VALDIG
VASCULAR LIVER DISEASE GROUP

Portal vein thrombosis meeting

Paris, 29-30 Nov 2022

Anticoagulation in patients with cirrhosis to prevent and treat portal vein thrombosis and to prevent decompensation

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Anticoagulation in patients with cirrhosis to prevent and treat portal vein thrombosis and to prevent decompensation

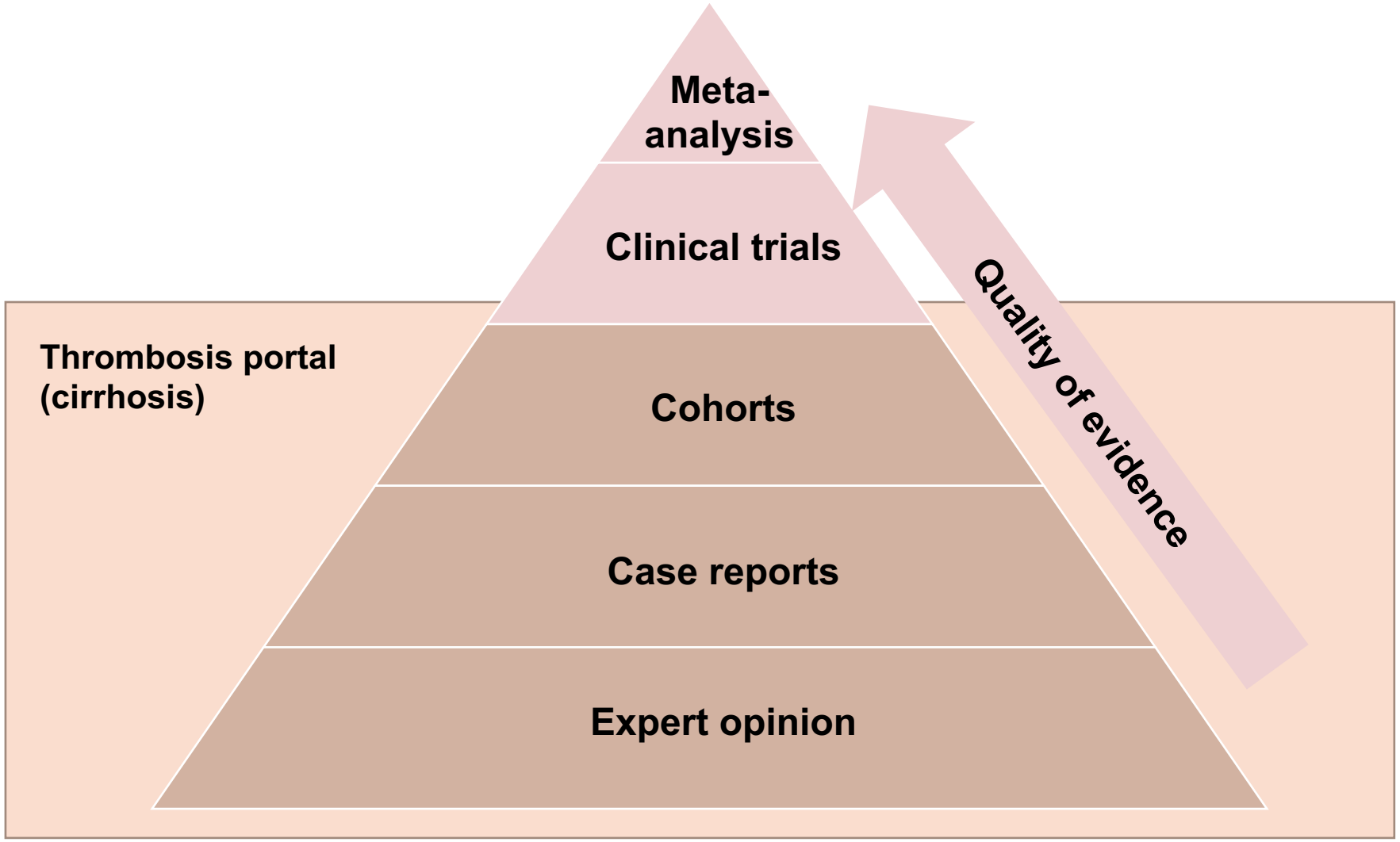
CONS

- 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 AG?

Quality of evidence in portal vein thrombosis in cirrhosis



Courtesy of L Téllez

Anticoagulation in patients with cirrhosis to prevent and treat portal vein thrombosis and to prevent decompensation

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?

Please address stopping rule, risk of re-thrombosis after anticoagulation withdrawal. Please also address bleeding complications unrelated to portal hypertension, and factors associated with progression and regression of the thrombus under anticoagulation

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

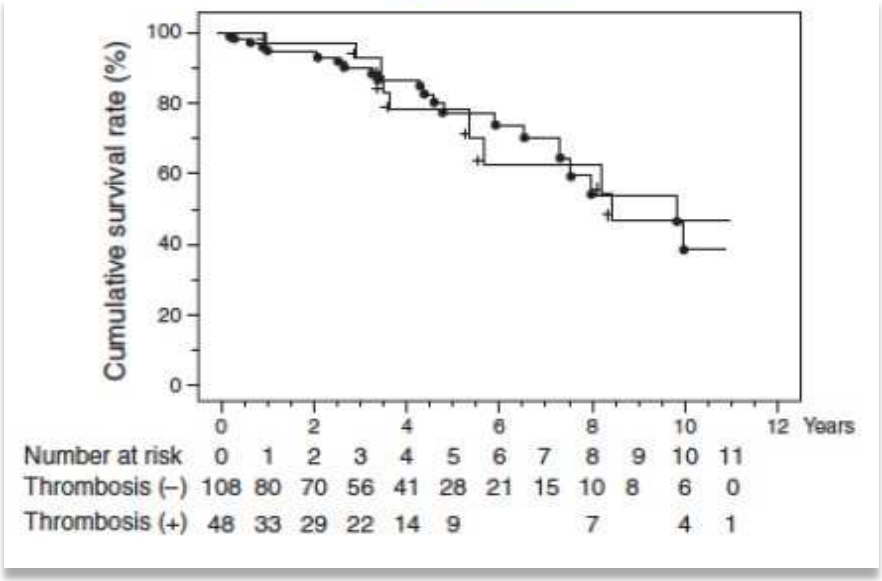
F Nery et al. Hepatology. 2014

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%)**

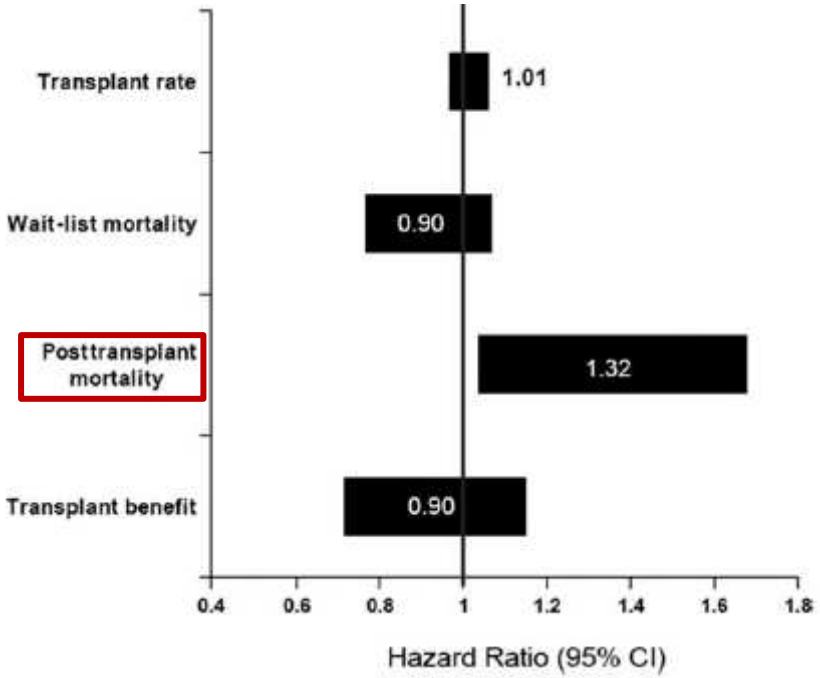
Correlation between the extension of PVT and clinical presentation

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

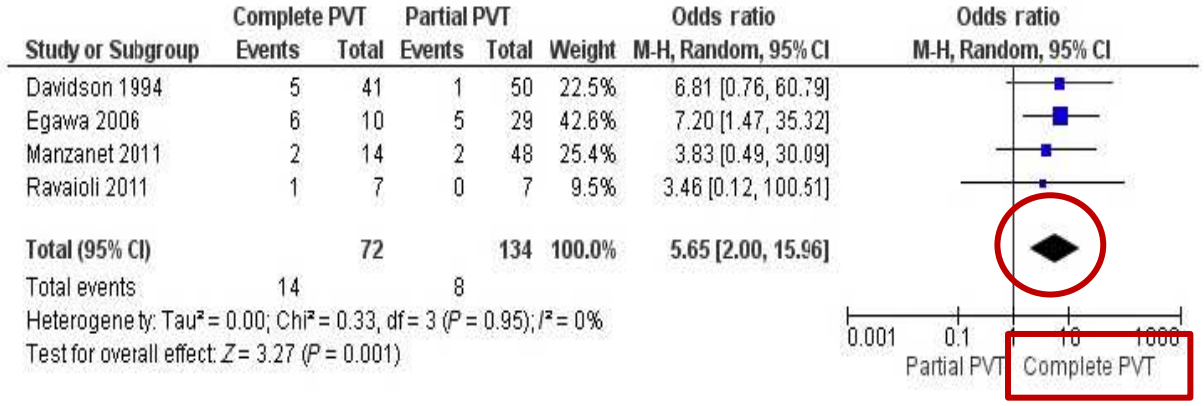
Impact of portal vein thrombosis on liver transplantation

SRTR 22291 receptors
PVT 4.02%

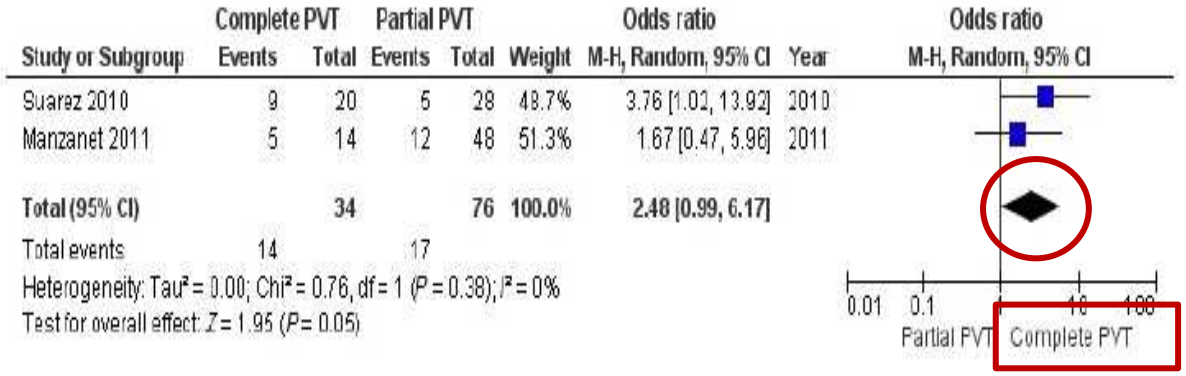


MJ Englesbe et al. Liver Transpl 2010

30-day post-transplantation survival



1-year post-transplantation survival



Zanetto A et al. Transplant Int 2018

Anticoagulation in patients with cirrhosis to prevent and treat portal vein thrombosis and to prevent decompensation

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

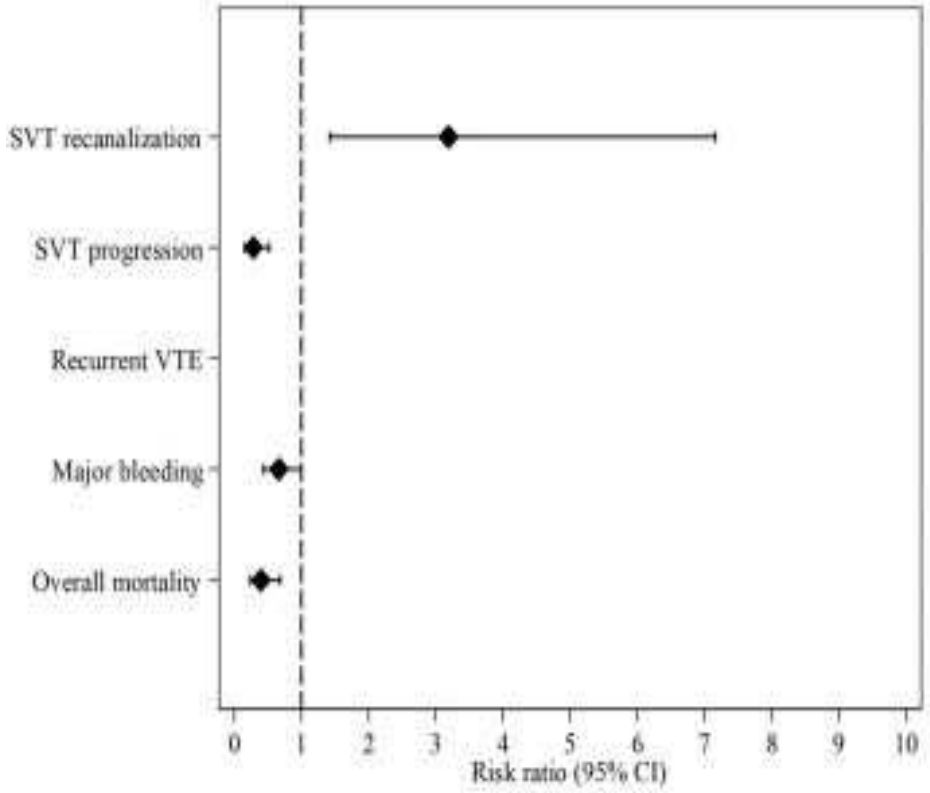
  Does anticoagulation modify the natural history of cirrhosis?
- Is anticoagulation safe?

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%
Cui, 2015	Prospective	65	LMWH	**6**	CR/PR 78%
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%
Pettinary, 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

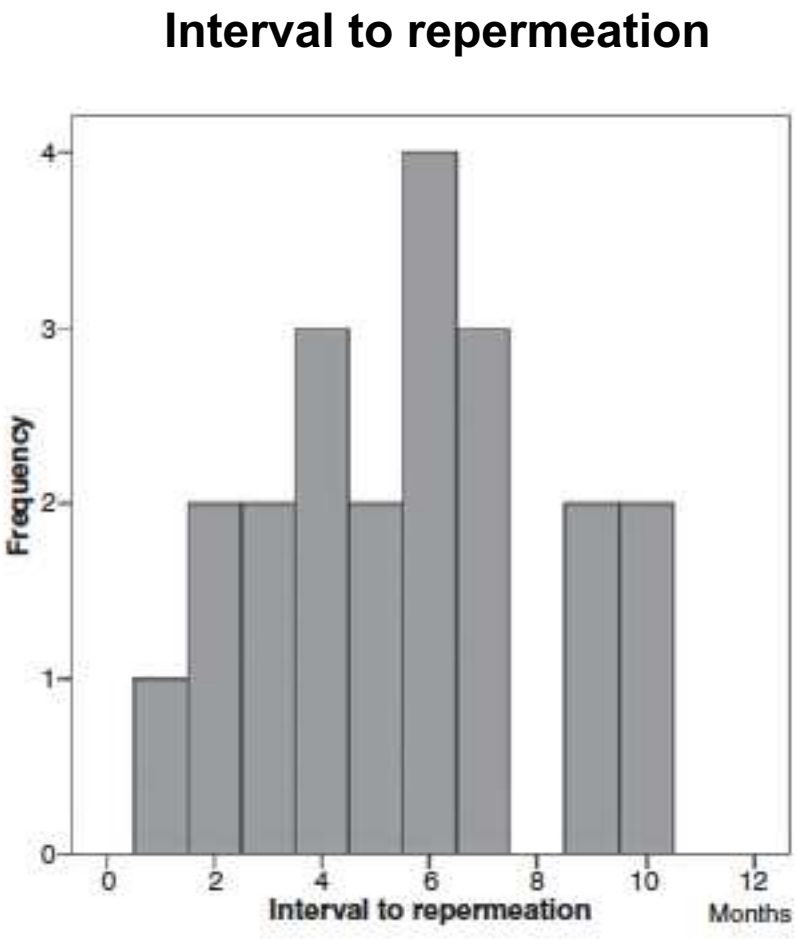
Meta-analysis of aggregate data
26 studies, 1475 patients, -2019



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. Throm 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

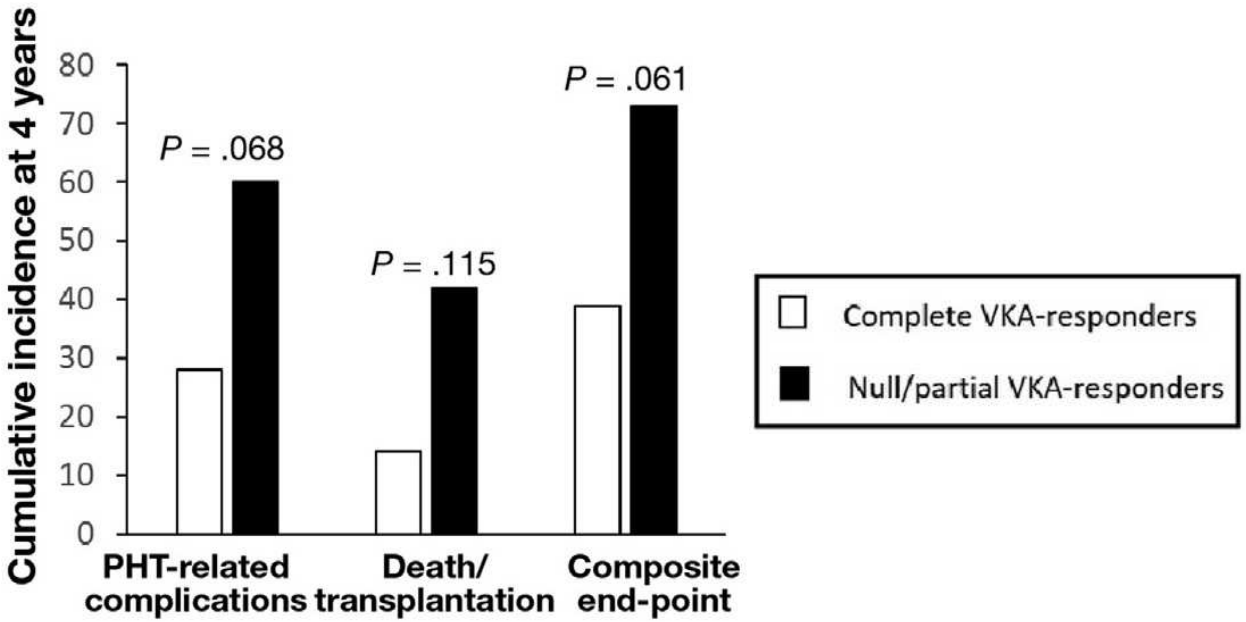
Interval to repermeation:

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

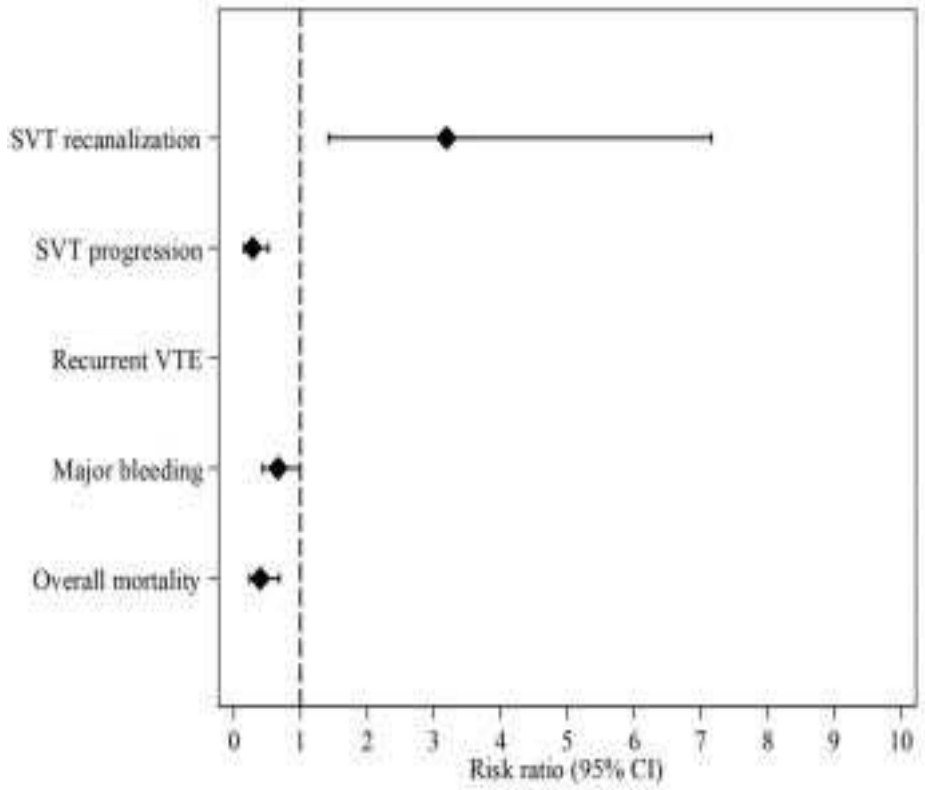
Le Wang et al. Adv Ther 2021

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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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)
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E Valeriani et al. Throm Haemost 2021

Anticoagulation in patients with cirrhosis to prevent and treat portal vein thrombosis and to prevent decompensation

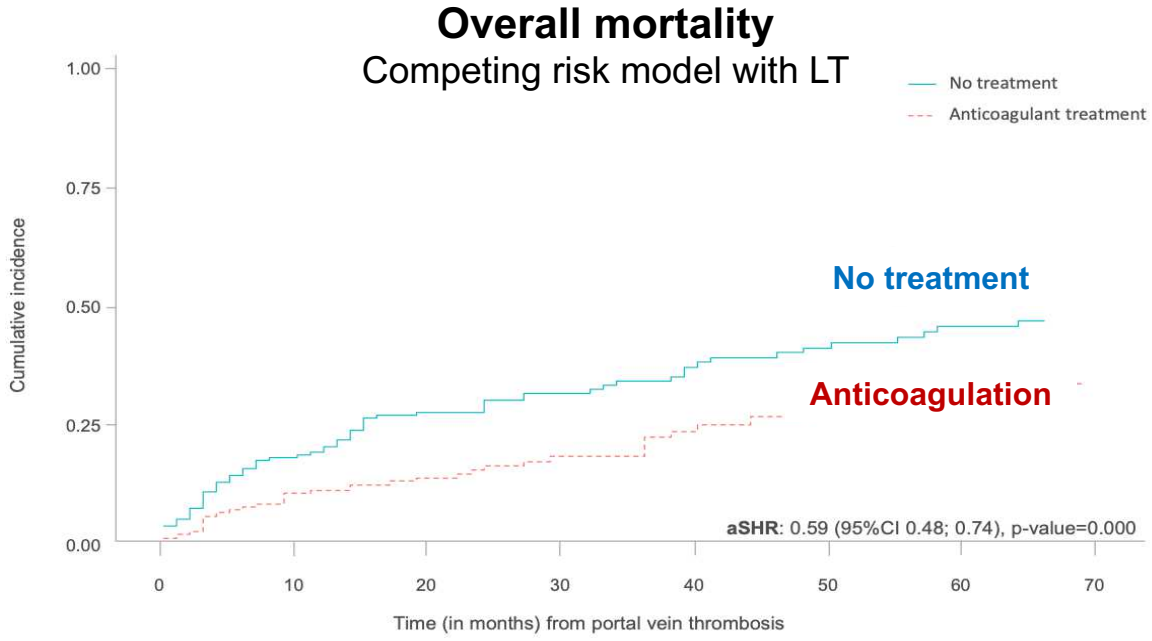
Agenda

- 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?

Decreased overall mortality in patients anticoagulated for portal vein thrombosis in cirrhosis

IPD meta-analysis
Studies comparing AC vs. no treatment cohorts
5 studies, **500 patients,** Until JUN-2020
Child B/C 68/49%%, Non-occlusive PVT 37/41%
AC (median): LMWH, VKA **9.1 m.** F-up (median): **26 m**



A Guerrero et al. Submitted

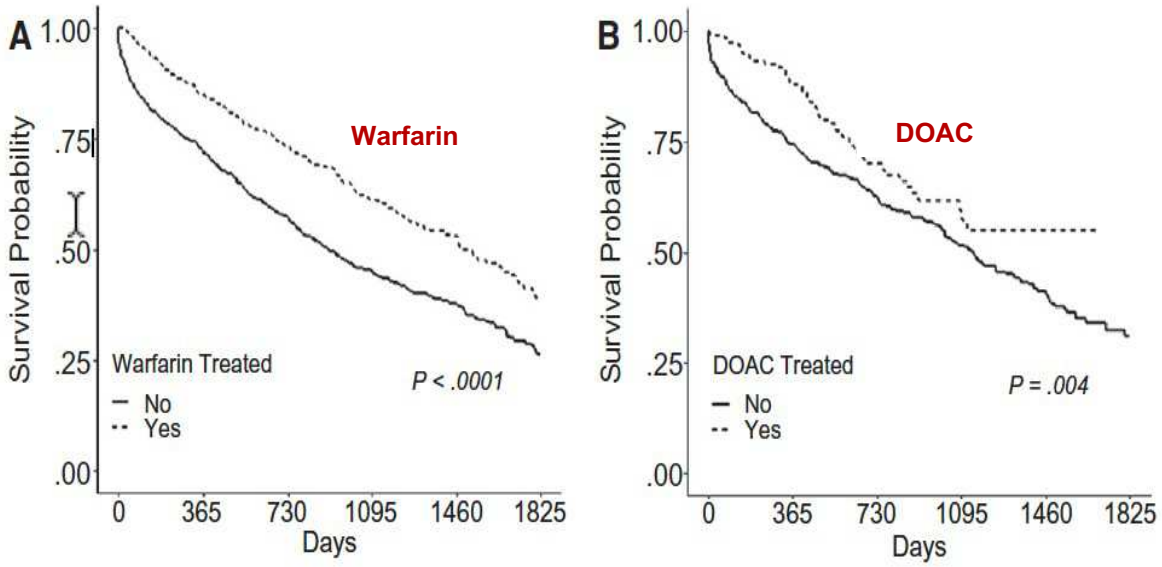
Anticoagulation reduces all-cause mortality and hepatic decompensation in patients with Child A/B cirrhosis and atrial fibrillation

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



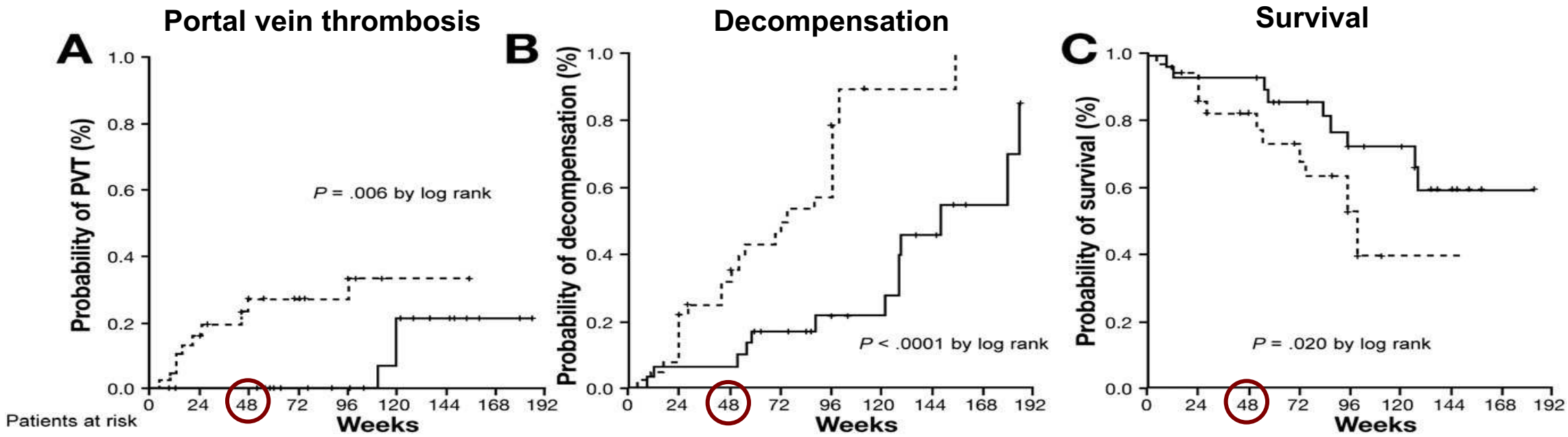
Incidence rates per 100 person-years

	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

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

Anticoagulation in patients with cirrhosis to prevent and treat portal vein thrombosis and to prevent decompensation

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?**

Efficacy of LMWH and VKA for portal vein thrombosis in cirrhosis

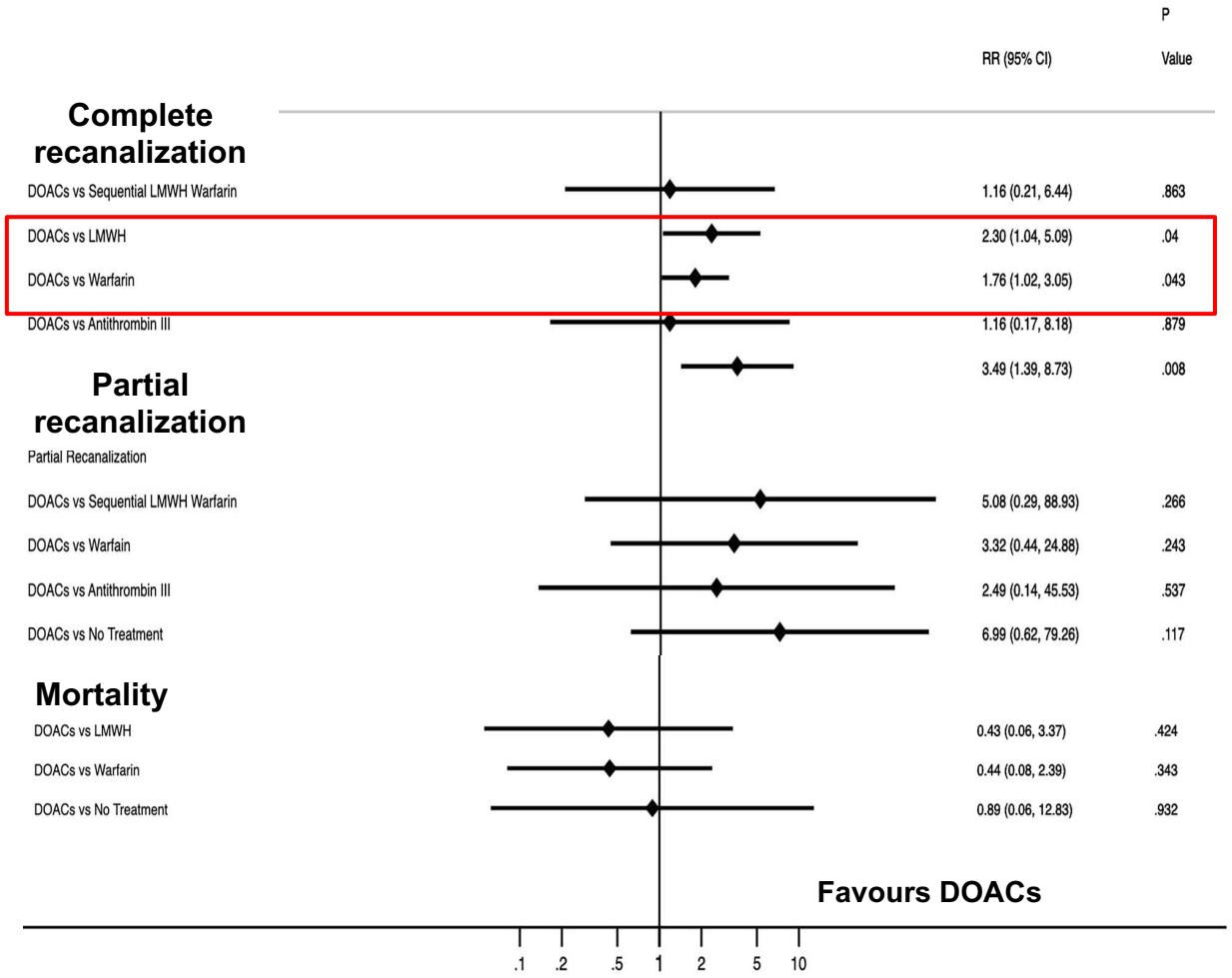
Aggregate data meta-analysis
8 studies, **353 patients**, until FEB-2017

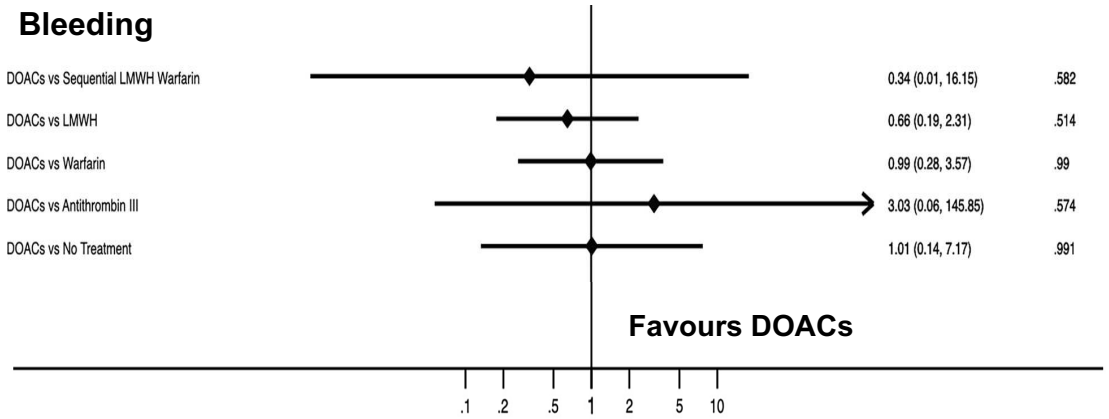
	Complete Recanalization of PVT			Progression of PVT			
Study-Level Factors	Pooled OR Over Subgroup	95% CI	*P*	Pooled OR Over Subgroup	95% CI	*P*	S
Duration of anticoagulation (*per mo*)	0.872	0.661–1.152	.389	1.100	0.826–1.467	.550	
Type of anticoagulation							
LMWH (vs untreated)	8.386	3.287–21.393	**.011**	0.062	0.040–0.097	**<.001**	
Warfarin (vs untreated)	2.232	0.742–6.720	.226	0.338	0.238–0.479	**.004**	
Warfarin (vs LMWH)	0.266	0.062–1.131	.147	5.446	3.089–9.960	**.004**	
Warfarin (vs LMWH), adjusted by study design Study design	0.057	0.002–1.651	.194	2.060	0.749–5.664	.256	
R (vs P)	0.420	0.075–2.349	.379	5.890	3.642–9.526	**.002**	

L Loffredo et al. Gastroenterology 2019

Efficacy and safety of DOACs in portal vein thrombosis in cirrhosis

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

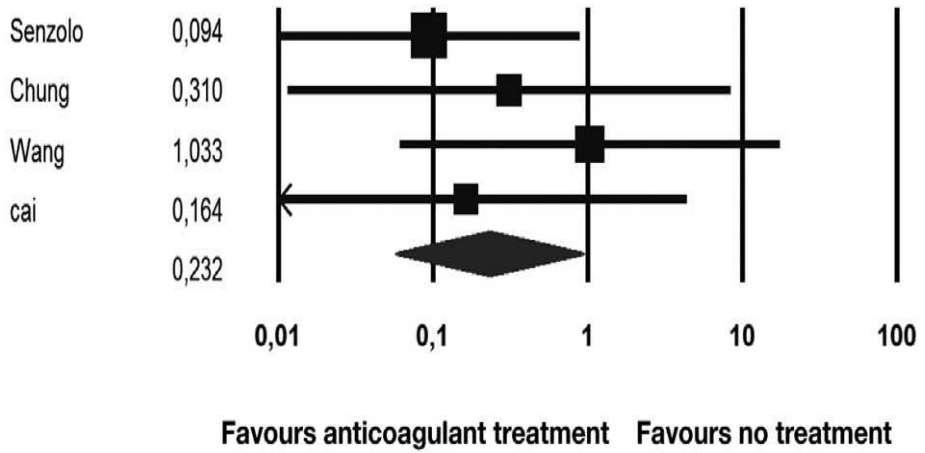




CH Ng et al. Hepatol Int 2021

Bleeding events in patients with cirrhosis and 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%)	0.1
Non-portal hypertension related, N (%)	20 (10%)	5 (1.7%)	0.1
Intracraneal hemorrhage **GI bleeding** **Epistaxis, gingivorrhagia** Abdominal hematoma for injection Other	**1** **6** **5** 3 6	4	

A Guerrero et al. Submitted

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

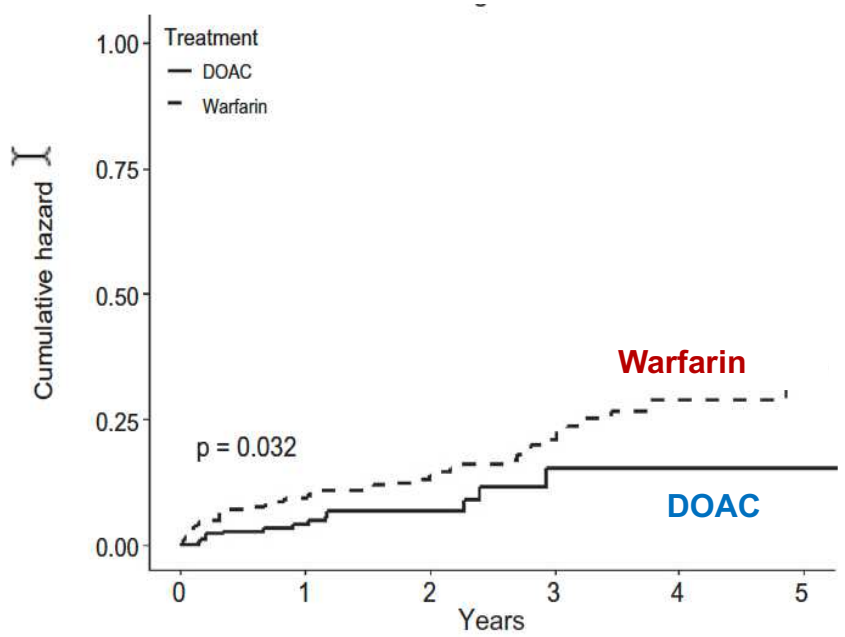
	Bleeding			
	Warfarin vs. No AC		DOAC vs. No AC	
Model Specification	n	HR (95% CI)	n	HR (95% CI)
ITT PS-matched cohorts	1,694	1.50* (1.10-2.06)		0.77 (0.40-1.48)
Marginal structural models†	2,694	1.29 (0.74-2.26)		0.37 (0.13-1.07)

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

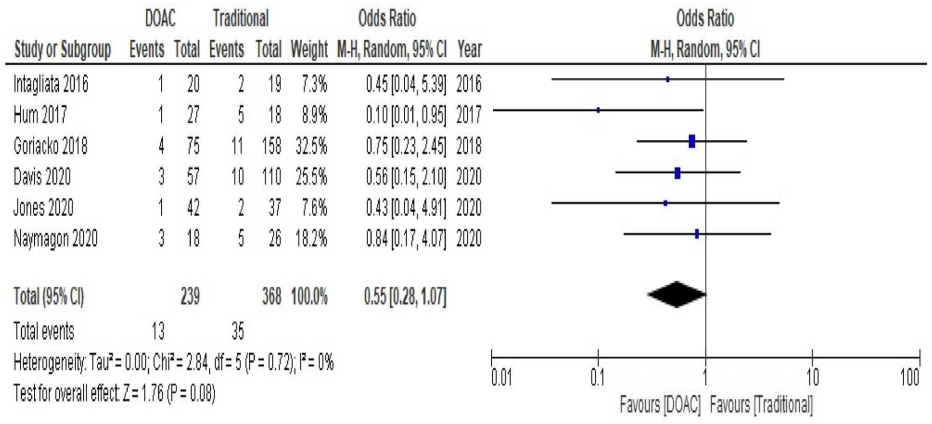


M Serper et al. Hepatology 2021

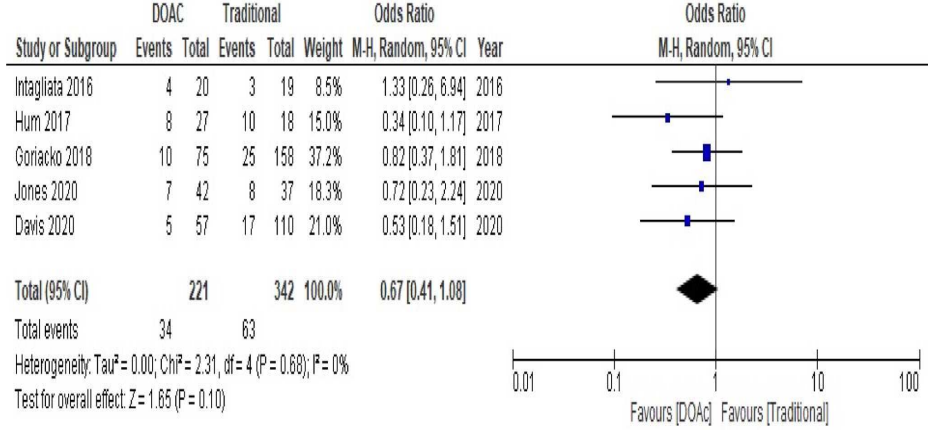
Bleeding events in patients with cirrhosis and atrial fibrillation treated with VKA or DOACs

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

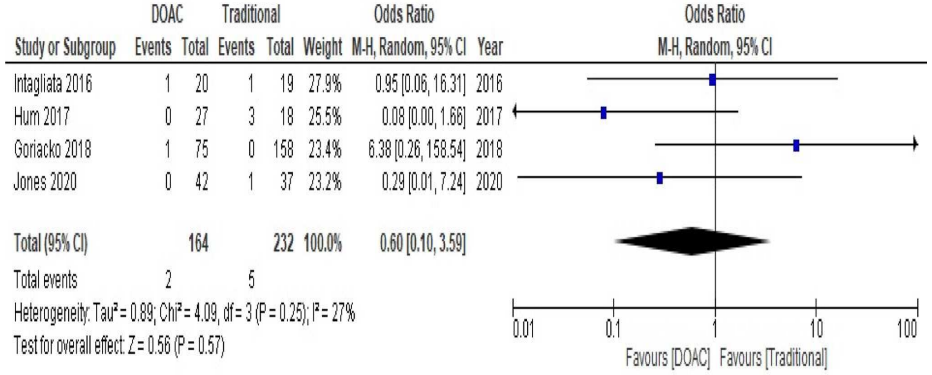
ISTH-Major bleeding



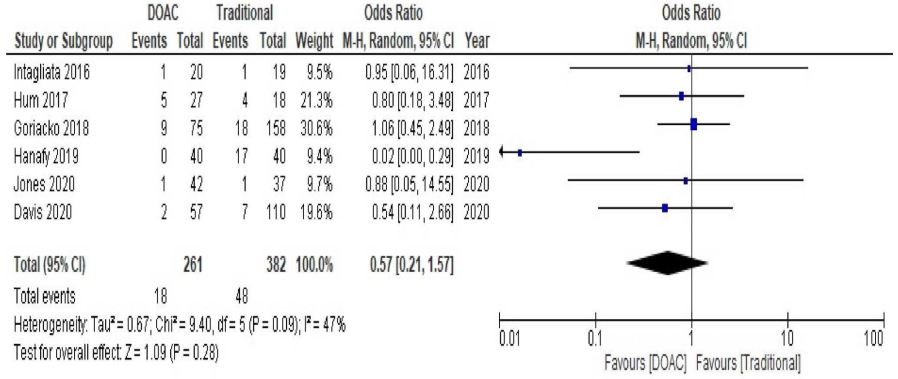
All bleeding



Intracraneal hemorrhage



GI bleeding



S Nisly et al. J Thromb Thrombol 2021

Anticoagulation in patients with cirrhosis to prevent and treat portal vein thrombosis and to prevent decompensation

Take-home messages

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**

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Portal vein thrombosis meeting
Paris, 29-30 Nov 2022

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Take-home messages

Aims of anticoagulation

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

Considerations for anticoagulation

Individualize indication, no firm recommendations: (→ favours anticoagulation)

- **LTx status** (→ candidate/waiting LT independent of extension/severity, prevent extension, keep SMV permeability!)
- **Symptoms** (→ symptomatic)
- **Acuity** (→ acute/recent, <6 m, no cavernoma)
- **Severity/extension** (→ occlusive >50%, progression)
- **Site** (→ main trunk, SMV)

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?)

Anticoagulation in patients with cirrhosis to prevent and treat portal vein thrombosis and to prevent decompensation

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