Joint CME/MOC Providership

American Society for
Gastrointestinal Endoscopy

Clots, Anticoagulants and Liver Disease How I Approach this Sticky Situation

PHILIPPE J. ZAMOR, MD, FAASLD
ASSOCIATE CLINICAL PROFESSOR OF MEDICINE
DIVISION OF HEPATOLOGY, ATRIUM HEALTH, CHARLOTTE, NC
WAKE FOREST SCHOOL OF MEDICINE

DISCLOSURES

NOTHING RELEVANT TO PRESENTATION

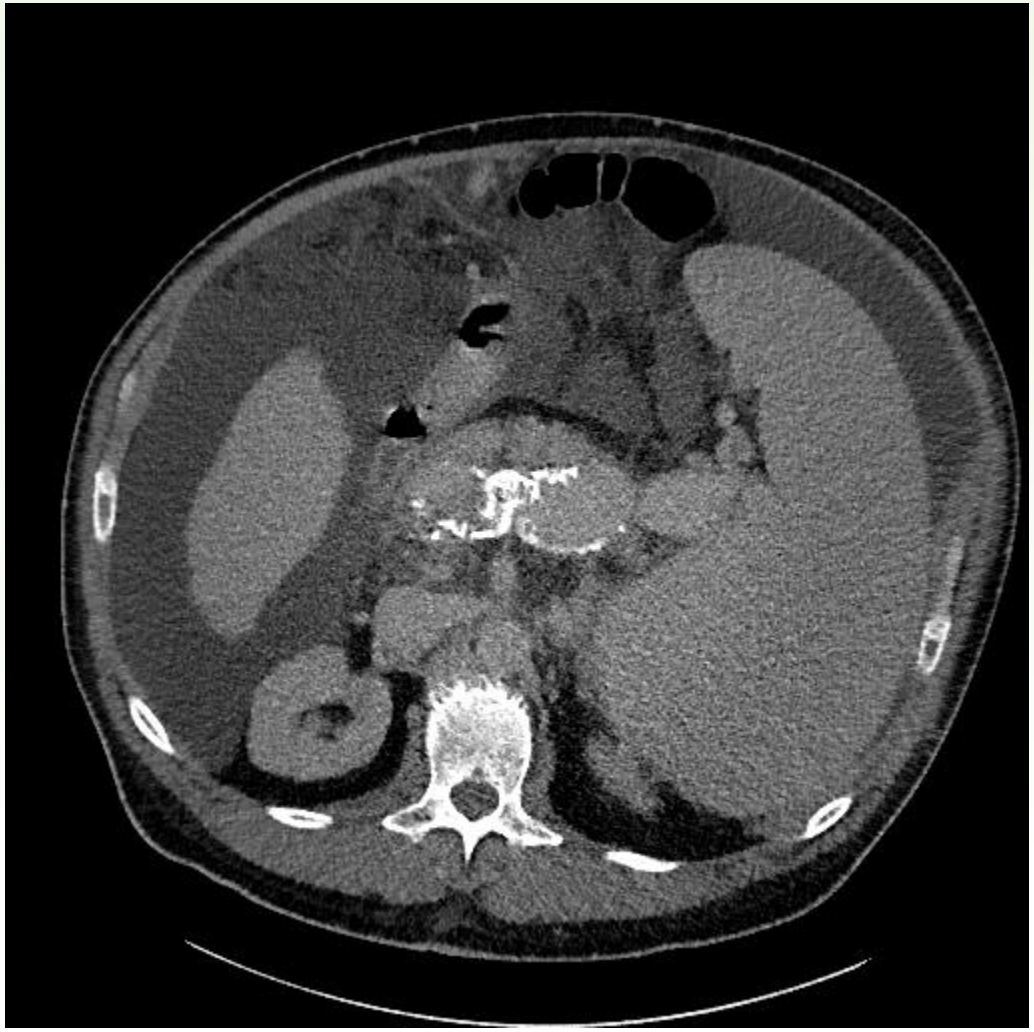
Speakers Bureau: AbbVie, Mallinckrodt

Advisory Board: Mallinckrodt

Case

54 yo man NASH/ASH cirrhosis undergoing evaluation for liver transplantation. MELD 16. Recurrent ascites and hepatic-hydrothorax, lg non-bleeding varices. Noted to have PVT on cross sectional imaging

- How common is PVT?
- How do we diagnose?
- What is the impact of PVT?
- Optimal management?
- Can PVT be prevented?



Epidemiology of PVT

- Relative risk of PVT is 7-fold higher in patients with cirrhosis than in general population
- Prevalence of PVT in patients with cirrhosis 10-25%
- Annual incidence of 3-17%

Ogren *World J Gastro* 2006
Noronha *Dig Dis Sci* 2019

Tsochatzis *Alimen Pharmacol Ther* 2010
Francoz *Gut* 2005. Zocco *J Hepatol* 2009

Risk Factors: Altered portal venous blood flow

- Threshold portal vein flow <15 cm/sec described as most predictive of PVT
  - OR = 44.9 (95% CI 5.3-382.7)
  - Increased severity of cirrhosis is inversely proportional to portal vein velocity
- Portal vein endothelial injury (splenectomy, hepatectomy, etc)
- Portal vein endothelial inflammation (pancreatitis, cholecystitis, appendicitis, or other intra-abdominal infection)

Zocco *J Hepatol* 2009
Lutz *Dig Dis Sci* 2012

Risk Factors: Local portal vein alterations

- Hemostatic alterations associated with cirrhosis
  - Derangement of balance due to ↓anticoagulants and procoagulants, ↑ procoagulants factors such as factor VIII and von Willebrand factor (vWF)

- Inherited and acquired prothrombotic disorders
  - Most cirrhotic pts do NOT carry protein C & S deficiency or other genetic alterations (Recommendation do NOT screen)
  - HCC seems to increase for PVT perhaps due to increase in local prothrombotic factors

Tripodi *NEJM* 2011

Risk Factors: Local portal vein alterations

- In patients with cirrhosis and portal hypertension: bacterial translocation, local inflammation and endotoxemia play role in promoting local hypercoagulable state
- LPS may favor hypercoagulable state by increasing endothelial factor VIII, decreasing thrombomodulin activity while also increasing platelet activation
- Endoscopic therapy for esophageal varices (band ligation or sclerotherapy) and history of variceal bleeding seem to play role in PVT

Carnevale *J Hepatol* 2017 Kapiotis *Blood* 1991 Queck *Gut* 2020 Fracoz *J Hepatol* 2012

Systemic Thrombotic Risk Factors

- Factor V Leiden mutation
- Prothrombin G20210A mutation
- MHTFR C677T mutation
- Positive anti-cardiolipin antibodies
- Positive lupus anticoagulant

Altered portal venous blood flow
(portal vein stasis)

-Low flow velocity from portal hypertension, portosystemic shunting

Portal Vein Thrombosis

Hypercoagulable state

-Alteration, imbalance in coagulation factors
  -Elevated von Willebrand factor
  -Increased ratio factor VIII/protein C
  -Thrombomodulin resistence
-Inherited and acquired prothrombotic disorders

Endothelial damage

-Infection, inflammation,endotoxemia
-Elevated von Willebrand factor

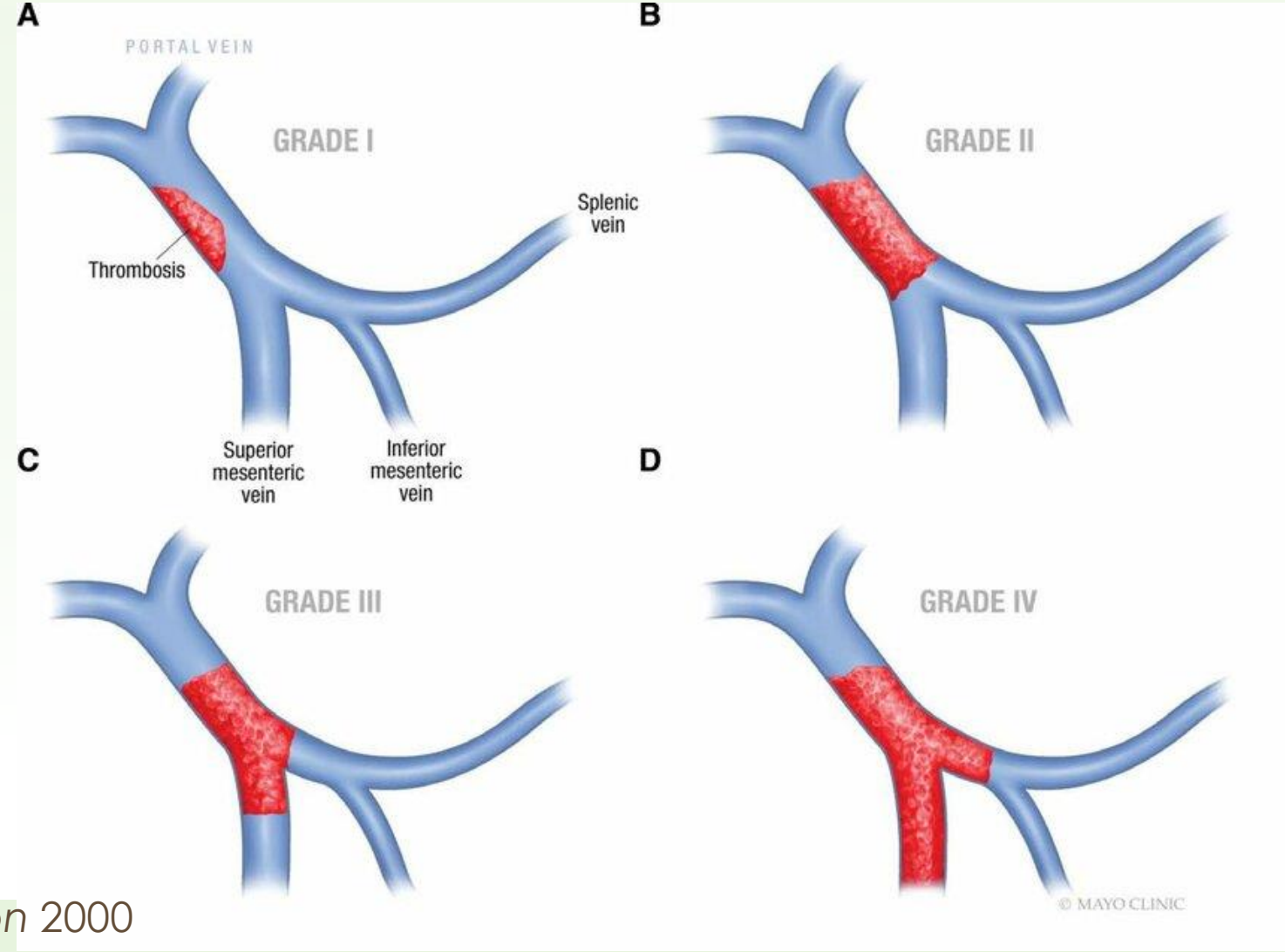
PVT increases adverse outcomes in cirrhosis and variceal bleed

Study	Patients	Hazard ratio
	Rebleeding	
Chen (J Hepatol 2012)	101	2.7 (95% CI 1.2, 6.1)
Hung (J Hepatol 2012)	95	4.0 (95% CI 1.9, 8.6)
	Mortality	
Wu J Clinical Gastroenterol 2002)	83	7.0 (95% CI 2.4, 20.2)
Hung (J Hepatol 2012)	95	3.4 (95% CI 1.5, 7.7)

PVT may increase pre-transplant mortality

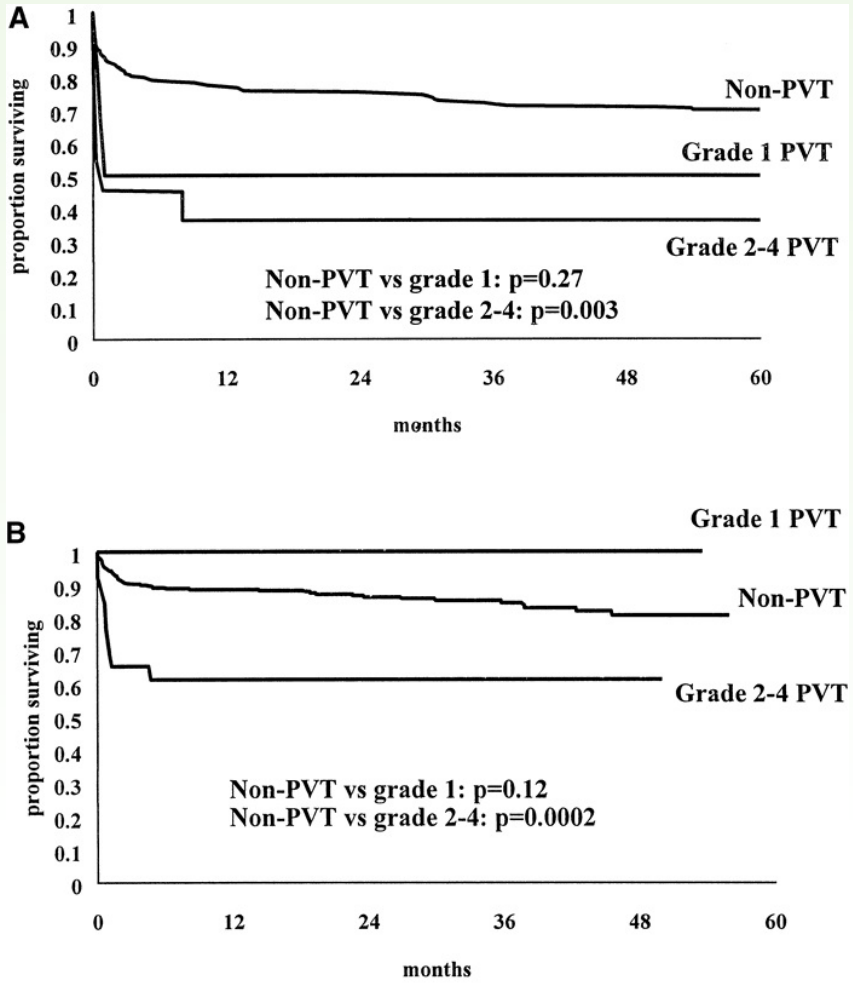
Study	Population	Patients	Effect Size
Englesbe (Liver Transpl 2010)	SRTR	46,530	HR 0.9 (p=0.23)
Englesbe (Liver Transpl 2010)	Single Center	3,295	HR 2.0 (95% CI 1.3, 3.2)
Law (AASLD 2014 Abstract 364)	Single Center	60	OR 4.0 (p=0.02)

Yerdel Classification



Yerdel *Transplantation* 2000

Post OLT survival PVT



Yerdel Transplantation 2000

Diagnosis

- Normally ultrasound is initial radiographic study used to diagnose PVT
- Most times PVT is asymptomatic, incidentally detected
- U/S 92% specific/89% sensitive, BUT 14-50% sensitivity for partial PVT
- Extension and occlusion of PV branches limited by OBESITY, ascites, bowel gas and operator
- Cross sectional imaging is recommended to confirm presence of PVT and for complete PVT staging and to rule out malignancy
  - While MRI offers no radiation exposure, may have lower specificity in small caliber vessels and may lack spatial resolution necessary to evaluate clot size

Tessler *Am J Roentgenol* 1991
Rodriguez-Castro *Transplantation* 2012

Natural History of PVT

- Debate as the influence of PVT on outcomes in patients with cirrhosis
  - Sparse studies, small number of pts, short follow up
- Important to distinguish between acute and chronic PVT

PVT and Liver Transplantation

- PVT prevalence among liver transplant candidates varies from 2.1% to 26%; up to 50% unrecognized at the time of transplant
- PVT can have a major impact on post OLTX outcomes: Grade III/IV had decreased 30 day and 1 year survival rates
- Variability in surgeon expertise in ability to establish portal anastomosis
- Recurrence rates of PVT after LT over time has dropped to 2%-3% in recent years

Rodriguez-Castro *Transplantation* 2012
Qi *J Gastro Liver Dis* 2015
Dumortier *Am J Transplant* 2002
Ponziani *Transplant Rev* 2014

Treatment Principles

- Still lack robust data on optimal management of PVT in cirrhosis
- Strong correlation between early initiation of treatment and likelihood of recanalization: treating less than 6 months after diagnosis most important factor
- Primary goal of treating PVT is recanalization
- Major goal is to prevent worsening/progression of thrombosis that may hinder future liver transplantation
- All major guidelines recommend assessment for gastroesophageal varices prior to treatment, AASLD recommends NO delay in initiating AC

Northup *Hepatology* 2021
Senzolo *J Hepatol* 2021

Treatment Principles

- Mean time to recanalization ranges from 5.5 to 8 months; ACG, AGA, and AISF suggest 6 month treatment course at minimum
  - Liver transplant candidates should be treated until liver transplant sx
- Should note recurrence of thrombosis is frequent ranging from 27%-38%; with recurrences usually between 2-5 months
- Can expect higher rates of recanalization with acute PVT
- NO role for anticoagulation in tumor associated PVT

Gastro 2020
ACG 2019

Guideline Recommendations

- **AASLD** recommend medical anticoagulation to recent PVT in patients with cirrhosis and recent occlusive or partially occlusive main PV thrombosis (>50% luminal obstruction)

- **EASL** guidelines recommend at least 6-month administration of anticoagulants, such as LMWH or VKAs at therapeutic doses for chronic PVT

- **ACG** recommends 6 months of anticoagulation in acute PVT and chronic PVT in those awaiting OLTx

Treatment: Choice of anticoagulation

- Acute PVT: LMWH initial treatment of choice
  - QOL can be an issue; adherence
- VKAs are also reasonable choice, but therapeutic range can be difficult to maintain

Complications of anticoagulation

- AC does not lead to higher rate of bleeding complications in patients with cirrhosis as compared to those without cirrhosis
- Meta-analysis by Loffredo et al showed no difference in risk of bleeding between LMWH and vit K antagonist (VKAs)

Loffredo *Gastro* 2017

Safety of therapeutic anticoagulation

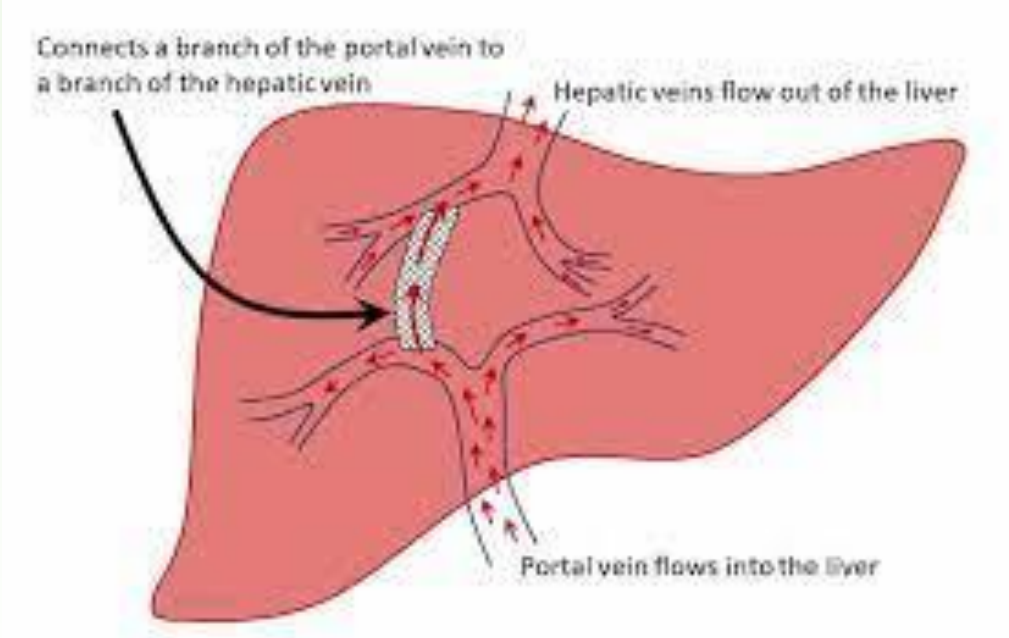
Study	Pts	Design	Anticoagulant	Complications of AC
Francoz (Gut 2005)	19	Single center, Retrospec	LMWH & Vit K antagonist	1 post-banding ulcer bleed
Amitrano (J Clin Gastro 2010)	28	Single center, Prospec	LMWH	No severe complications
Bento (Blood 2011)	28	Single cnter, Retrospec	LMWH	No severe complications
Delgado (Clin Gastro Hepatol 2012)	55	Multicenter, Retrospec	LMWH or Vit K antagonist	5 bleeding complications (all in vit K antagonist recipients)
Senzolo (Liver Int 2012)	33	Single center, Prospective	LMWH	1 cerebral bleed 1 variceal bleed 1 HIT
Werner (Dig Dis Sci 2013)	28	Single center, Retrospec	Vit K antagonist	1 vaginal bleeding

Summary of anticoagulation for PVT in cirrhosis

- Studies support anticoagulant use
- Earlier use is associated with higher recanalization rates
- Unresolved issues
  - Choice of anticoagulant
  - Optimal anticoagulant dosing
  - Duration of treatment
  - Monitoring of anticoagulation- can we follow INR or anti-Xa levels?
  - Optimal candidates for anticoagulation

TIPS for PVT

- Less commonly used for PVT than anticoagulation
  - Typically used in symptomatic portal HTN (variceal bleeding/refractory ascites) or progression of thrombus on AC
- Technical strategies:
  - TIPS followed by portal vein recanalization via portosystemic shunt
  - Portal vein recanalization via percutaneous approaches followed by TIPS placement
  - TIPS insertion between a hepatic vein and large collateral vessel without main portal vein recanalization



Pros and Cons of TIPS for PVT

- Advantages
  - Recanalize PV with endovascular techniques
  - Resolve symptomatic portal HTN
  - Prevent extension of thrombus by creating portosystemic shunt

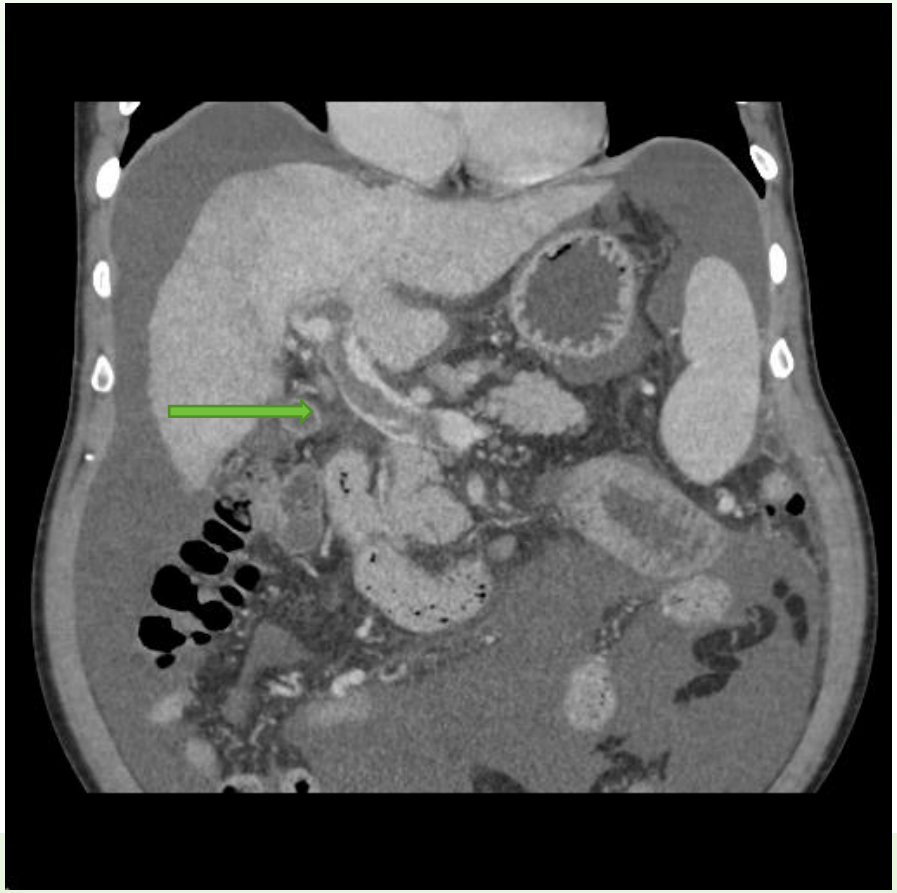
- Disadvantages
  - Technically challenging
  - Complications of TIPS

TIPS for PVT

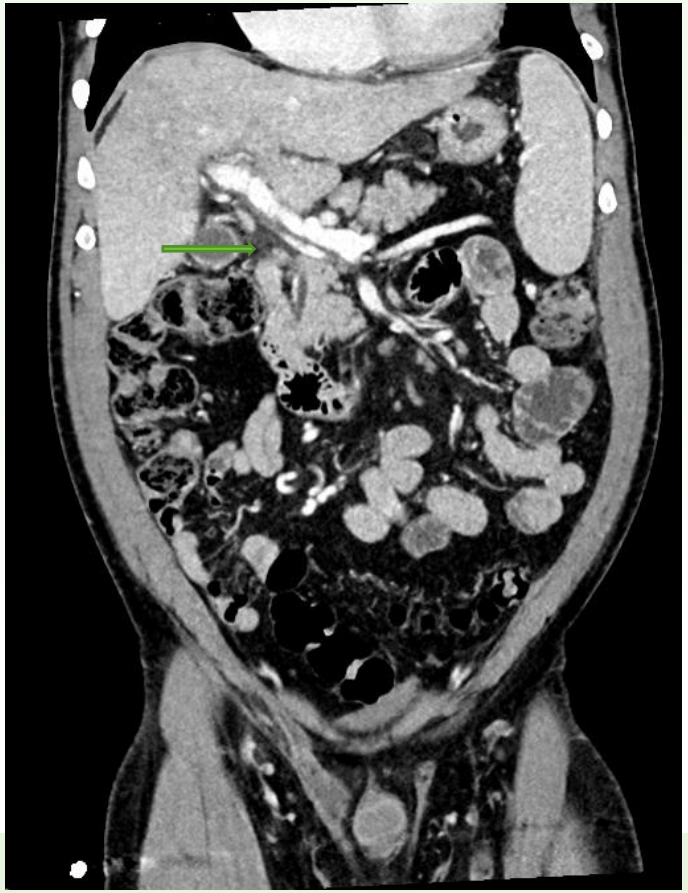
- Technically successful in 67-100%
  - Rate of portal vein recanalization with successful TIPS insertion is up to 80%
- Procedure-related complications vary
- Optimal timing is unclear
- Feasibility of TIPS reduced:
  - PV cavernoma
  - Complete occlusion of PVT
  - No patent intrahepatic PV branches available

52 yo man with symptomatic portal HTN: ascites, bleeding esophageal varices

BEFORE TIPS



POST TIPS



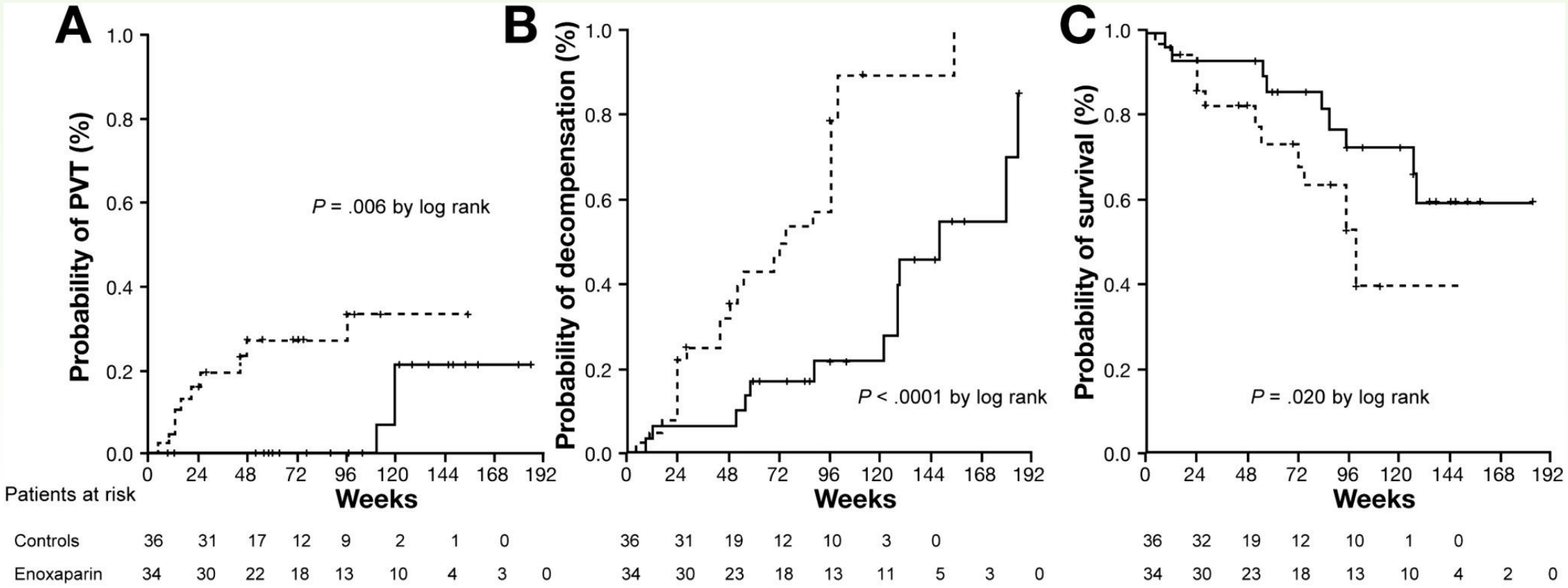
Chronic PVT in Cirrhotics: Prophylaxis?

- Randomized controlled trial, 70 subjects (Child B and C)
  - 12 months of treatment, 12 months follow up
  - 1 patient withdrawn 2/2 HIT
  - 3 episodes EV bleed (2 in treatment group)

	Enoxaparin 4000 u/day N=34	**Placebo N=36**
Acute PVT on tx (p=0.025)	0%	16%
PVT (end of f/u) (p=0.048)	8%	27%
Hepatic decompensation (p<0.001)	12%	59%
Survival (p=0.251)	60%	40%

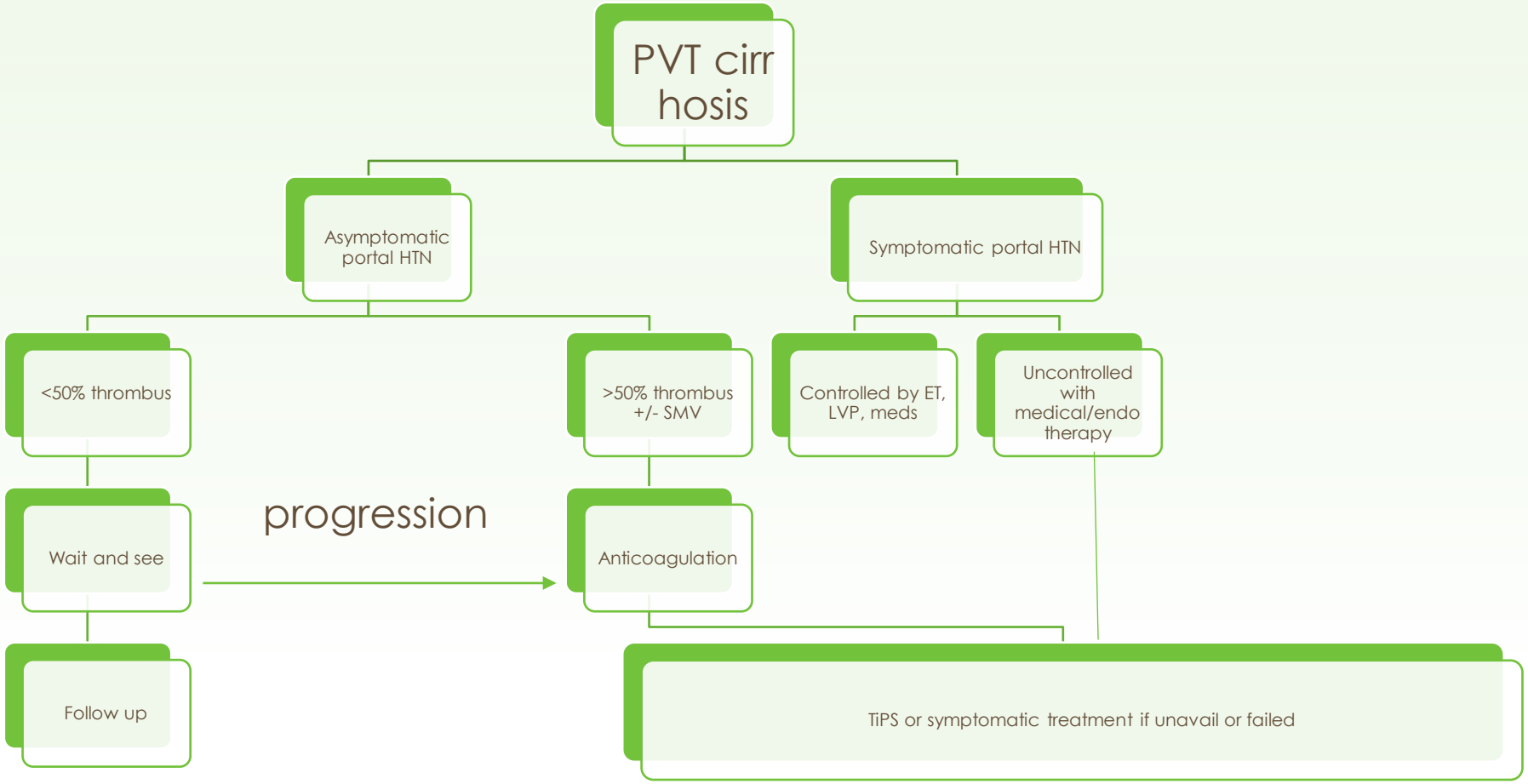
Villa *Gastro* 2012

Chronic PVT in Cirrhotics: Prophylaxis?



Villa *Gastro* 2012

Algorithm for management of PVT



Thank You

PHILIPPE.ZAMOR@ATRIUMHEALTH.ORG

Atrium Health
Wake Forest Baptist

CME/MOC QUESTION

- Recommended treatment course of portal vein thrombosis with anticoagulation

A. 3 months

B. 6 months

C. 9 months

D. 12 months

CME/MOC ANSWER

- Recommended treatment course of portal vein thrombosis with anticoagulation

- 6 months