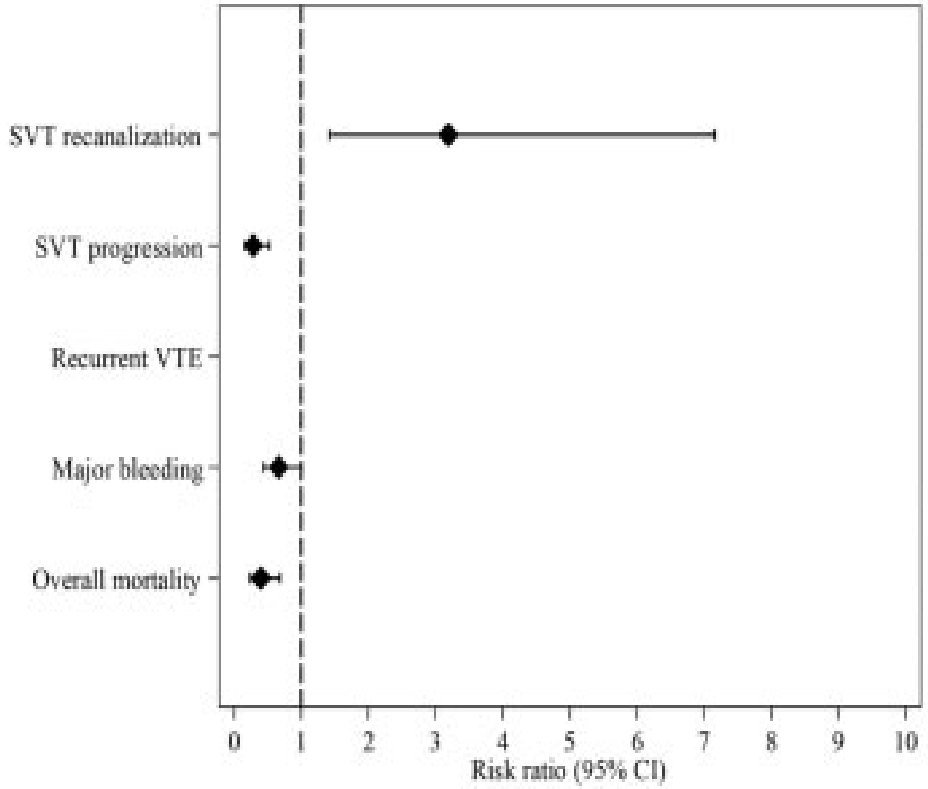
  Does anticoagulation modify the natural history of cirrhosis?
- Is anticoagulation safe?

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	LMWH	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

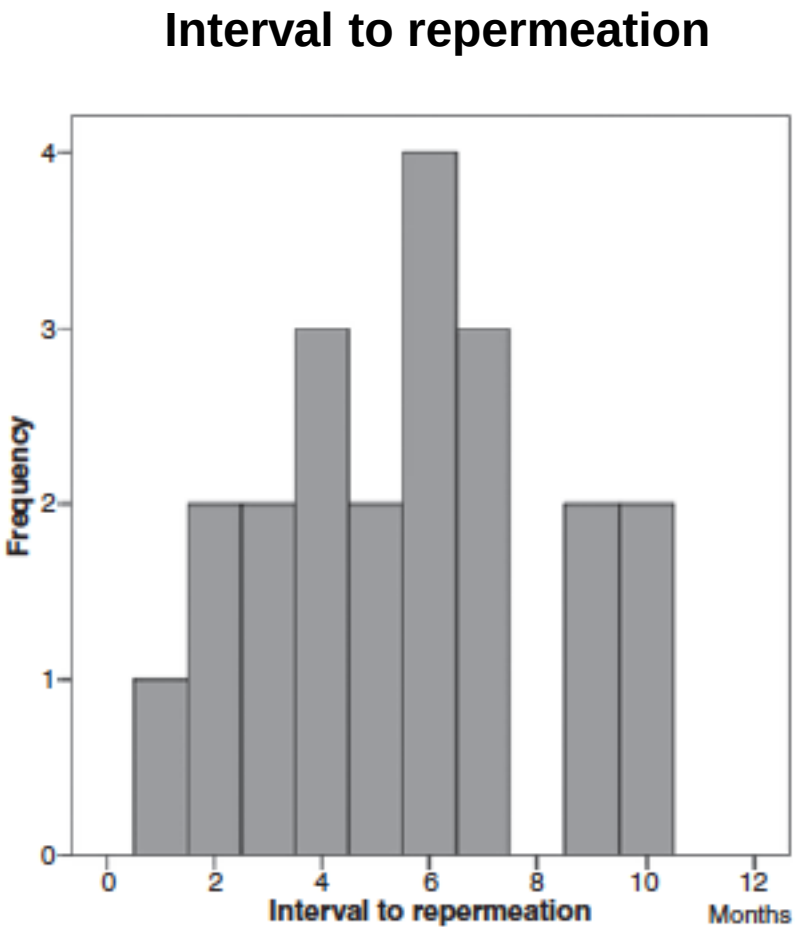
Meta-analysis of aggregate data
26 studies, 1475 patients, -2019



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. Thromb Haemost 2021

Anticoagulant for portal vein thrombosis in cirrhosis: Interval to repermeation



M Senzolo et al. Liver Int 2012

182 patients with cirrhosis and PVT, 2008-2016

81 on anticoagulation, 101 untreated

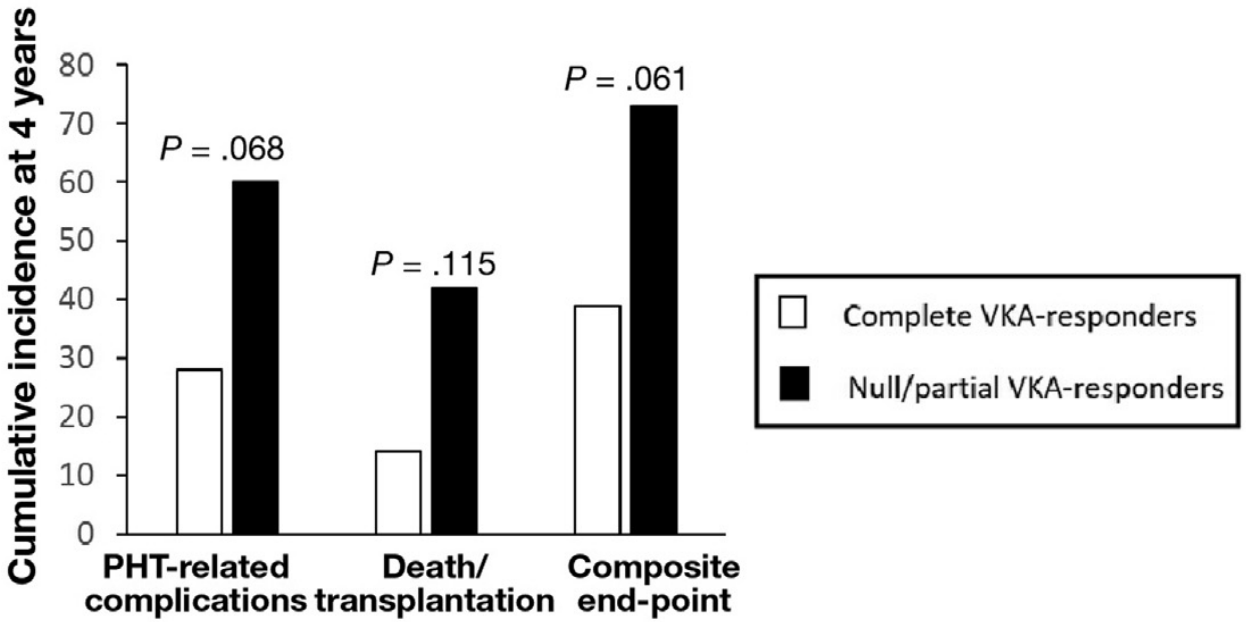
Interval to repermeation:

61% at **3 m**, 28% at **6-12 m**, 11% after 12 m

I Pettinari et al. AJG 2019

Anticoagulation for portal vein thrombosis in cirrhosis
Relationship between 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

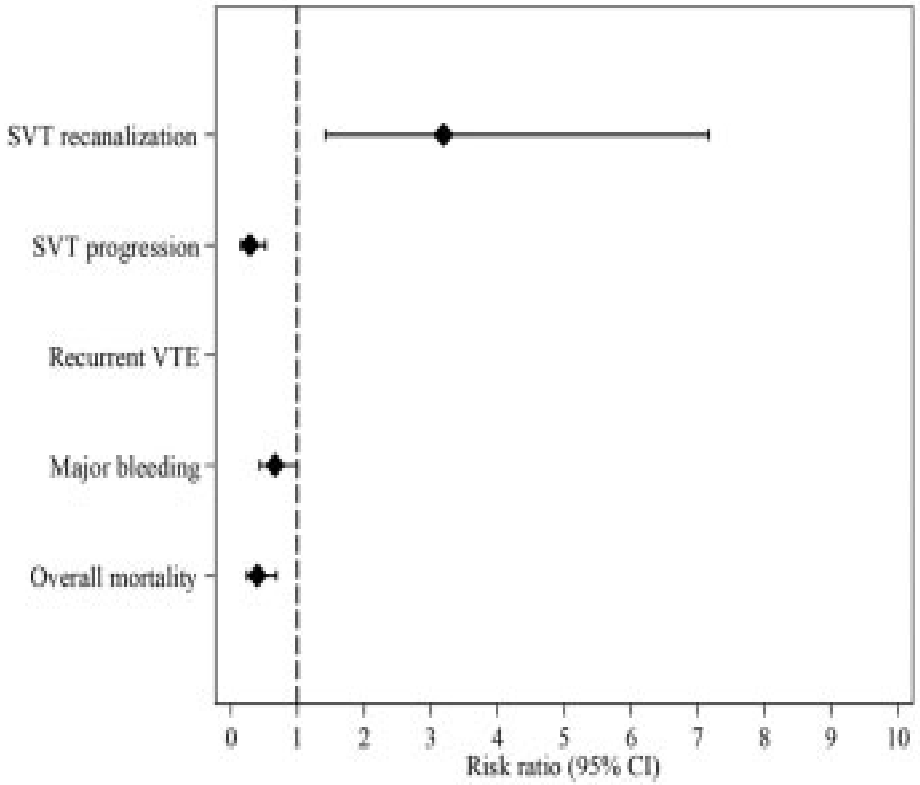
Le Wang et al. Adv Ther 2021

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

Anticoagulation for portal vein thrombosis in cirrhosis

Meta-analysis of aggregate data
26 studies, 1475 patients, -2019



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E Valeriani et al. Throm Haemost 2021

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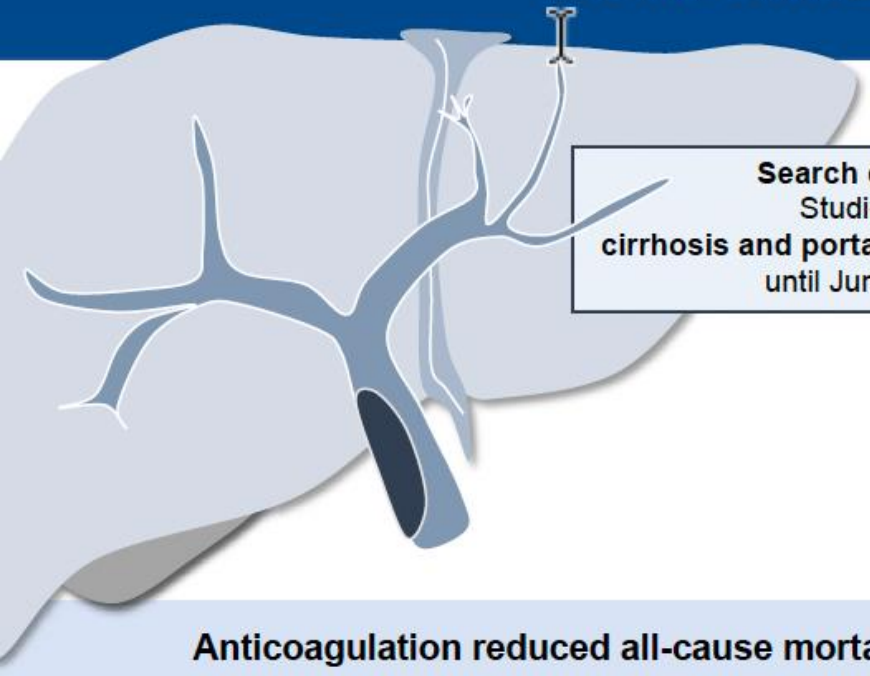
The IMPORTAL competing-risk individual patient data meta-analysis



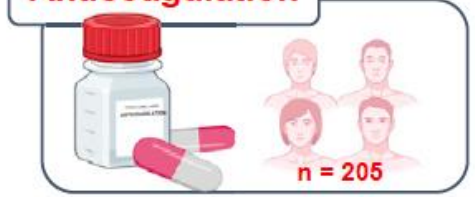
Search criteria:
Studies of
cirrhosis and portal vein thrombosis
until June 2020

Selection
✓ 5 studies
✓ 500 patients

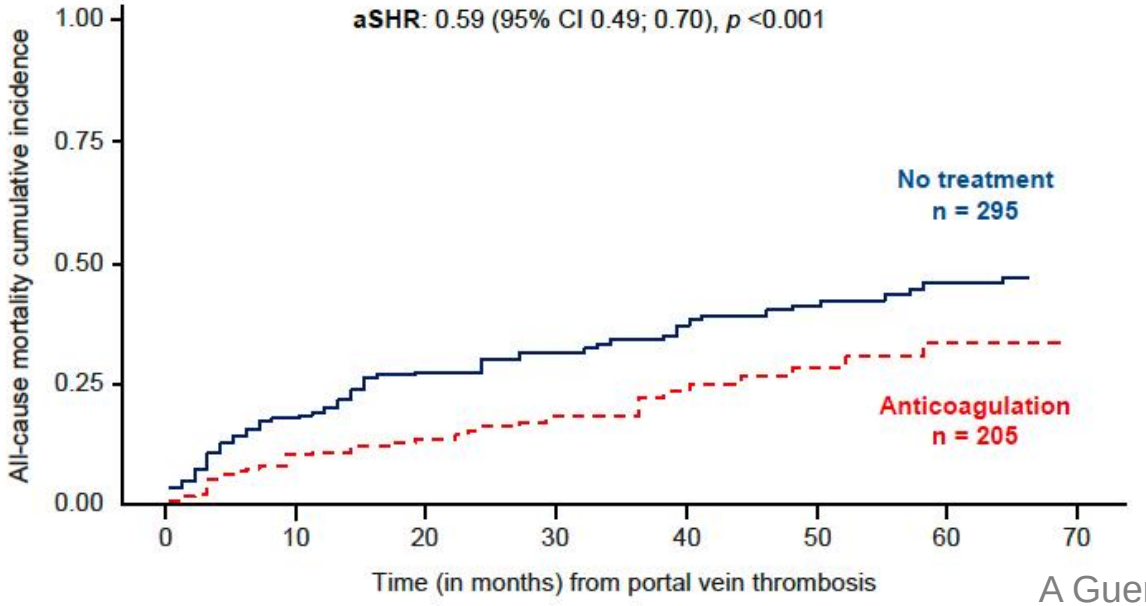
Primary outcome:
All-cause mortality

Method:
One-step meta-analysis
Competing-risk model with liver transplantation

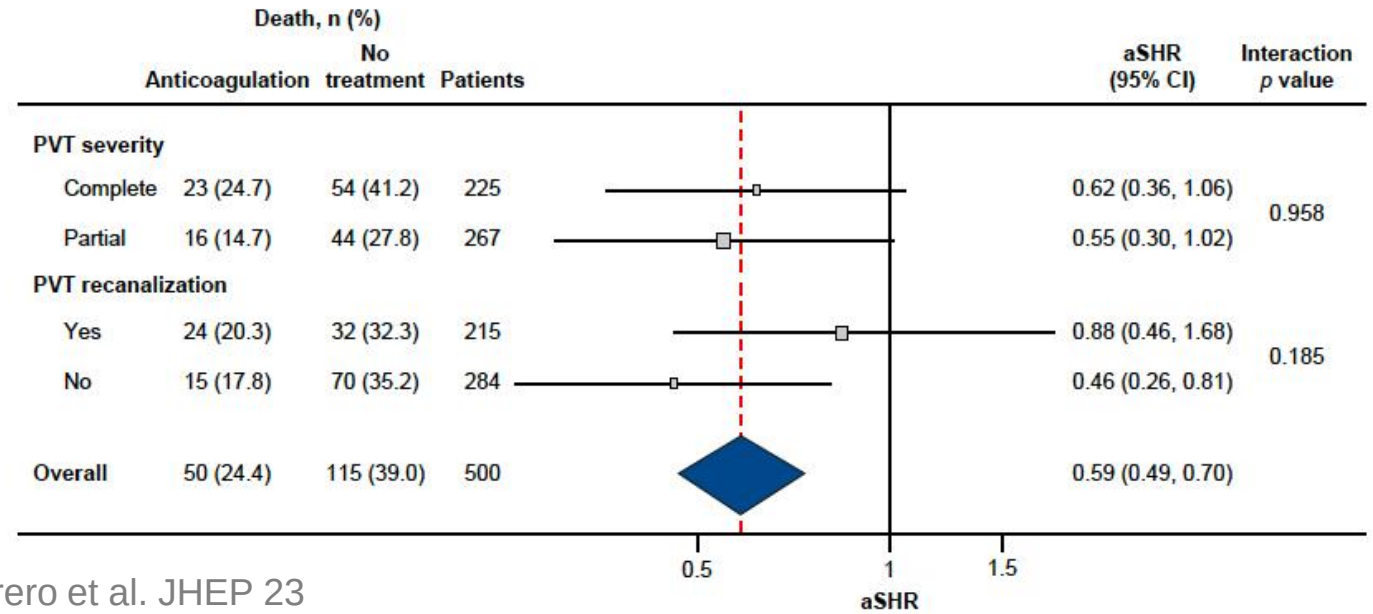
Anticoagulation *vs.* **No treatment**



Anticoagulation reduced all-cause mortality…



…independently of thrombosis severity and recanalization



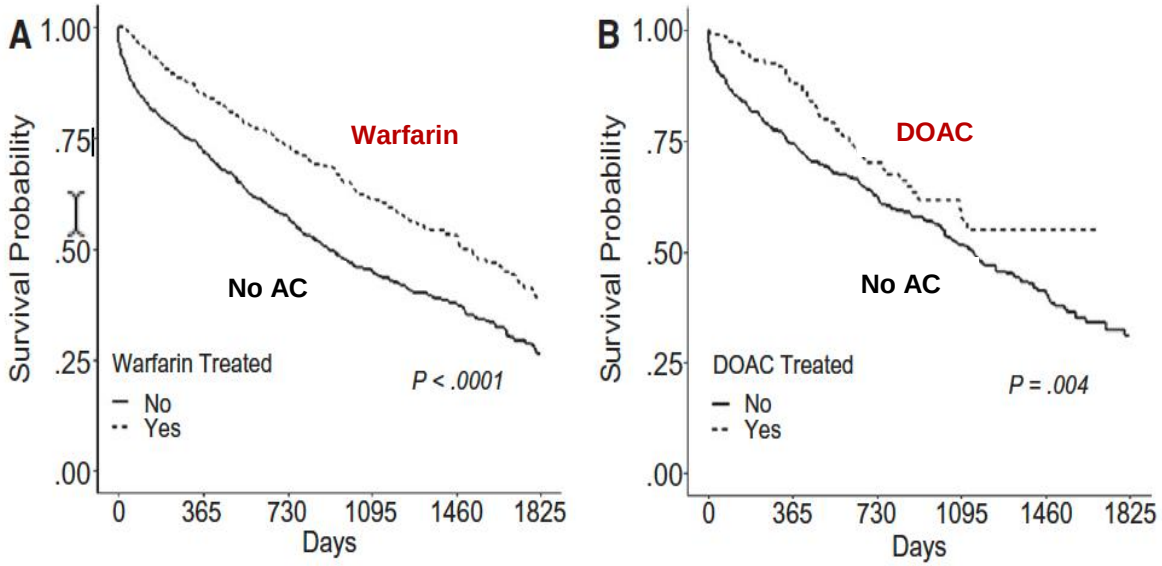
Anticoagulation reduces all-cause mortality and hepatic decompensation in patients with Child A/B cirrhosis and atrial fibrillation

Retrospective longitudinal study, US Veterans data
Cirrhosis with incidental atrial fibrillation
1694 controls, 614 warfarin, 704 DOAC

Child A/B (%): **warfarin** 70/30, **DOAC** 90/10
4.6 yr f-up

Survival probability

KM curve in a propensity-matched cohort



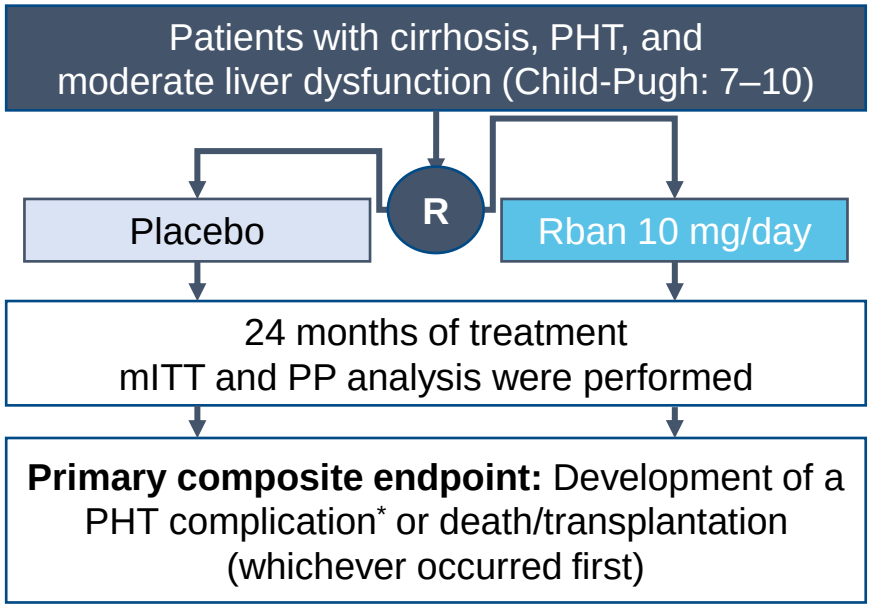
Incidence rates per 100 person-years

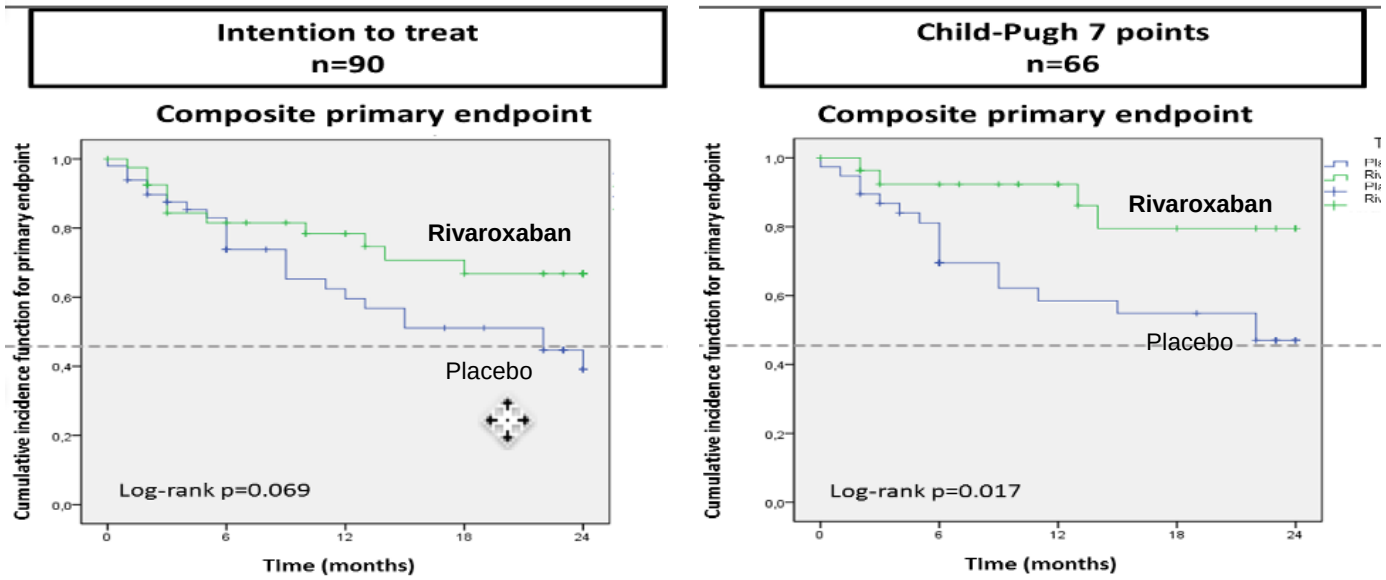
	Warfarin-Matched Cohort			DOAC-Matched Cohort		
	No AC n = 1,080	Warfarin n = 614	*P* Value	No AC n = 503	DOACs n = 201	*P* Value
All-cause mortality	27.2	17.0	<0.001	23.1	16.1	<0.01
HD	7.1	5.3	0.02	6.3	4.6	0.14
Death after hepatic decompensation	12.4	7.6	<0.001	6.7	4	0.12
Ischemic stroke	1.7	2.3	0.11	2.0	1.3	0.18
MACE	3.8	3.4	0.21	3.5	3.2	0.36
Splanchnic thrombosis	0.5	0.3	0.05	0.5	0.3	0.27
Bleeding	5.4	5.9	0.29	4.8	3.6	0.21

M Serper et al. Hepatology 2021

Rivaroxaban improves survival and decompensation in cirrhotic patients with moderate liver dysfunction: a double-blind, placebo-controlled trial

Randomized, double-blind, placebo-controlled multicenter trial (EduraCT: 2014-005523-27)





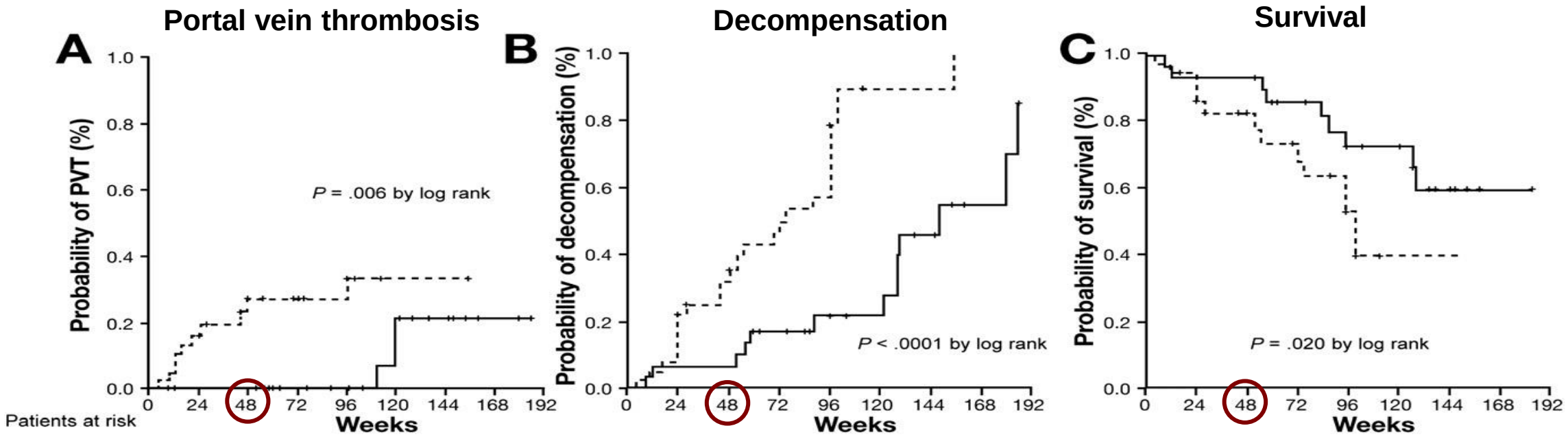
Adverse events

- **Non-PHT bleeding** OR 4.2 [95% CI: 1.54–11.7 p=0.004]
- **Major bleeding events** OR 4.02 [95% CI: 0.767–21.167, p=NS]

A Puente et al. JHEP 2023

Enoxaparin prevents portal vein thrombosis and liver decompensation in advanced cirrhosis

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 (HR)

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

… Survival (HR)

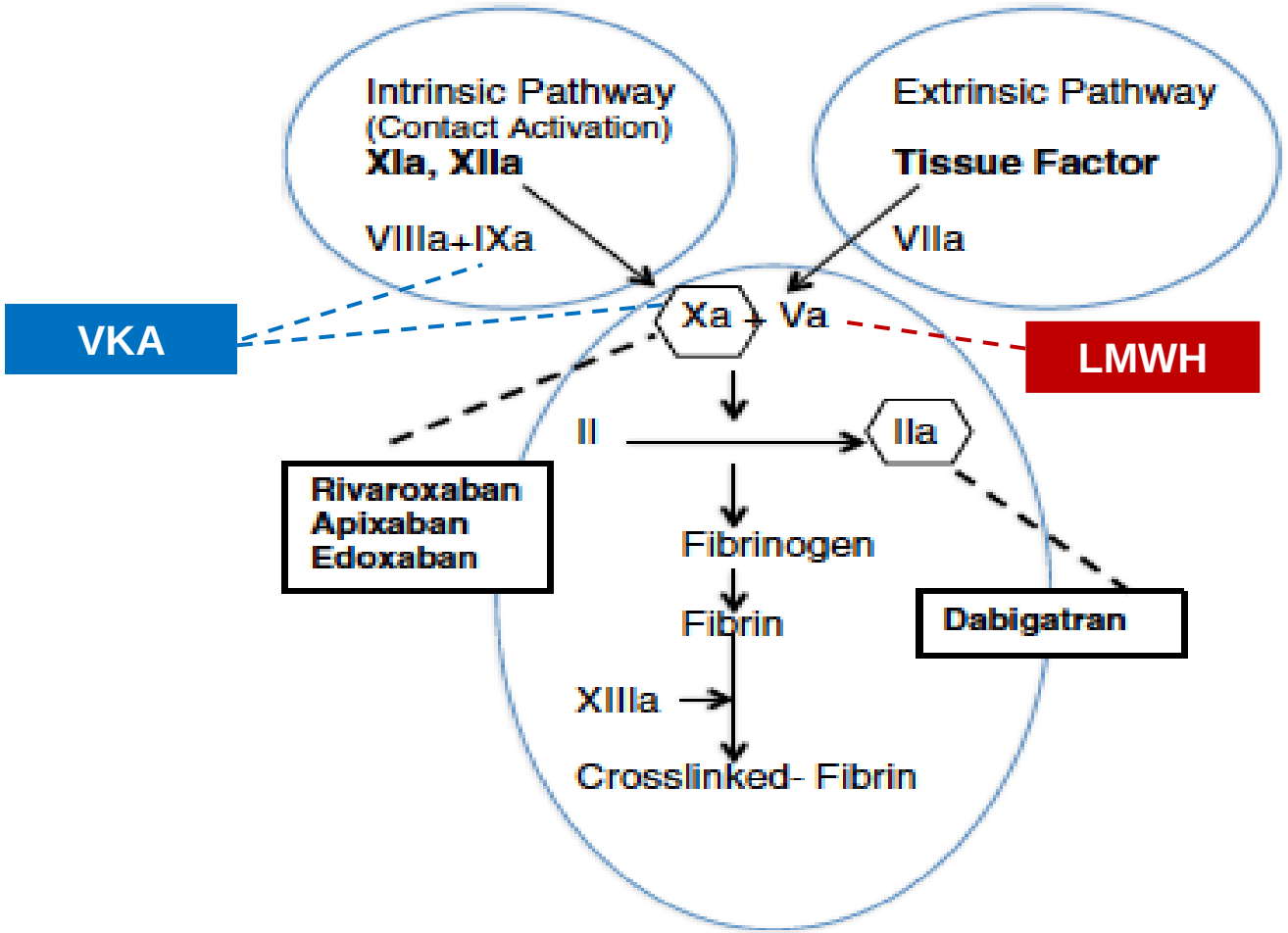
Enoxaparin treatment	0.36
Portal vein diameter	1.34

E Villa et al. Gastroenterology 2012

Agenda

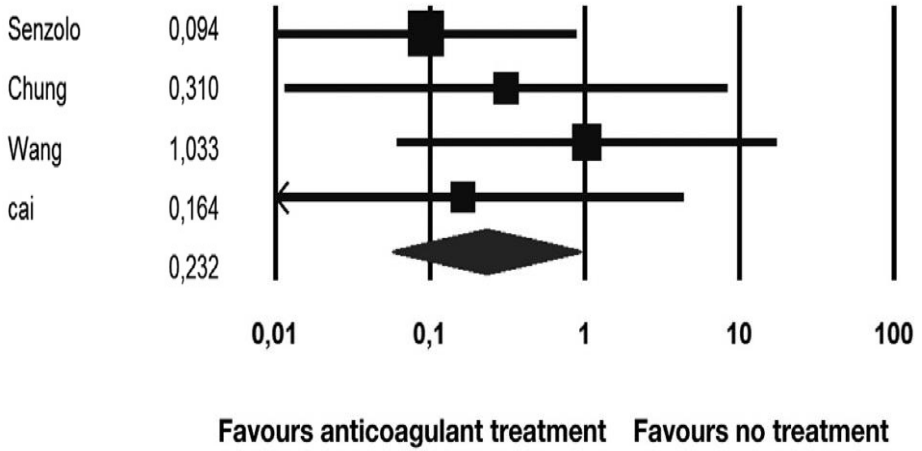
- Does portal vein thrombosis (PVT) influence meaningful outcomes (decompensation, LTx, death) in cirrhosis?
- Does anticoagulation reverse PVT more often than no treatment? Does anticoagulation modify the natural history of cirrhosis?
- **Is anticoagulation safe?**

Mechanism of action of anticoagulants



Bleeding events in patients with cirrhosis and portal vein thrombosis on LMWH and/or VKA

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	.0924
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

Bleeding events in patients with cirrhosis and portal vein thrombosis on LMWH and/or VKA

IPD meta-analysis

Studies comparing AC vs. no treatment cohorts

5 studies, **500 patients,** Until JUN-2020

AC: **LMWH, VKA**. **Child B/C 62%**. AC (median): **9.1 m.** F-up (median): **26 m**

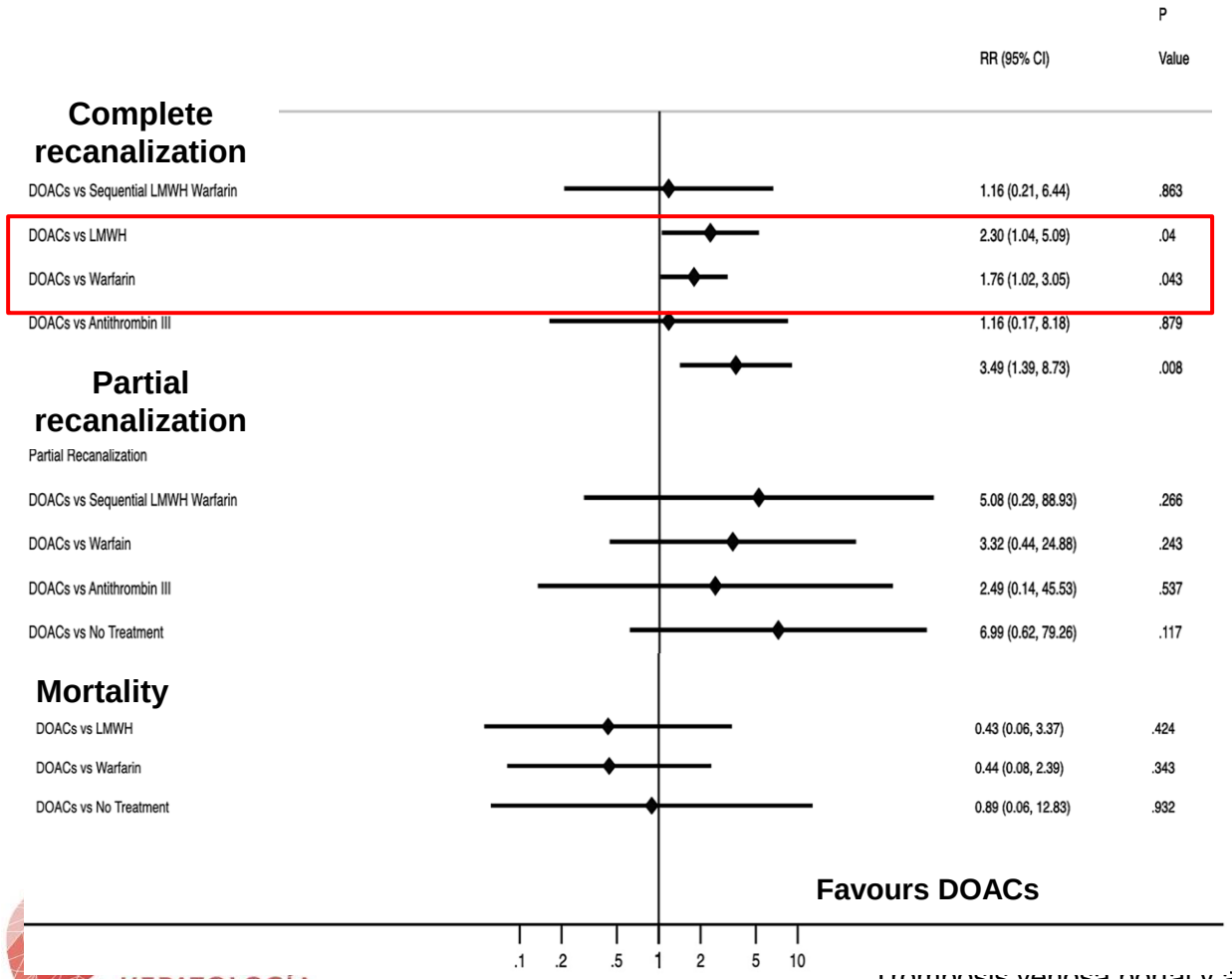
Bleeding events	Anticoagulation n=205	No treatment n=295	P
Global, N (%)	39 (19.0%)	46 (15.6%)	0.3
Portal hypertension related, N (%)	19 (9.3%)	41 (13.9%)	0.12
Non-portal hypertension related, N (%)	20 **(10%)**	5 **(1.7%)**	0.001
Intracraneal hemorrhage **GI bleeding** **Epistaxis, gingivorrhagia** Abdominal hematoma for injection Other Hemoptysis (1), post-surgical hemorrhage (1), purpura (1), unspecified (2)	**1** **6** **5** 3 5	4	

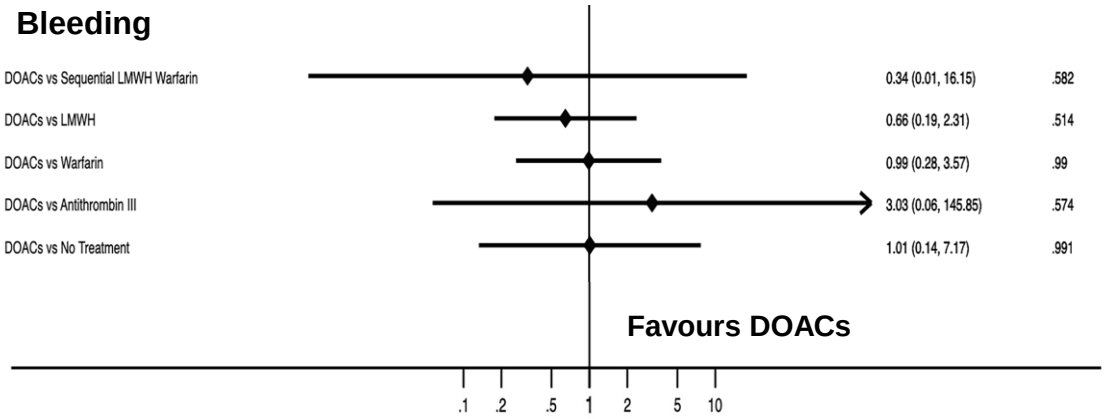
"Trombosis venosa portal y anticoagulación en la cirrosis"

A Guerrero et al. JHEP 23

Efficacy and safety of DOACs in portal vein thrombosis in cirrhosis

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





CH Ng et al. Hepatol Int 2021

Bleeding events in patients with cirrhosis and atrial fibrillation on VKA or DOACs

Retrospective longitudinal study US Veterans data
Cirrhosis with incidental atrial fibrillation
1694 controls, 614 warfarin, 704 DOAC

Child A/B (%): **warfarin** 70/30, **DOAC** 90/10
4.6 yr f-up

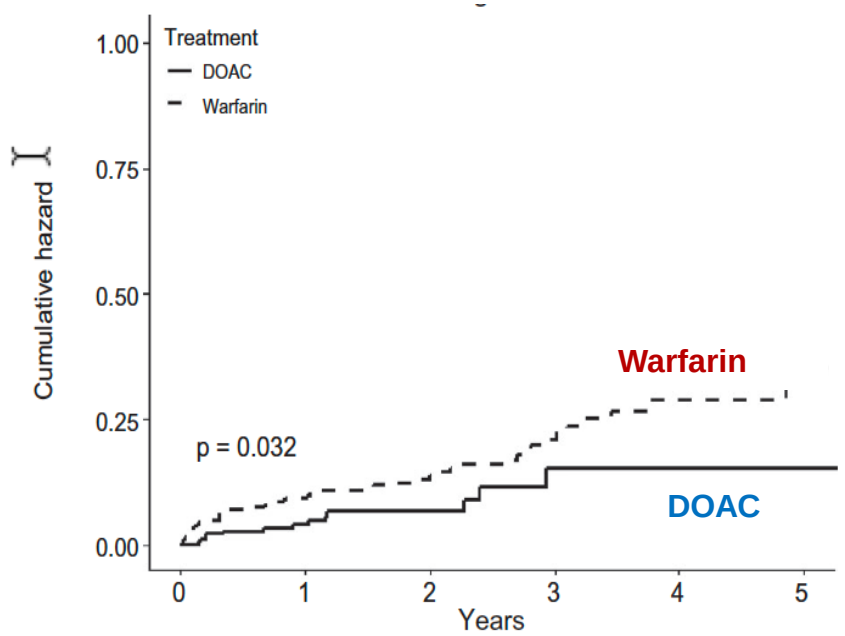
	Bleeding			
	Warfarin vs. No AC		DOAC vs. No AC	
Model Specification	n	HR (95% CI)	n	HR (95% CI)
ITT PS-matched cohorts	1,694	1.50* (1.10-2.06)		0.77 (0.40-1.48)
Marginal structural models†	2,694	1.29 (0.74-2.26)		0.37 (0.13-1.07)

Incidence rates per 100 person-years

	Warfarin-Matched Cohort			DOAC-Matched Cohort		
	No AC n = 1,080	Warfarin n = 614	*P* Value	No AC n = 503	DOACs n = 201	*P* Value
Bleeding	5.4	5.9	0.29	4.8	3.6	0.21

Bleedings: ~88% GI in both groups

Cumulative risk of bleeding

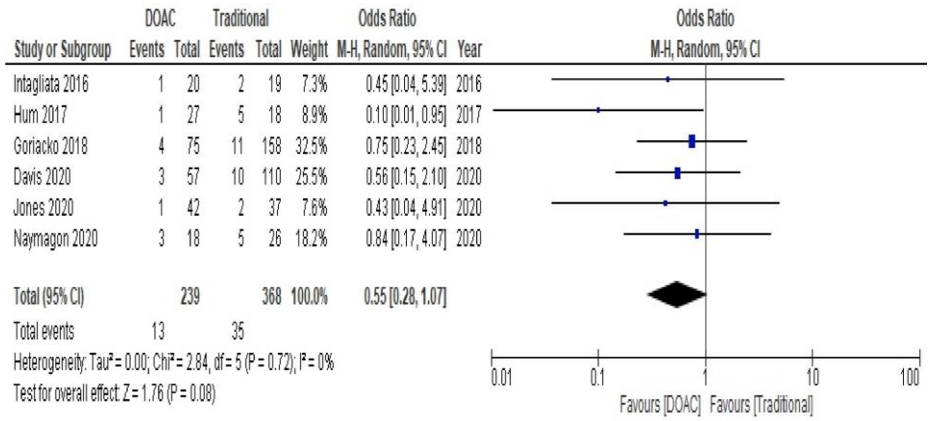


M Serper et al. Hepatology 2021

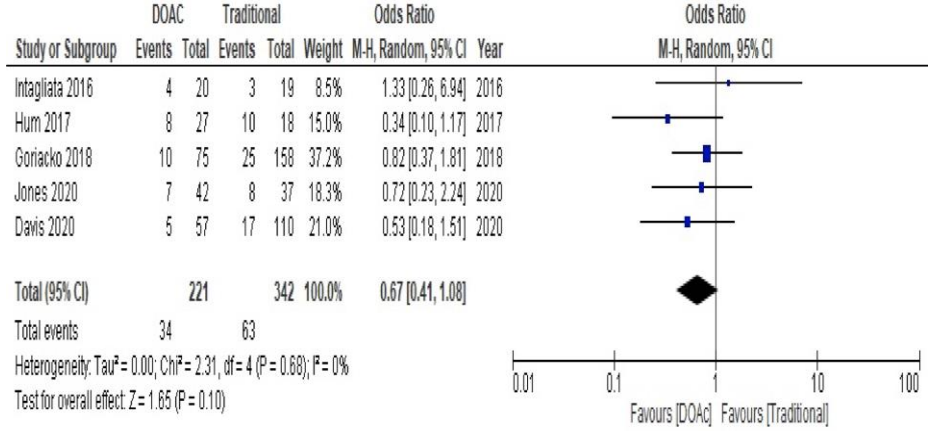
Bleeding events in patients with cirrhosis and atrial fibrillation treated with VKA or DOACs

Agregate data meta-analysis
Studies comparing DOAC vs. traditional AC
Child A/B cirrhosis with atrial fibrillation
7 studies, **683 patients, ISTH definitions**

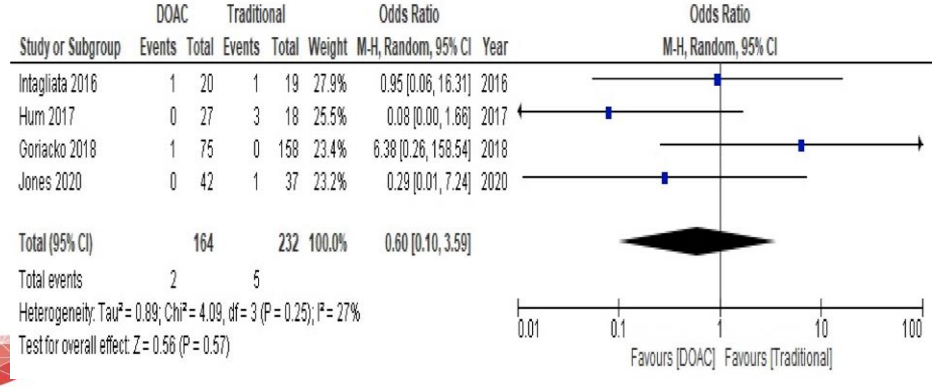
ISTH-Major bleeding



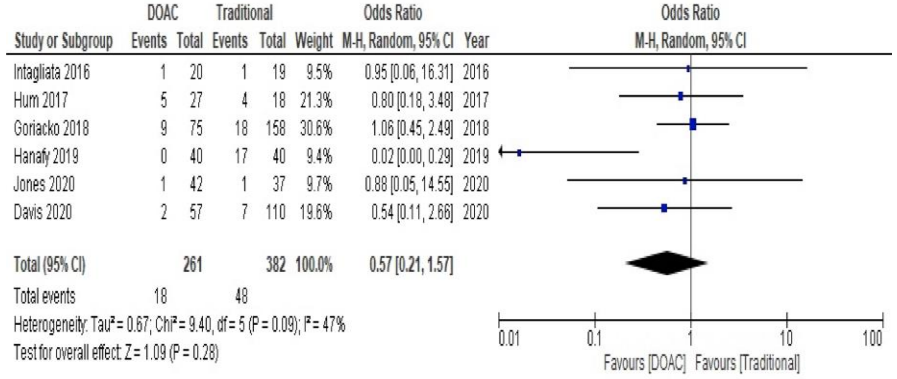
All bleeding



Intracraneal hemorrhage



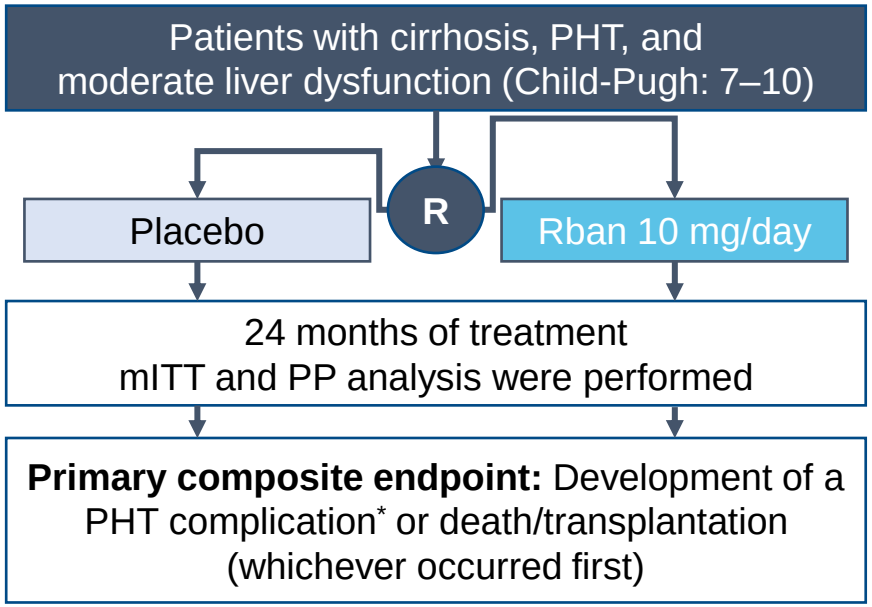
GI bleeding

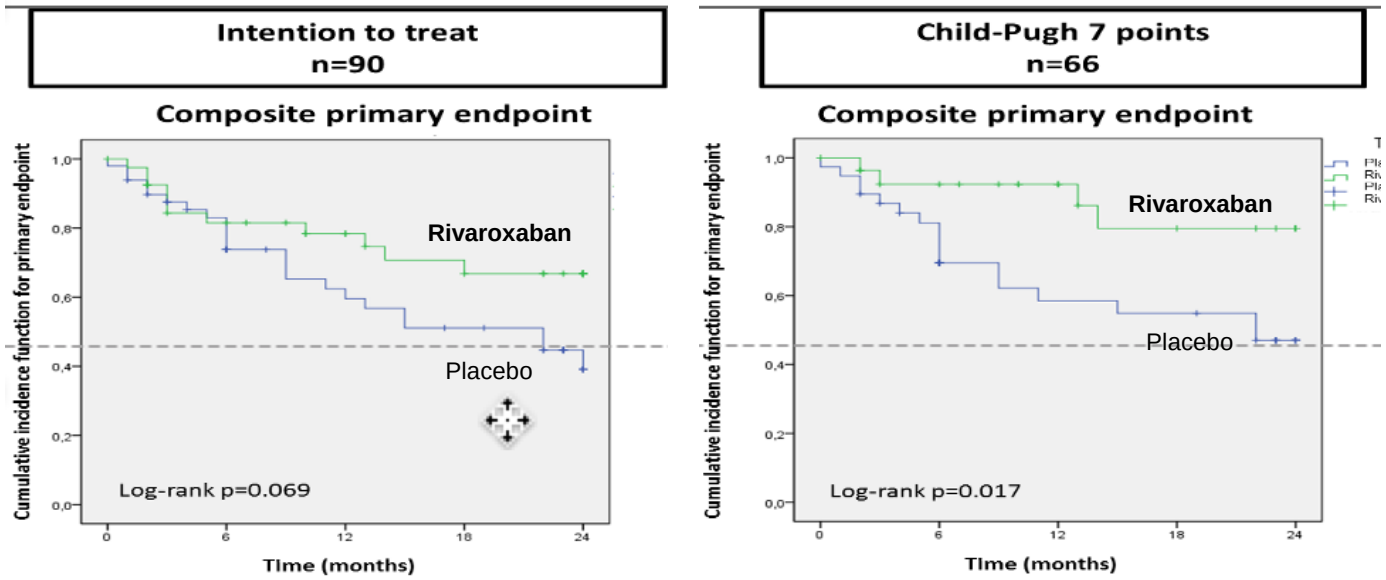


S Nisly et al. J Thromb Thrombol 2021

Rivaroxaban improves survival and decompensation in cirrhotic patients with moderate liver dysfunction: a double-blind, placebo-controlled trial

Randomized, double-blind, placebo-controlled multicenter trial (EduraCT: 2014-005523-27)





Adverse events

- **Non-PHT bleeding** OR 4.2 [95% CI: 1.54–11.7 p=0.004]
- **Major bleeding events** OR 4.02 [95% CI: 0.767–21.167, p=NS]

A Puente et al. JHEP 2023

Anticoagulation to treat portal vein thrombosis in cirrhosis

Type, dosing and bleeding risk

- **Recanalization**: LMWH>VKA?, 6-9 months. Progression ~**7%**: LMWH=VKA
- VKA risk increases in ↑creatinine, ↓albumin, **platelet <30-50k/µl**
- Enoxaparin 1-1.5 mg/kg.d SC, no monitoring. VKA INR 2-3
- Similar efficacy of LMWH→VKA, LMWH, VKA, DOACs
- **Similar (or lower) bleeding risk** with DOACs than with traditional AC in **Child A/B**

Anticoagulation to treat portal vein thrombosis in cirrhosis

Aims of anticoagulation
- Achieve recanalization
- Halt progression
- Avoid recurrence
- Reduce decompensation and death?

Considerations → individualize decisions

	Anticoagulation	
Characteristics	**Favours**	**Not favours**
Patient		
Transplant status	Waiting list Potential candidate	Not candidate
Clinical status	Child A	Encephalopathy, Risk of falls Platelet count <30-50k/µl
Thrombosis		
Symptoms	Yes	No
Time course	Recent (<6 m)	Chronic Cavernoma
Severity	Partially occlusive (>50%) Complete	Minimally occlusive (<50%)
Location	Main trunk Superior mesenteric vein	Isolated of intrahepatic branches
Evolution	Progression without treatment	Stability or regression

Anticoagulation to treat portal vein thrombosis in cirrhosis

Aims of anticoagulation

- Achieve recanalization
- Halt progression
- Avoid recurrence
- Reduce hepatic decompensation and mortality?

Considerations for anticoagulation

Individualize stopping AC: (→ favours maintaining anticoagulation)

- Maintain until recanalization or for at least 6-9 months if no recanalization
- Continued after recanalization (→ candidate/waiting LT, symptomatic, recurrent, others?)

Take-home messages

- Potential benefit of long-term anticoagulation on hepatic decompensation and survival in cirrhosis
- Portal vein thrombosis might identify a subset of patients with cirrhosis that could benefit of long-term anticoagulation
- The benefit on liver outcomes and survival seems to be independent of the type of anticoagulant, traditional or DOAC