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# Management of Portal Vein Thrombosis With and Without Cirrhosis

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# Extrahepatic Portal Vein Obstruction

## Causal factors

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Malignancy	1/3
Cirrhosis	1/3
Others	1/3

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Janssen Blood 2000. Ogren WJG 2006. Rajani APT 2010

# Portal Vein Thrombosis

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- In patients without cirrhosis
  - In patients with cirrhosis
-

# Non-cirrhotic, non-malignant PVT

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## Risk factors for venous thrombosis

- At least one 67%
- Multiple 18%
- Local factor 21%

# Non-cirrhotic, non-malignant PVT

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## Risk factors for venous thrombosis

- At least one 67%
- Multiple 18%
- Local factor 21%

**General factor in 36% of patients with local factors**

# Prothrombotic disorders in PVT

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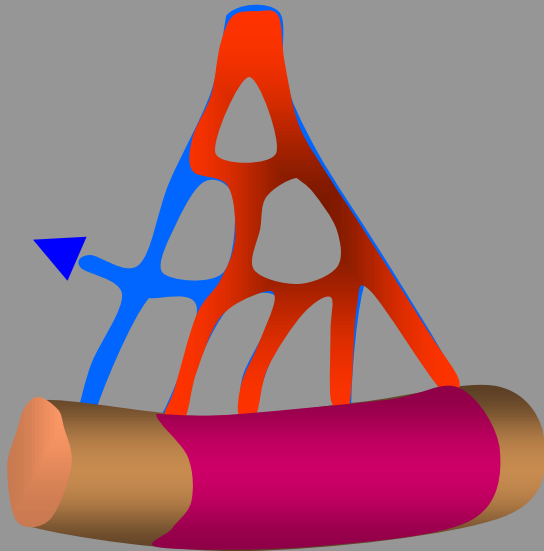
Myeloproliferative neoplasms %	35
Inherited disorders %	35
Antiphospholipid syndrome %	15
Others (IBD, ...) %	10

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Janssen, HLA Blood 2000. Denninger, MH Hepatology 2000.  
Primignani, Hepatology 2006. Plessier, Hepatology 2010. Rajani, APT 2010

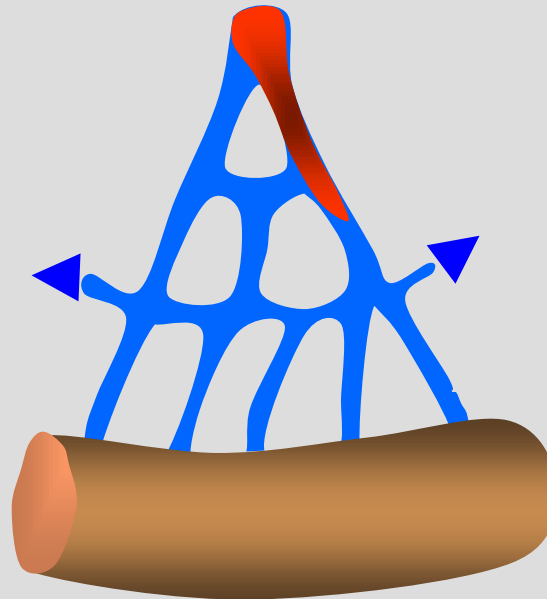
# Portal Vein Thrombosis

Intestinal  
Ischemia



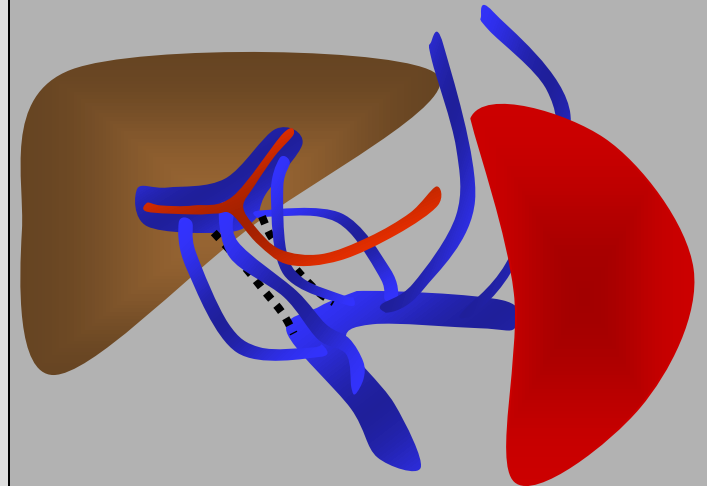
Bleeding  
Ascites  
MOF

Uncomplicated  
Acute PVT



Abdo<sup>minal</sup> Pain  
SIRS

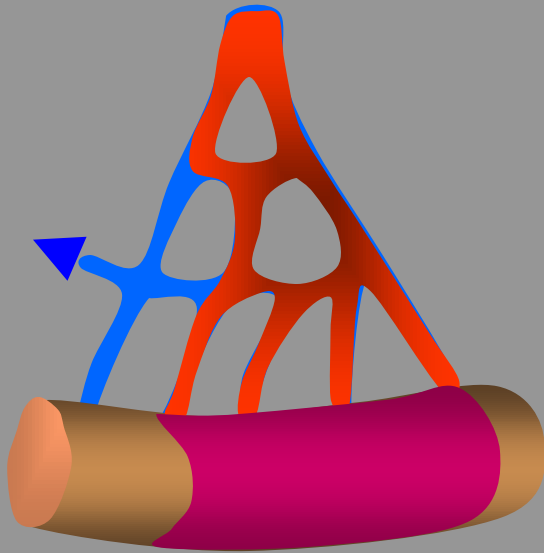
Chronic PVT



Bleeding  
Encephalopathy  
Cholangiopathy

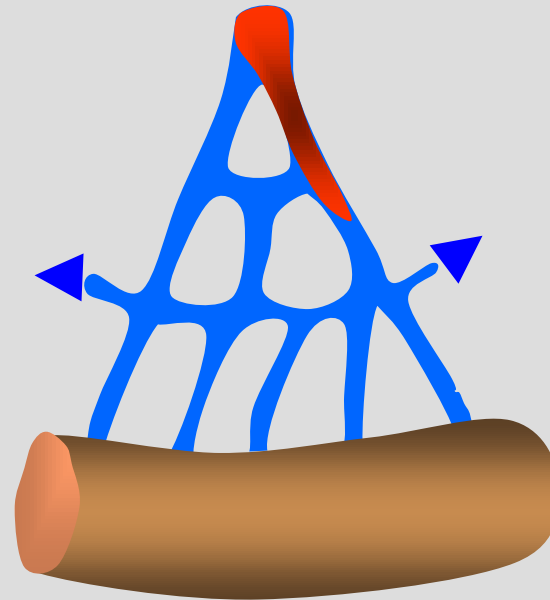
# Portal Vein Thrombosis

Intestinal  
Ischemia



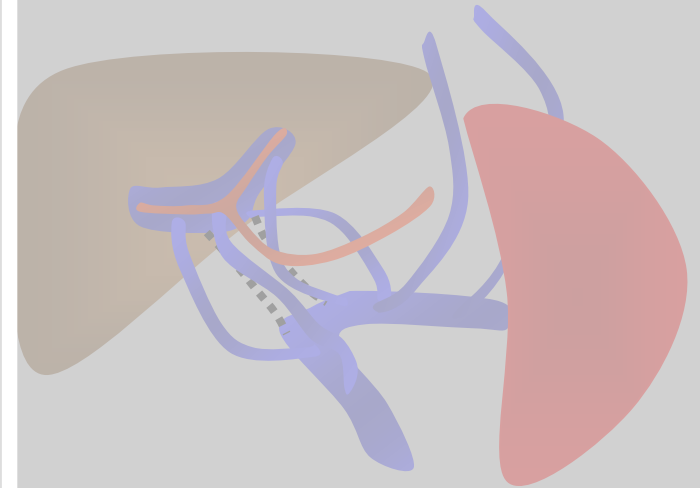
Bleeding  
Ascites  
MOF

Uncomplicated  
Acute PVT



Abdo<sup>minal</sup> Pain  
SIRS

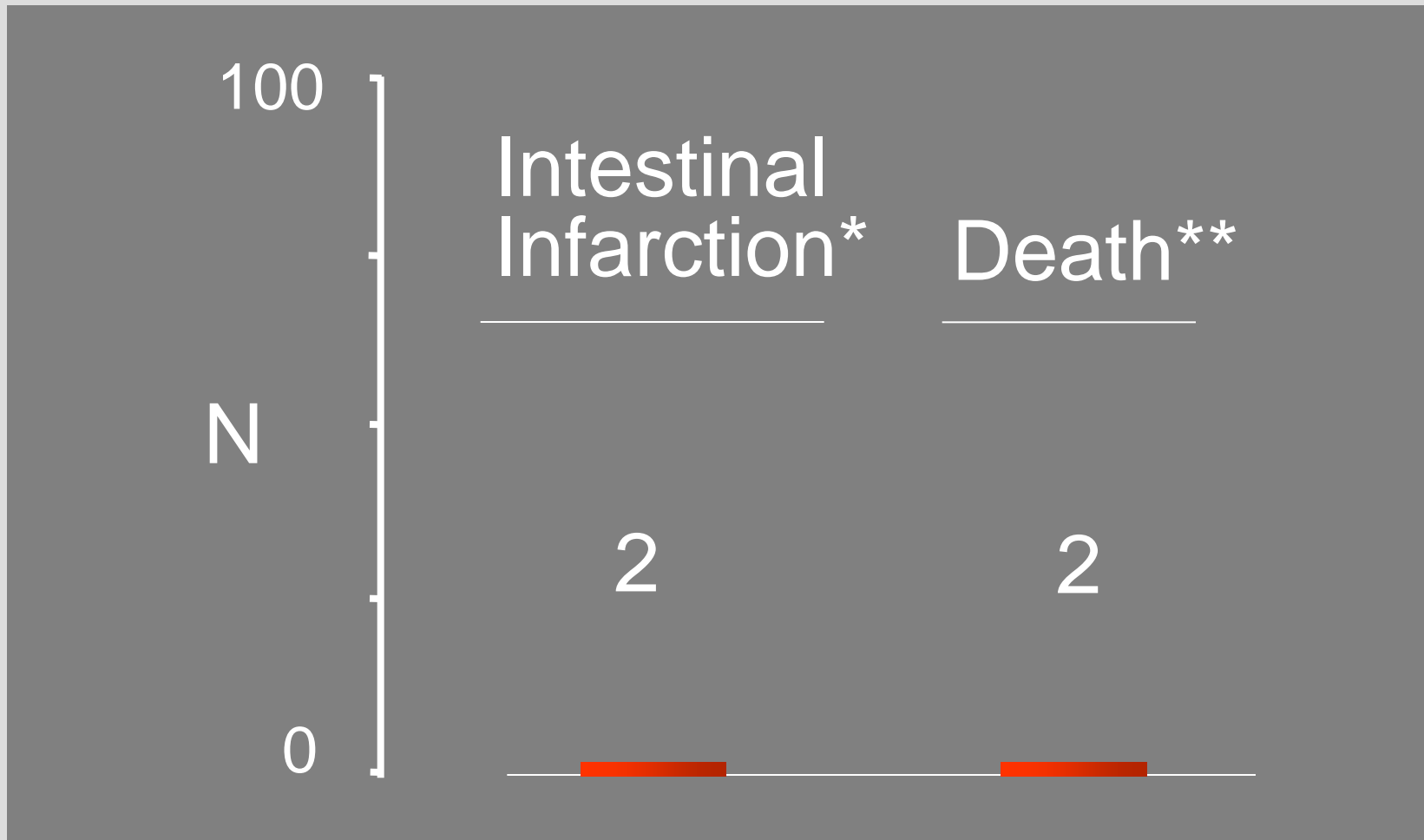
Chronic PVT



Bleeding  
Encephalopathy  
Cholangiopathy



# Acute PVT. Anticoagulation in 95 Patients



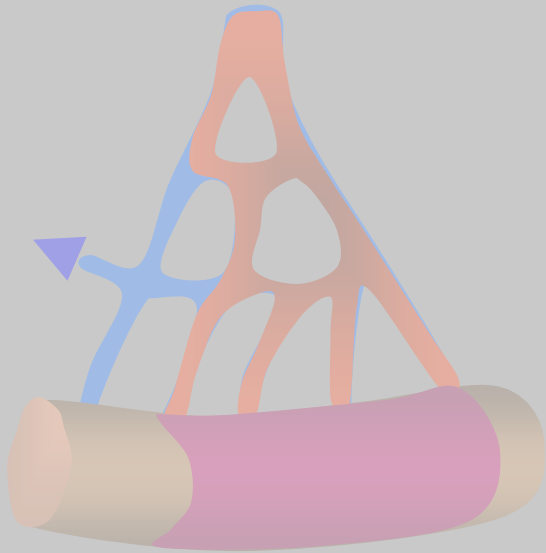
Plessier.  
Hepatology  
2010

\* Limited intestinal resection. Both survived.

\*\* Late malignancy in 1. Sepsis in 1

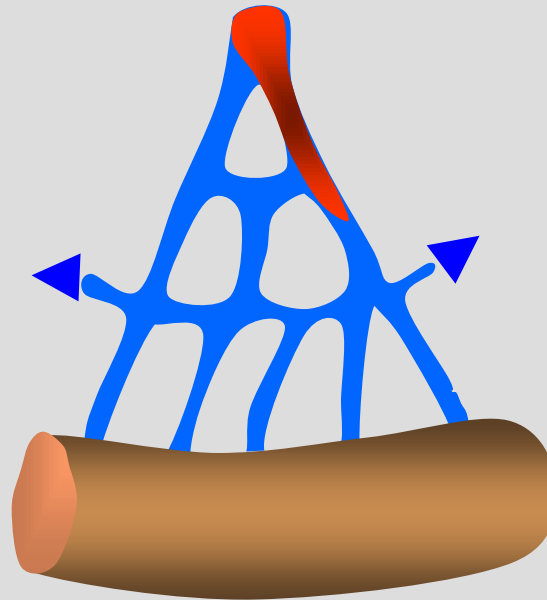
# Portal Vein Thrombosis

Intestinal  
Ischemia



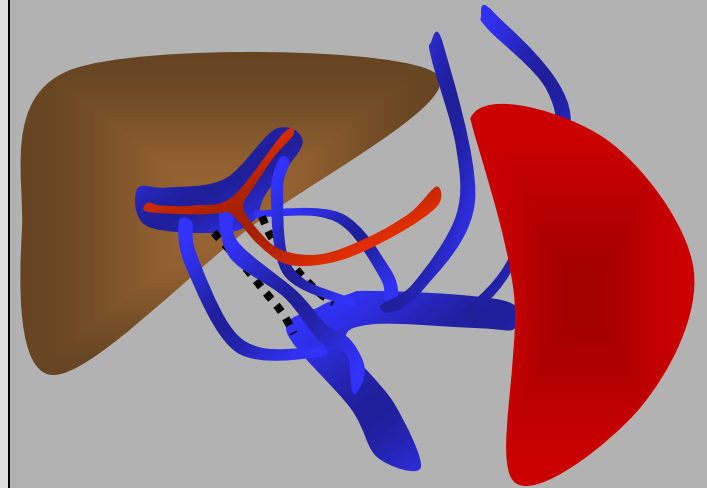
Ascites  
MOF

Uncomplicated  
Acute PVT



Abdo<sup>minal</sup> Pain  
SIRS

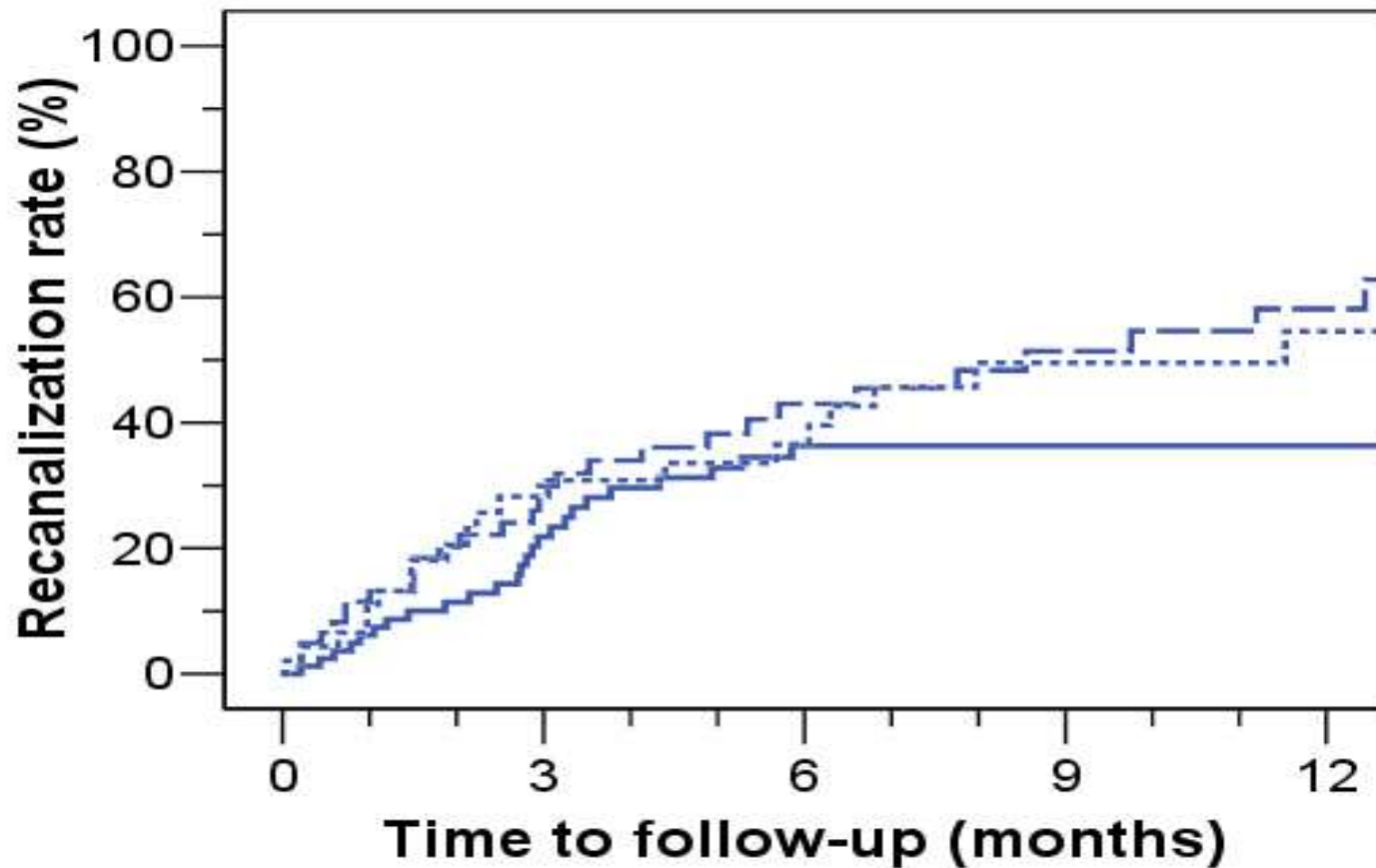
Chronic PVT



Bleeding  
Encephalopathy  
Cholangiopathy

# Acute Portal Vein Thrombosis

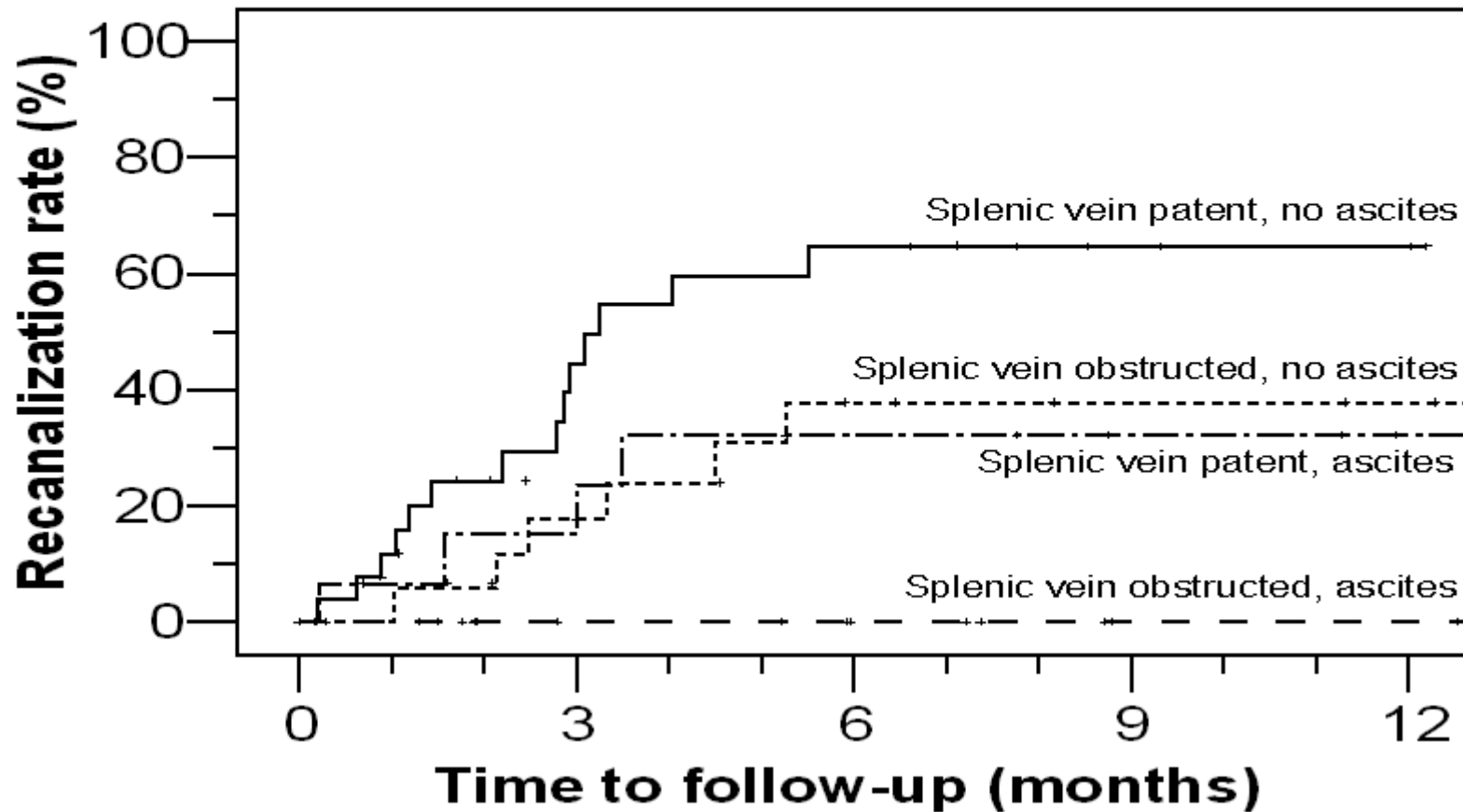
EN-Vie Cohort: 95 anticoagulated patients



Sup. mesenteric  
Splenic  
Portal

# Acute PVT: EN-Vie Cohort

## Predictive Factors for Portal Vein Recanalization



# Acute PVT

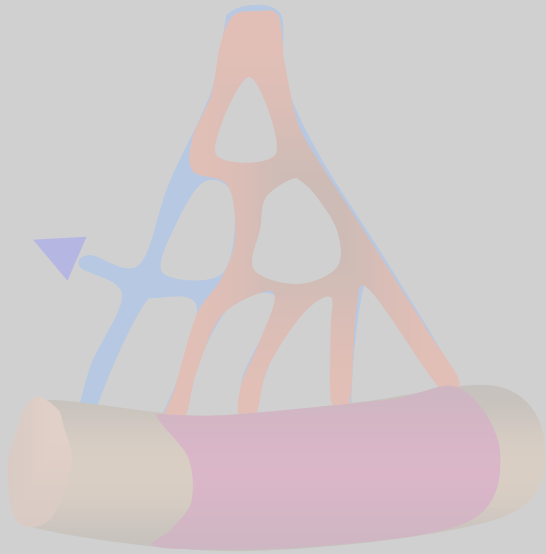
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## Alternative therapy ?

- TIPS: unclear
  - Thrombolysis
    - Systemic or SMA: hazardous
    - Transhepatic intraportal : hazardous
    - Transjugular intraportal : appealing
-

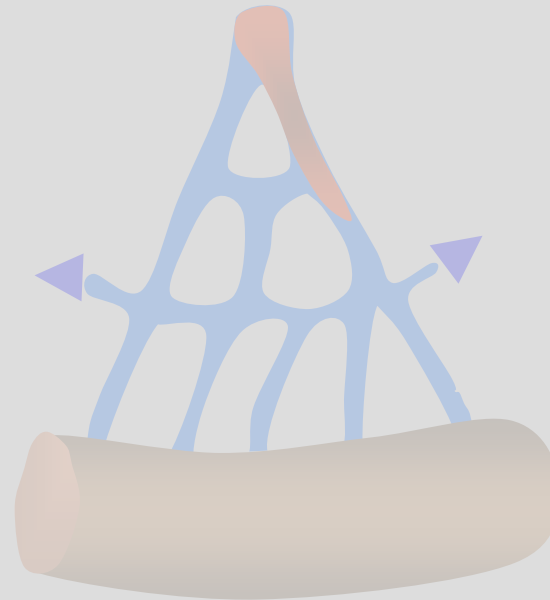
# Portal Vein Thrombosis

Intestinal  
Ischemia



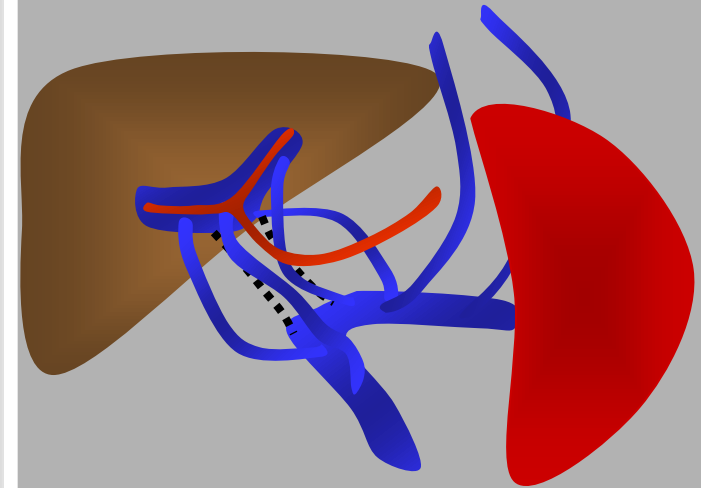
Ascites  
MOF

Uncomplicated  
Acute PVT



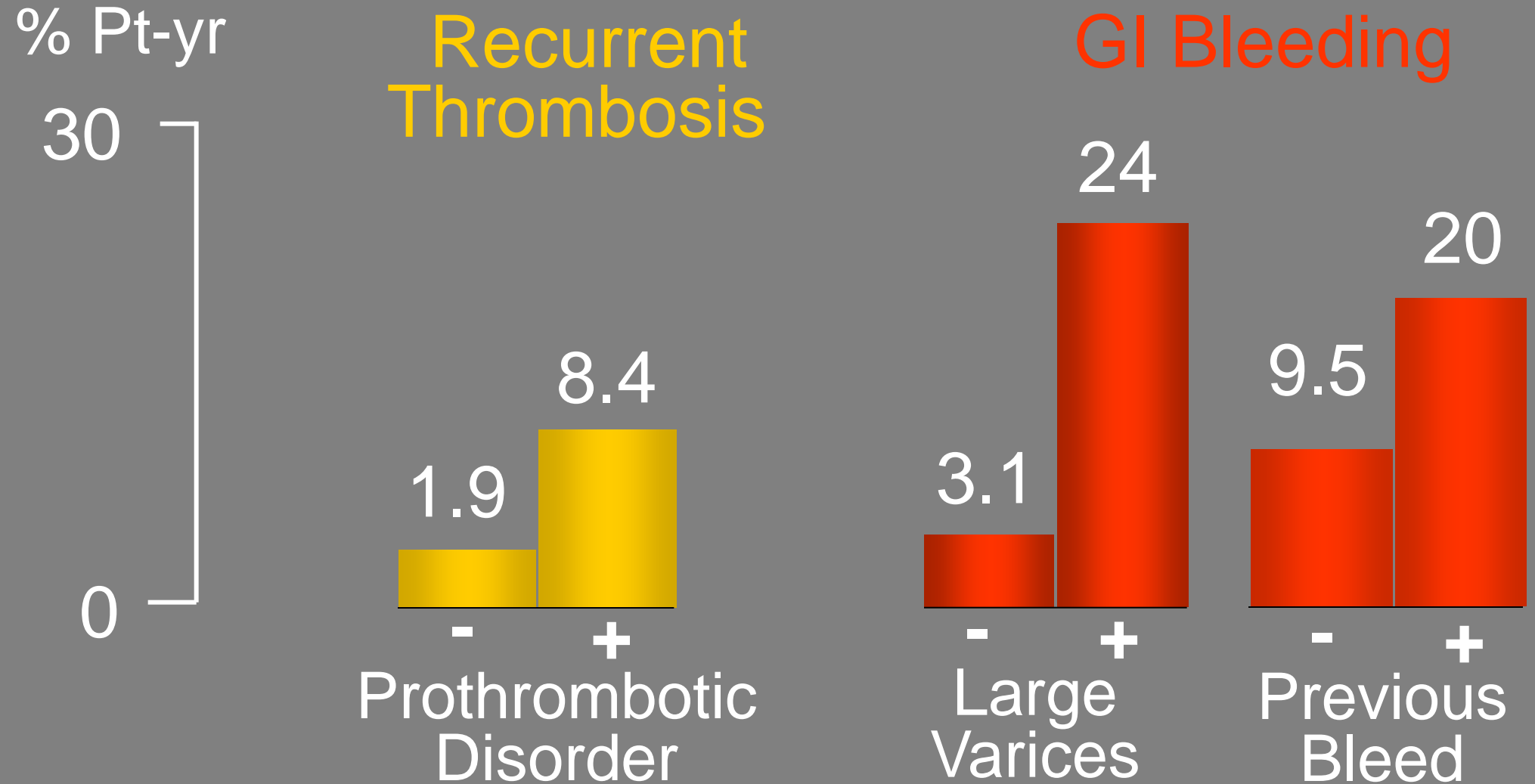
Abdo<sup>minal</sup> Pain  
SIRS

Chronic PVT



Bleeding  
Encephalopathy  
Cholangiopahy

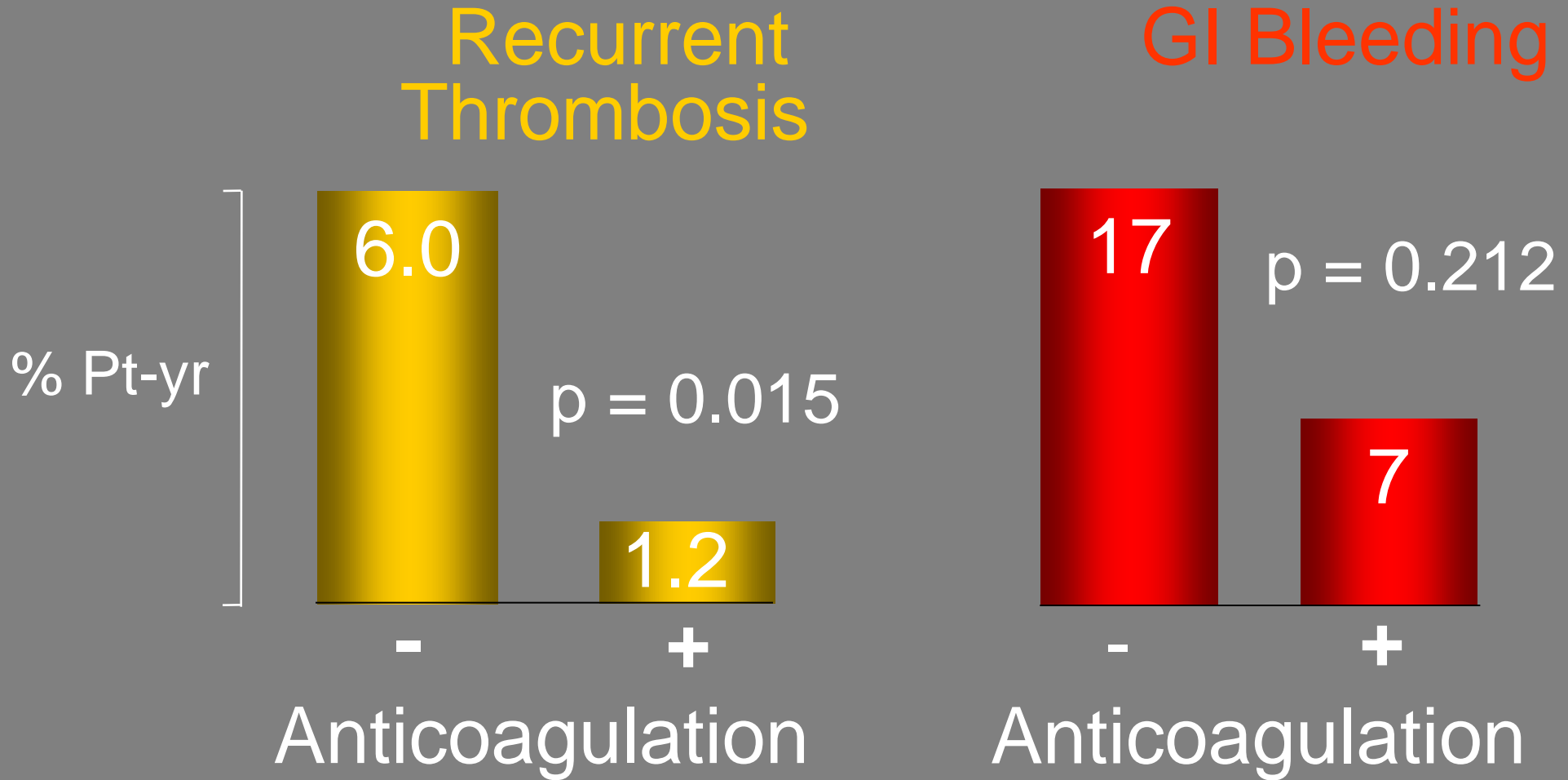
# Chronic Portal Vein Thrombosis - Complications



$p = 0.04, 0.07$  and  $0.004$

Condat, Gastroenterology 2001

# Extrahepatic PHT : Anticoagulation





# Prophylaxis for bleeding in adults with PVT

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- Beta blockers
  - Endoscopic therapy
  - Recanalization/Mesentericoportal bypass
  - Portosystemic shunting/Devascularization
- 

Sarin Gastroenterology 2010. Plessier J Hepatol 2012

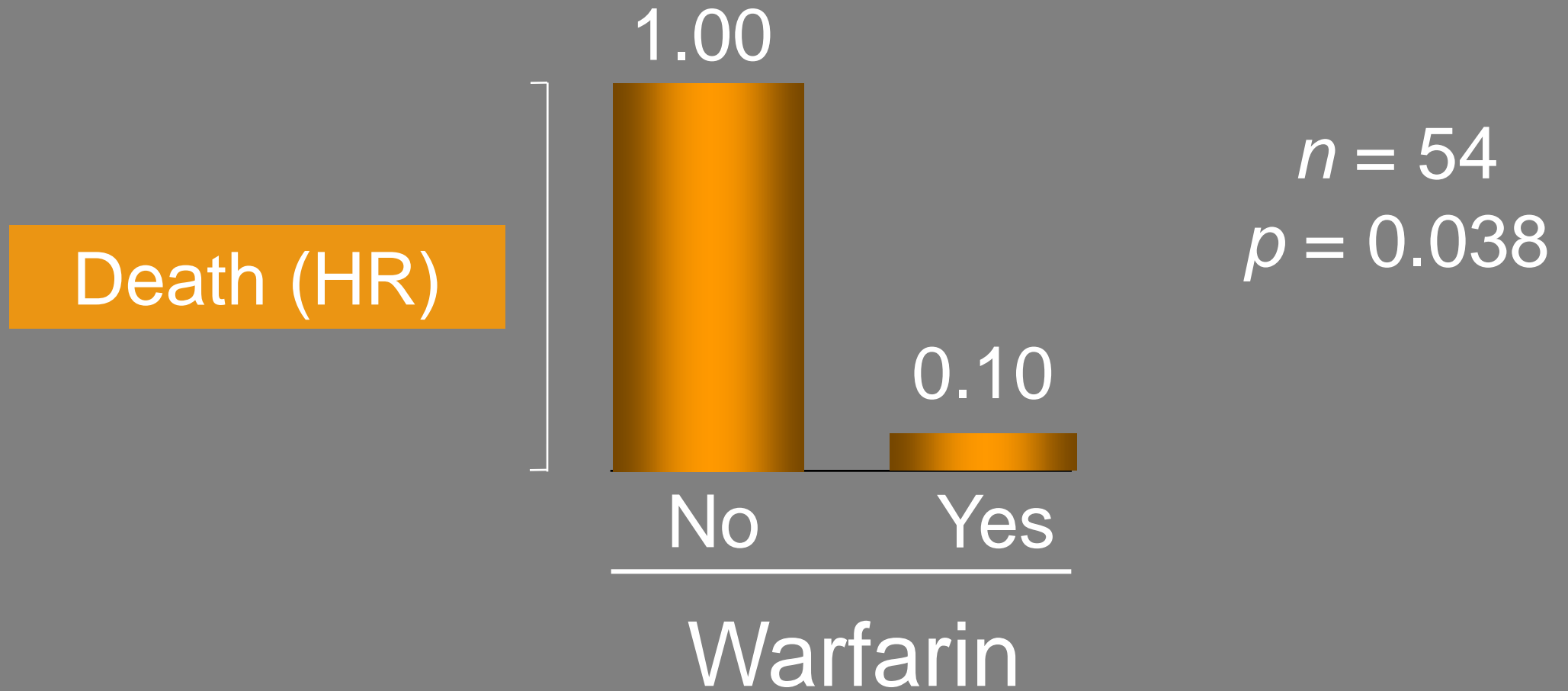
# Portal Vein Thrombosis - Bleeding Severity

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	Anticoagulation		<i>p</i>
	No	Yes	
Hemoglobin (g/dL)	8.0	7.9	NS
Length of stay (days)	9.6	14.0	NS
Transfusion (N units)	4.3	2.9	NS

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# Chronic Porto-Mesenteric Vein Thrombosis



# PVT in Patients without Cirrhosis

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1. The benefit:risk ratio of anticoagulation for acute PVT seems to be favorable. Alternative therapies potentially hazardous.
  2. Prophylaxis of GI bleeding in chronic PVT based on non selective beta blockers and endoscopic ligation.
  3. Benefit from anticoagulation for chronic PVT still unclear (SMV thrombosis, thrombophilia ?)
  4. Bleeding on anticoagulation apparently not a problem. Further studies needed.
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# Portal Vein Thrombosis

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- In patients without cirrhosis
  - **In patients with cirrhosis**
-

# Would you prescribe anticoagulation?

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- 54 year-old male patient
- Chronic hepatitis C  
Long-standing alcohol use
- Ruptured esophageal varices
- Platelets 60 000/ $\mu$ L, PT 68%,  
bilirubin 25  $\mu$ mol/L,  
albumin 39 g/L,  
créatinine 87  $\mu$ mol/L
- Partial portal vein thrombosis

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1 - YES

2 - NO

# Would you prescribe anticoagulation?

---

- 54 year-old male patient
- Chronic hepatitis C  
Long-standing alcohol use
- Ruptured esophageal varices
- Platelets 60 000/ $\mu$ L, PT 68%,  
bilirubin 25  $\mu$ mol/L,  
albumin 39 g/L,  
créatinine 87  $\mu$ mol/L
- Partial portal vein thrombosis

---

1 - YES

2 - NO

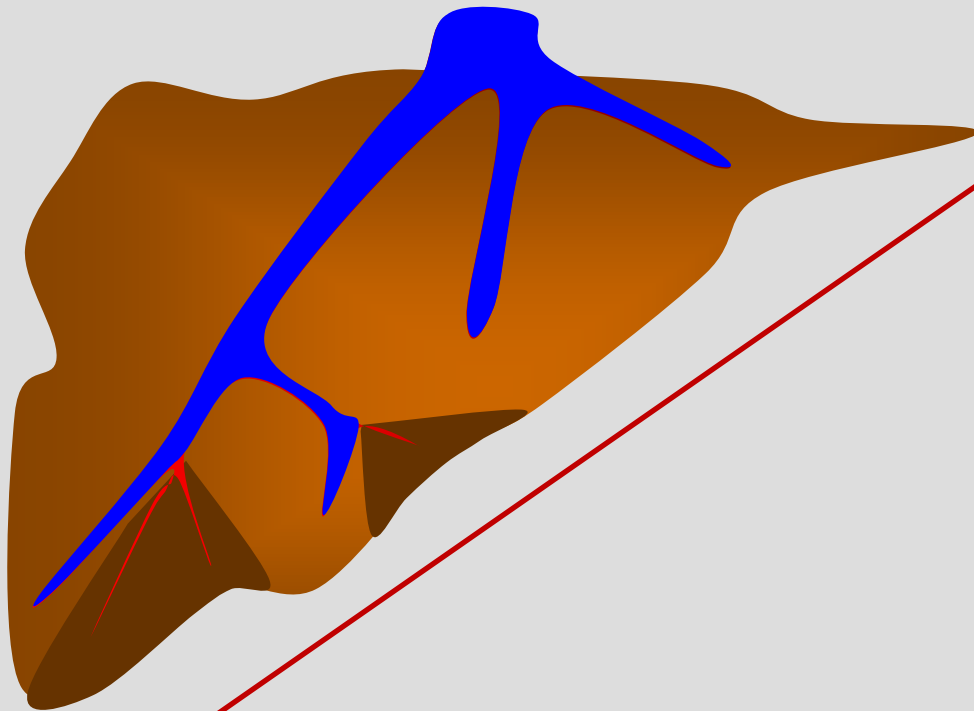
# Cirrhosis Splanchnic Vein Thrombosis

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- Thrombosis of intrahepatic veins
  - Thrombosis of extrahepatic portal vein
-

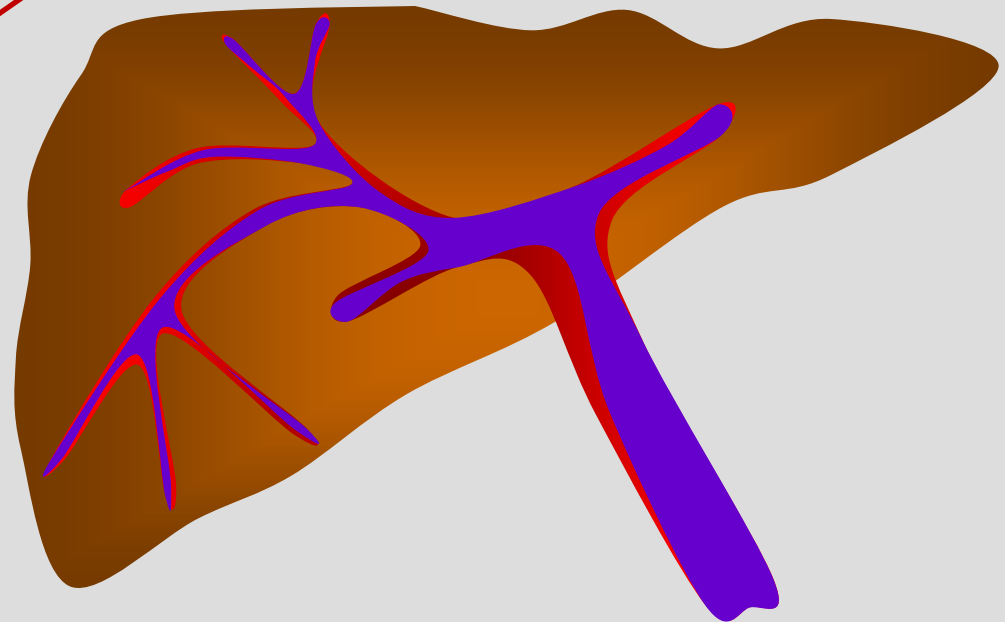


70% hepatic veins thrombosed



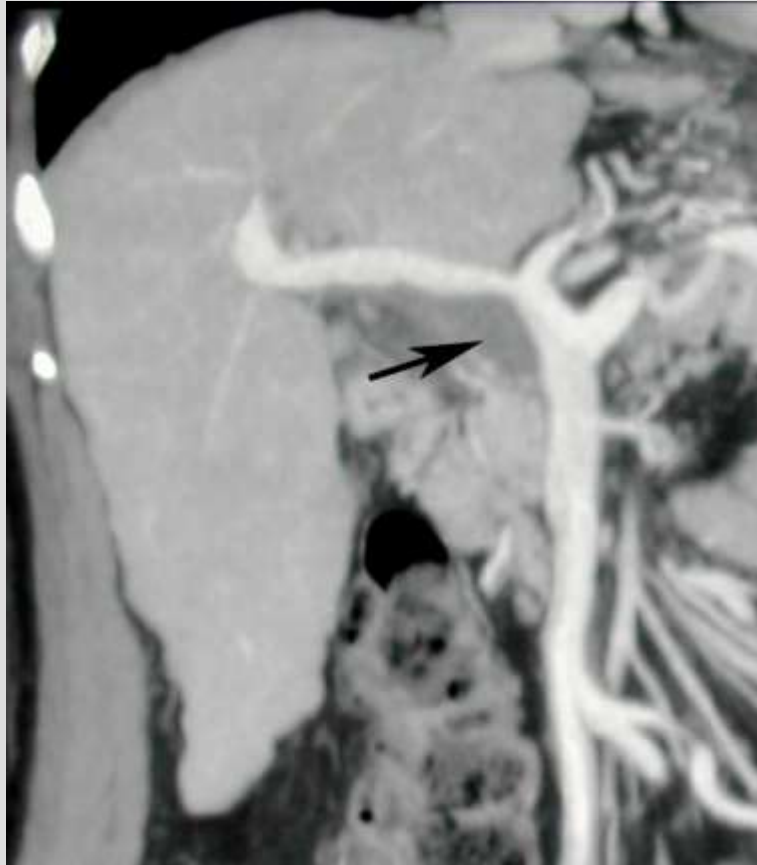
Wanless, Hepatology 1995  
Shimatzu, Hepatology 1997

Explanted  
Cirrhotic Livers



40% of portal veins thrombosed

# Extrahepatic Portal Vein Thrombosis in Cirrhosis



Partial PVT	Occlusive PVT
10% (5-16)	3% (1-4)
Spontaneous regression	
40% (31-71)	

# Extrahepatic Portal Vein Thrombosis in Cirrhosis



Only PV	Radicles
85%	15%

Cavernoma	10-20%
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Yerdel 2000. Manzanet 2001. Francoz 2005. Dumortier 2010.  
Englesbe 2010. Ravaioli 2011. Luca 2012, Maruyama 2013

# PVT and Cirrhosis Presentation

Context of Diagnosis	79 patients
Screening for HCC	34 (43 %)
GI bleeding related to PHT	31 (39 %)
Abdominal pain	4 (5 %)
Intestinal infarction	10 (13 %)
Complete SMV obstruction	10/10
Intestinal resection	6/10
Death	4/10

# PVT and Cirrhosis Severity

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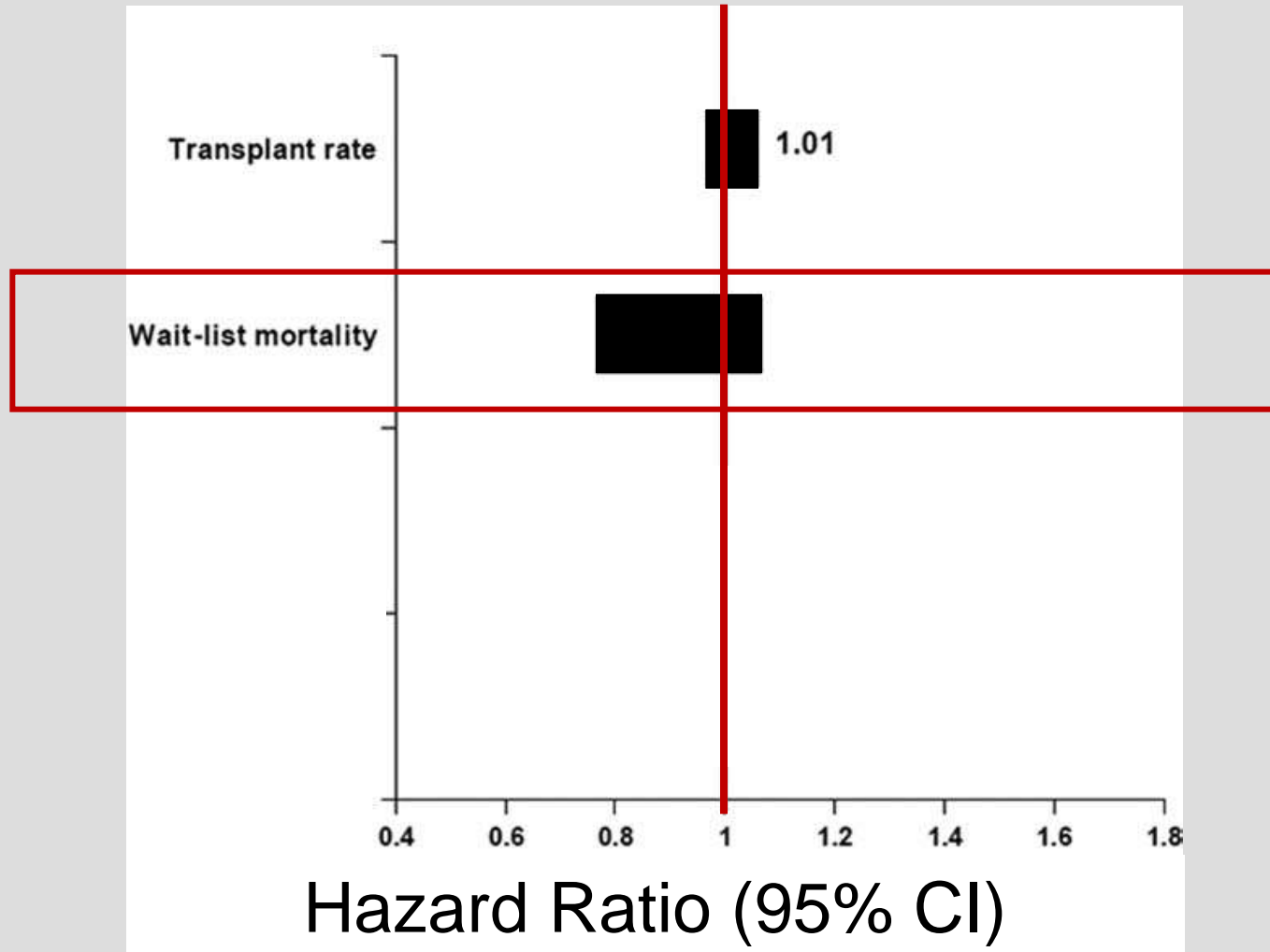
## PVT associated with

- Small liver
- High Child-Pugh or MELD scores
- Portal hypertensive bleeding, failure to control bleeding, failure to eradicate varices
- Ascites
- Hepatic encephalopathy

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Wanless, Hepatology 1995. Shimamatsu, Hepatology 1997. Nonami, Hepatology 1992. Orloff, J Gastrointest Surg 1997. D'Amico, Hepatology 2003. Amitrano, J Hepatol 2004. Englesbe, Liver Transplant 2010

# Impact of PVT before LTx



Englesbe. Liver Transplant 2010. SRTR 22,291 listed candidates. Occlusive PVT 4.02%

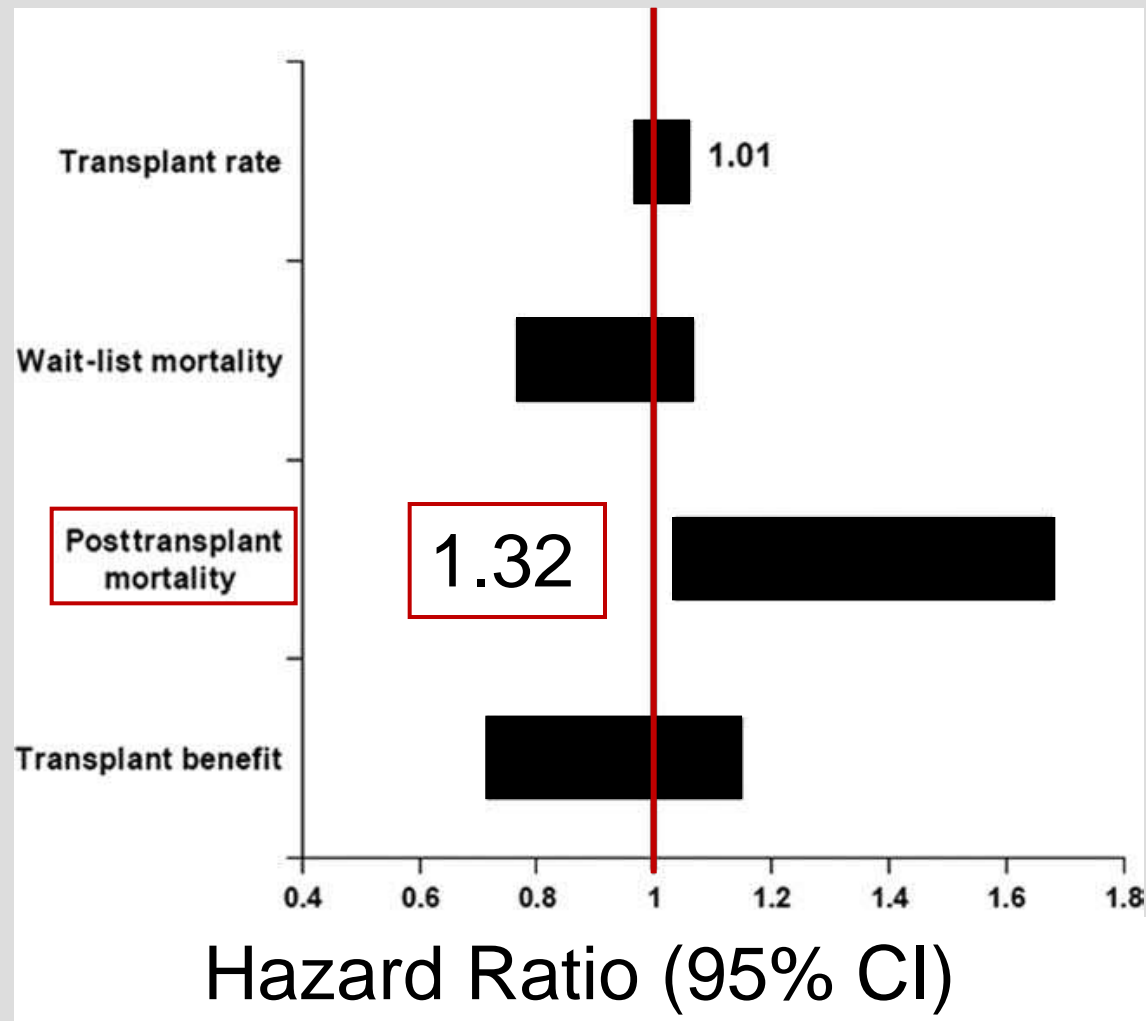
**Advanced  
Cirrhosis**



**Portal Vein  
Thrombosis**

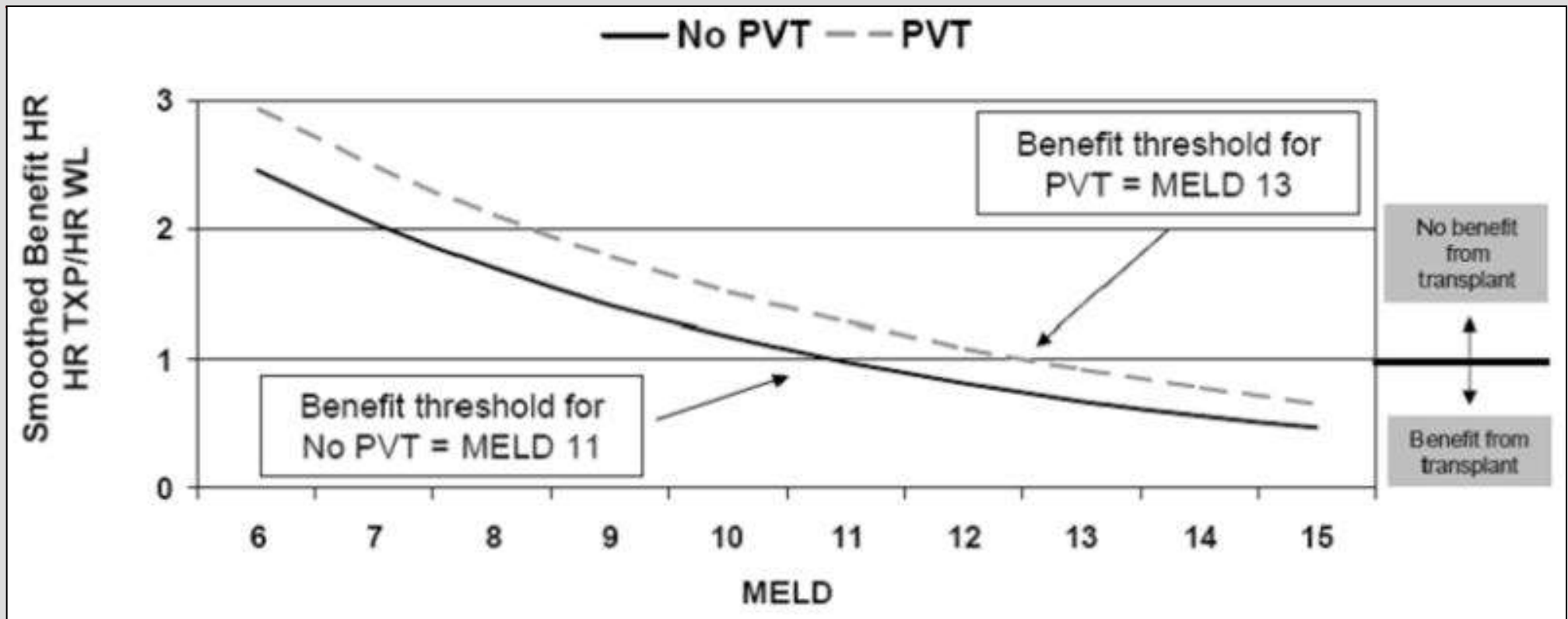
# Impact of PVT before and after LTx

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# Impact of PVT before and after LTx



Englesbe. Liver Transplant 2010.

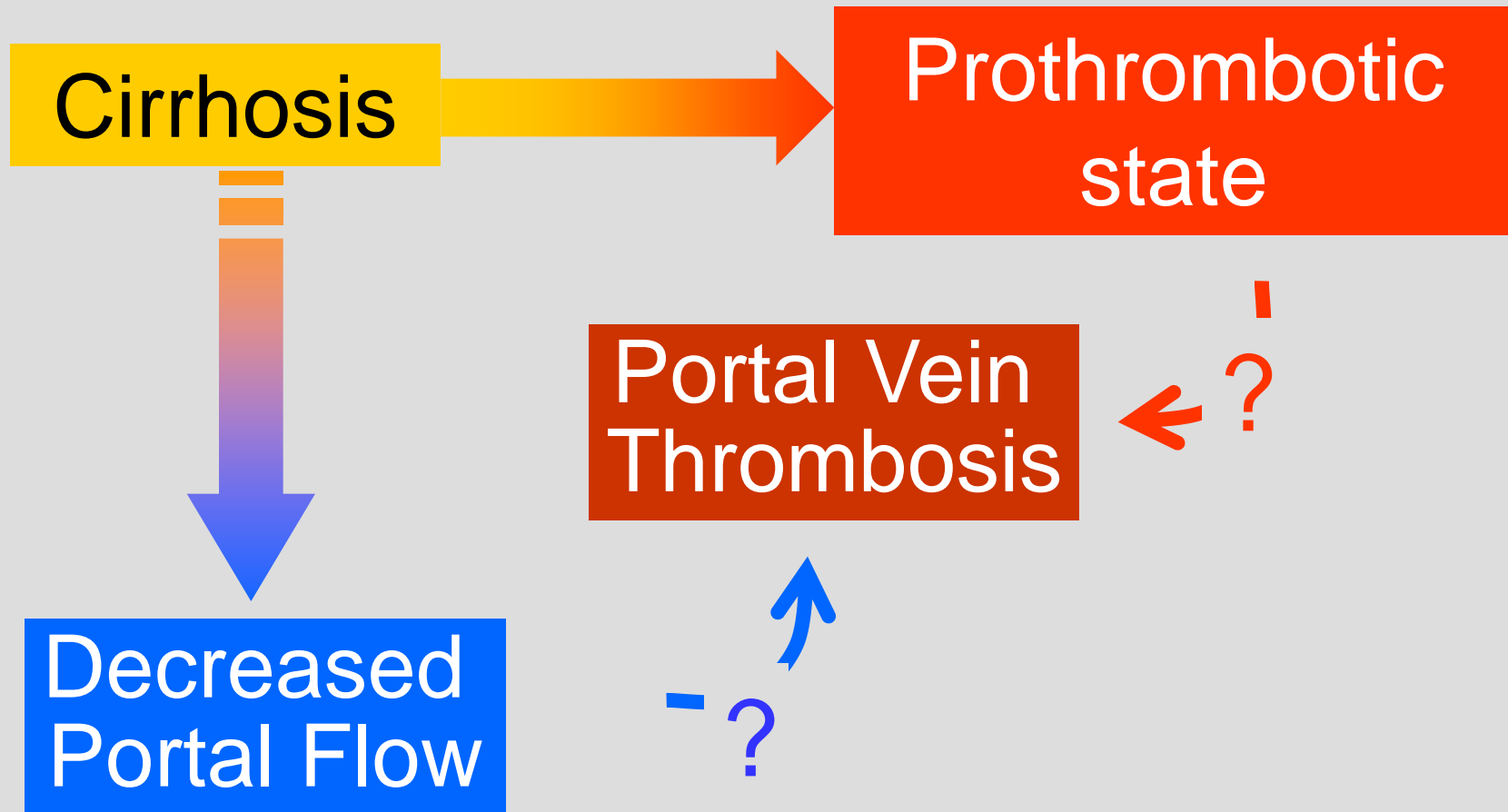
SRTR 22,291 Candidats sur liste. TVP totale 4.02%

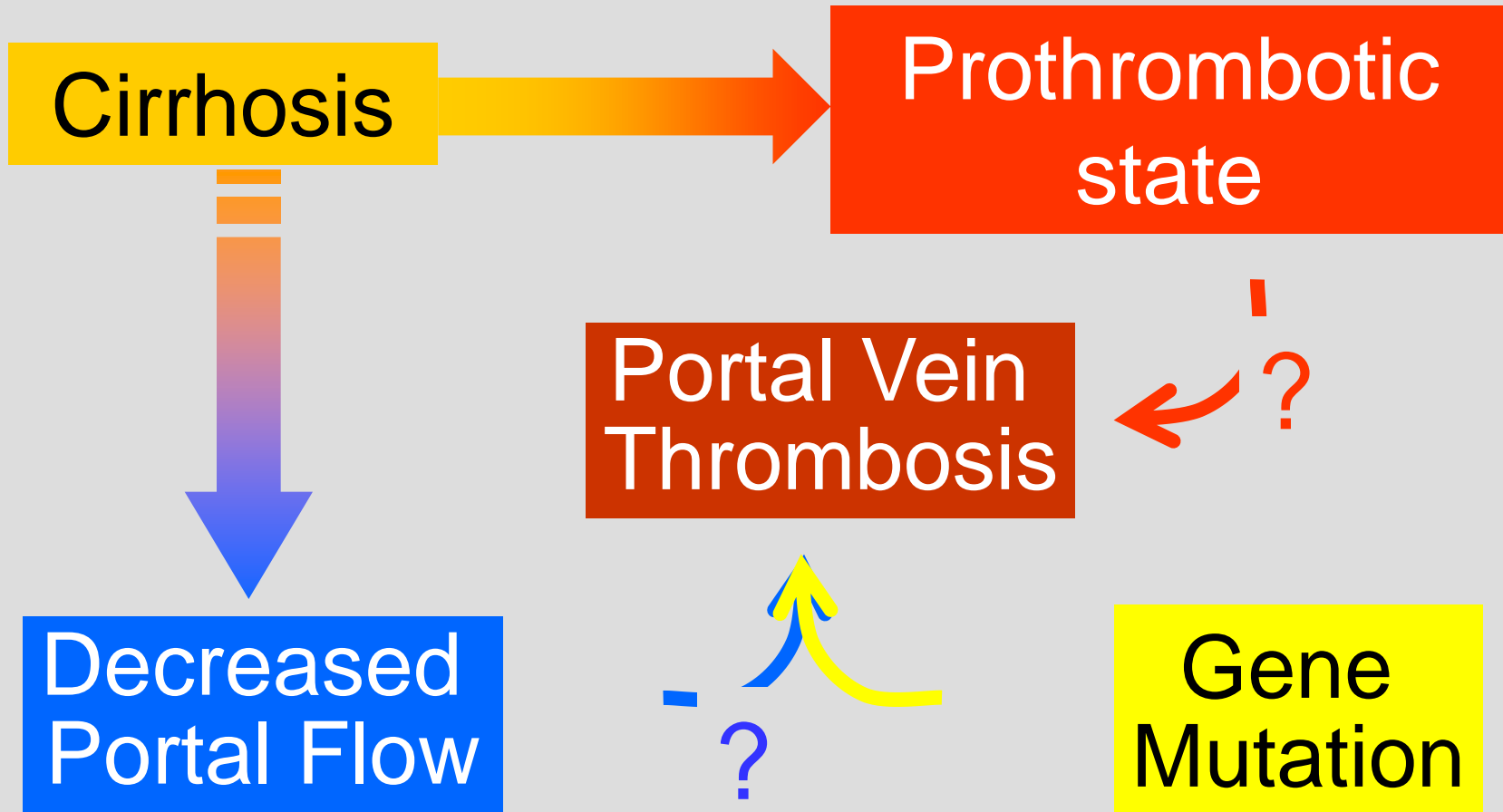
[Résultats similaires Doenecke, Clin Transplant 2009]

**Advanced  
Cirrhosis**



**Portal Vein  
Thrombosis**





Pellicelli. ILC 2011. Erkan EJGH, 2005. Amitrano, J HEP 2004.

**Advanced  
Cirrhosis**



**Portal Vein  
Thrombosis**

# THROMBOCIR Study

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- Screening for HCC (US-Doppler /3 ou /6 mo.)
- 898 patients, Child A, median follow-up 47 mo.

Progression  
N = 221

PVT  
N = 101

Both  
N = 43

- Baseline data, F.V & F.II Leiden
- PVT, portal flow velocity, progression

**Advanced  
Cirrhosis**



**Portal vein  
Thrombosis**

Variables associated  
with PVT

EV – *Baseline*

Bilirubin – *Baseline*

**NOT**

Progression (before PVT)

Portal flow (↓before PVT)

## Variables associated with Progression

Age – *baseline*

EV – *baseline*

Bilirubin – *baseline*

Creatinine – *baseline*

PT – *baseline*

PVT before – *Time depend.*

**NOT**

PVT < 6 mo – *Time depend.*

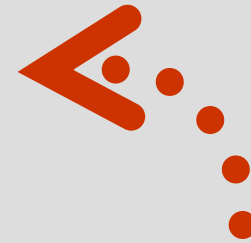
# Portal vein Thrombosis



# Advanced Cirrhosis

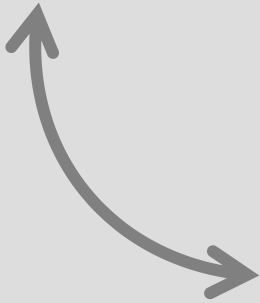
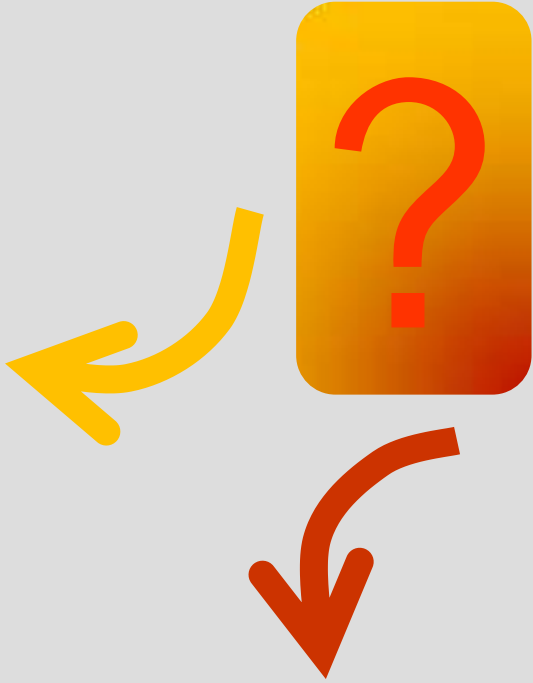


**Advanced  
Cirrhosis**



**Portal vein  
Thrombosis**

**Advanced  
Cirrhosis**



**Portal vein  
Thrombosis**

# Management of Portal Vein Thrombosis

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- Treatment
  - Prophylaxis
-

# Anticoagulation and PVT in Cirrhosis

Author	N	Treatment	% Recanalization Compl./Part./Nil		
Francoz	19	LMWH → VKA	42	5	53
Amitrano	28	LMWH	75	8	17
Senzolo	33	LMWH	36	27	36
Seijo	55	LMWH → VKA	45	15	40

Francoz, Gut 2005. Amitrano, Clin Gastroenterol Hepatol 2010. Senzolo, Liver Int 2012.  
Seijo Clin Gastroenterol Hepatol 2012

# Anticoagulation and PVT in Cirrhosis

Author	N	Treatment	Bleeding related deaths
Francoz	19	LMWH →VKA	0%
Amitrano	28	LMWH	0%
Senzolo	33	LMWH	0%
Seijo	55	LMWH →VKA	0%

Francoz, Gut 2005. Amitrano, Clin Gastroenterol Hepatol 2010. Senzolo, Liver Int 2012.  
Seijo Clin Gastroenterol Hepatol 2012

# Treatment of PVT in Patients with Cirrhosis

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Anticoagulation or TIPS for recanalization ?

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# TIPS in Cirrhosis with PVT

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- ≈ 250 patients reported
  - Feasible when intrahepatic veins are visible.
  - Effective for recanalization of partial occlusion.
  - TIPS dysfunction, encephalopathy & mortality were similar to TIPS patients without PVT.
  - Impact on complications and mortality unclear.
- 

Senzolo, AP&T 2006. Van Ha, Cardiovasc Intervent Radiol 2006.

Perarnaud, Eur J Gastro Hepato 2010. Han, J Hepatol 2010.

Luca, Gut 2011. Senzolo, Liver Intern 2012

# Management of Portal Vein Thrombosis

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- Treatment
  - Prophylaxis
-



# PVT Prophylaxis – Cirrhosis (CTP B7-C10)

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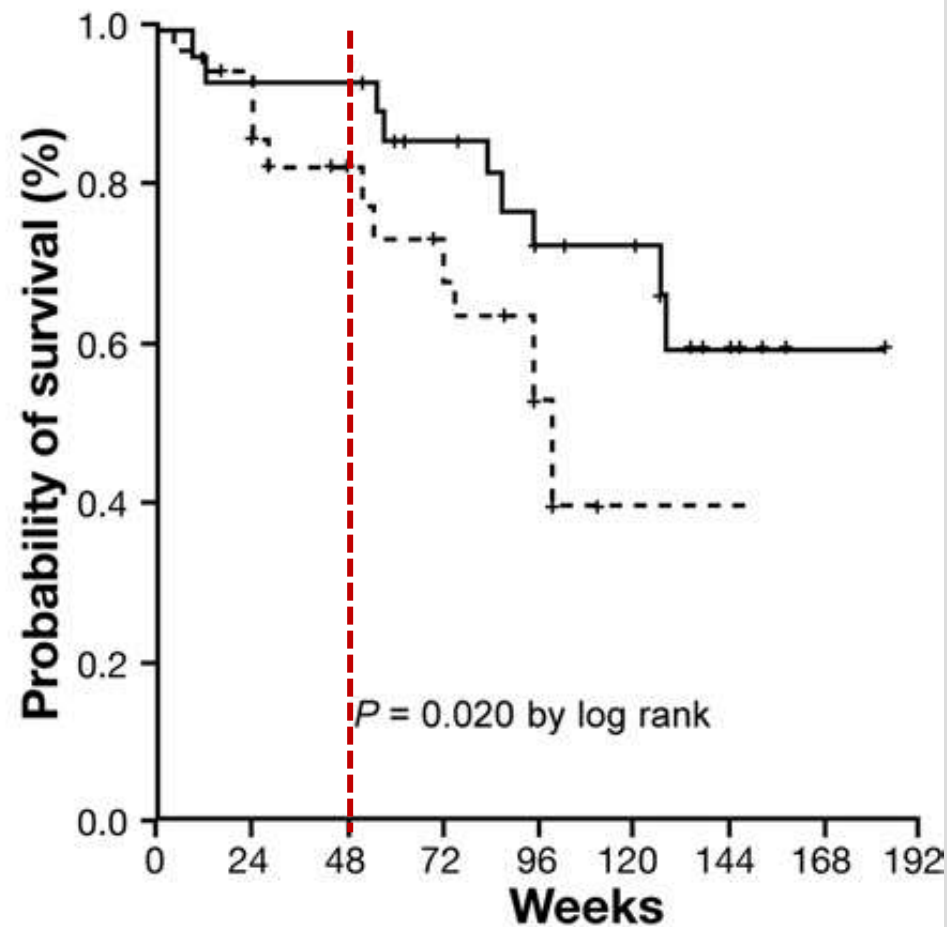
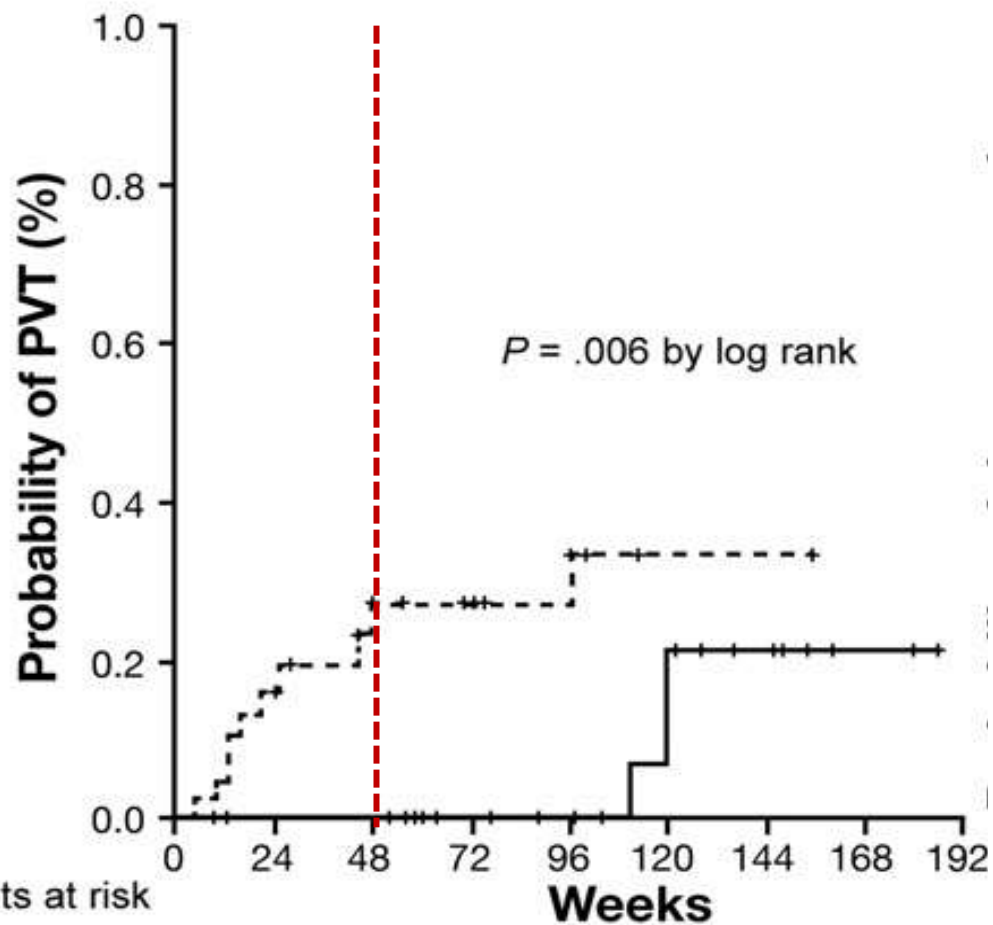
	<u>Control</u>	<u>Enoxaparin</u>
N. of patients	36	34
Partial PVT	3	0
Complete PVT	3	0
Decompensation	19	4

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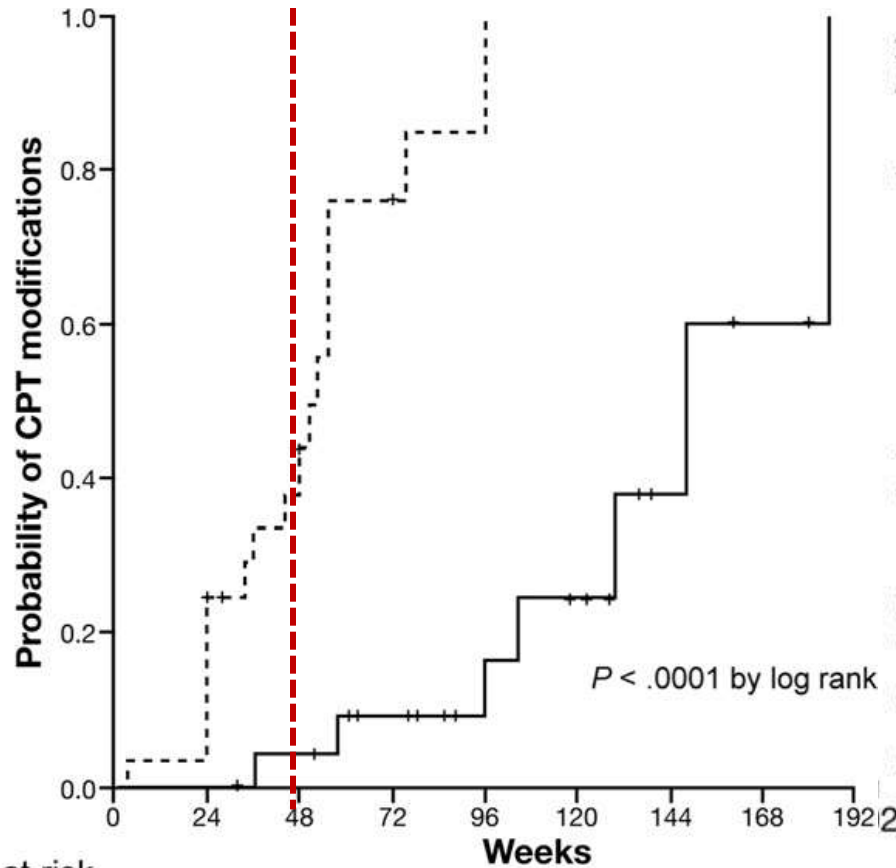
Villa. Gastroenterology 2012. Enoxaparin 4.000 UI/d, for 12 mo.

## CP score modification

## Survival



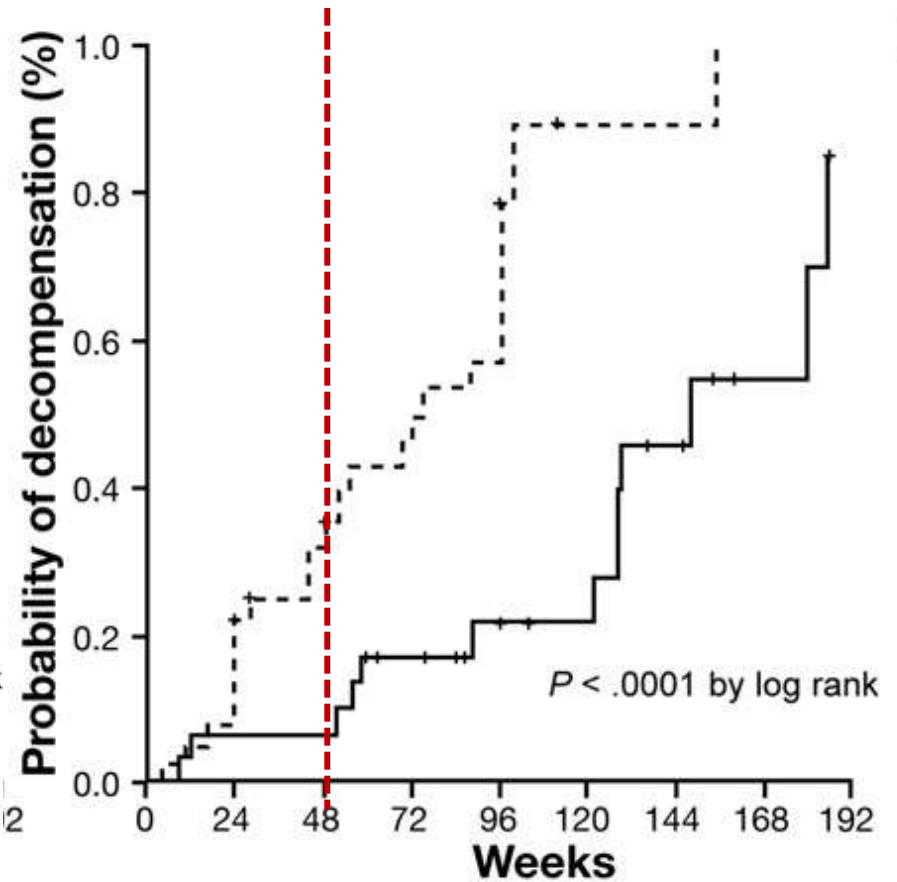
## CP score modification



Patients at risk

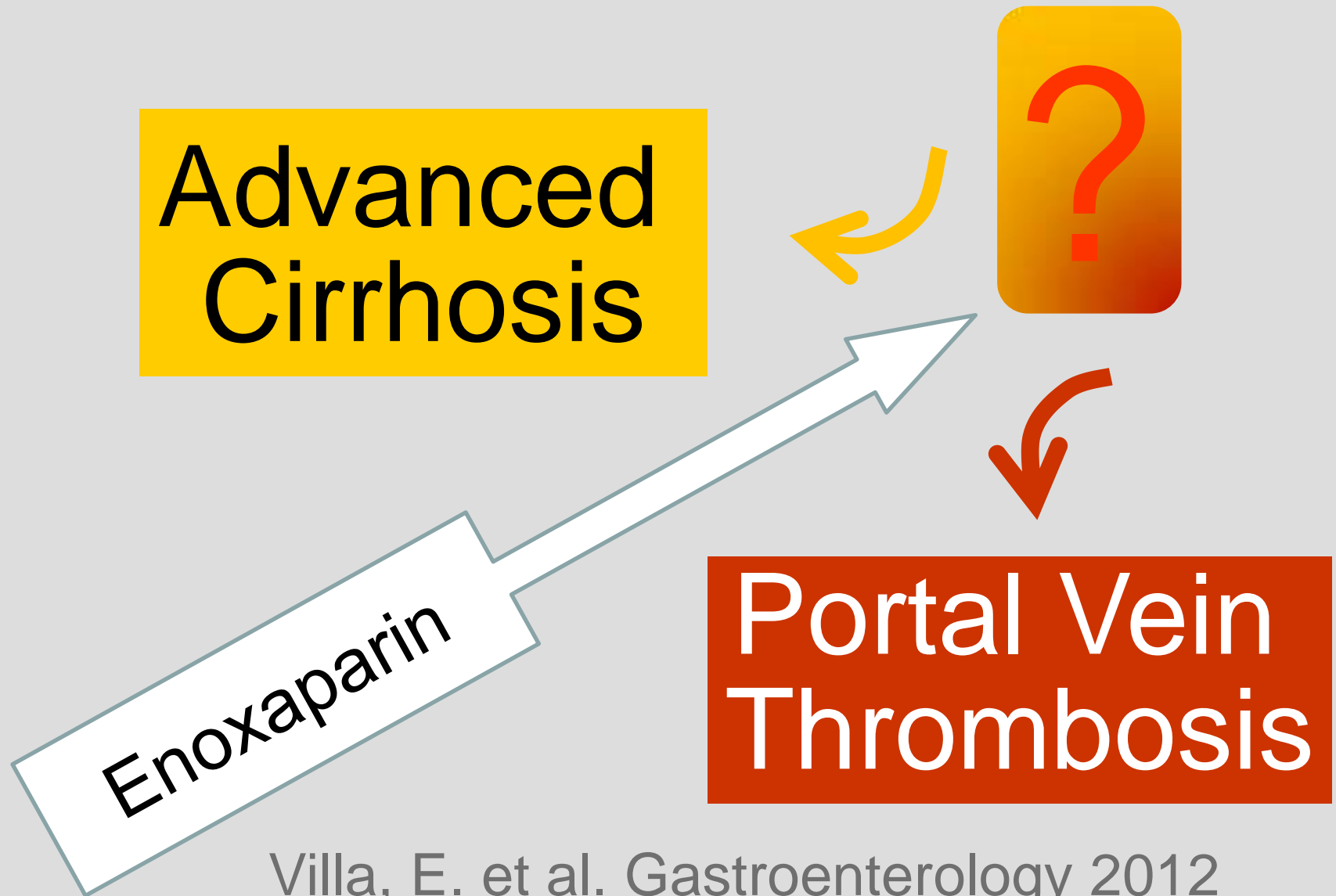
Controls	36	30	19	12	10	1	0		
Enoxaparin	34	32	23	18	13	11	5	0	0

## Decompensation



Controls	36	31	19	12	10	3	0		
Enoxaparin	34	30	23	18	13	11	5	3	0

Villa. Gastroenterology 2012. Enoxaparin 4.000 UI/d, for 4 weeks.



Villa, E. et al. Gastroenterology 2012

Nery, F. et al The Liver Meeting 2013. Communication #127

# Conclusions

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- Patients with cirrhosis are not ‘naturally anticoagulated’.
  - Extrahepatic PVT points to a severe disease.
  - PVT does not obviously make cirrhosis more severe.
  - PVT and worsening of cirrhosis share a common factor.
  - Enoxaparin appears to benefit patients with cirrhosis of Child-Pugh 7-10.
-

# Open questions

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- What is the mechanism of enoxaparin beneficial effect in patients with cirrhosis?
  - Is there a benefit from anticoagulation therapy in patients with established PVT (recanalization, decompensation, transplantability, mortality) ?
  - Which modalities for anticoagulation therapy (agent, duration, monitoring) ?
-

# Recommendations

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## Proposed indications of anticoagulation therapy in patients with cirrhosis

- PVT in a liver transplantation candidate  
→ benefit plausible but unproved
  - Mesenteric venous ischemia  
→ benefit plausible and reasonable
  - Strong underlying prothrombotic disorder  
→ benefit plausible and reasonable
-

# Collaborations

## Hôpital Beaujon

A. Plessier, B. Condat, E. de Raucourt, L. Boudaoud,  
A. Sibert, V. Vilgrain, D. Cazals Hatem, P. Bédossa,  
O. Goria, JJ Kiladjian

## Réseau Français des Maladies Vasculaires du Foie

European network for vascular diseases of  
the liver (VALDIG)

(JC. Garcia-Pagan, H. Janssen)





# Questions

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In cirrhosis, portal vein thrombosis is due to

- 1 - hepatic dysfunction
  - 2 - portal vein blood stasis
  - 3 - underlying thrombophilia
  - 4 - spontaneous bacterial peritonitis
  - 5 - hepatocellular carcinoma
-

# Proposed Answers

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In cirrhosis, portal vein thrombosis is ~~due to~~  
**associated with**

- 1 - hepatic dysfunction
  - 2 - portal vein blood stasis
  - 3 - underlying thrombophilia
  - ~~4 - spontaneous bacterial peritonitis~~
  - ~~5 - hepatocellular carcinoma~~
-

# Questions

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In patients with cirrhosis, it is clear that PVT

1 - worsens hepatic dysfunction

2 - worsens portal hypertension

3 - induces liver atrophy

4 - makes liver transplantation more difficult

5 - increases the risk of hepatocellular carcinoma

---

# Proposed Answers

---

In patients with cirrhosis, it is clear that PVT

1 - worsens hepatic dysfunction

2 - worsens portal hypertension

3 - induces liver atrophy

4 - makes liver transplantation more difficult

5 - increases the risk of hepatocellular carcinoma

---

# Questions

---

In patients with cirrhosis, anticoagulation therapy for PVT is indicated

- 1 - only for Child-Pugh class A
  - 2 - should be associated with a TIPS
  - 3 - only in liver transplant candidates
  - 4 - is not associated with an increased risk of bleeding
  - 5 - improves liver condition
-

# Proposed Answers

---

In patients with cirrhosis, anticoagulation therapy for PVT is indicated

1 - only for Child-Pugh class A

2 - should be associated with a TIPS

3 - only in liver transplant candidates

4 - is not associated with an increased risk of bleeding

5 - improves liver condition

---

# EVL, bleeding and anticoagulation

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	PVT & VKA	PVT no VKA
Hospitalisation	75 %	69 %
Days in hospital	7,4	11
Days in USI	2,3	0,6
Blood units	3,2 ± 1,9	4,2 ± 2,2

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