Anticoagulation Therapy for Liver Disease: A Panacea ?

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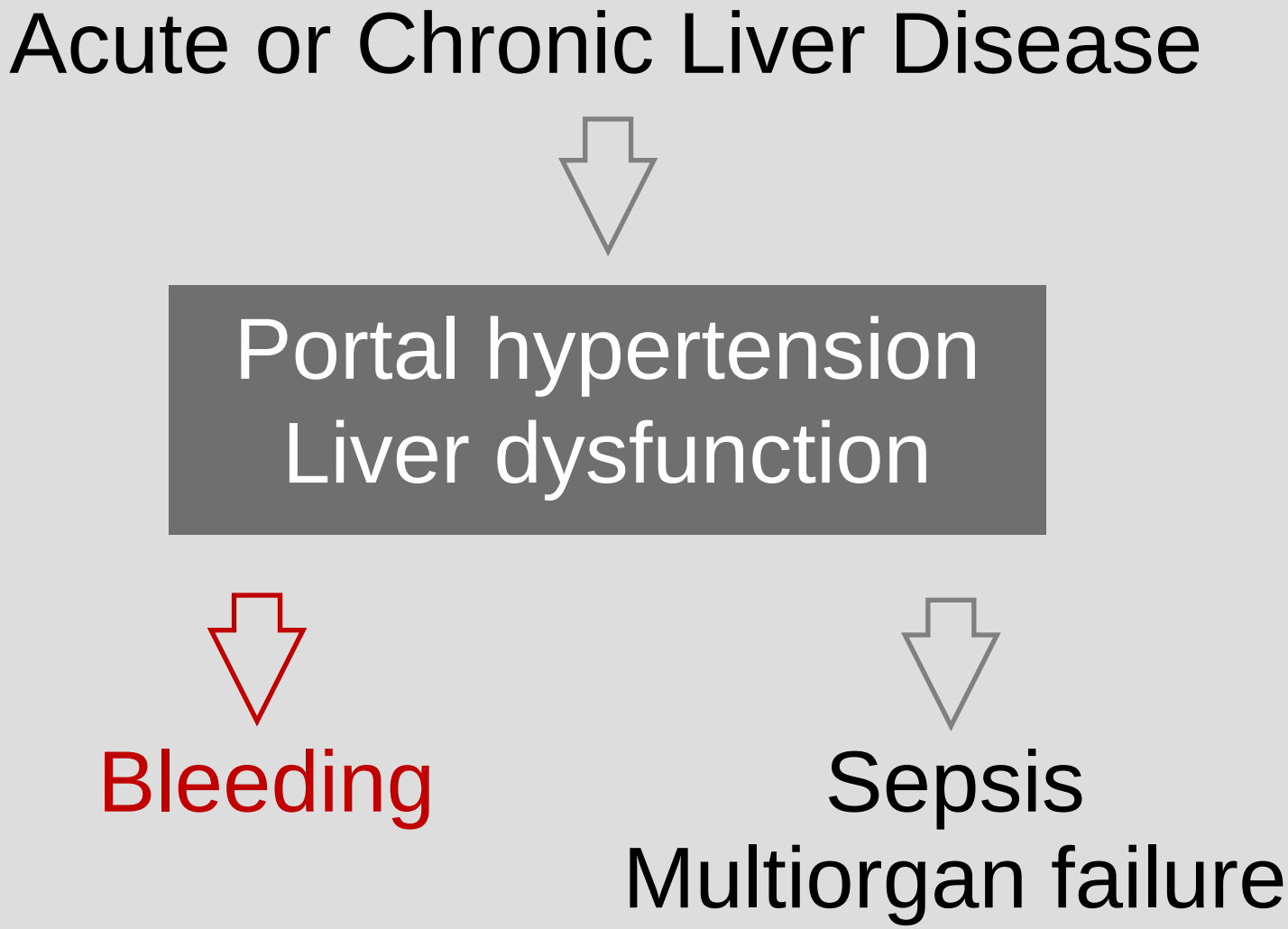
Nothing to disclose


Acute or Chronic Liver Disease
Portal hypertension
Liver dysfunction
Bleeding
Sepsis
Multiorgan failure

Anticoagulation Therapy for Liver Disease

- Vascular diseases of the liver
- Parenchymal diseases of the liver

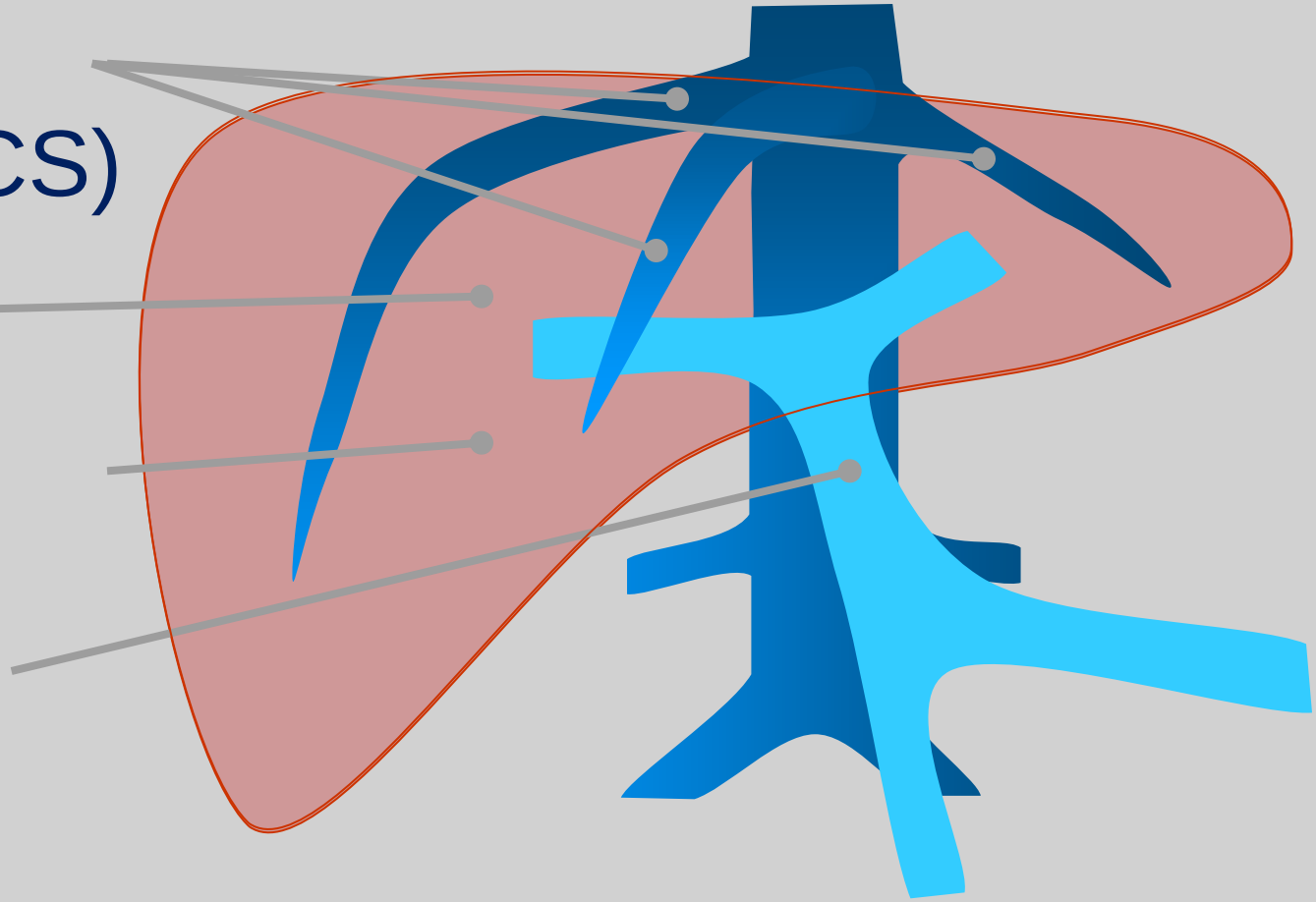
Vascular Liver Diseases

Hepatic veins thrombosis (BCS)

SOS/VOD

IPH/OPV/NRH

Portal vein thrombosis



Risk Factors for Venous Thrombosis in Patients with Splanchnic Vein Thrombosis

	HVT	PVT
• At least one	84%	67%
• Multiple	46%	18%
• Local factor	5%	21%

Murad. Ann Intern Med 2009. N = 163. Plessier. Hepatology 2010. N = 102

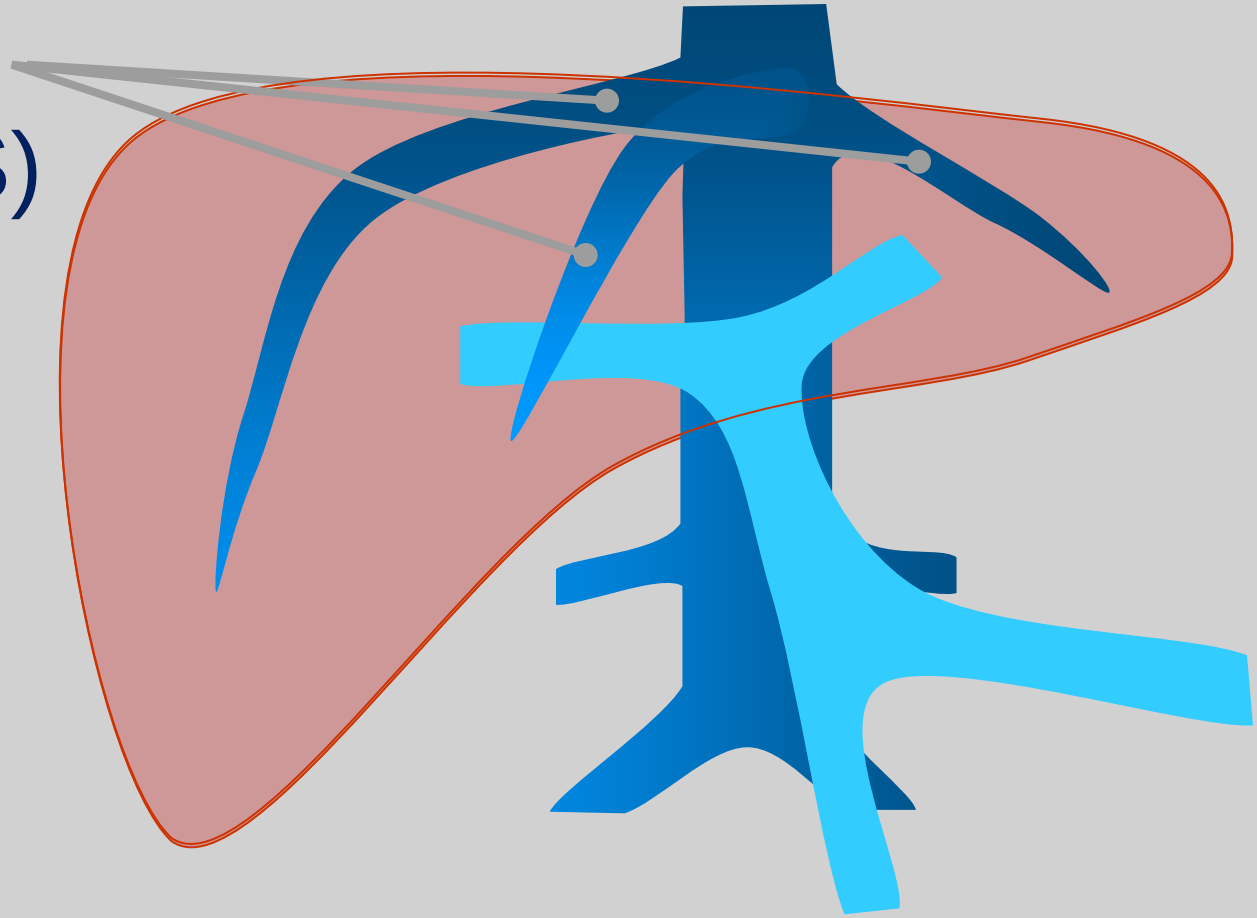
Prothrombotic Diseases in HVT & PVT

	HVT	PVT
Myeloproliferative neoplasms %	50	35
Antiphospholipid syndrome %	15	15
Inherited disorders %	35	35
Others (PNH, Behcet, IBD, …) %	10	10

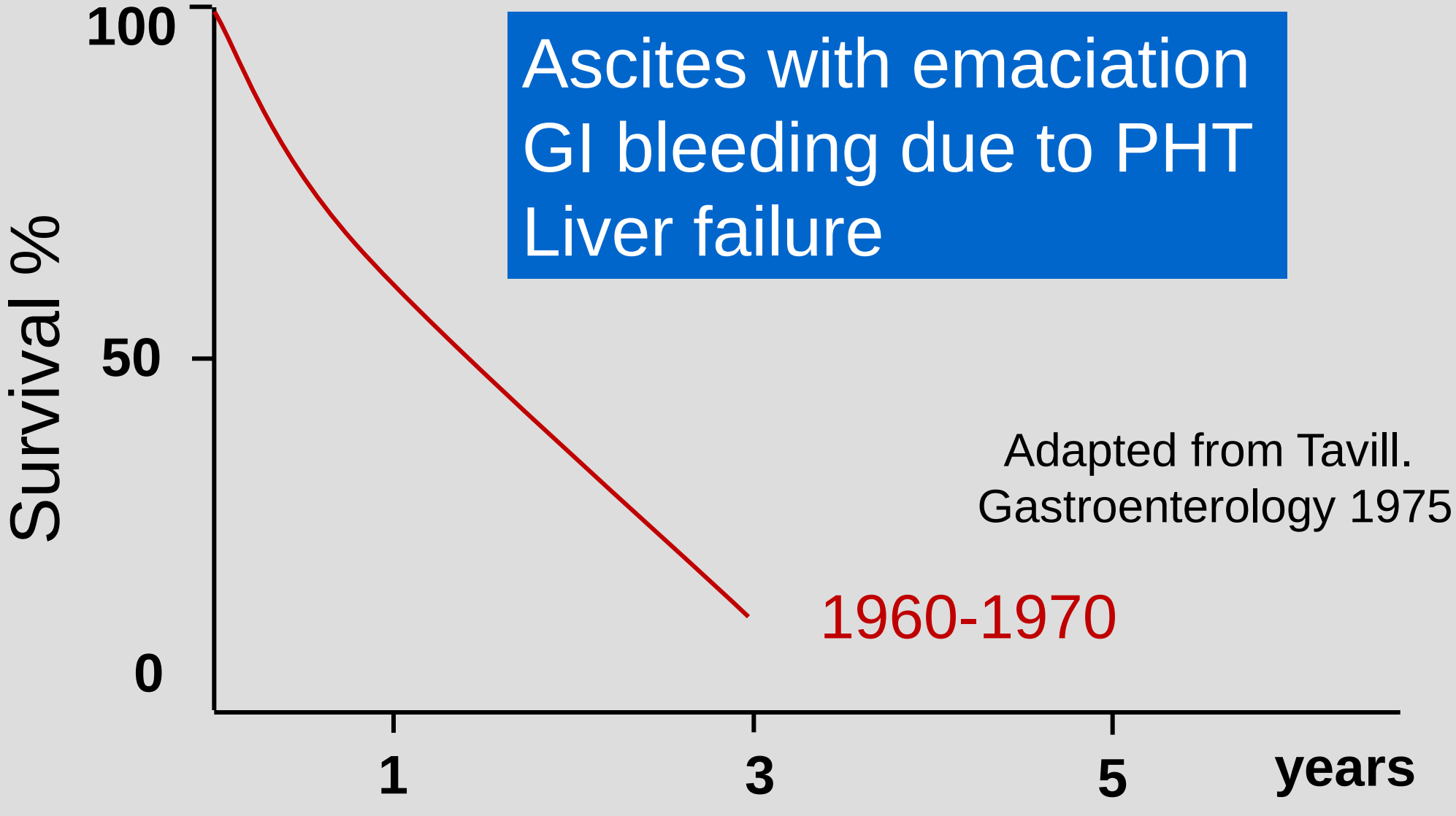
Hirschberg J Hepatol 2000. Janssen, Blood 2000. Denninger, Hepatology 2000. Primignani, Hepatology 2006. Murad, Ann Intern Med 2009. Plessier, Hepatology 2010.

Vascular Liver Diseases

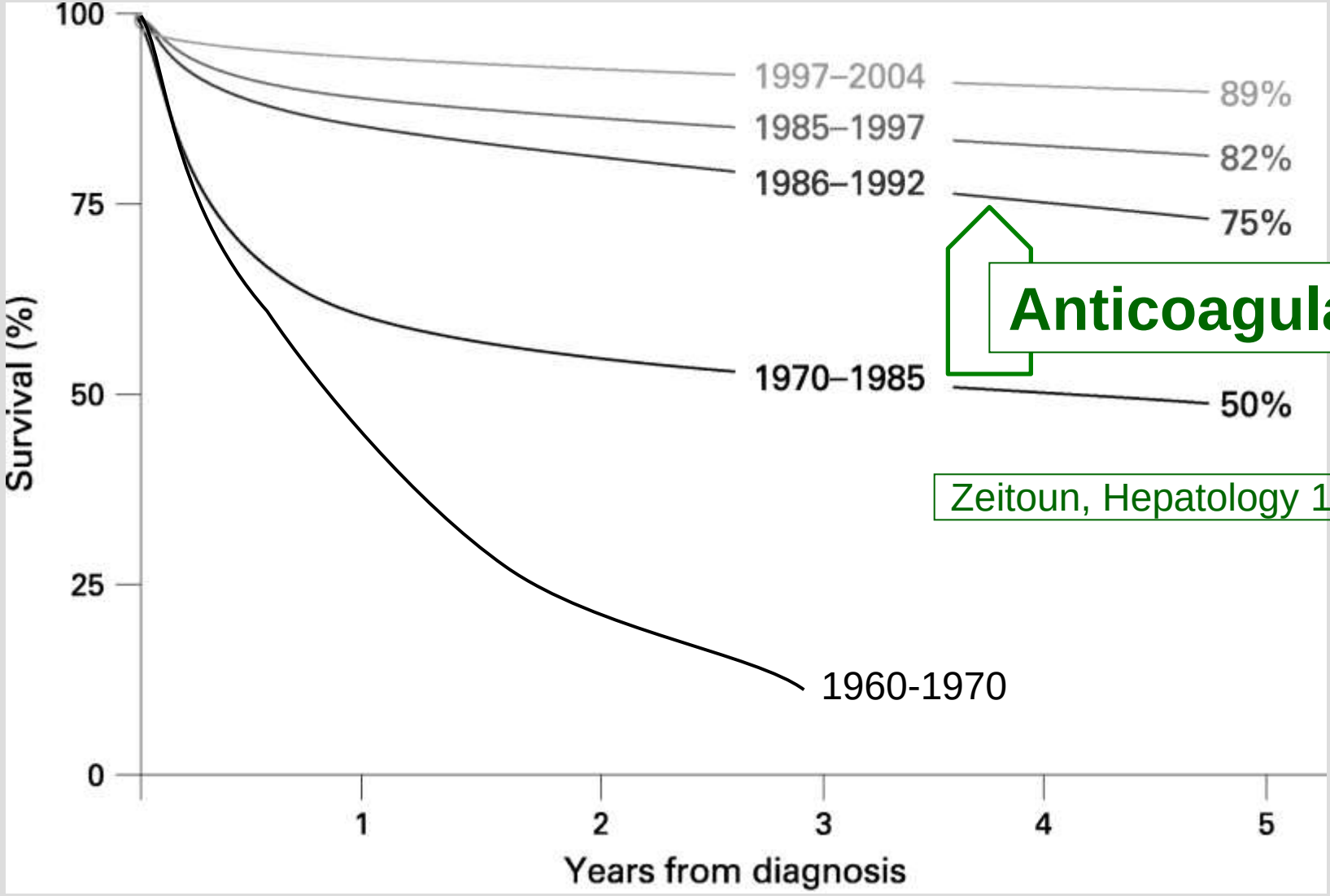
Hepatic veins thrombosis (BCS)



Primary BCS – Natural History

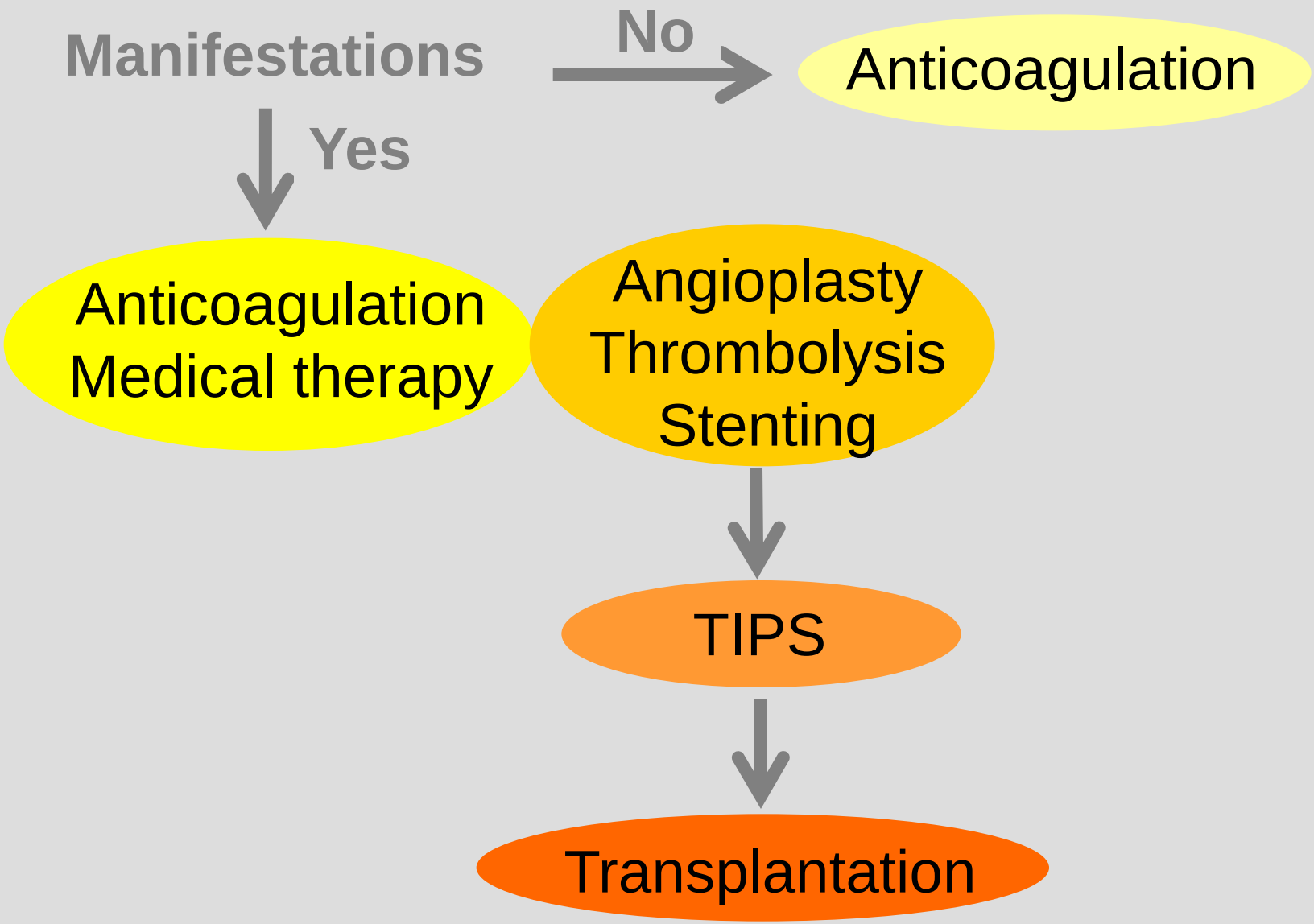


BCS : Improved Survival Over 3 Decades



Zeitoun, Hepatology 1999

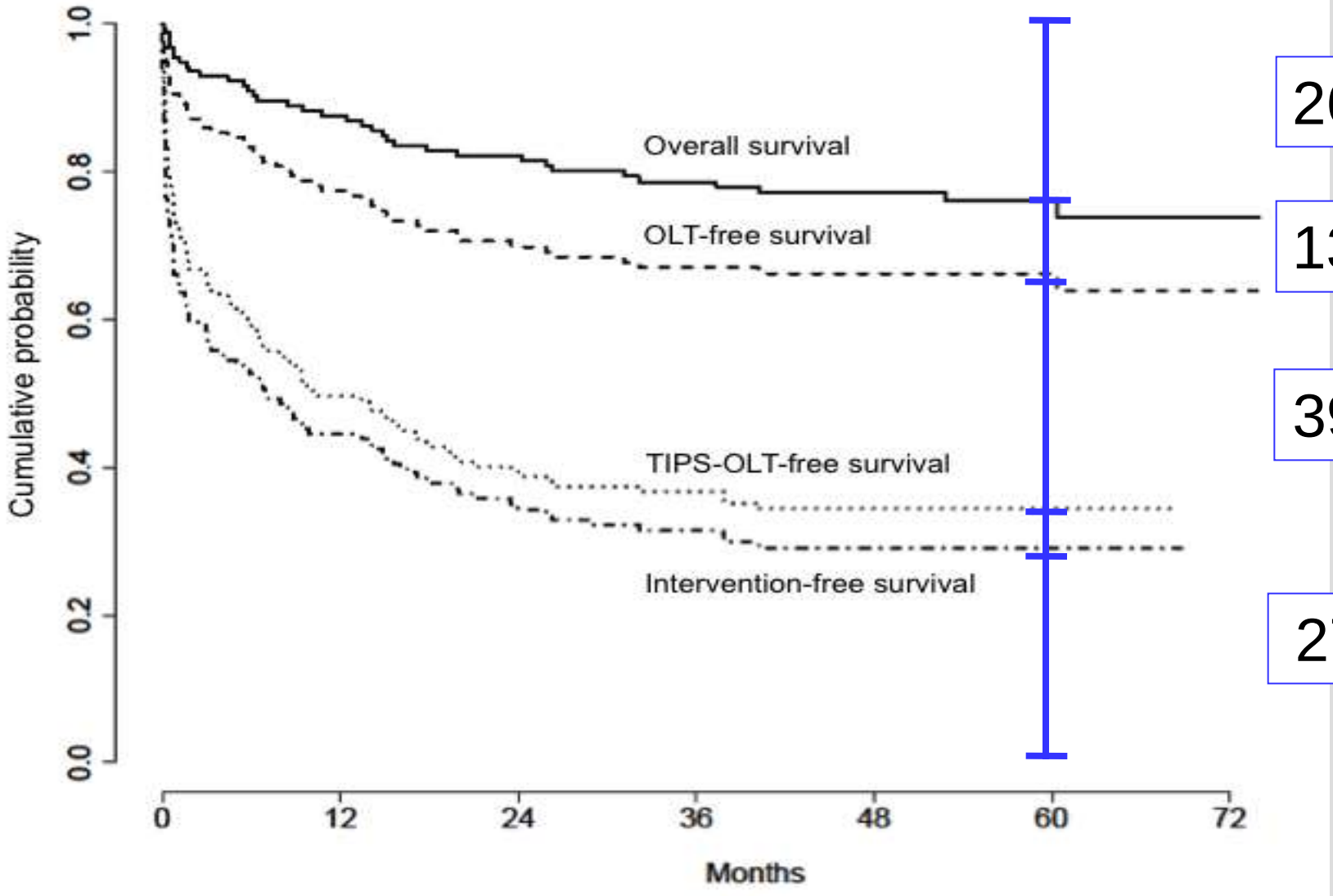
Valla, D-C Gut 2008;57:1469-1478



EASL CPG and Baveno VI Recommendations, 2015

J Hepatol 2015

BCS - Current Survival



26% Died

13% LTx

39% TIPS

27% Med. Rx.

EN-Vie cohort. Seijo. Hepatology 2013

BCS - Major Bleeding on Anticoagulation Therapy

	N		Deaths	
Permanent anticoagulation	139	89%		
Bleeding	24	17%	3	2%
Portal hypertension	14		2	
Intracranial	3		1	
Other	7		0	

Seijo. Hepatology 2013

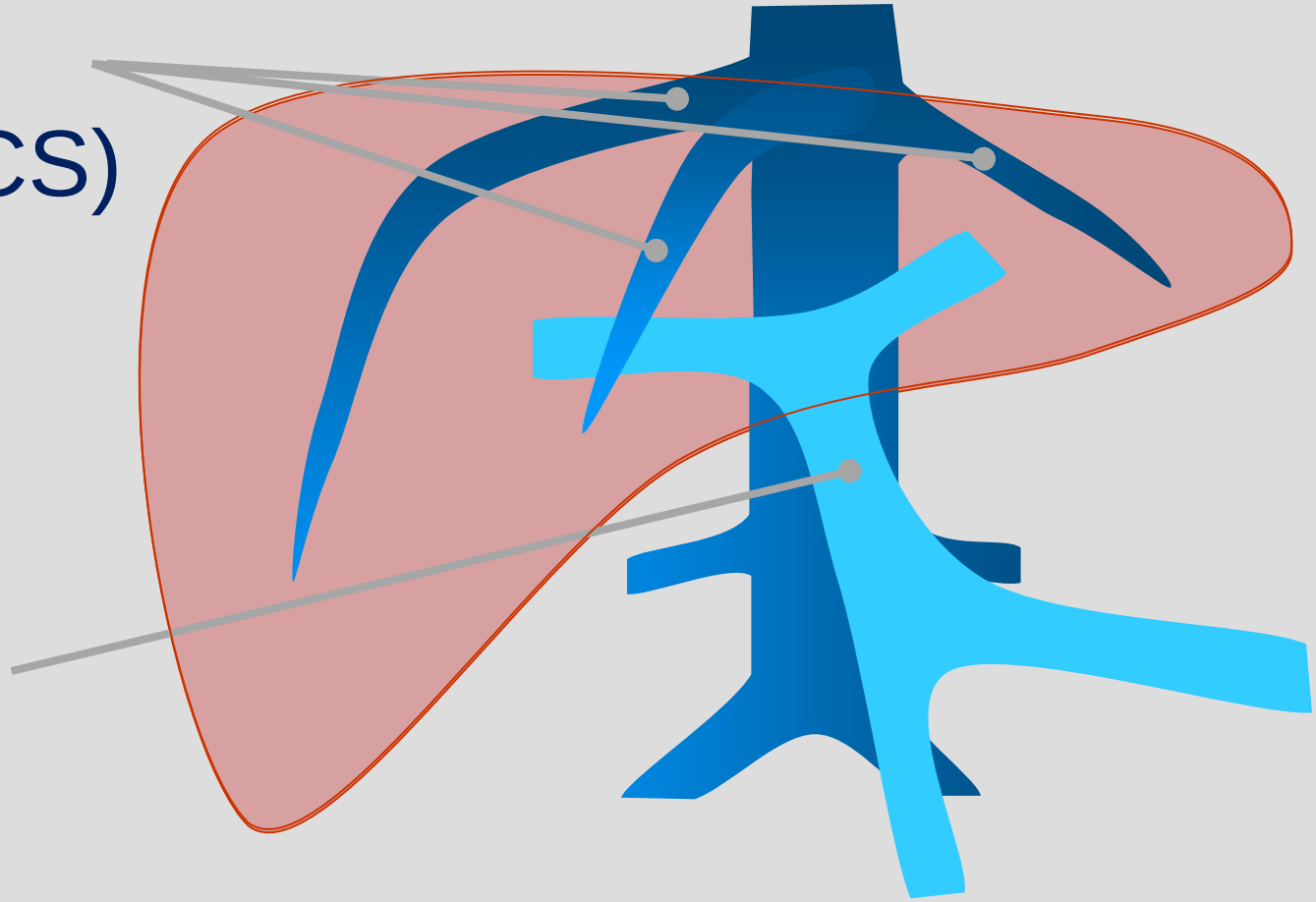
Anticoagulation for BCS

- Acceptable pathophysiological rationale.
- Circumstancial clinical evidence for a favorable benefit:risk ratio.
- Still high incidence of adverse events related to anticoagulation therapy.
- Solid evidence unlikely to appear soon due to rarity. Solid expert consensus.

Vascular Liver Diseases

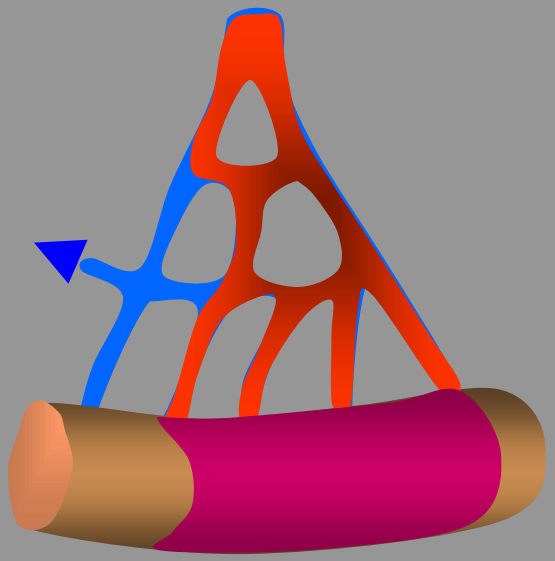
Hepatic veins thrombosis (BCS)

Portal vein thrombosis



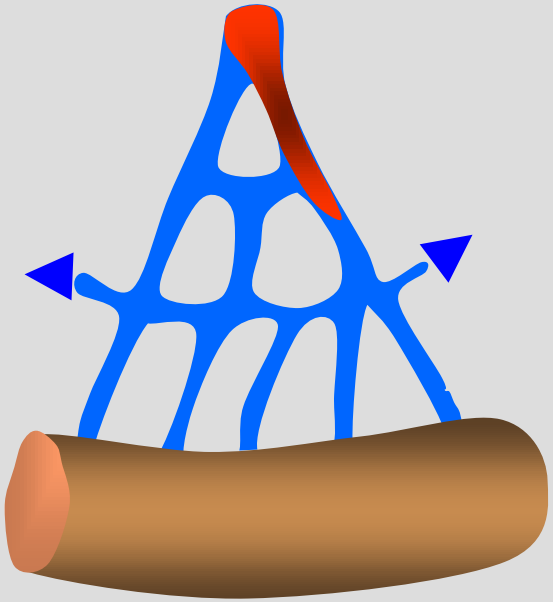
Portal Vein Thrombosis

Intestinal Ischemia



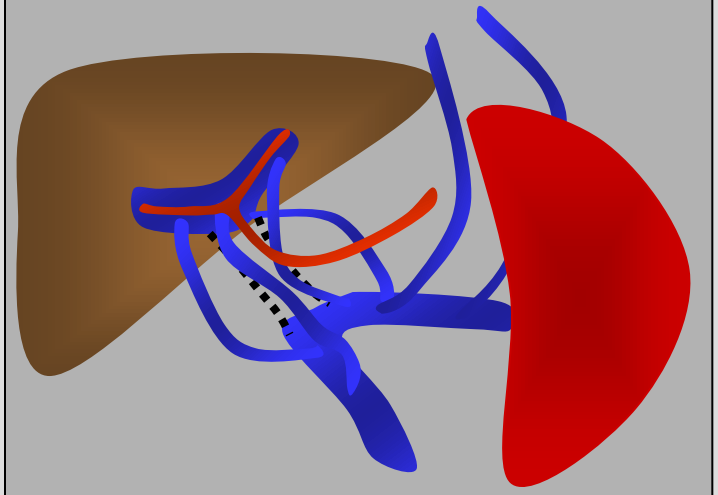
Bleeding
Ascites
MOF

Uncomplicated Acute PVT



Abdominal Pain
SIRS

Chronic PVT



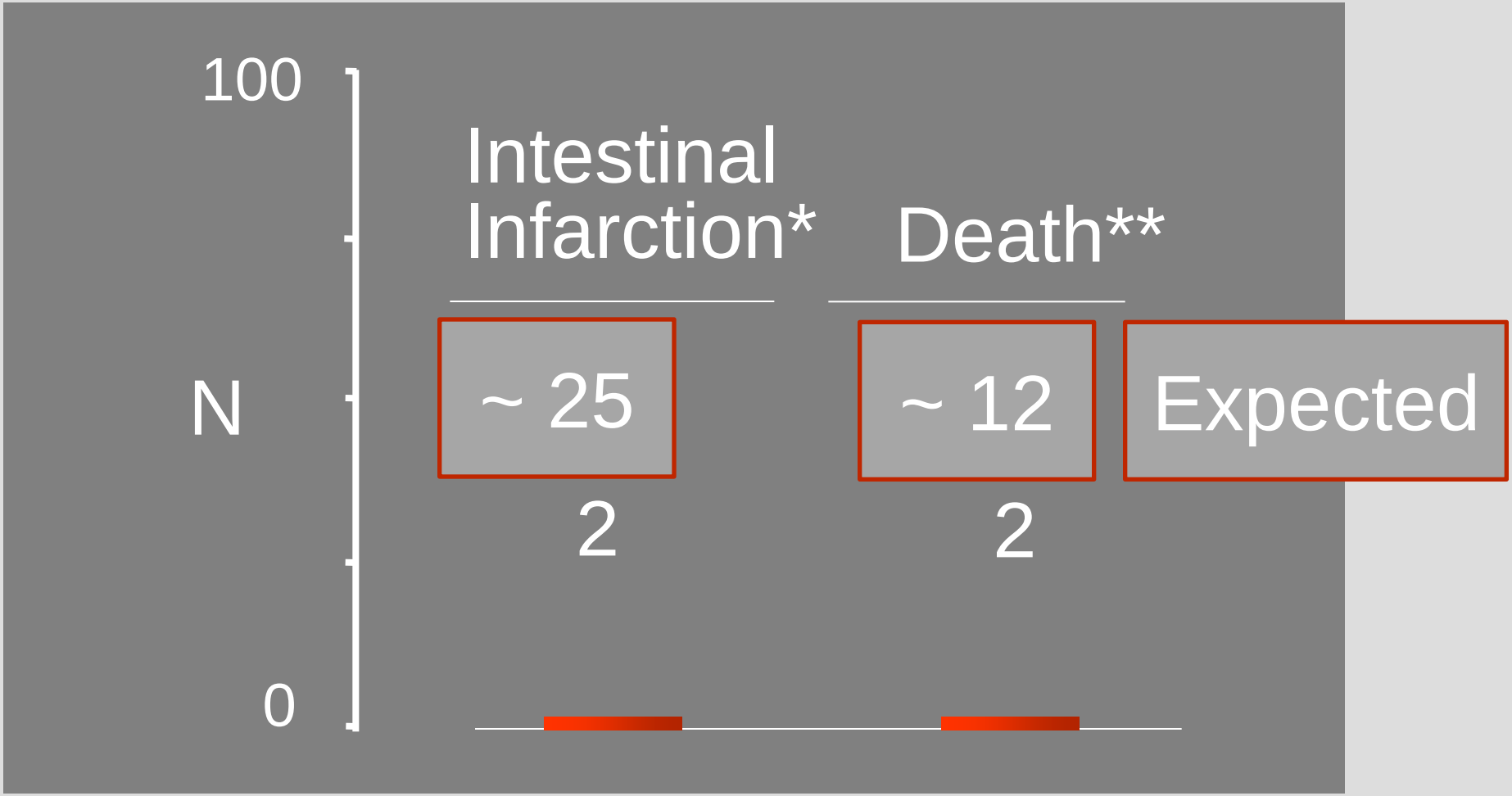
Bleeding
Encephalopathy
Cholangiopathy

Non-cirrhotic, non-malignant PVT Treatment

Preventing potentially lethal complications

- Intestinal infarction
- Recurrent thrombosis
- Portal hypertension

Recent PVT. Anticoagulation in 95 Patients



*Limited intestinal resection. Both survived. **Malignancy 1. Sepsis 1

Plessier. Hepatology 2010. Hmoud, J Clin Exp Hepatol 2014

Non-cirrhotic, non-malignant PVT Treatment

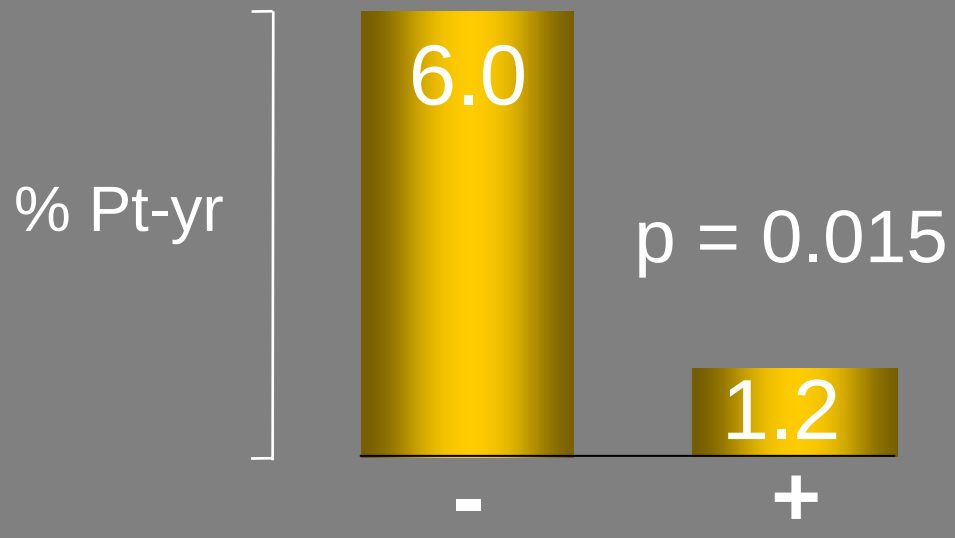
Preventing potentially lethal complications

- Intestinal infarction
- Recurrent thrombosis
- Portal hypertension

PVT – Anticoagulation and thrombosis

1

New thrombosis



Condat, Gastroenterology 2001

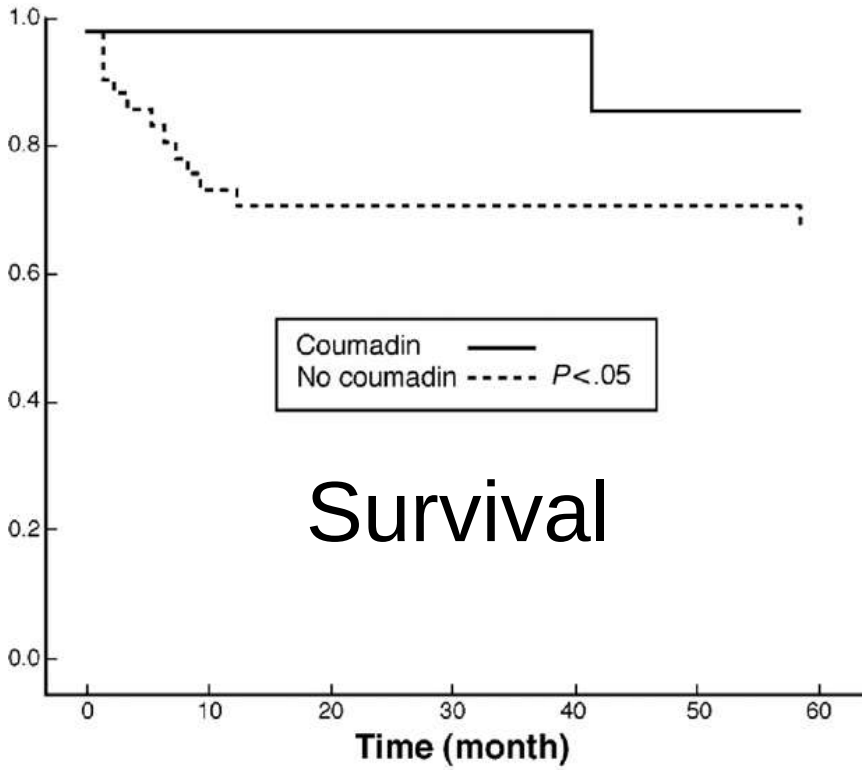
2

New thrombosis

HR 0.2, p = 0.1

Spaander, JTH 2013

3



Survival

Orr, CGH 2007

Non-cirrhotic, non-malignant PVT Treatment

Preventing potentially lethal complications

- Intestinal infarction
- Recurrent thrombosis
- Portal hypertension

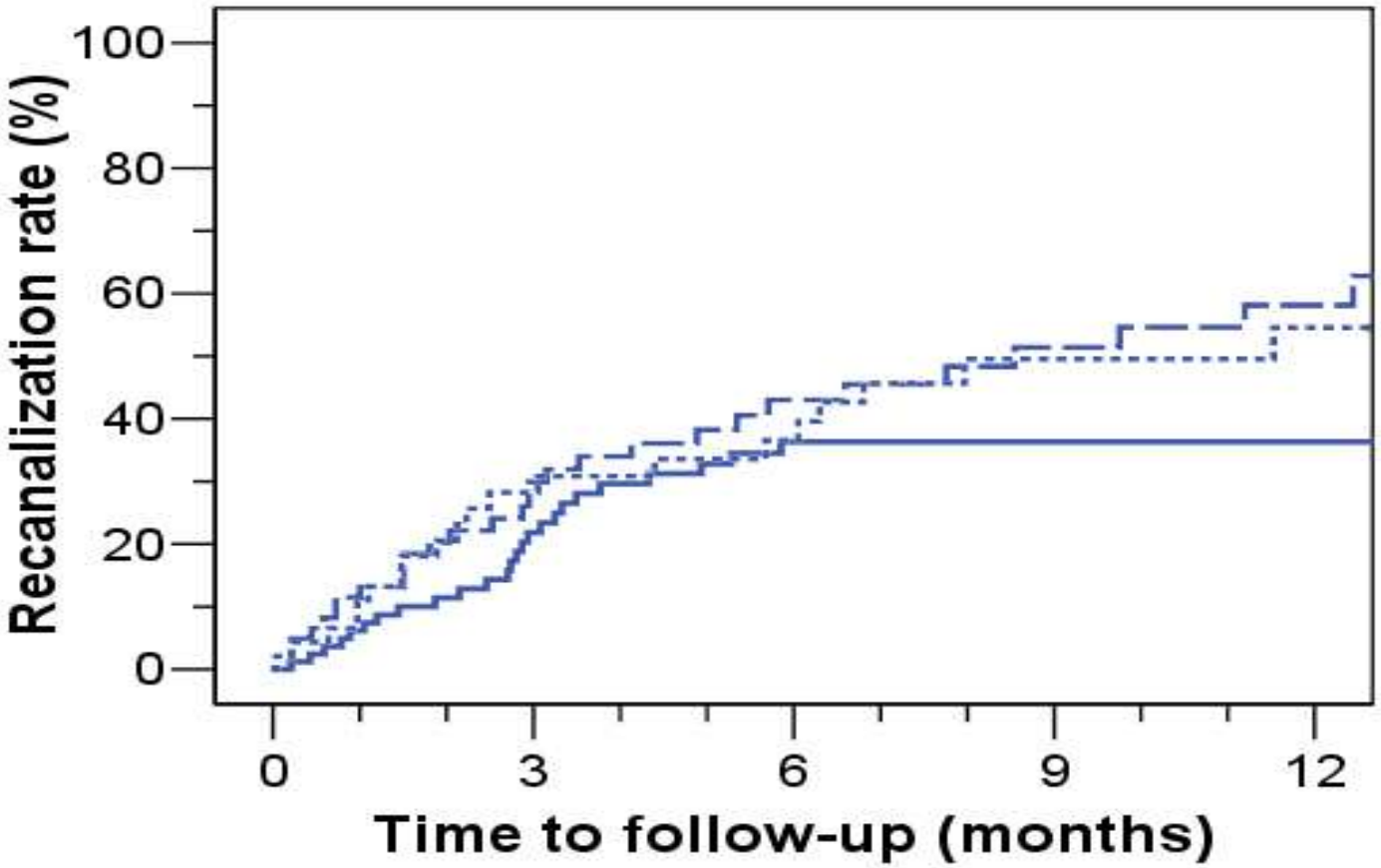
Anticoagulation for recent (acute) PVT

Anticoagulation		No anticoagulation
Complete recanalization	Partial recanalization	Recanalization
38.3%	14.0%	<< 17%

Hall. World J Surg 2011

Recent PVT: EN-Vie Cohort

EN-Vie Cohort: 95 anticoagulated patients

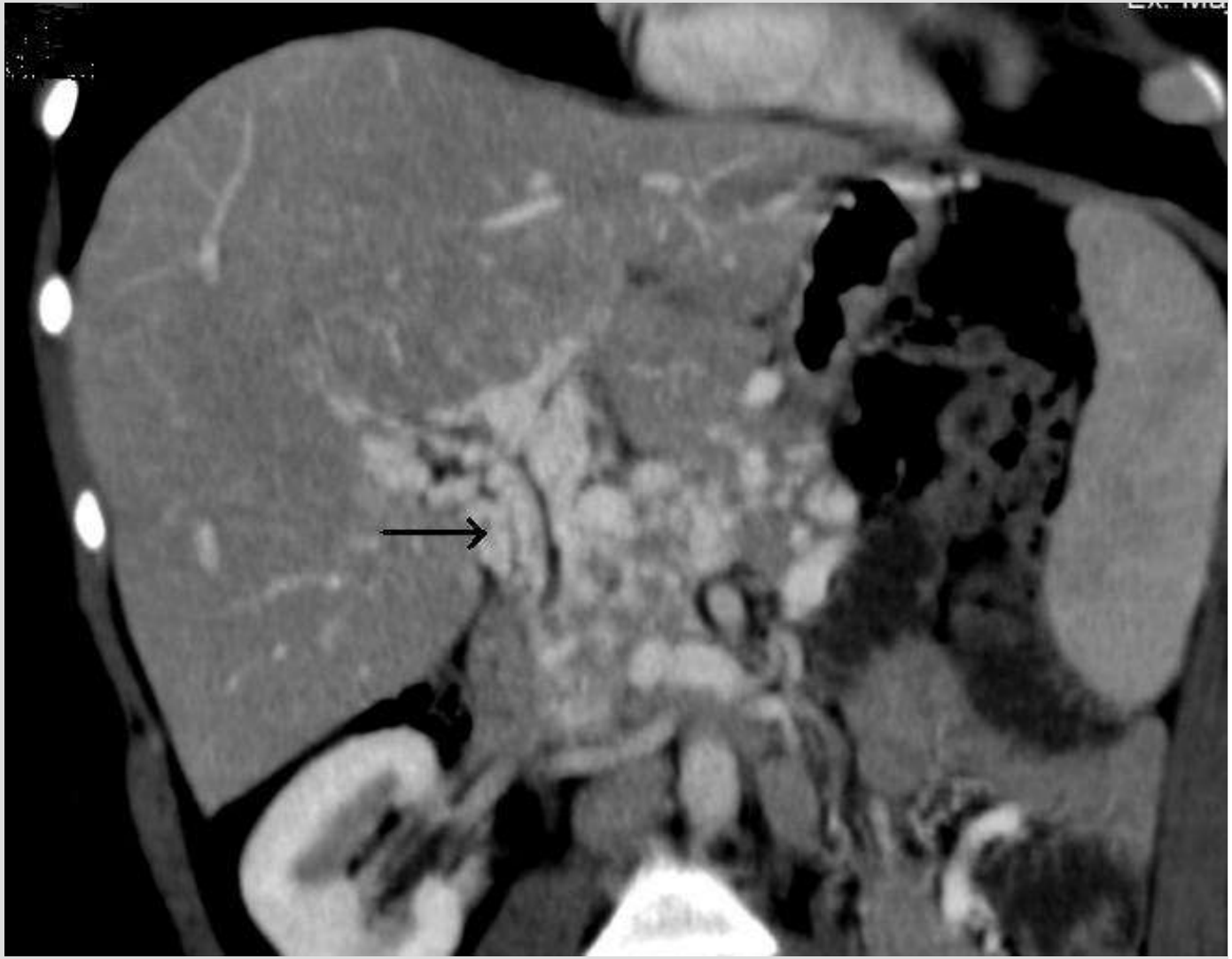


Sup. mesenteric
Splenic
Portal

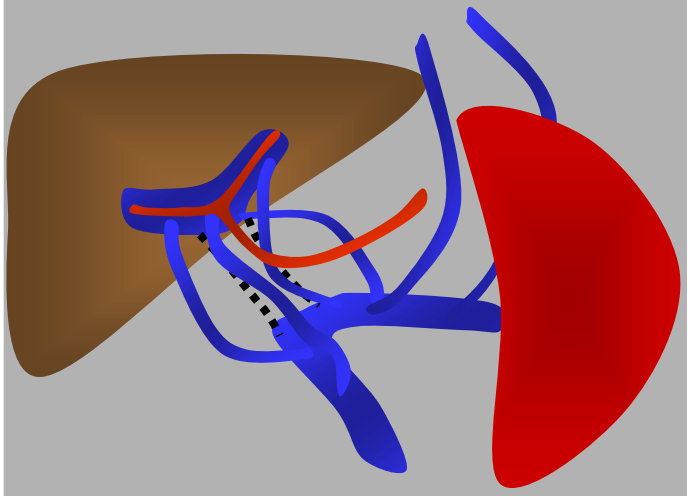
Plessier. Hepatology 2011.

Hall. Hepatogastroenterol 2013

Portal Vein Thrombosis



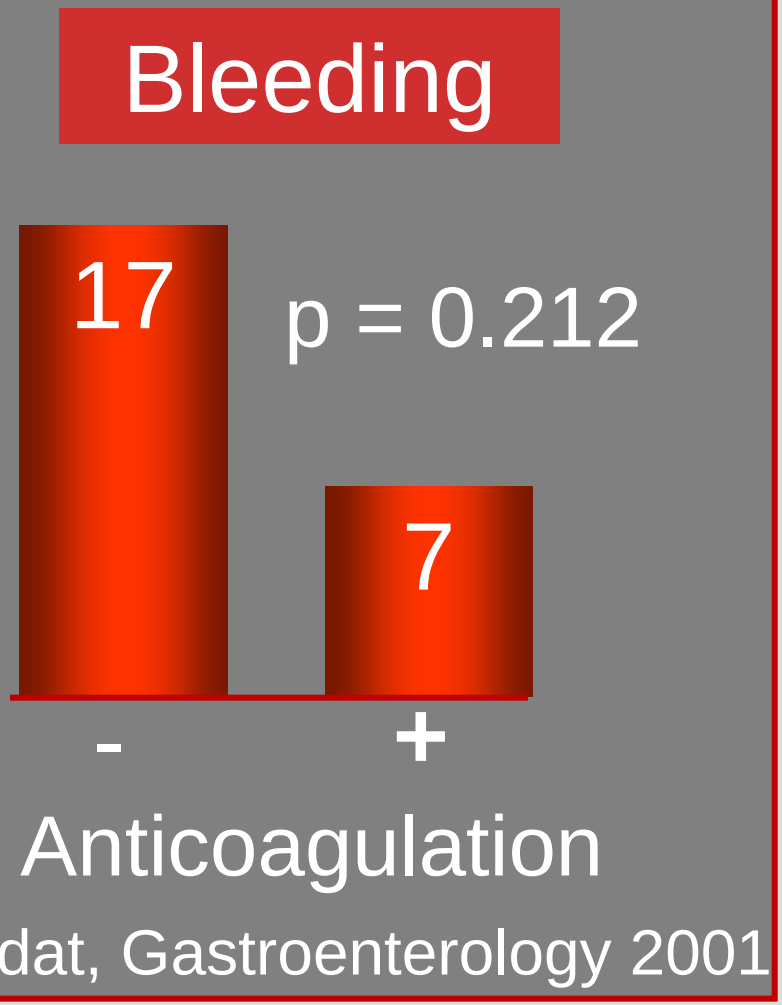
Chronic PVT



Bleeding
Encephalopathy
Cholangiopahy

PVT – Anticoagulation and bleeding

1



Condat, Gastroenterology 2001

2

Bleeding	HR	*P*
GI bleed*	2.1	<.01
Ascites*	2.0	=.01
Anticoagulant	2.1	<.01

* At baseline

Spaander, JTH 2013

PVT - Severity of Bleeding

No impact of anticoagulation therapy on

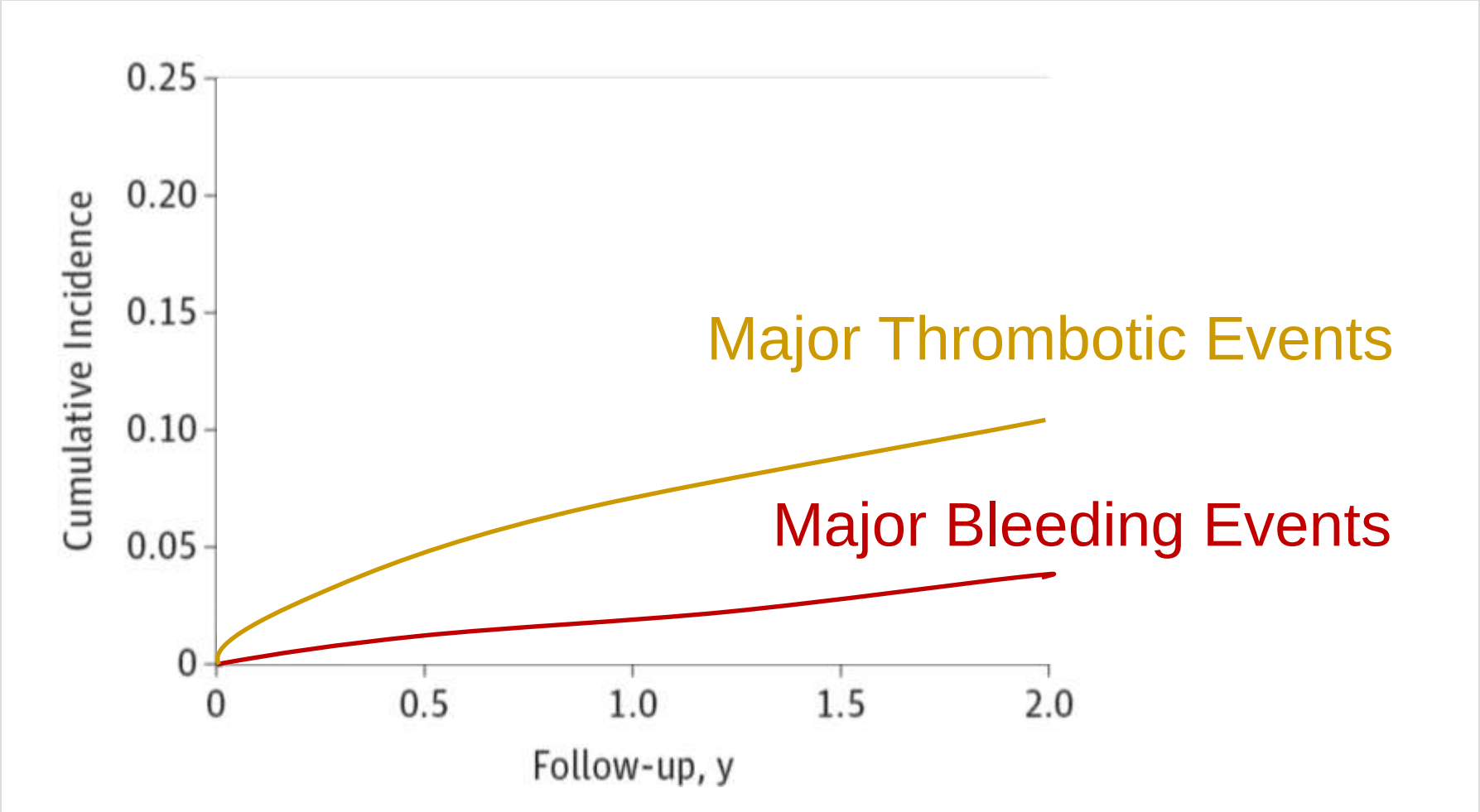
Hemoglobin (g/dL)

Length of stay (days)

Transfusion (N units)

Condat, Gastroenterology 2001. Spaander, JTH 2013. Christol, ILC 2012

Noncirrhotic Splanchnic Vein Thrombosis



From Ageno, JAMA Intern Med 2015

Anticoagulation for PVT without cirrhosis

- Allows recanalization in 40% of patients seen at the acute stage.
- Prevents extension/recurrence of thrombosis.
- May improve long-term outcome in patients with extensive thrombosis.
- Does not appear to increase the severity of PHT-related bleeding.
- Has unclear impact on the risk of bleeding.

PVT : Unresolved treatment issues

→ Permanent anticoagulation therapy for all?

→ Which criteria for a precision medicine ?

- Degree of venous involvement
- Causes and risk factors
- Personal or familial history

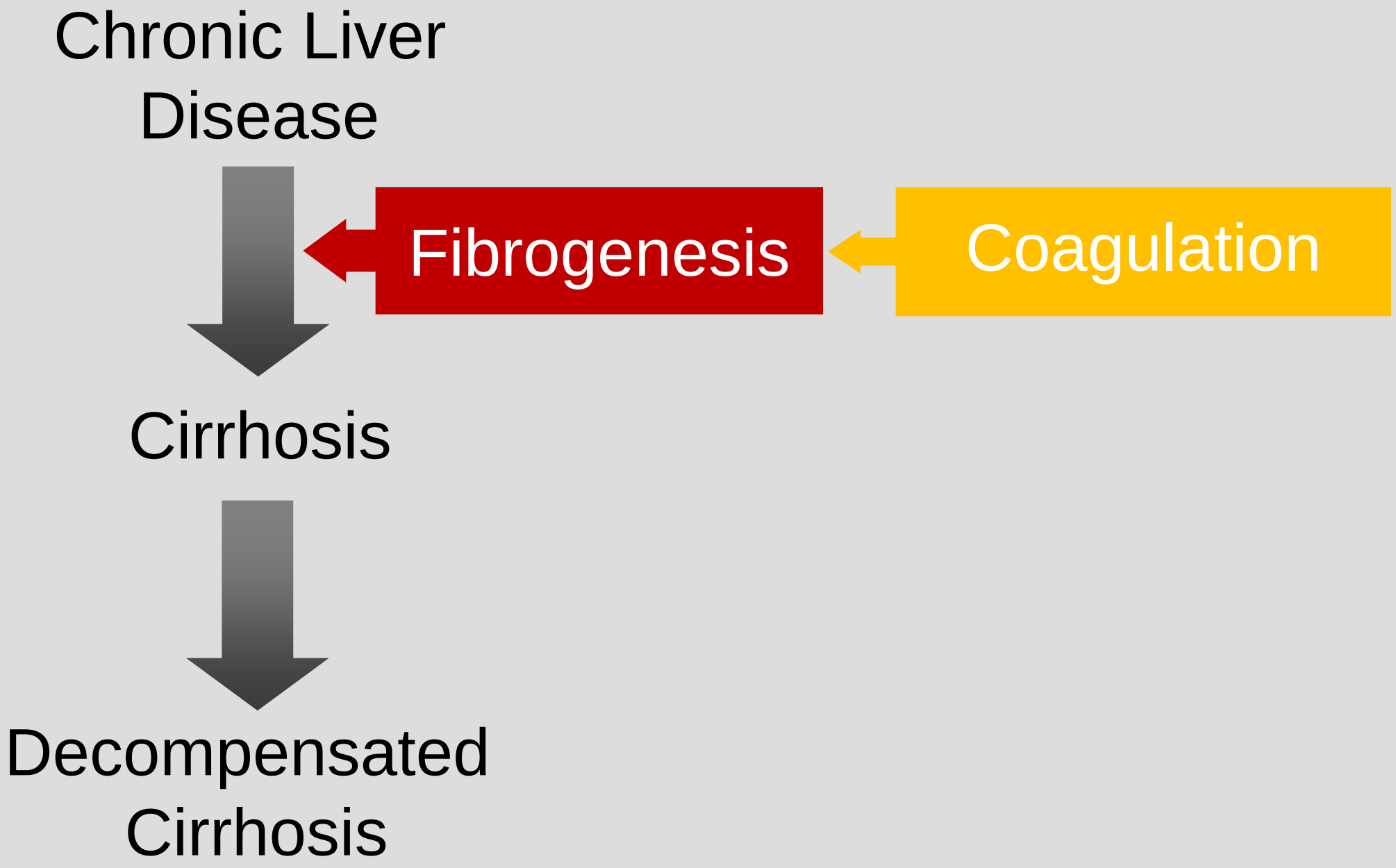
RIPORT
A randomized control trial in patients without highly prothrombotic conditions or previous intestinal ischemia

Anticoagulation therapy for liver disease

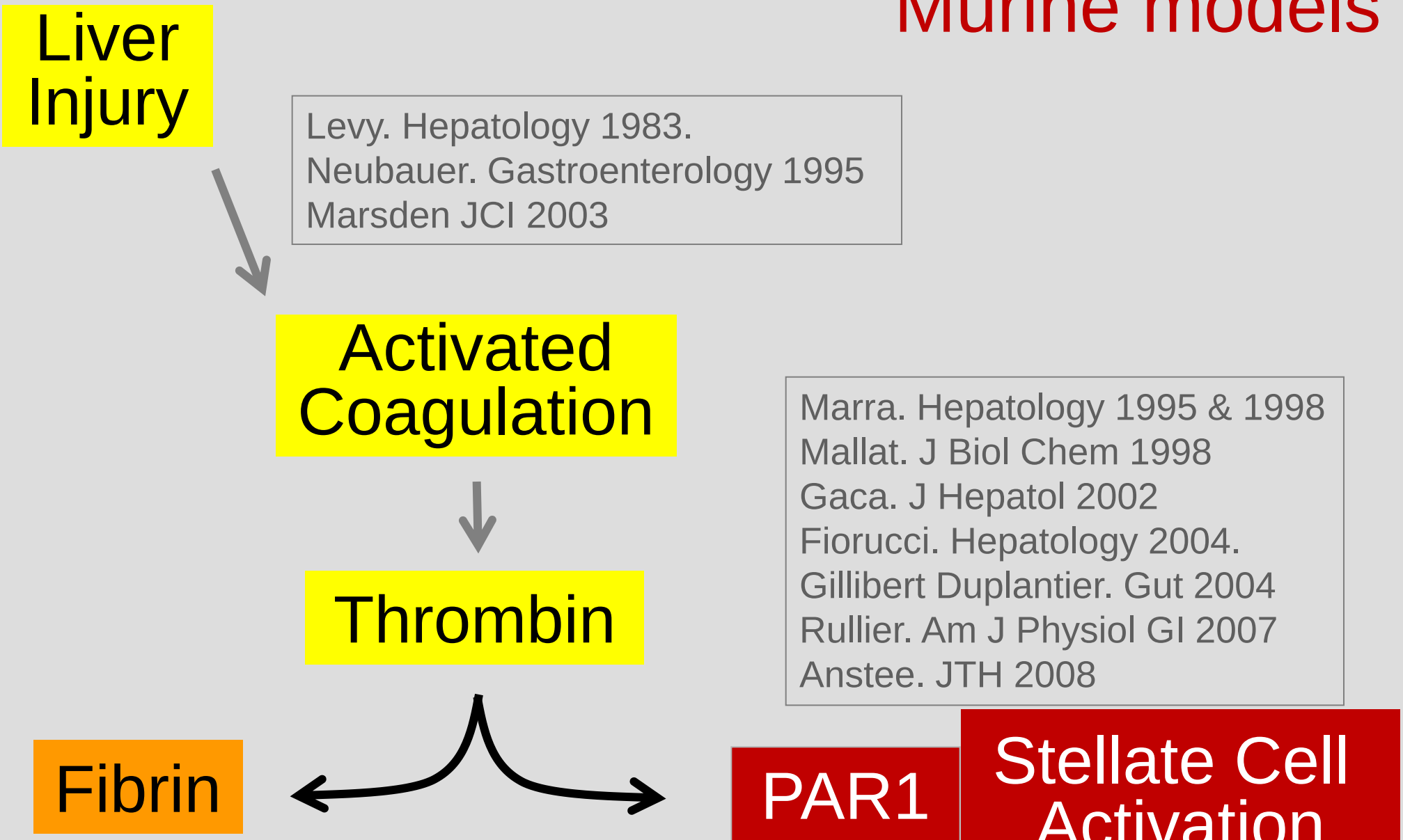
- Vascular diseases of the liver
- Parenchymal diseases of the liver

Parenchymal Liver Disease

- Coagulation and hepatic fibrogenesis
- Coagulation anomalies in liver disease
- Thrombosis and cirrhosis progression

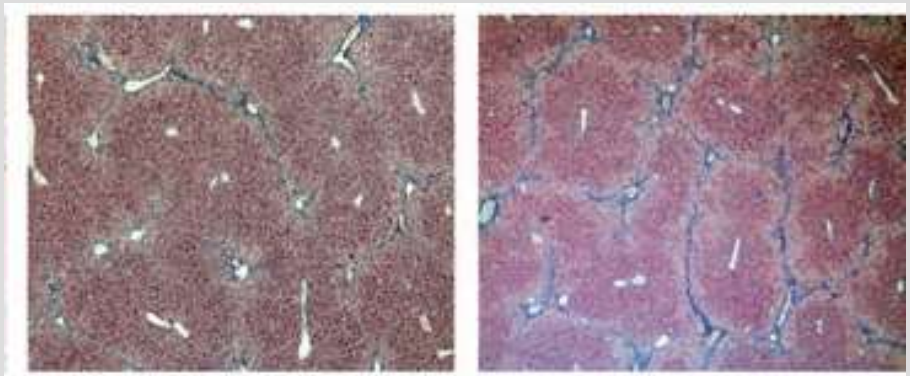
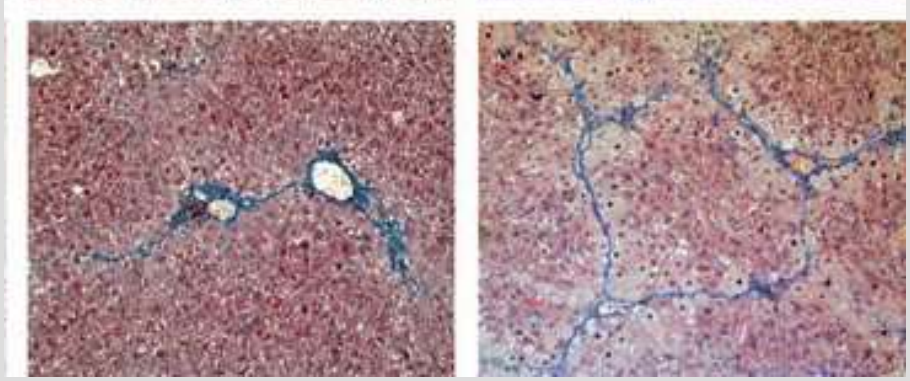

Chronic Liver Disease
Fibrogenesis
Coagulation
Cirrhosis
Decompensated Cirrhosis

Murine models

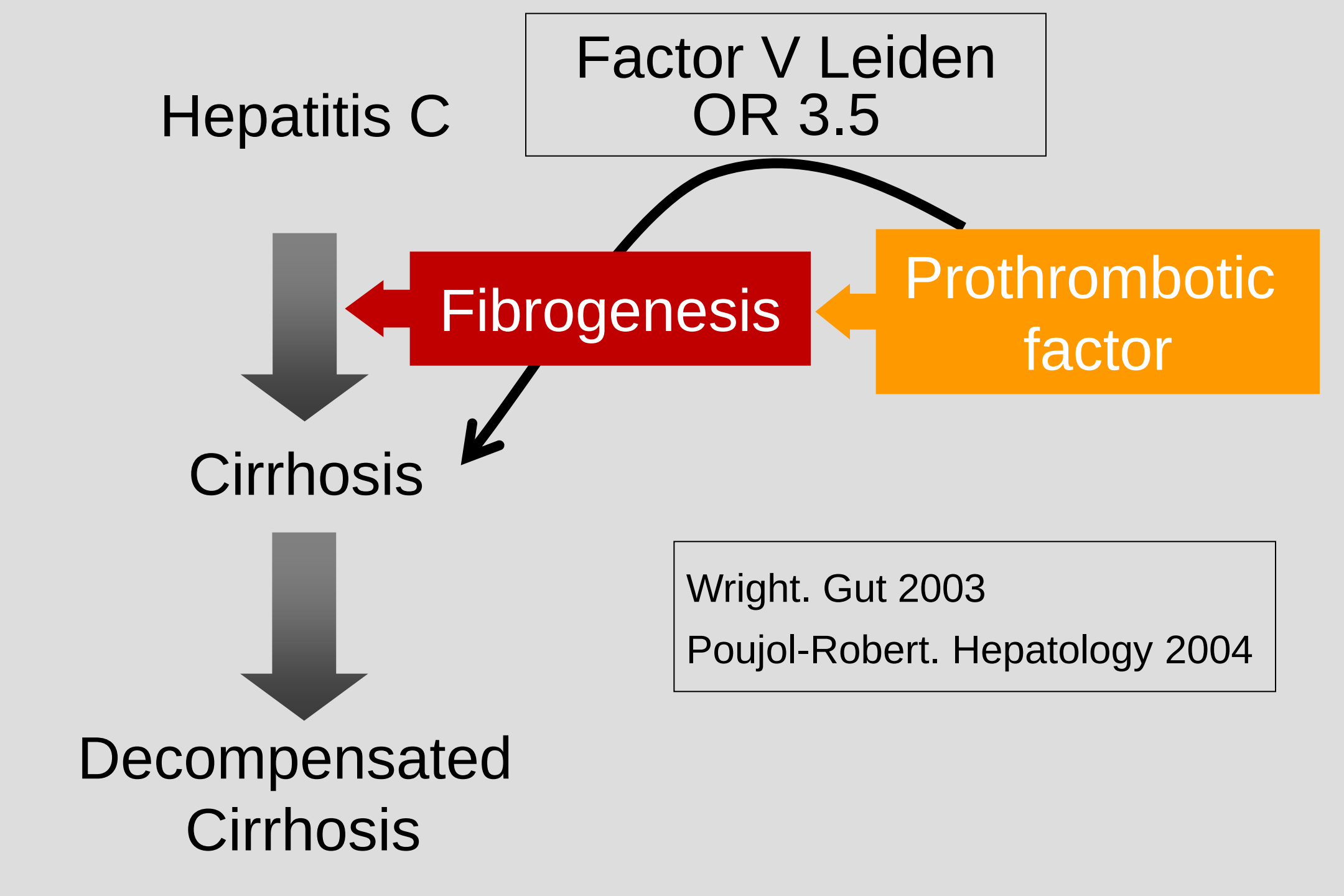


Anstee. Clin Res Hepatol Gastroenterol 2011

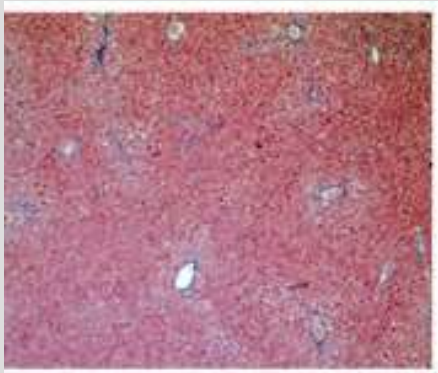
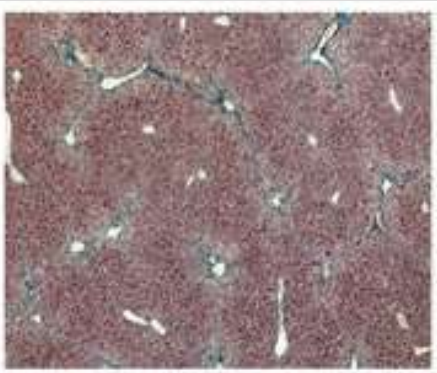
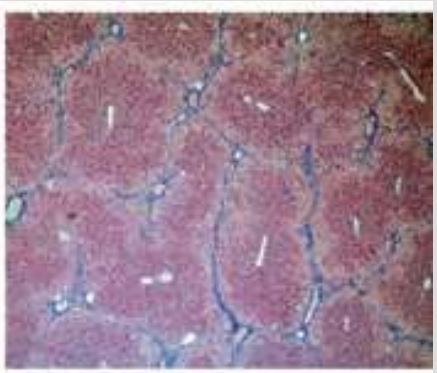
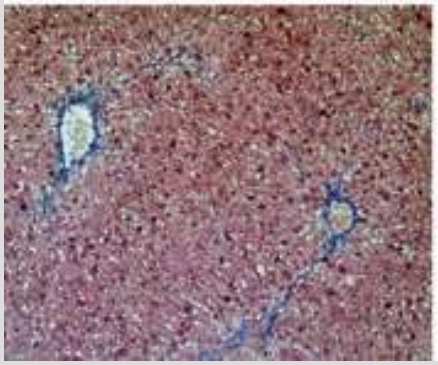
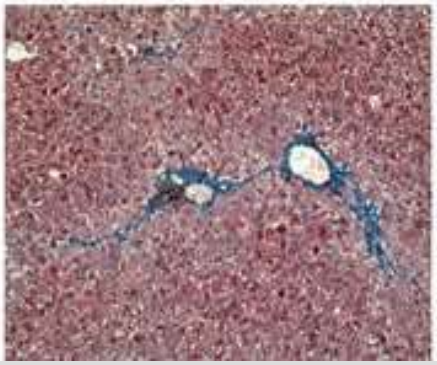
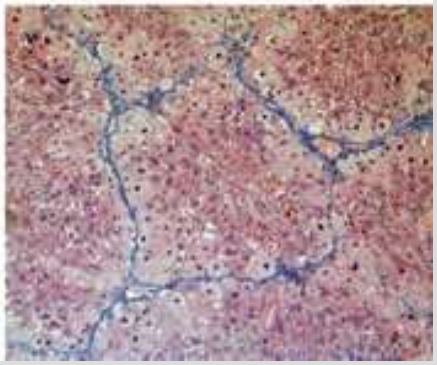
CCl4 Murine Model

	C57BL/6 Control	C57BL/6 FVL Mutant
Four weeks Low power		
Four weeks High power		

Anstee. J Thromb Haemost 2008

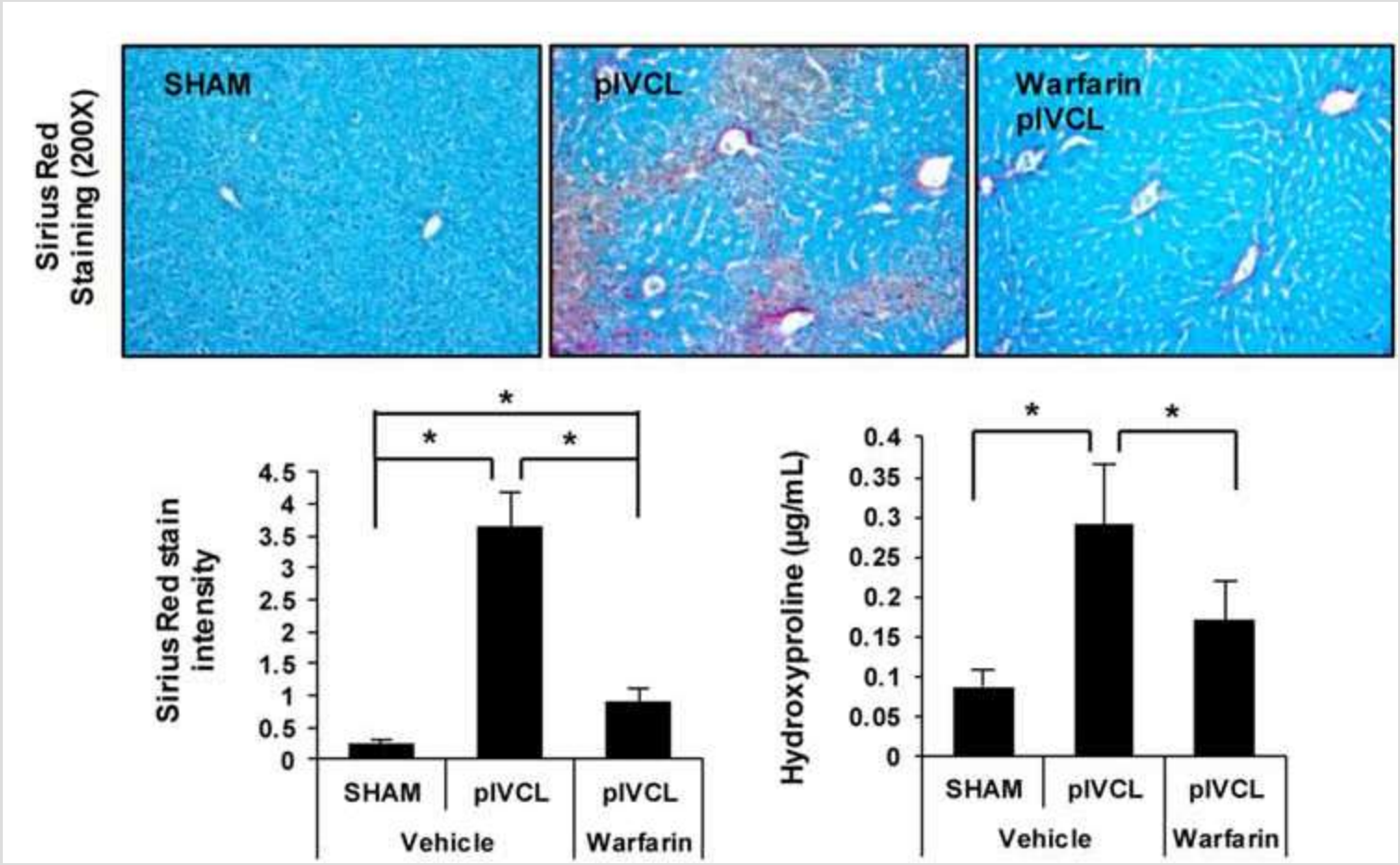

Hepatitis C
Factor V Leiden
OR 3.5
Fibrogenesis
Prothrombotic factor
Cirrhosis
Decompensated Cirrhosis
Wright. Gut 2003
Poujol-Robert. Hepatology 2004

CCl4 Murine Model

	C57BL/6 Warfarin	C57BL/6 Control	C57BL/6 FVL Mutant
Four weeks Low power			
Four weeks High power			

Anstee. J Thromb Haemost 2008

Murine model of congestive hepatopathy



Simonetto, Hepatology 2015

Parenchymal Liver Disease

- Coagulation and fibrogenesis
- Coagulation anomalies in liver disease
- Thrombosis and cirrhosis progression

Coagulation in Cirrhosis

- Platelet counts decreased
- Factor II, VII, IX and X levels decreased
- Tissue factor levels increased
- Coagulation factor VIII increased
- Von Willebrandt factor increased
- Clearance of activated factors decreased
- Coagulation inhibitors decreased

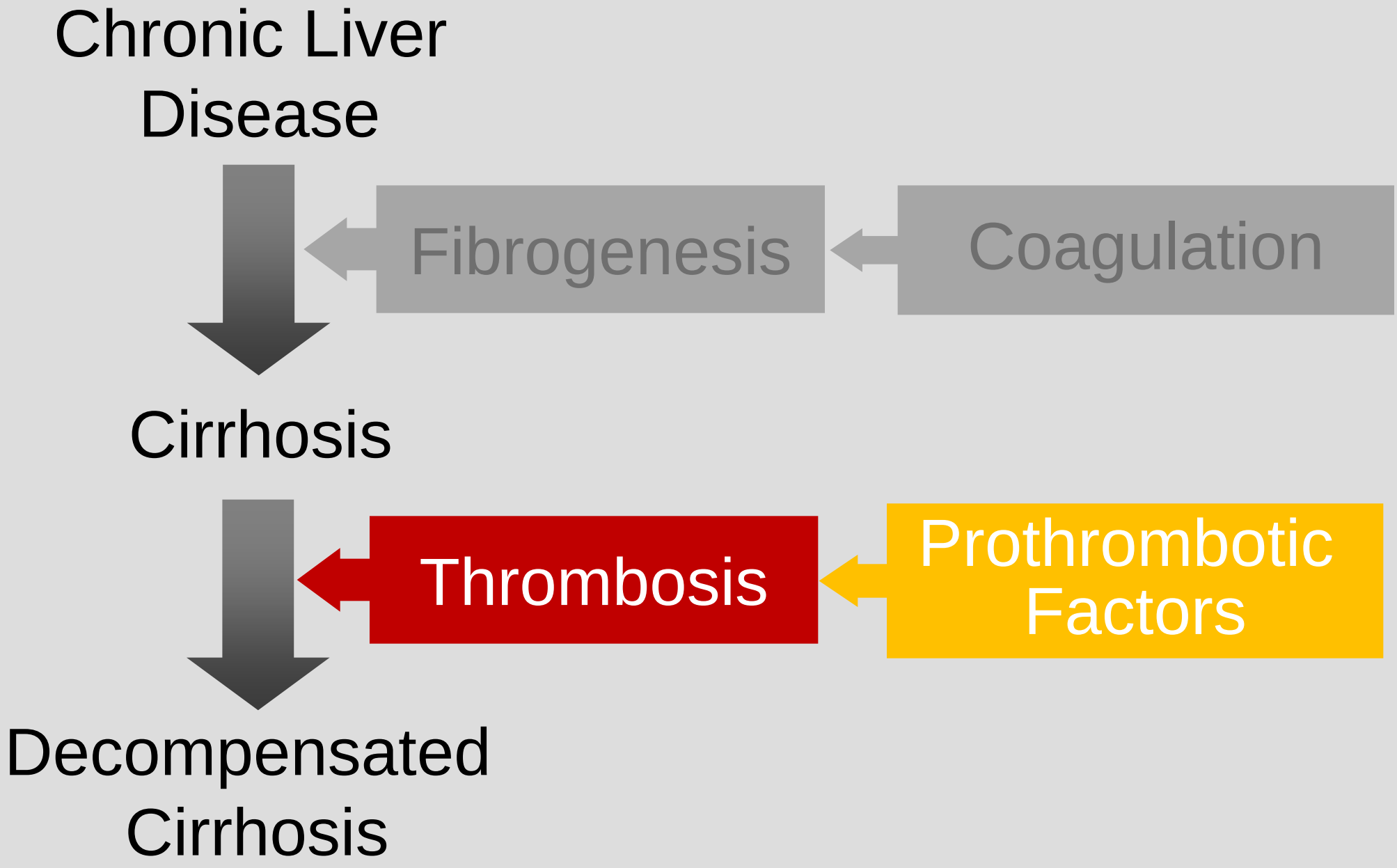
Cirrhosis as a Prothrombotic State ?

- Maintained thrombin generation potential in plasma in vitro
- In vitro resistance to the anticoagulant action of thrombomodulin (↑ factor VIII, ↓ protein C)
- TAT, D-dimers and TF microparticles increased
- Moderate increase in the risk of DVT

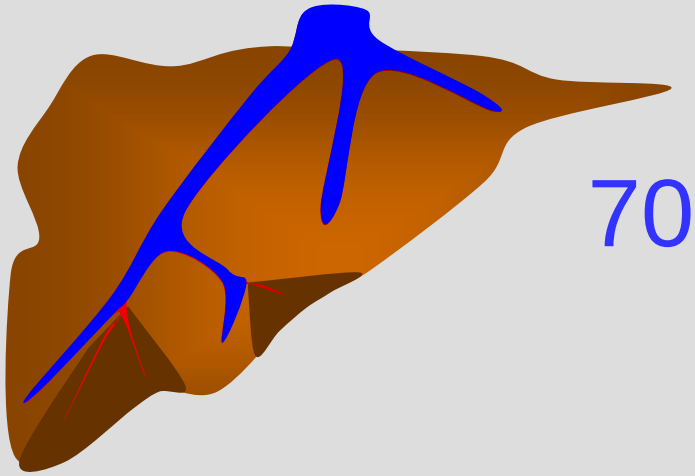
Tripodi, JTH 2011. Rautou J Hepatol 2015

Parenchymal Liver Disease

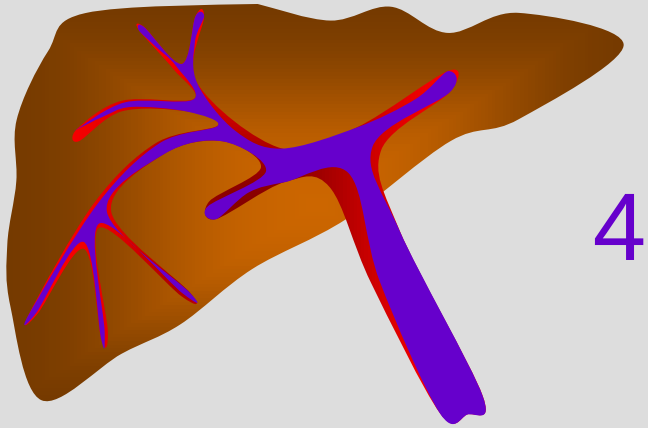
- Coagulation and fibrogenesis
- Coagulation anomalies in liver disease
- Thrombosis and cirrhosis progression


Chronic Liver Disease
Fibrogenesis
Coagulation
Cirrhosis
Thrombosis
Prothrombotic Factors
Decompensated Cirrhosis

Explanted Cirrhotic Livers



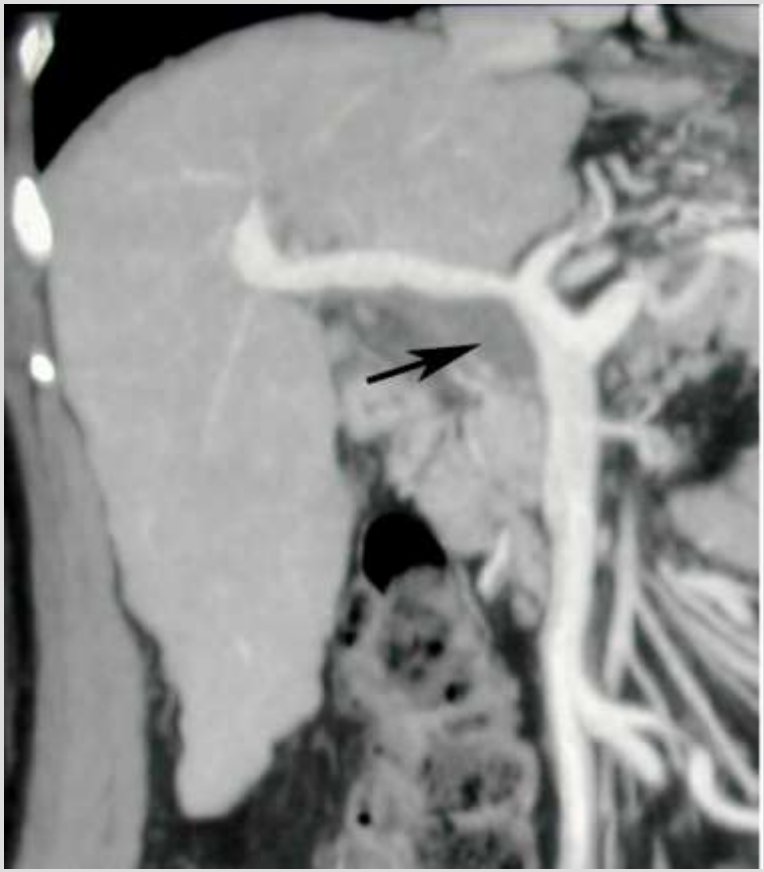
70% intrahepatic HV thrombosed



40 % intrahepatic PV thrombosed

Wanless, Hepatology 1995. Shimamatsu, Hepatology 1997

Extrahepatic Portal Vein Thrombosis in Cirrhosis

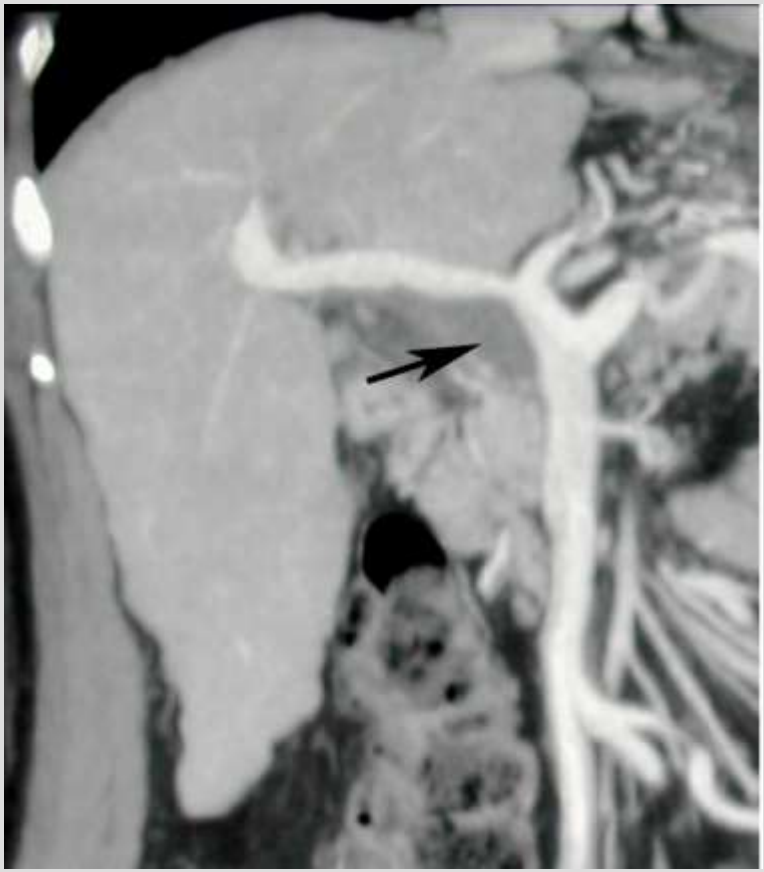


Partial PVT	Occlusive PVT
10% (5-16)	3% (1-4)

Spontaneous regression
40% (31-71)

Nery, Hepatology 2014. Maruyama, Am J Gastro 2013. Luca, Radiology 2012

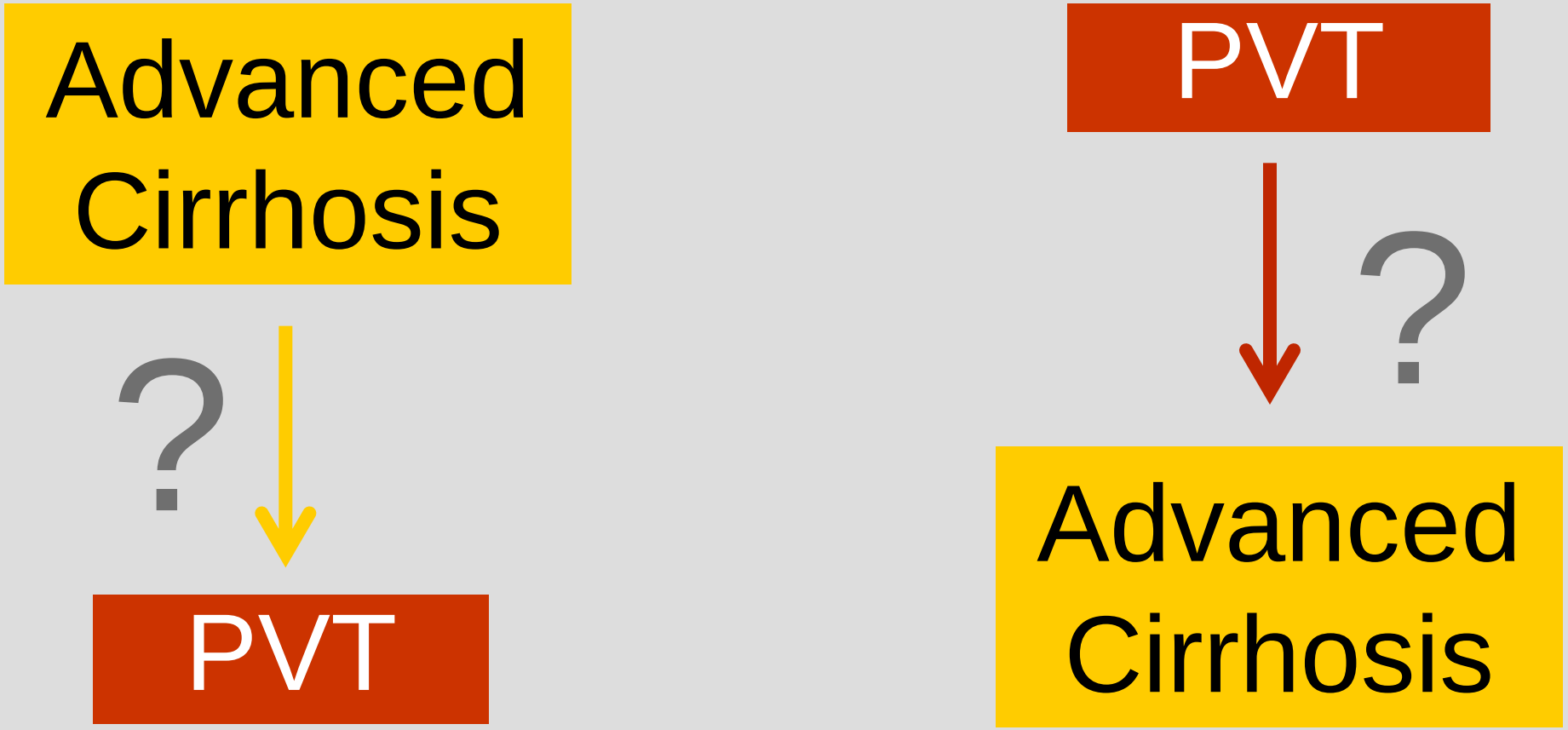
Extrahepatic Portal Vein Thrombosis in Cirrhosis



Associated with severity in cross-sectional studies

Inconsistent impact on mortality in follow-up studies

Nery, Hepatology 2014. Maruyama, Am J Gastro 2013. Luca, Radiology 2012
Englesbe. Liver Transplant 2010. SRTR 22,291 listed candidates. Occlusive PVT 4.02%


Advanced Cirrhosis
?
PVT
PVT
?
Advanced Cirrhosis

THROMBOCIR Study

- 1243 patients, Child A-B, median f-up 47 mo
- Baseline features, F.V & F.II Leiden
- Portal vein thrombosis, portal flow velocity, liver disease progression

Progression	PVT	Both
N = 355	N = 118	N = 52

US-Doppler screening for HCC q 3 or 6 mo. Trinchet, Hepatology 2011
Nery, Hepatology 2014

PVT and severity of cirrhosis

- Time dependent analysis for PVT

  → Severity of liver disease at baseline

  Not : progression of liver disease

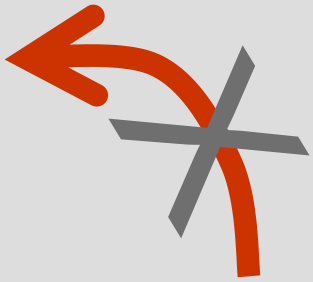
- Time dependent analysis for progression

  → Age, severity of liver disease at baseline

  Not : PVT

Nery, Hepatology 2014

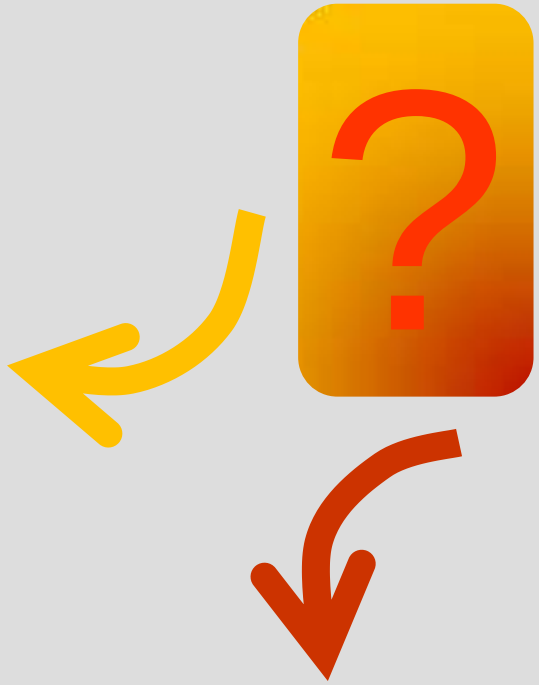
Advanced Cirrhosis



Portal vein Thrombosis

Nery. Hepatology 2014

Advanced Cirrhosis



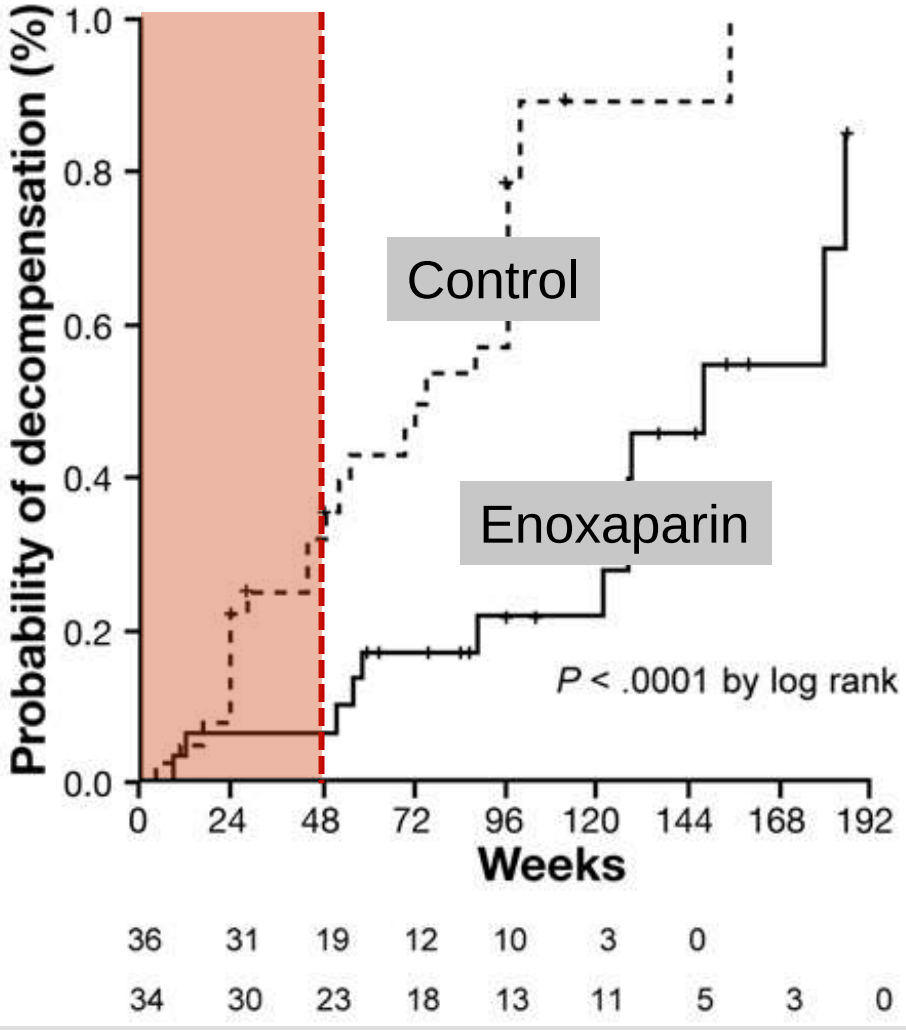
Portal vein Thrombosis

PVT Prophylaxis – Cirrhosis (CTP B7-C10)

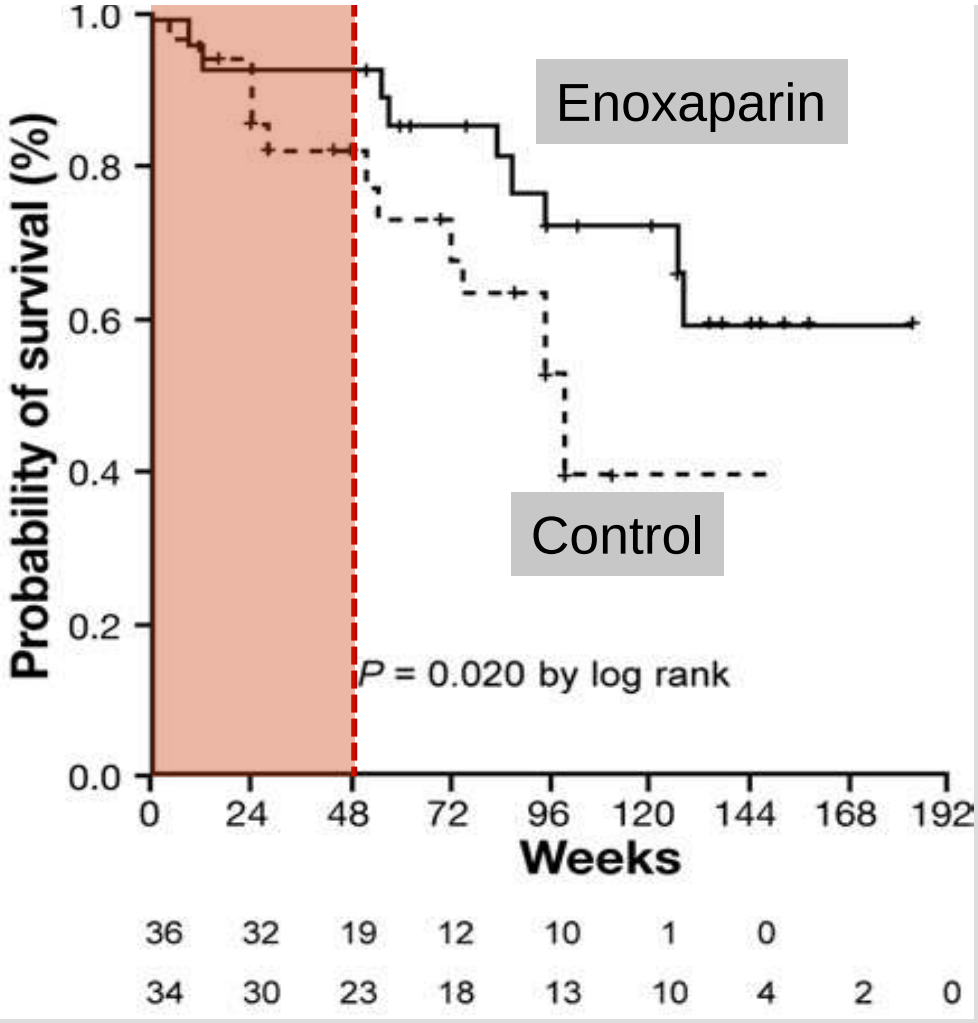
	Control	Enoxaparin
N. of patients	36	34
Partial PVT	3	0
Complete PVT	3	0
Decompensation	19	4

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

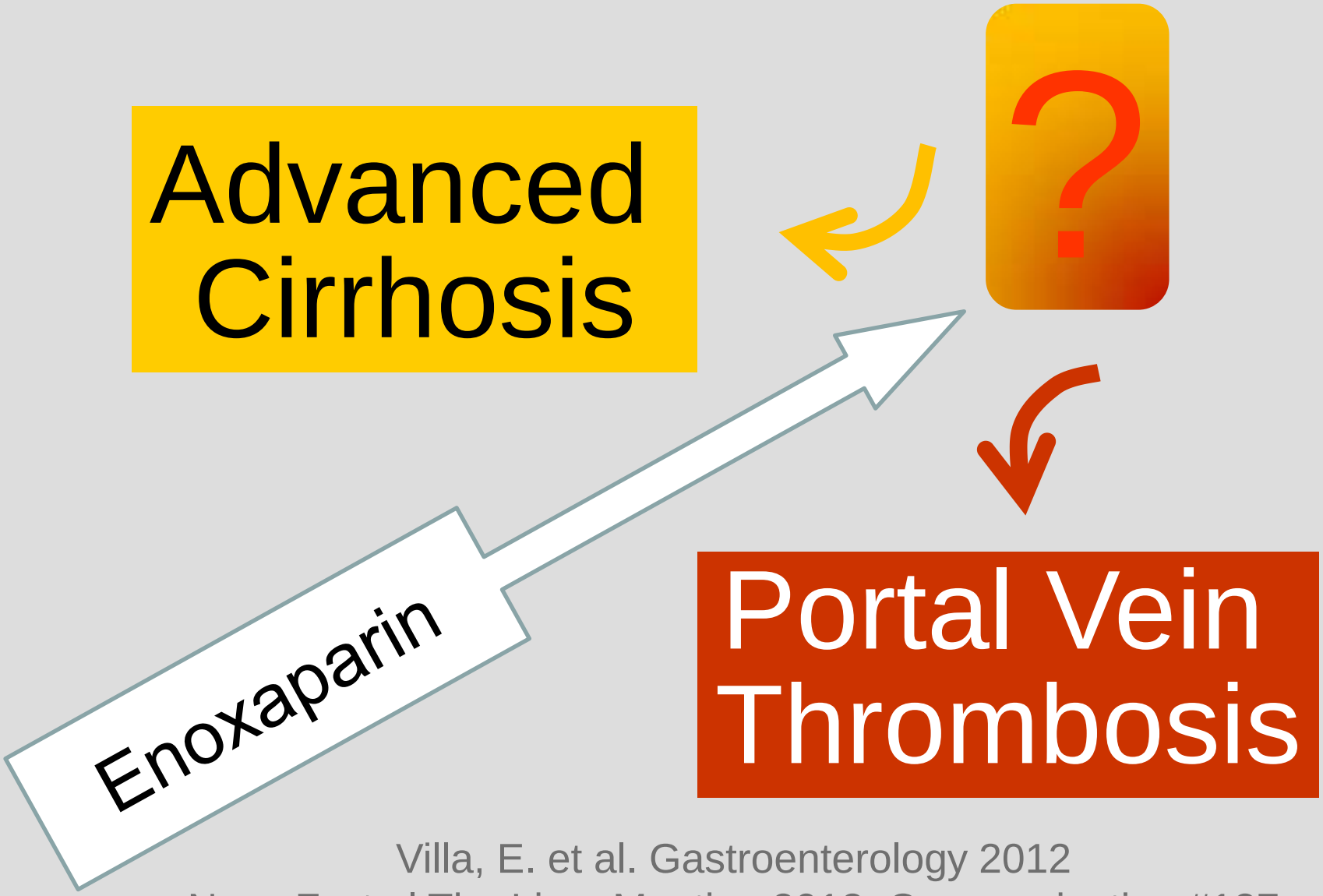
Decompensation



Survival



Villa. Gastroenterology 2012. Enoxaparin 4.000 UI/d, for 48 weeks.



Villa, E. et al. Gastroenterology 2012

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

Anticoagulation therapy (AT) for PVT in cirrhosis

Complete recanalization	41.5%
Major AT related complication	3%
AT related death	0

OR for recanalization 4.16 (1.88-9.20)

Qi, Eur J Intern Med 2014

Anticoagulation for Parenchymal Liver Disease (I)

- Detrimental role of coagulation activation in hepatic fibrogenesis.
- Favorable effect of anticoagulation in animal model of hepatic fibrogenesis; to be ascertained in patients.
- Thrombin generation potential normal or increased in patients with cirrhosis.
- Intrahepatic thromboses associated with severe disease.

Anticoagulation for Parenchymal Liver Disease (II)

- PVT is a marker, but not a direct cause, for progression of liver disease.
- A common determinant to PVT and progression would best explain the findings.
- This common determinant could be targeted by enoxaparin therapy.
- Curative therapy for PVT has not yet been shown to ameliorate outcome

Anticoagulation for Parenchymal Liver Disease (III)

In waiting for additional data from randomized controlled trial,

Anticoagulation can be considered in patients with cirrhosis and established portal vein thrombosis when

- in a context of acute intestinal ischemia;
- there is an associated highly prothrombotic condition;
- the patient is a transplant candidate

Collaborations

Hôpital Beaujon

A. Plessier, PE.Rautou, B. Condat, E. de Raucourt, L. Boudaoud, A. Sibert, V. Vilgrain, D Cazals Hatem, V. Paradis, 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)

Progression of Fibrosis in Experimental Cirrhosis

- Hypoxia is associated with angiogenesis and the progression of fibrosis
- Hypoxia induces VEGF and Collagen 1 expression in stellate cells

Transjugular Intrahepatic Porto-Systemic Shunt (TIPS)