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- Presented 2014 with abdominal pain and ascites
  - Hepatic vein and portal vein thrombosis
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  - JAK2 positive polycythaemia

# Thrombotic complications and liver disease - to anticoagulate or not?

Jeffrey S Wong

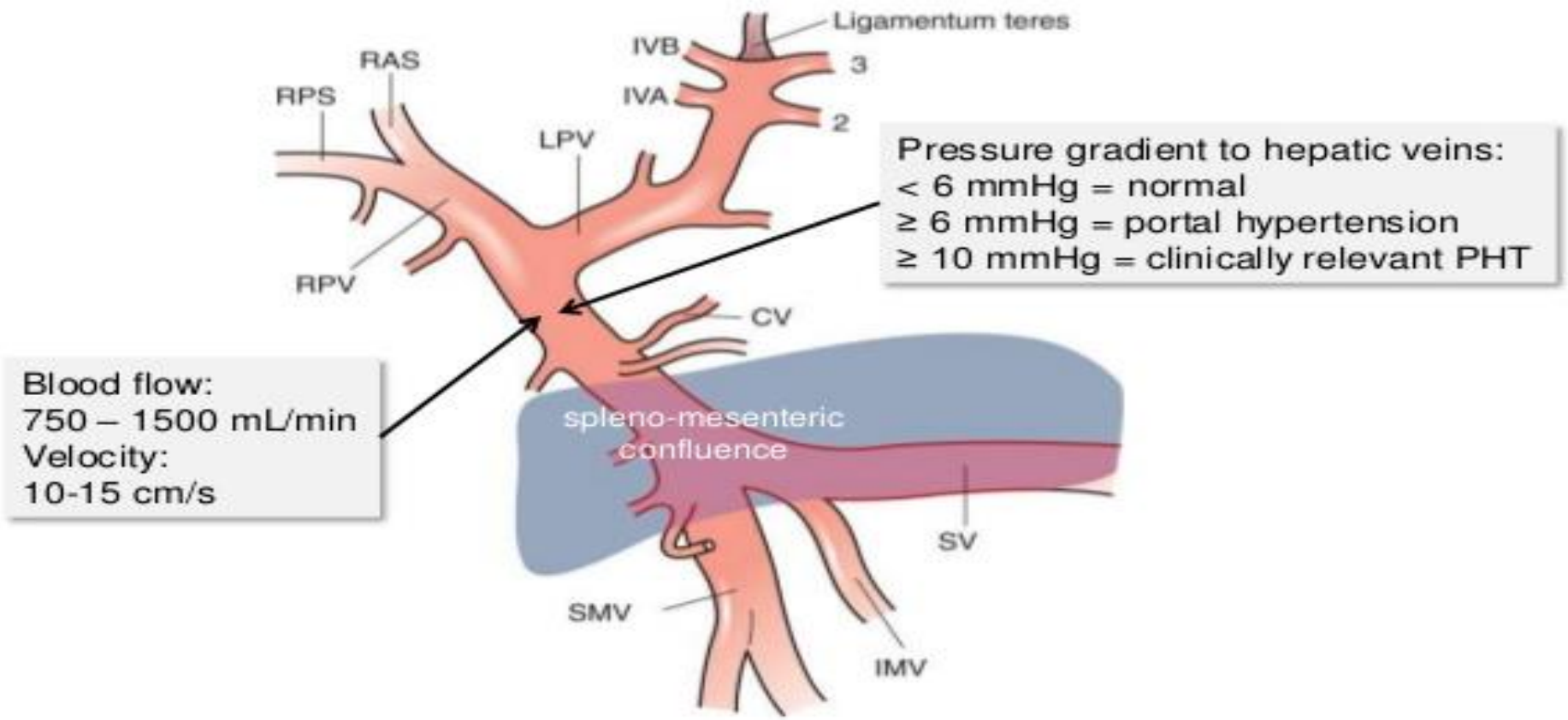
November 2019

Hepatology network meeting

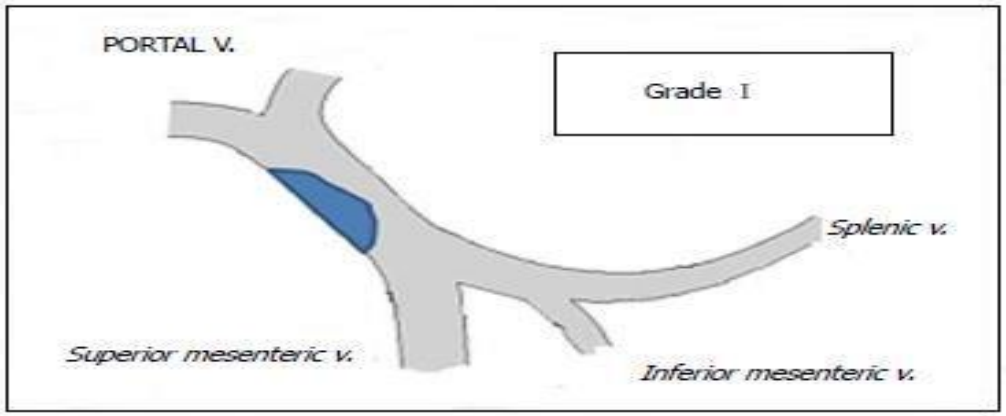
# PVT: presentation

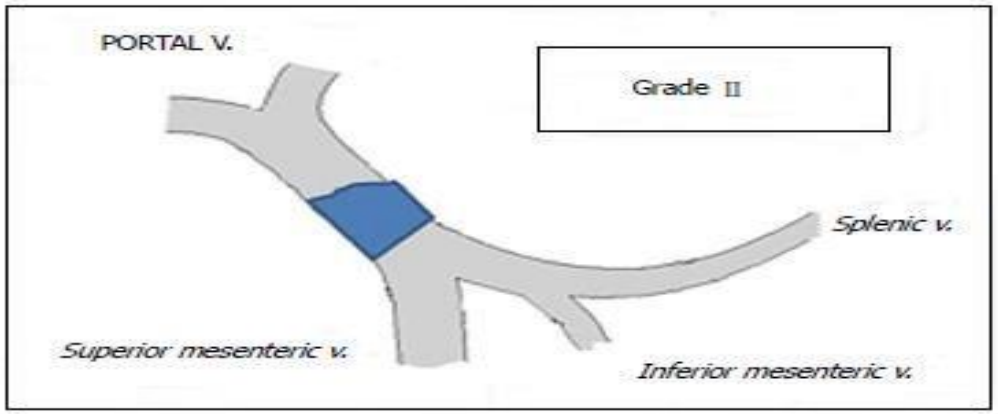
- Often asymptomatic detected on US
- Portal Hypertension: new or increased
  - Variceal bleeding
  - Ascites
  - Intestinal ischaemia/infarction
- Acute vs Chronic

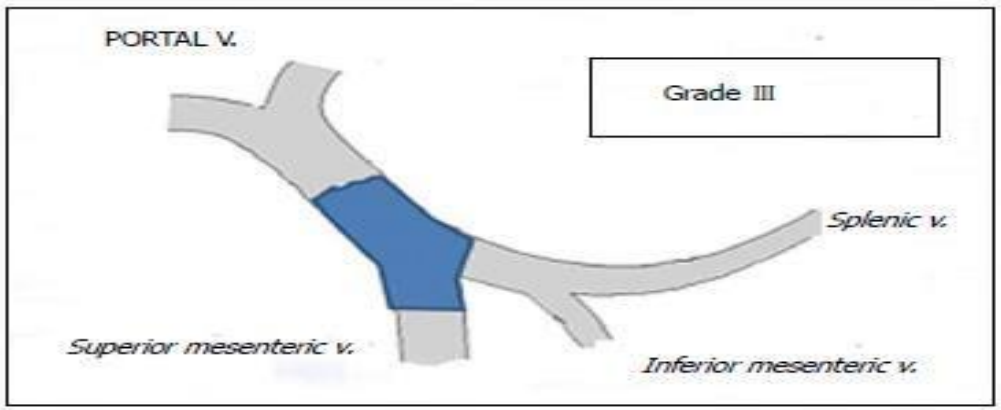
# Anatomy of the portal system

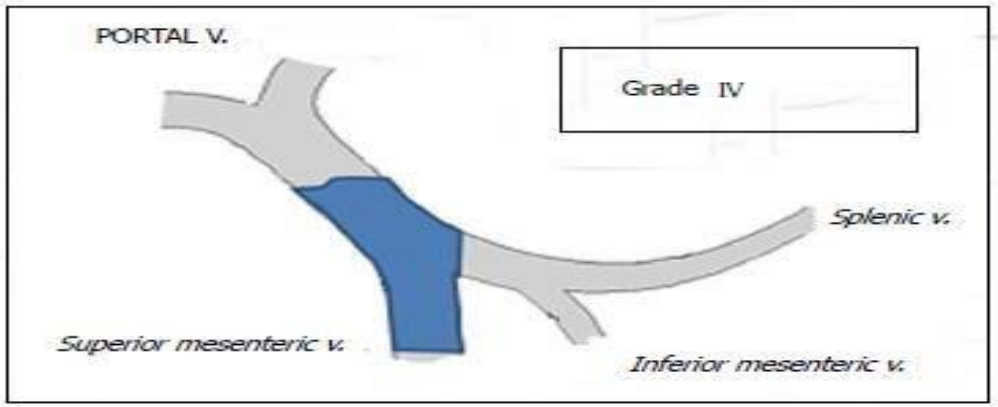


# Classification of PVT




| Venous involvement | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| PV | < 50% | > 50% | Complete | Complete |
| "Proximal" SMV | ± Minimal | ± Minimal | Complete | Complete |
| "Distal" SMV | None | None | None | Complete |

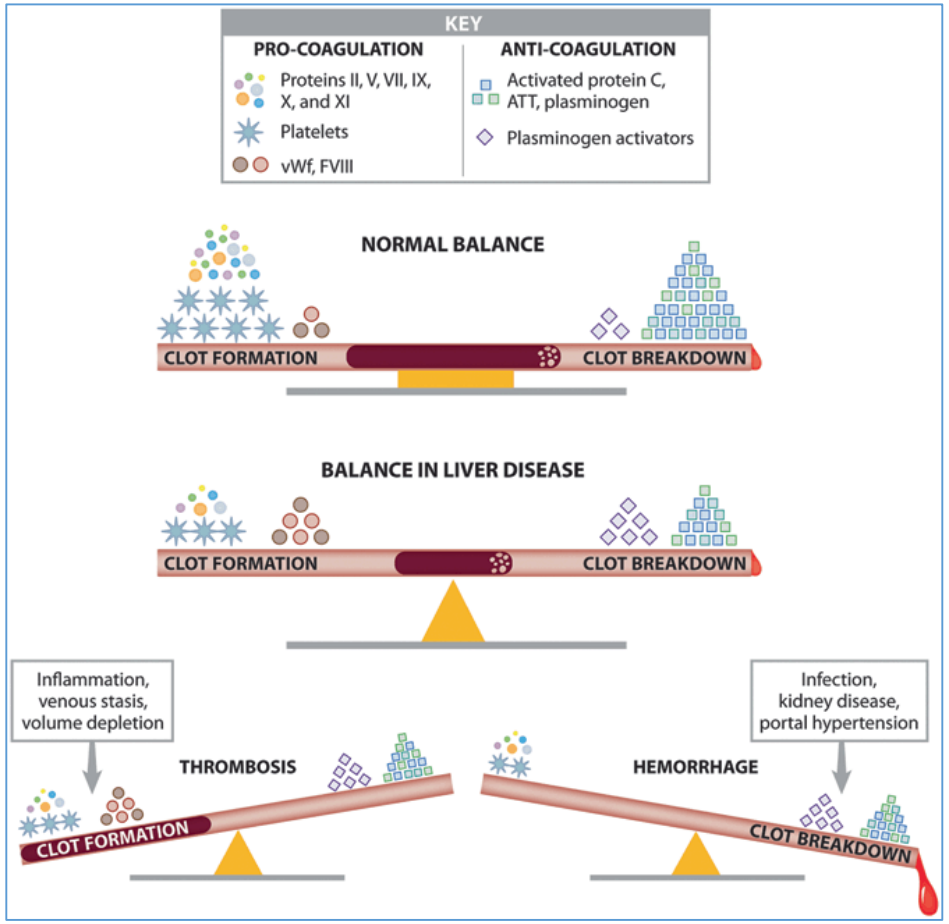
# Why do thromboses occur in cirrhosis?

Virchow’s triad

- Stasis
- Endothelial injury
- Hypercoagulability

# Coagulability in Cirrhosis

- Coagulation in Cirrhosis is considered “rebalanced”
- Minimal disruption required to unbalance
- Clinically we see
  - Increased thrombotic events
  - Increased bleeding events



# Coagulability in Cirrhosis

## Cirrhosis and coagulation abnormalities

| Antihemostatic | Prohemostatic |
|---|---|
| Thrombocytopenia<br>Alteration of platelet functions | ↑↑ FvW and FVIII |
| ↓↓ Factors II, V, VII, IX, X, XI<br>Abnormalities of fibrinogen | ↓↓ Protein C, protein S, protein Z, AT(III), heparin-CoFII, $\alpha_2$-macroglobulin |
| ↓↓ $\alpha_2$-anti-plasmine, TAFI<br>↑ t-PA | ↓↓ plasminogen<br>↑ PAI-1 |

T. Lisman *et al*. J Hepatol 2002;37:280-7

# PVT: Incidence

**Table 3**
**Incidence of portal vein thrombosis (PVT) in different patient cohorts**

| Associated Pathology | No. of Subjects | Incidence of PVT (%) | Type of Study | Reference |
|---|---|---|---|---|
| Liver cirrhosis | 701 | 11.2 | Doppler ultrasonography | 10 |
| | 512 | 16.6 | Retrospective | 11 |
| Liver carcinoma | 435 | 21.4 | Retrospective | 13 |
| | 101 | 20 | Retrospective | 15 |
| | 72 | 44 | Autopsy | 14 |
| Liver transplant | 885 | 13.8 (no portosystemic shunt)<br>38.9 (prior portosystemic shunt) | Cohort study | 12 |

# Prognosis in PVT

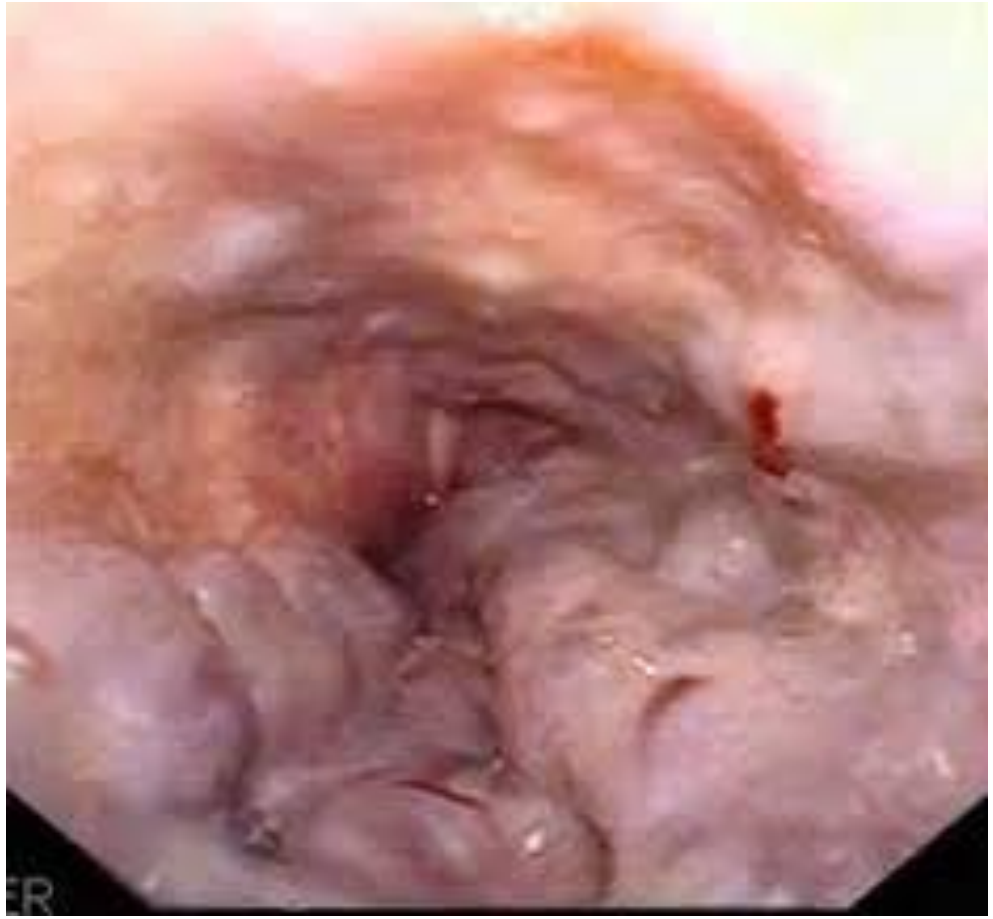
## Minimal good data

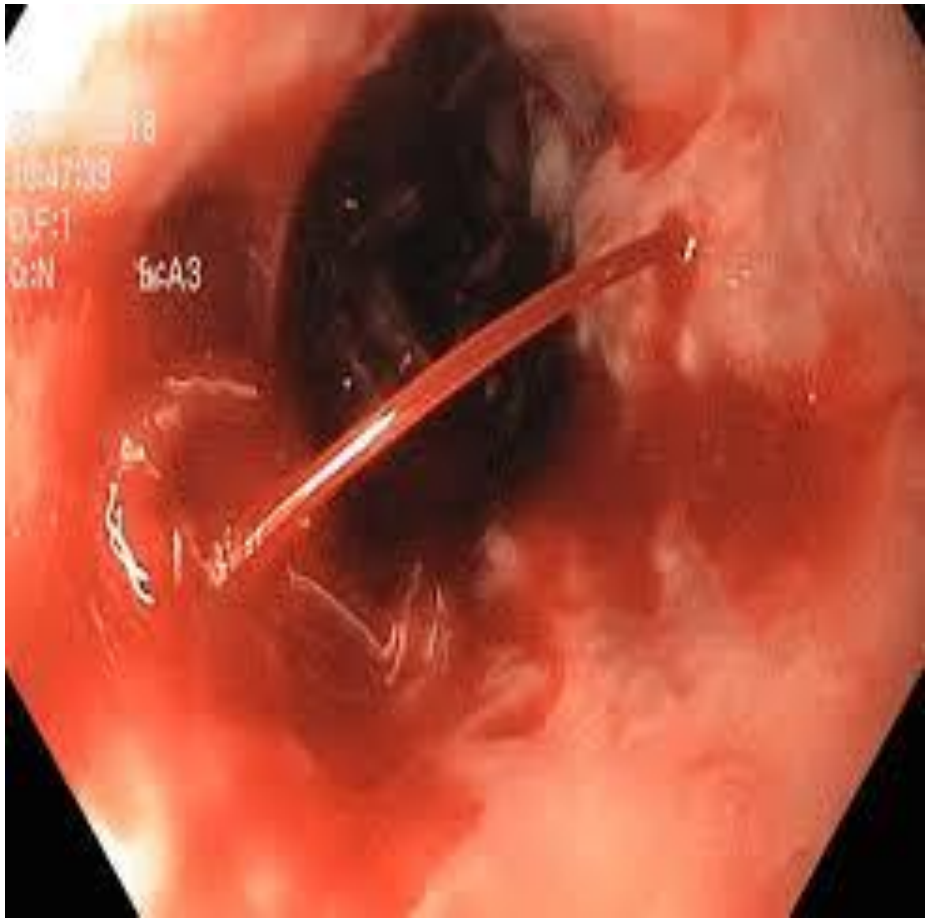
- Refractory variceal bleeding increased
- Overall worse survival
  - Meta-analysis 3 studies
    - Mortality OR 1.62
    - Decompensation OR 2.52
  - Impact of the PVT or a marker of decompensation
  - Partial PVT appears to have no impact on survival

## LT candidates

- May impact on transplantability
- Worse post LT survival for occlusive thrombus

# Traditional reluctance to anticoagluate those with advanced liver disease





# Treatment of PVT

Aims of treatment

- Recanalisation
- Prevent extension
- Maintain transplantability

26 studies of LMWH/VKA/DOAC

- Majority are retrospective or case reports
- Impossible to determine survival advantage

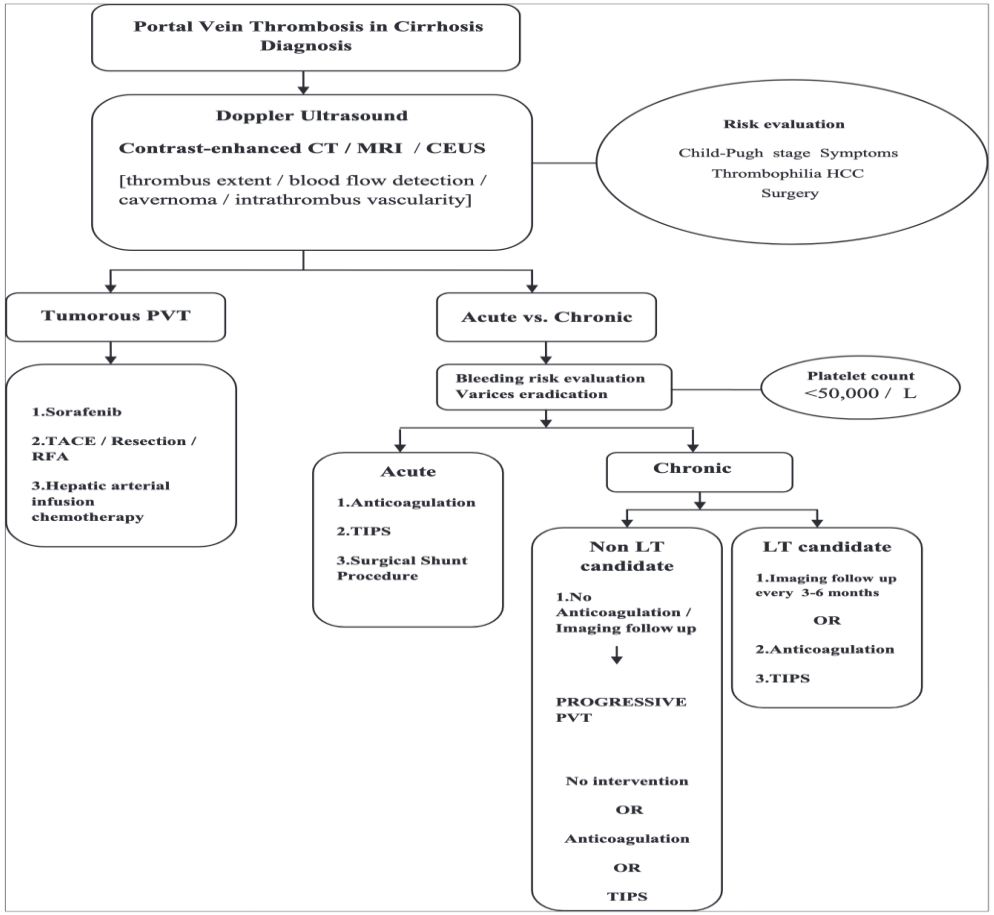
# Meta-analysis of treatment

| | AC | No AC | p |
|---|---|---|---|
| Recanalisation | 71% | 42% | <0.0001 |
| Recanalisation: complete | 53% | 33% | 0.002 |
| Progression | 9% | 33% | <0.0001 |
| Major and minor bleeding | 11% | 11% | |
| Variceal bleeding | 2% | 12% | 0.04 |

**Effects of Anticoagulants in Patients With Cirrhosis and Portal Vein Thrombosis: A Systematic Review and Meta-analysis**
Loffredo, Lorenzo et al. Gastroenterology, Volume 153, Issue 2, 480 - 487.e1

Note: Only trials of LMWH and VKA

# Assessment and treatment of PVT




*Annals of Gastroenterology* (2018) **31,** 315-329

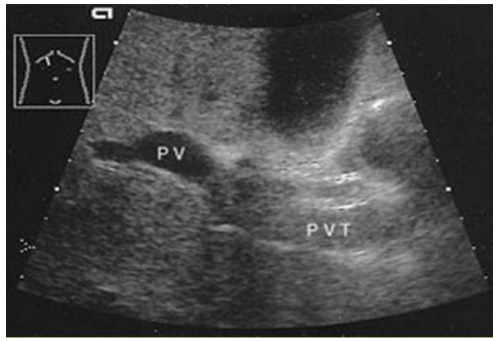
# Another guideline

| Portal vein thrombosis in cirrhosis | |
|---|---|
| Anticoagulation | • Symptomatic cases and asymptomatic cases with:<br>  ○ Concomitant thrombosis of other venous segments apart from portal veins, such as extension into mesenteric or splenic veins<br>  ○ Non-reversible risk factors or persistent hypercoagulable states<br>  ○ Interval increase in thrombus burden while not anticoagulated<br>  ○ Awaiting liver transplantation |
| Conservative management with no anti-coagulation or interventions | • Asymptomatic cases with partial non-obstructive PVT not involving other venous segments and not awaiting liver transplantation<br>• Very high bleeding risk on anticoagulation or active bleeding not yet cor-rected<br>• Other related short-term, poor prognosis co-morbidities or end-stage liver cirrhosis |
| Thrombectomy and/or thrombolysis | • Worsening abdominal pain with thrombus extension while on therapeutic anticoagulation<br>• Impending or ongoing intestinal necrosis and infarction from venous thrombosis (typically seen when multiple splanchnic veins are involved) |
| TIPS | • Select cases of obstructive PVT with worsening portal hypertension and its symptoms and only in select institutions where expertise in performing this procedure optimally is available |

Vascular Medicine 2016, Vol. 21(1) 61–69

# Other questions

- When should we do a thrombophilia screen?
- Duration of treatment?
- Need to control varices prior to treatment?
- DOAC
- Primary prevention?



# Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis

| | Enoxaparin | Control |
|---|---|---|
| PVT at week 48 | 0.0% | 16% |
| PVT at end of FU | 8.8% | 27.7% |
| Decompensation | 11.7% | 59.4% |
| Deaths | 8 | 13 |

Single Centre RCT 34 Enoxaparin 36 control
Enoxaparin 4000u OD
Villa et al Gastroenterology. 2012 Nov;143(5):1253-1260.e4

# DOAC in PVT

- Rivaroxaban/Dabigatran
- Insufficient data in PVT
  - Moderate data in Cirrhotics with no PVT
- Considerations
  - FDA ”not recommended”: Rivaroxaban CPT B/C Dabigatran CPT C
  - Pharmacokinetic concerns with both
  - “More” studies of Rivaroxaban
  - Rivaroxaban reversal not available in NZ
- Experts suggest that the decision should be individualised

# My attempt at humour!

DOACs are generally not recommended due to a lack of large-scale studies and should only be considered under the guidance of a thrombosis or vascular medicine specialist

Vascular Medicine
2016, Vol. 21(1) 61–69

# EASL Guidelines 2015

1. Evaluate portal vein patency in all patients with cirrhosis listed or potential candidates for liver transplantation (B2)
2. Always evaluate the extension of PVT with CT scan or MR imaging (A1)
3. In patients with underlying HCC, rule out neoplastic PVT by contrast enhanced ultrasound/CT scan/MR imaging or biopsy of the thrombus (A1)
4. Consider screening for underlying genetic thrombophilic conditions in patients with PVT and cirrhosis (B2)
5. Anticoagulation must be started always after implementing an adequate prophylaxis for gastrointestinal bleeding (A1)
6. Consider anticoagulation at therapeutic dose for at least 6 months (B1)
7. In patients with superior mesenteric vein thrombosis, with a past history suggestive of intestinal ischemia or liver transplant candidates, consider lifelong anticoagulation (C2)
8. Once PVT has been repermeated, consider prolonging anticoagulation for some months and until transplant in liver transplant candidates (B2)
9. In liver transplant candidates, who have progressive PVT not responding to anticoagulation, consider referring the patients for TIPS (B2)

# Key points

- Need to exclude malignancy
- PVT treatment should be individualized
- Anticoagulation is safe but varices need to be controlled first
- DOAC can be considered
- May need to consult NZLTU

# Final Slide

In this context of uncertainty on the benefit/risk ratio of anticoagulation, we believe that anticoagulation in cirrhotic patients with PVT should be decided on a case-by-case basis

Riva N, Ageno W. Timing of anticoagulation for portal vein thrombosis in liver cirrhosis: An Italian internist's perspective. J Transl Intern Med 2018; 6: 6-10.