Vascular Liver Disease
Recent developments

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☐ I do not have any potential conflict of interest

Vascular Liver Disease
Recent developments

- Congenital extrahepatic portosystemic shunt (CEPS)
- Portal vein thrombosis in patients with cirrhosis
- Recanalization of the thrombosed portal vein
- Direct oral anticoagulants

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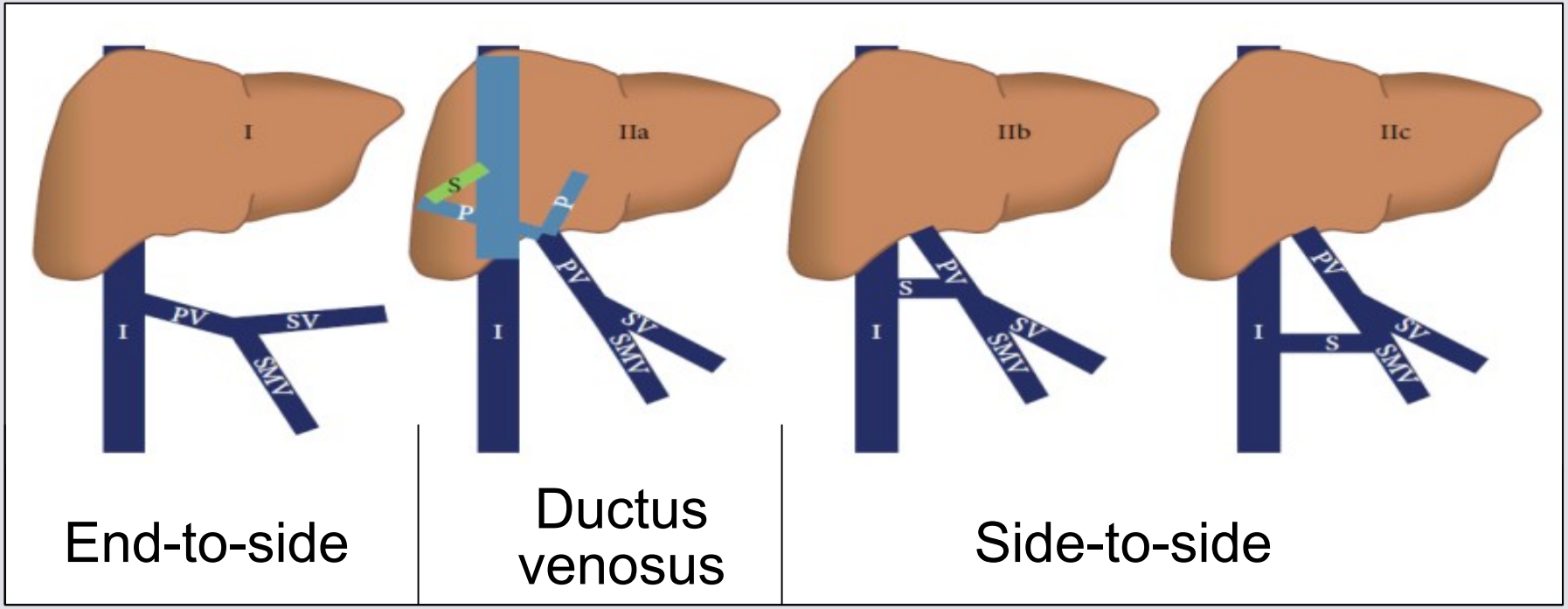
Congenital Extrahepatic Portosystemic Shunts (CEPS)



Gupta. Radiol Res Practice 2015

CEPS – VALDIG's experience in 66 adults

Main complications	N	%
HE	19	29
PAHT	10	15
HPS	2	3
HCC	8	12
Adenoma	10	15
Benign nodules	25	38
None	21	32

Baiges (VALDIG), Hepatology 2019 – median age 30 years

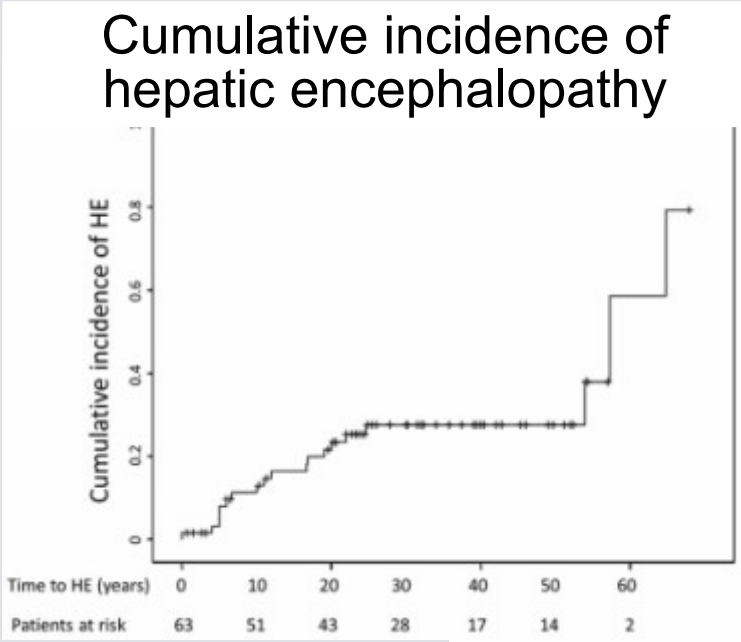
CEPS – VALDIG's experience in 66 adults

Main complications	N	%	Age Med. (range)
HE	19	29	12 (5-65)
PAHT	10	15	20 (2-42)
HPS	2	3	41 (41-41)
HCC	8	12	39 (32-53)
Adenoma	10	15	18 (4-46)
Benign nodules	25	38	20 (7-52)
None	21	32	30 (0-67)*

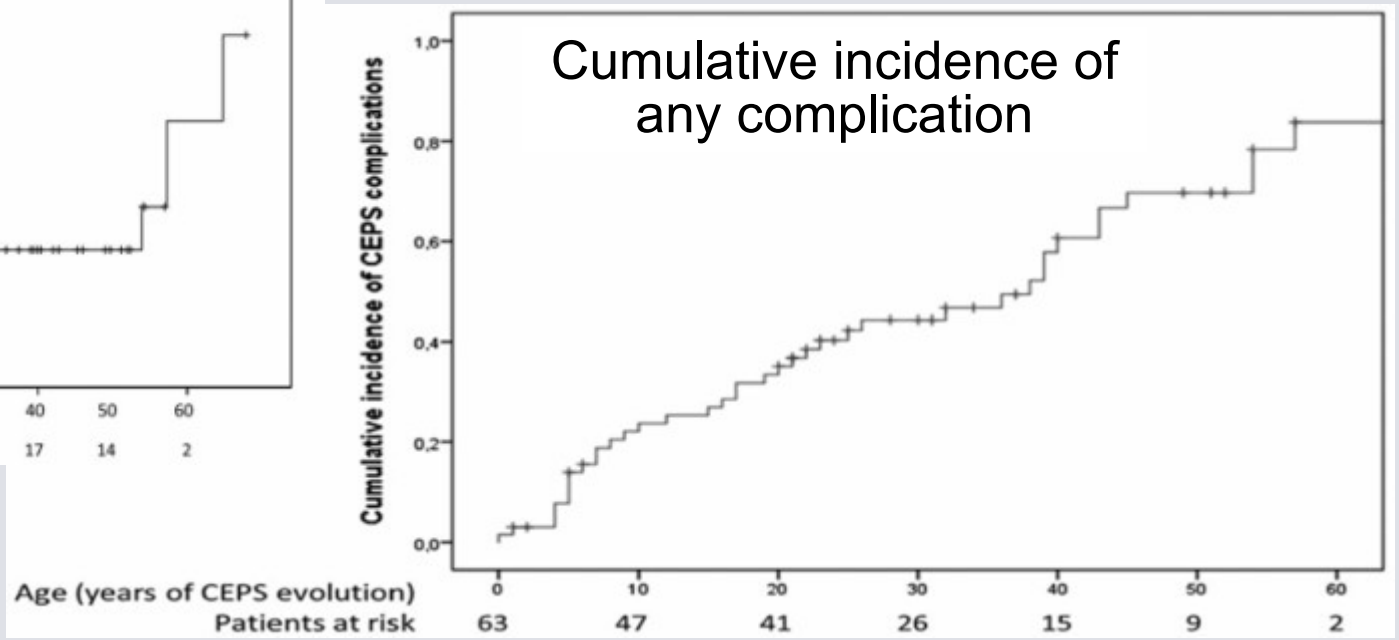
Baiges (VALDIG), Hepatology 2019 – * Follow-up

CEPS

Cumulative incidence of hepatic encephalopathy



Cumulative incidence of any complication



Baiges (VALDIG), Hepatology 2019

CEPS – VALDIG's experience in 66 adults

Main Complications	N	%	Age Med. (range)	Male sex
HE	19	29	12 (5-65)	47%
PAHT	10	15	20 (2-42)	60%
HPS	2	3	41 (41-41)	50%
HCC	8	12	39 (32-53)	87%
Adenoma	10	15	18 (4-46)	0%
Benign nodules	25	38	20 (7-52)	-
None	21	32	30 (0-67)*	76%

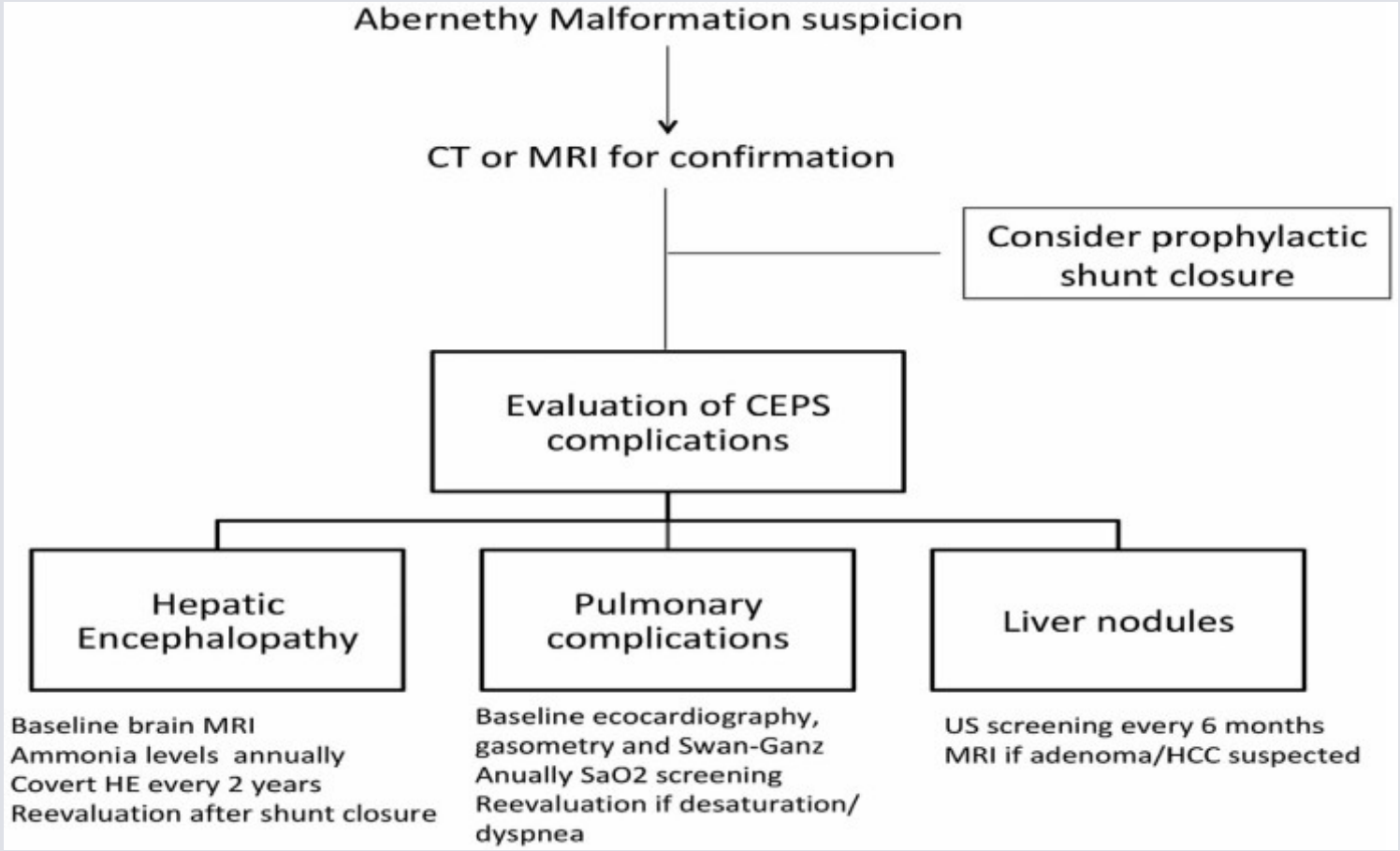
Baiges (VALDIG), Hepatology 2019 – * Follow-up

CEPS – VALDIG's experience in 66 adults

Main complications	N	%	Shunt closure	Outcome after closure
HE	19	29	4	4 improved
PAHT	10	15	3	2 resolution
HPS	2	3	2	2 resolution
HCC	8	12	0	
Adenoma	10	15	1	No change
None	21	32	5	No complication

Baiges (VALDIG), Hepatology 2019 – median age 30 yrs

CEPS



Baiges (VALDIG), Hepatology 2019

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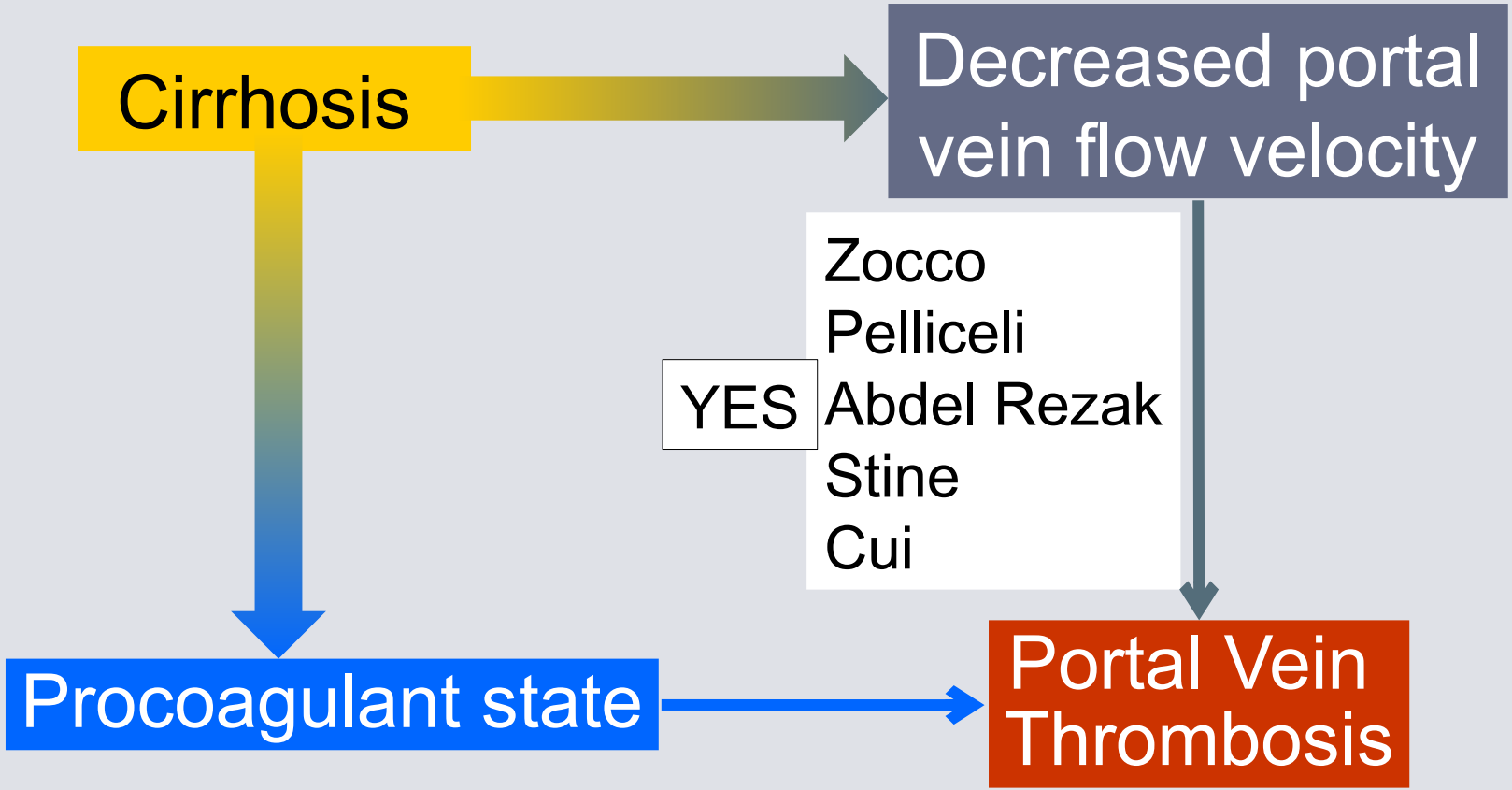
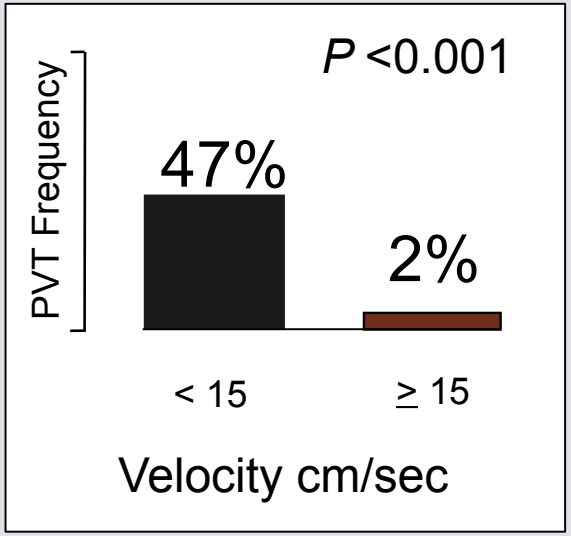
Portal vein thrombosis in cirrhosis

- Portal vein flow velocity
- Non specific beta adrenergic blockers
- Transient portal vein thrombosis

Predicting PVT with portal vein flow velocity



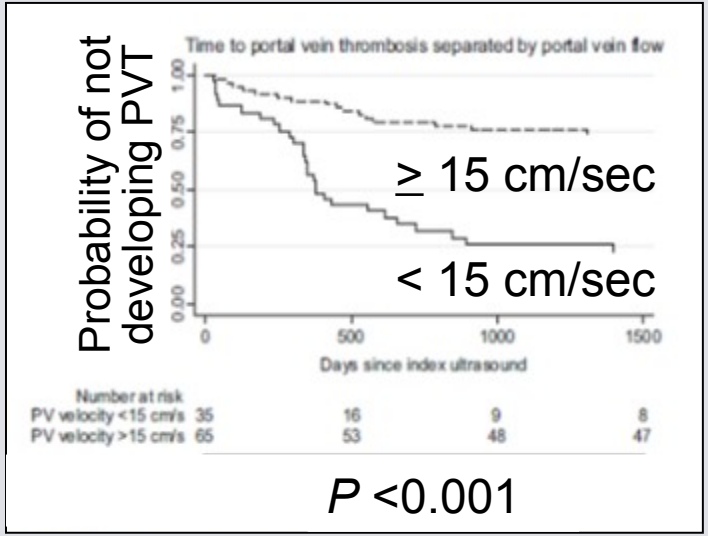
Predicting PVT with portal vein flow velocity



Zocco, J HEP 2009

Similar to

Abdel-Razik EJGH 2015

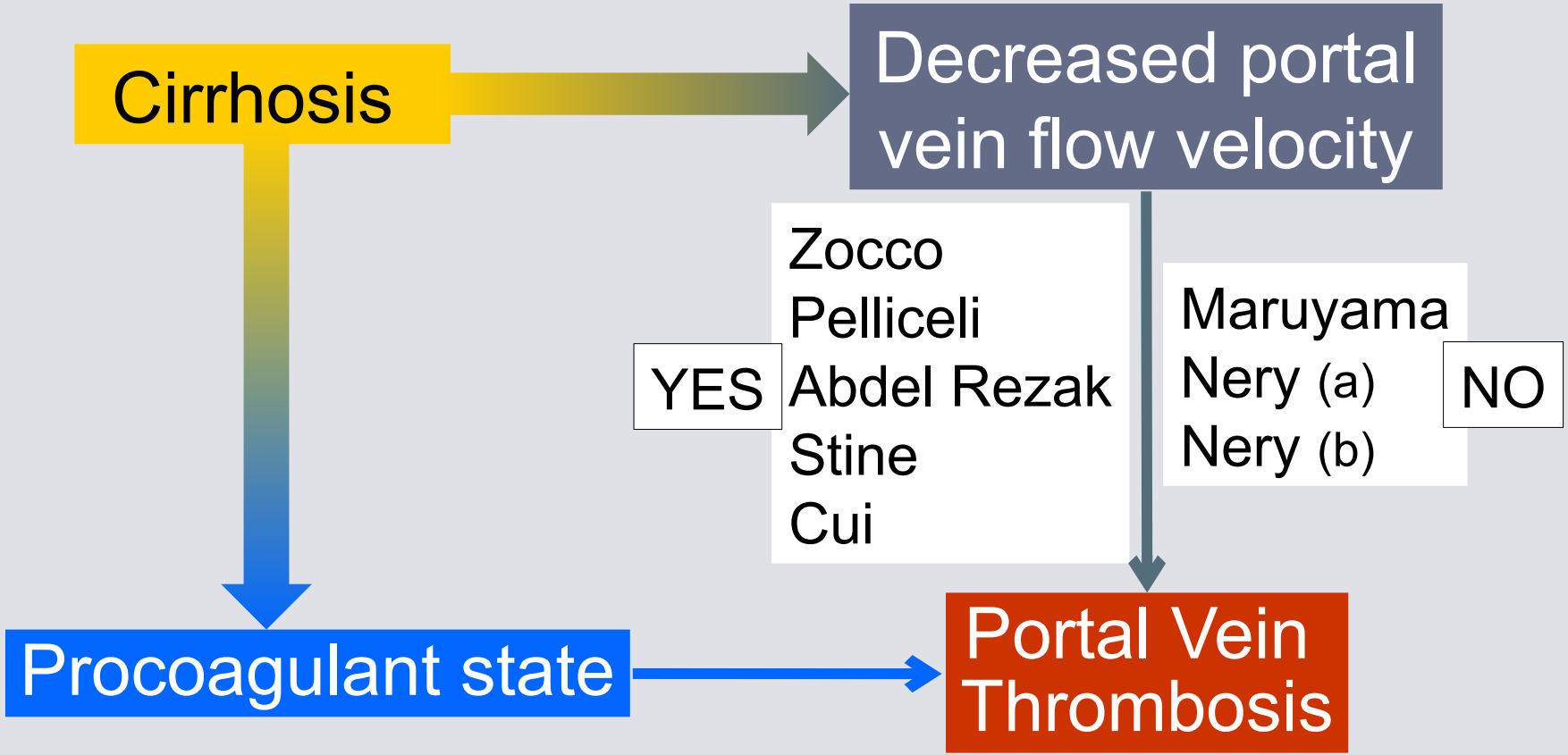


Stine Liver Int 2018

Variable	AUC
PVFV	0.709
D-Dimer	0.732
CP score	0.778
DIC	0.845

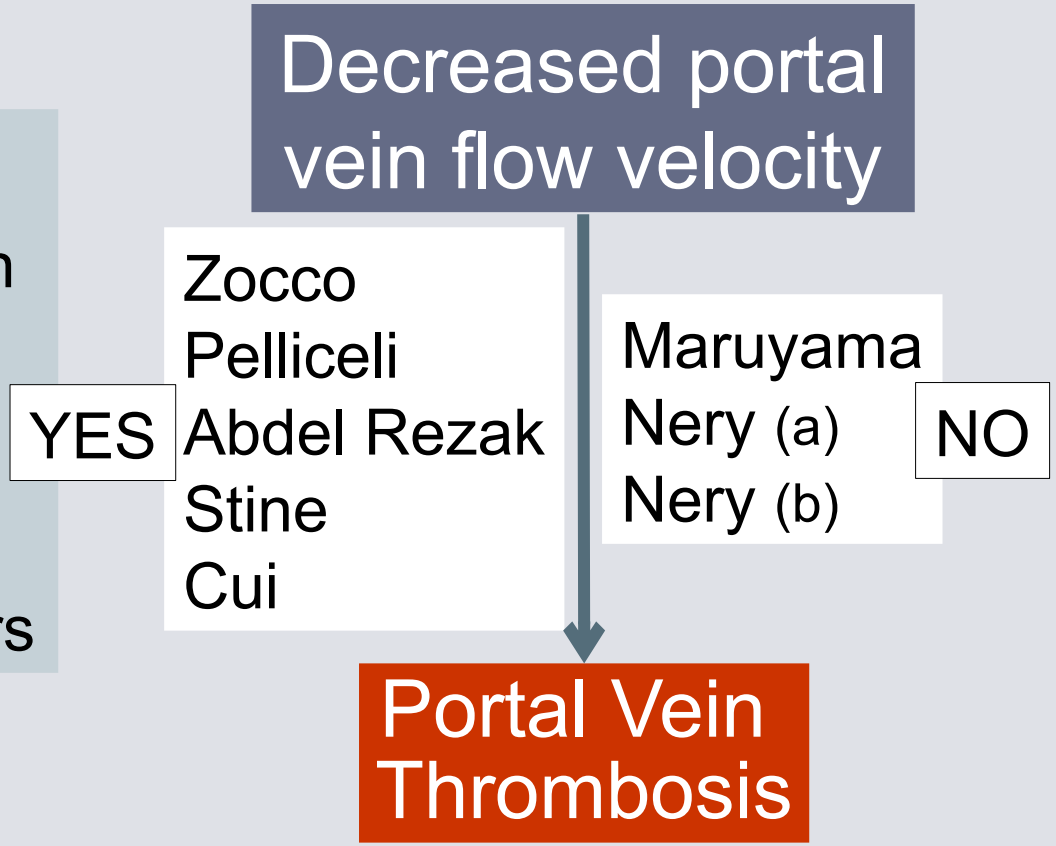
Cui, Thrombosis Res 2018

Predicting PVT with portal vein flow velocity



Predicting PVT with portal vein flow velocity

- Reproducibility
- Interaction of velocity with
  - Severity of liver disease
  - Obesity/NASH
  - Treatment of the cause
  - Nonspecific beta-blockers



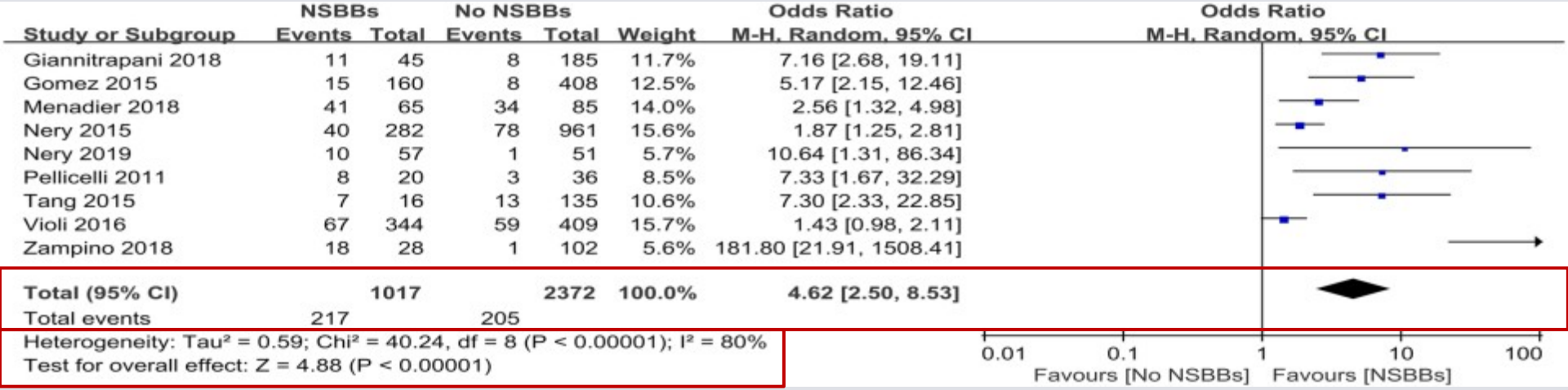
Predicting PVT with portal vein flow velocity

- Tight relationship between portal vein blood flow velocity and severity of liver disease
- The independent impact of each factor difficult to evaluate
- Decreased velocity likely to contribute
- Not discriminant enough to serve as a trigger point for therapy

Portal vein thrombosis in cirrhosis

- Portal blood flow velocity
- Non specific beta adrenergic blockers
- Transient portal vein thrombosis

PVT in cirrhosis: Nonspecific beta-blockers



Study or Subgroup	NSBBs Events	NSBBs Total	No NSBBs Events	No NSBBs Total	Weight	Odds Ratio M-H, Random, 95% CI
Giannitrapani 2018	11	45	8	185	11.7%	7.16 [2.68, 19.11]
Gomez 2015	15	160	8	408	12.5%	5.17 [2.15, 12.46]
Menadier 2018	41	65	34	85	14.0%	2.56 [1.32, 4.98]
Nery 2015	40	282	78	961	15.6%	1.87 [1.25, 2.81]
Nery 2019	10	57	1	51	5.7%	10.64 [1.31, 86.34]
Pellicelli 2011	8	20	3	36	8.5%	7.33 [1.67, 32.29]
Tang 2015	7	16	13	135	10.6%	7.30 [2.33, 22.85]
Violi 2016	67	344	59	409	15.7%	1.43 [0.98, 2.11]
Zampino 2018	18	28	1	102	5.6%	181.80 [21.91, 1508.41]
Total (95% CI)		**1017**		**2372**	**100.0%**	**4.62 [2.50, 8.53]**
Total events	217		205			

Heterogeneity: Tau² = 0.59; Chi² = 40.24, df = 8 (P < 0.00001); I² = 80%
Test for overall effect: Z = 4.88 (P < 0.00001)

Xu, Hepatol Int 2019

Portal vein thrombosis : Non-specific beta-blockers

Independent variables	P	OR	C.I.
Platelets	0.32	0.99	0.99-1.0
Child-Pugh	0.19		
Esophageal varices	0.007		
Hypertension	0.06	4.4	-0.2-3.1
Beta-blocker use	0.0003	17.8	1.03-4.7

Zampino, Saudi J Gastroenterol 2018
Retrospective - 130 Italian patients.
19 PVT

	PVT hazard ratio	95% confidence interval	P
Oesophageal varices (Medium/Large vs Null/small)			
Crude	5.67	1.49-21.63	0.011
Adjusted for NSBB	2.45	0.55-10.89	0.238
NSBB (yes vs no)			
Crude	10.56	1.35-82.73	0.025
Adjusted for PBFV	12.47	1.58-98.43	0.017
Adjusted for heart rate	13.66	1.51-123.85	0.020
Adjusted for OV	6.15	0.63-59.96	0.118

NSBB, nonselective beta-blocker; PBFV, portal blood flow velocity (cm/s); OV, oesophageal varices.

Nery, AP&T 2019
Prospective - 108 Portugese patients.
11 PVT

PVT in cirrhosis – Nonspecific beta-blockers

- Tight relationship between nonspecific beta-adrenergic blockade and esophageal varices
- The independent impact of each factor is difficult to evaluate.
- The mechanism (if any) remains elusive.
- Additional data are needed before management is modified (NSBB increase survival and decrease bleeding).

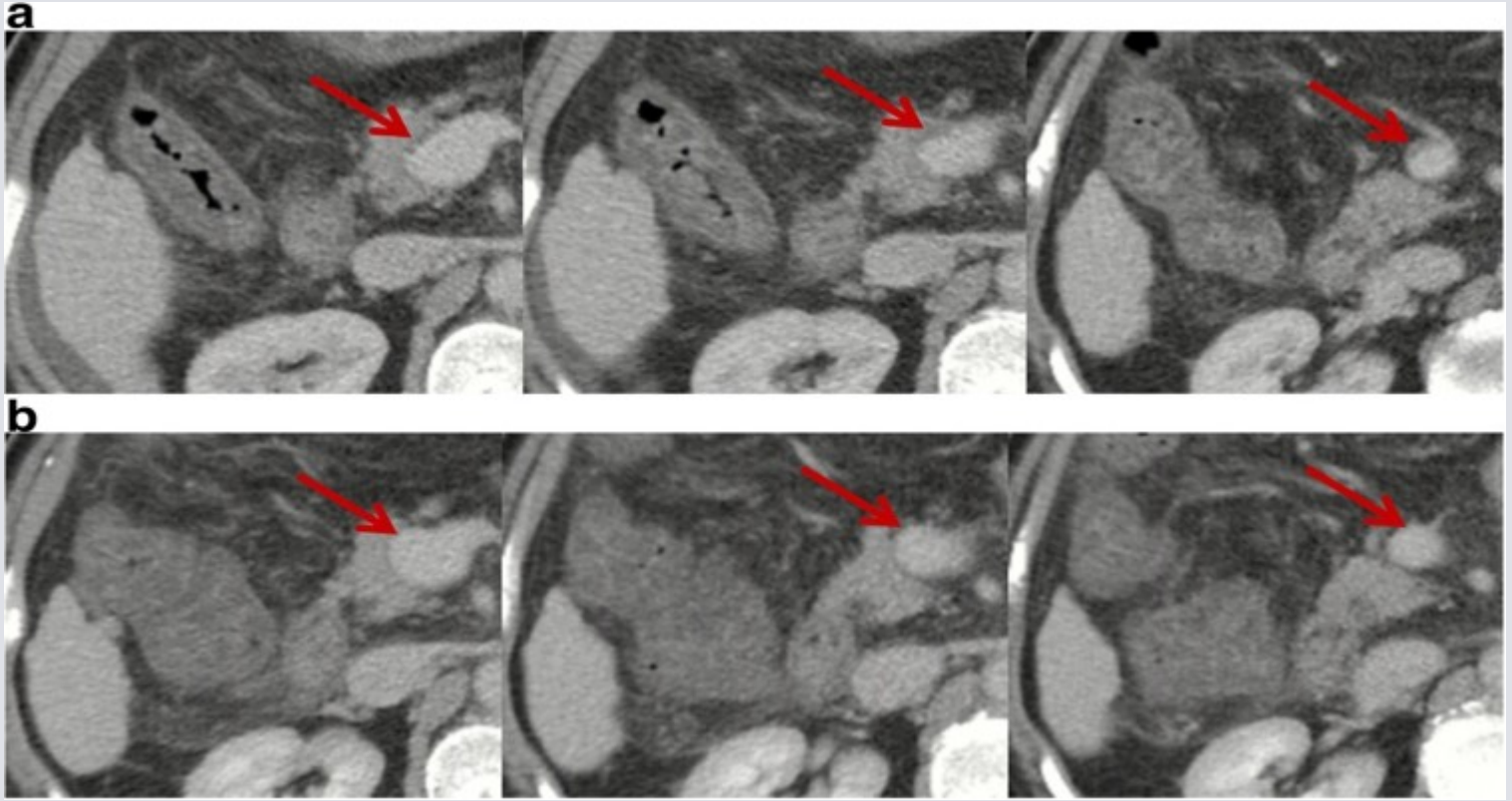
Portal vein thrombosis in cirrhosis

- Portal blood flow velocity
- Non specific beta adrenergic blockers
- Transient portal vein thrombosis

Transient Portal Vein Thrombosis in Cirrhosis

Feb 2017

Apr 2017

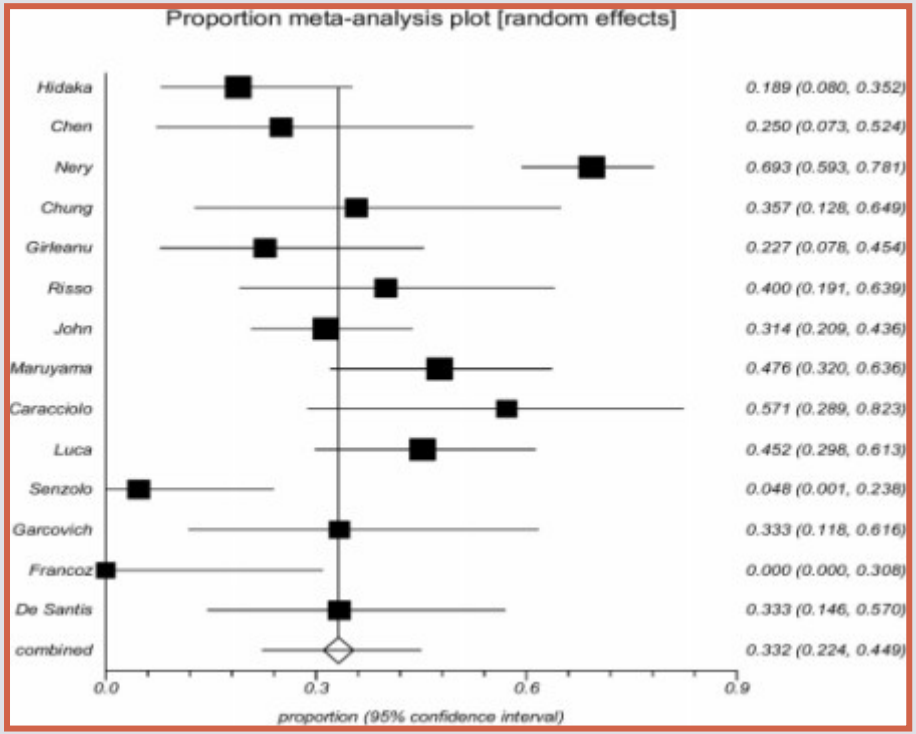


Qi, BMC Medicine 2018

Extrahepatic PVT in cirrhosis

% Partial	76%
%Transient	33%

Ponziani, Transplant Rev 2014.
Francoz, J Hep 2014.
Harding, WJG 2015



Proportion of transient thrombus

(Forest plot of 14 studies. Qi, BMC Medicine 2018)

Transient Portal Vein Thrombosis in Cirrhosis

- Causes/risk factors for partial and/or transient PV thrombus could differ from complete permanent occlusion.
- Prognostic meaning/consequences of partial and/or transient PV thrombus could differ from complete permanent occlusion.

Definition for transient PVT

The condition where a PV thrombus resolves

Issues

- Which imaging procedure?
- Schedule for reevaluation?
- Regression without resolution
- Recurrence

Definition for transient PVT

The condition where a PV thrombus resolves

Issues

- Which imaging procedure? → CT or MR
- Schedule for reevaluation?
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Definition for transient PVT

The condition where a PV thrombus resolves

Issues

- Which imaging procedure? → CT or MR
- Schedule for reevaluation? → 3 monthly
- Regression without resolution
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Definition for transient PVT

The condition where a PV thrombus resolves

Issues

- Which imaging procedure? → CT or MR
- Schedule for reevaluation? → 3 monthly
- Regression without resolution → morphometry
- Recurrence

Definition for transient PVT

The condition where a PV thrombus resolves

Issues

- Which imaging procedure? → CT or MR
- Schedule for reevaluation? → 3 monthly
- Regression without resolution → morphometry
- Recurrence → to be neglected

Impact of spontaneous recanalization

Longitudinal studies

- de novo PV thrombosis: N = 3
- changes in thrombus size: N = 1

→ No independent impact on outcome and prognosis

Qi, BMC Medicine 2018. John, Ann Hepatol 2013.
Maruyama, Am J Gastroenterol 2013. Nery, Hepatology 2015. Luca, Radiology 2012

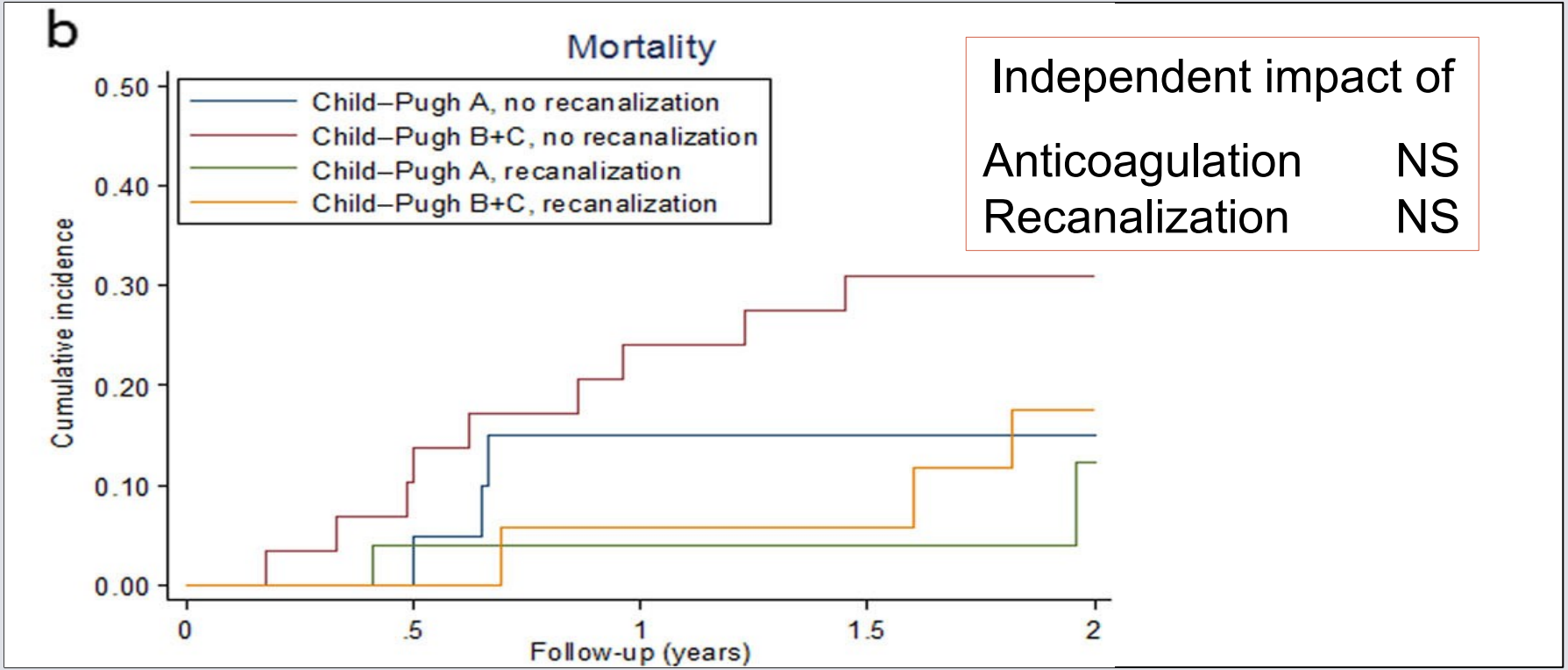
Impact of recanalization on anticoagulation therapy

- Improved event free survival suggested
- Improved liver function tests suggested
- Decreased mortality suggested

→ Requires further evaluation

Delgado, Clin Gastro Hepato 2012. Endo, Scand J Gastroenterol 2018.
La Mura Clin Gastro Hepato 2018.Senzolo, Clin Translat Gastroenterol 2018. Noronha Ferreira, Dig Dis Sci 2019

Recanalization with anticoagulation therapy

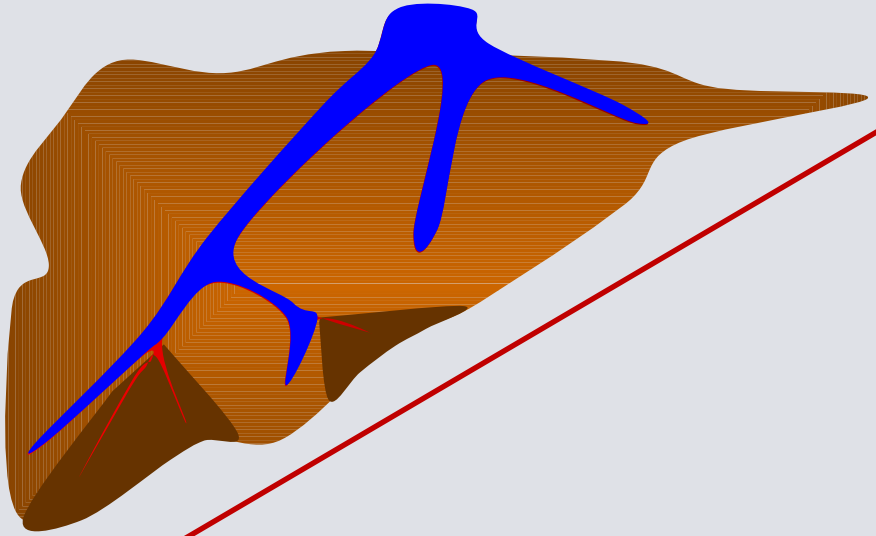


Independent impact of

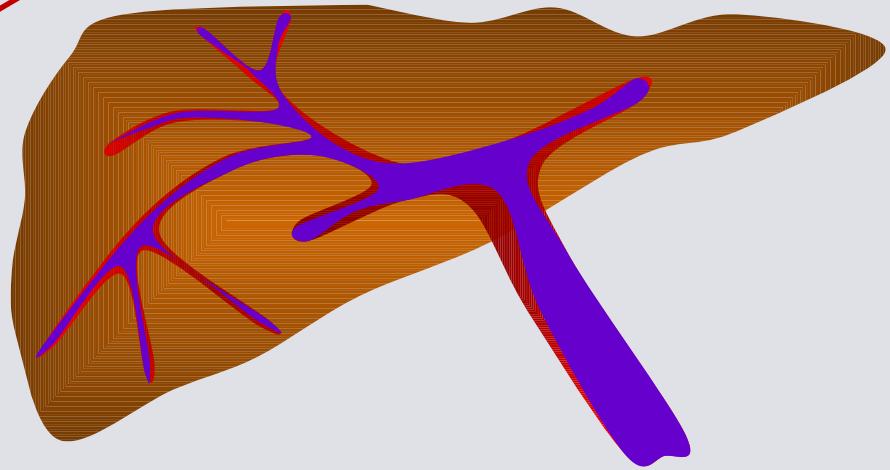
Anticoagulation	NS
Recanalization	NS

Senzolo, Clin Translat Gastroenterol 2018

70% hepatic veins thrombosed



Explanted Cirrhotic Livers



40% of portal veins thrombosed

Wanless, Hepatology 1995
Shimatzu, Hepatology 1997

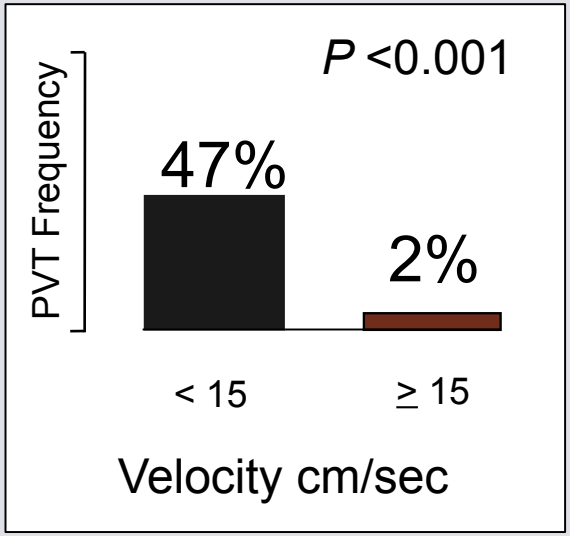
Conclusions

- Diagnosis of congenital extrahepatic portosystemic shunt, and its closure, should be liberally considered.
- Slowing of portal blood flow parallels progression of cirrhosis and development of PVT. Still, no threshold of velocity triggering anticoagulation therapy has yet been established.
- Nonspecific beta-blockers may contribute to PVT. Direct evidence and exact mechanism still to be provided. No changes in current practice are yet warranted.
- Transient PVT is most common in cirrhosis. Its role as an indicator for subsequent extrahepatic extension or a factor for aggravating liver disease requires further studies.

Possible explanations for discrepant results

- Reproducibility of measurements
- Interaction of velocity with
  - Severity of liver disease
  - Obesity/NASH
  - Treatment of cause (HBV, HCV, alcohol)
  - Nonspecific beta-blockers
  - Size of varices at baseline (actual vs history)

Predicting PVT with portal vein flow velocity



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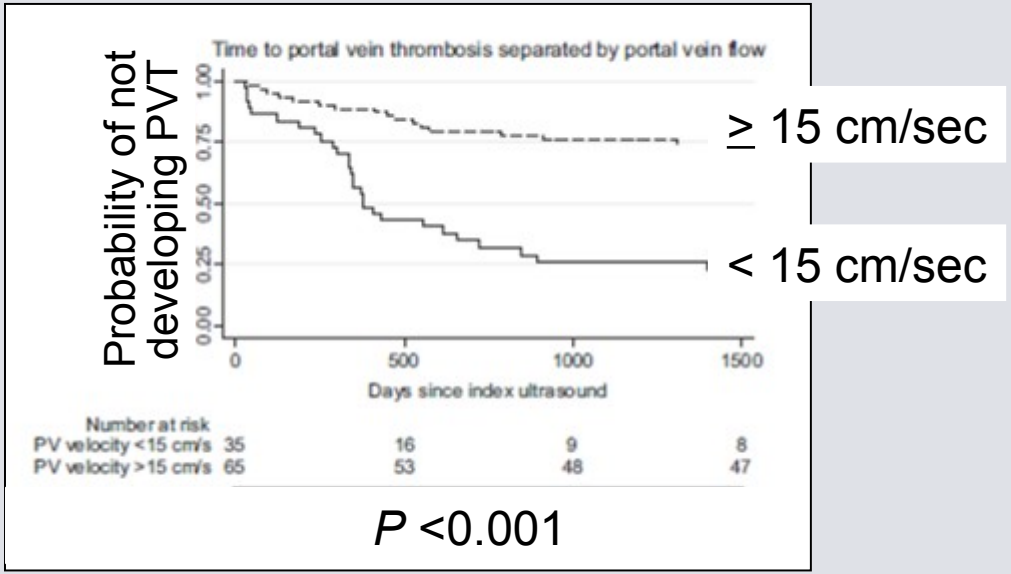

Stine Liver Int 2018

Predicting PVT with portal vein flow velocity

Baseline variables	Multivariate	
	HR	*P*
Prothrombin	0.82	0.03
EV grade ≥ 2	2.14	0.004

Nery. Hepatology 2015
N = 1243 patients - PVT n = 118

Time dependent variables	Univariate		Multivariate
	HR	*P*	*P*
Decreasing PBF velocity	0.98	0.19	NS
De novo ascites	1.81	0.01	NS
Recent decompensation	2.11	0.007	NS
NSBB before PVT	1.67	0.04	NS

Portal vein flow velocity in cirrhosis