Hemostasis and Thrombosis in Cirrhotic Patients

Dominique-Charles Valla
Hôpital Beaujon, APHP, Université Paris-7, Inserm CRB3

Nothing to disclose

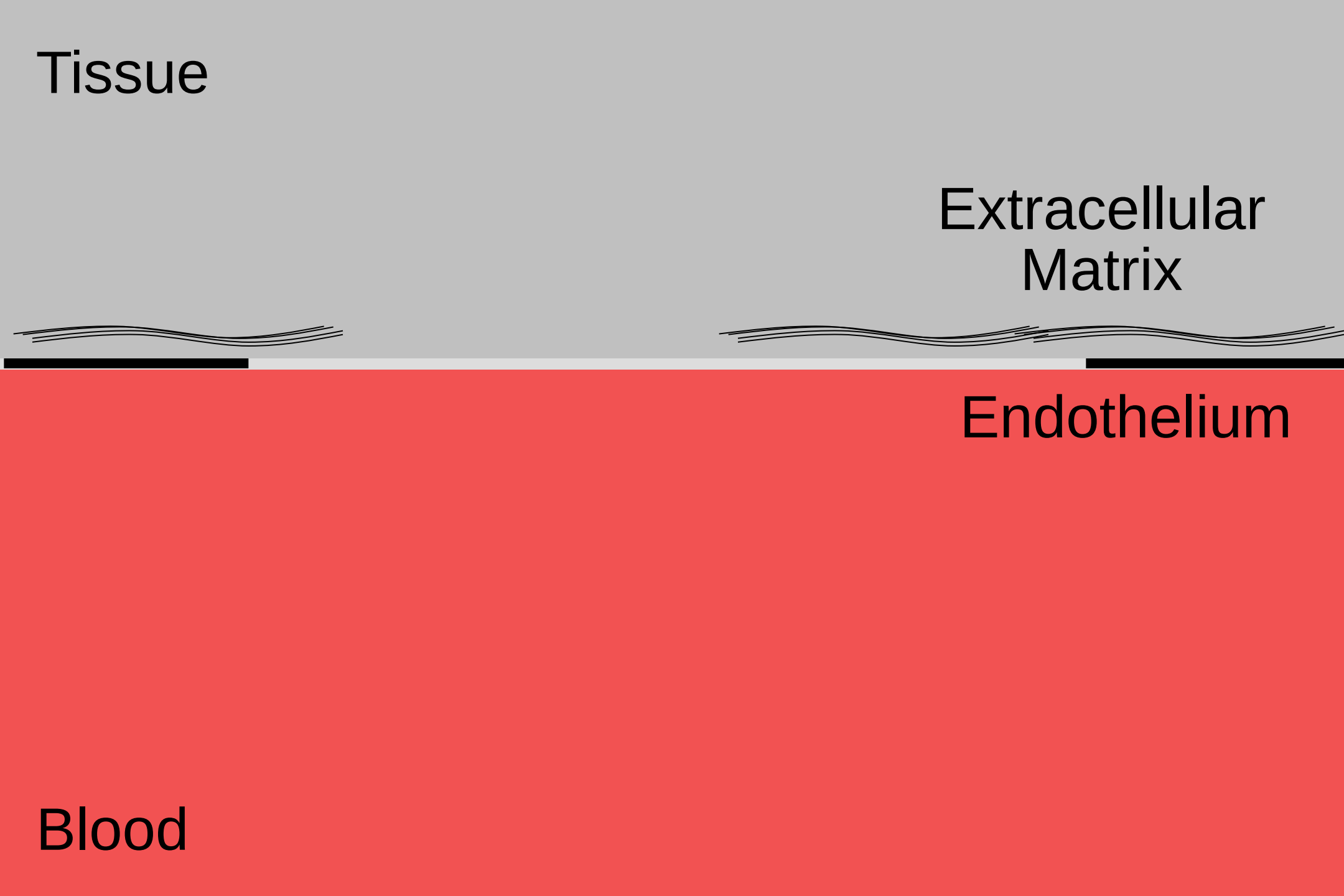
Hemostasis and Thrombosis in Cirrhotic Patients

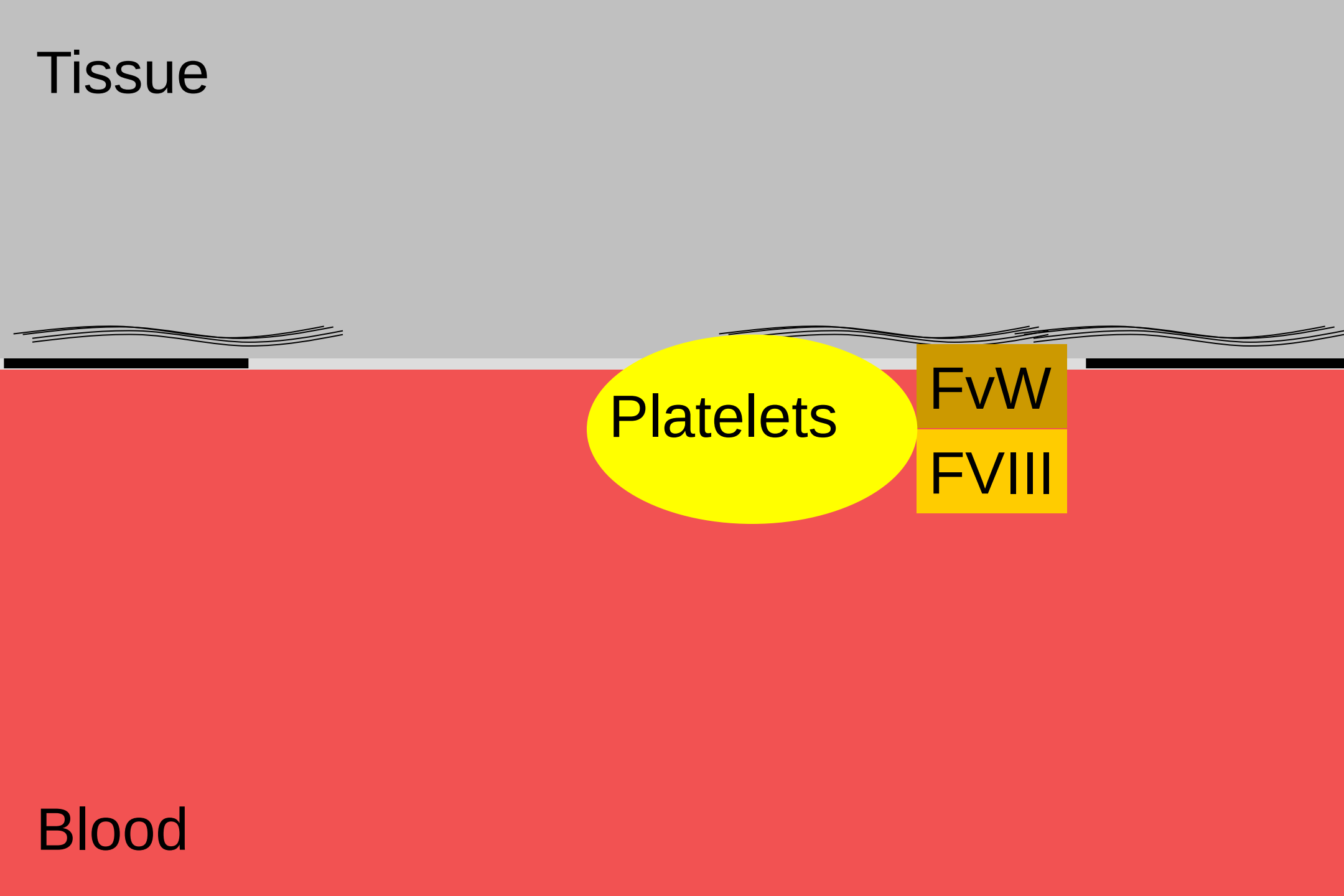
1. Cirrhosis could be a prothrombotic state
2. Coagulation activation is a fibrogenic factor
3. HVT & PVT associated with cirrhosis severity
4. PVT constitutes a limitation to LTx
5. A strengthening rationale for anticoagulation

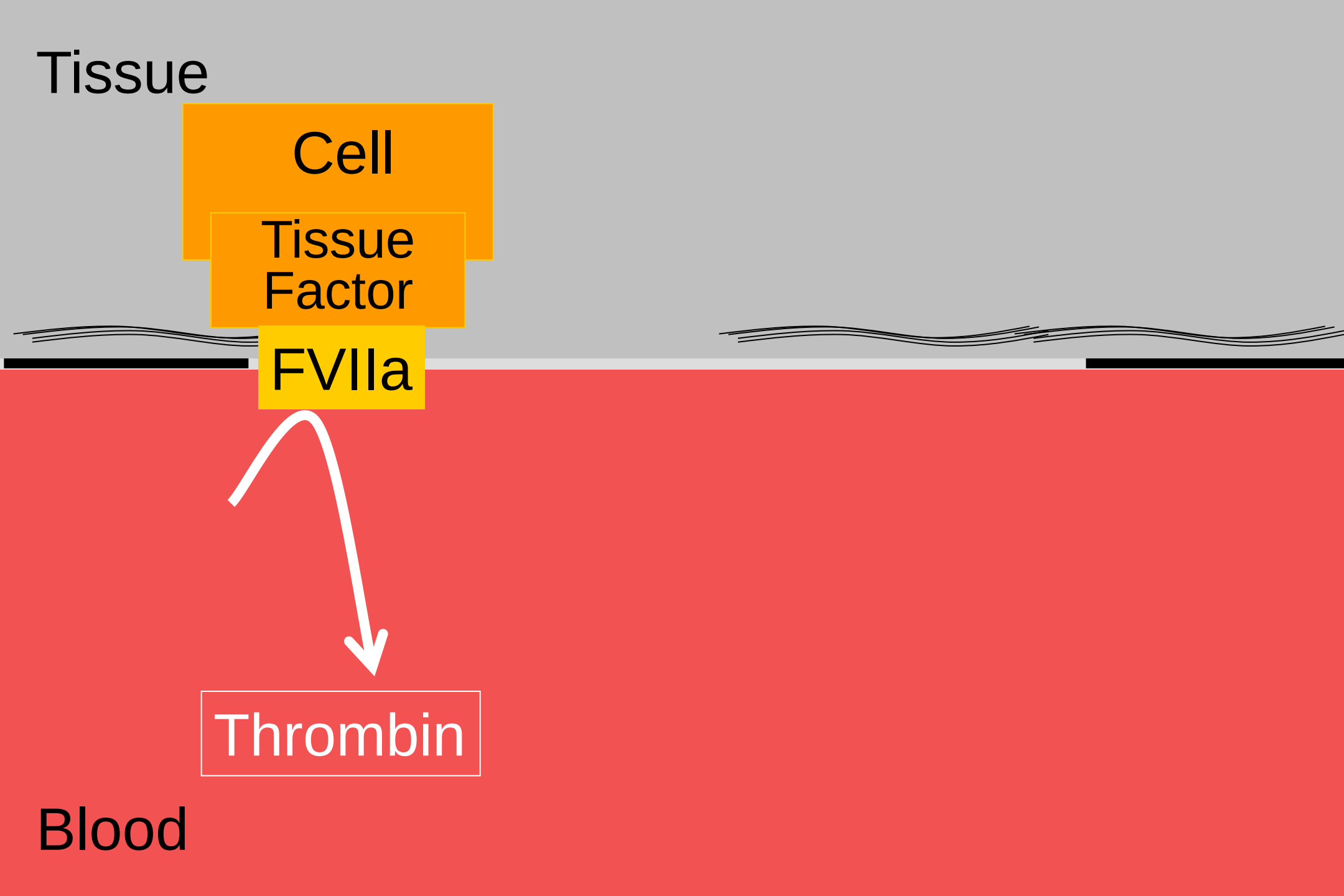
HVT, hepatic vein thrombosis. PVT, Portal vein thrombosis

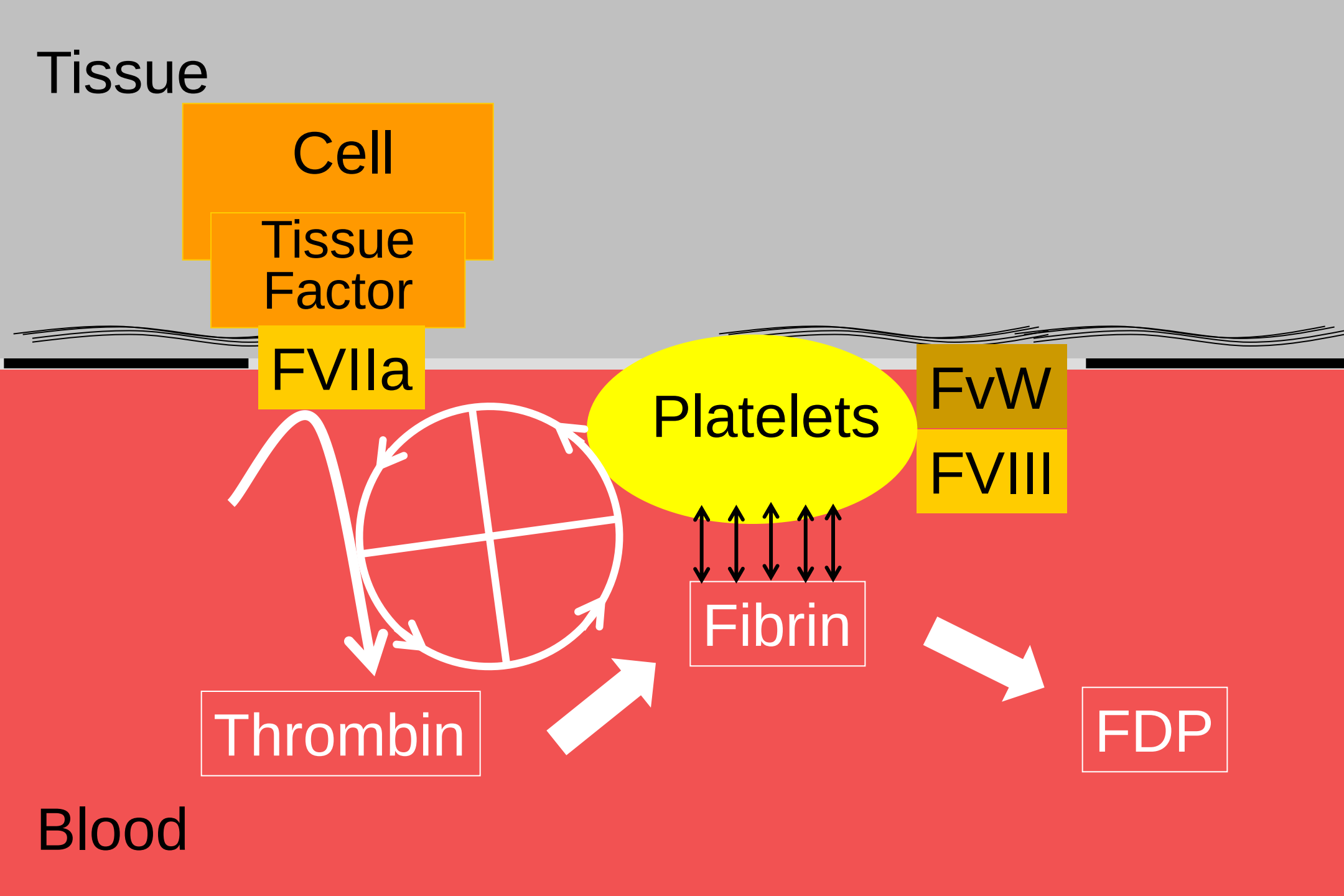
Cirrhosis could be a prothrombotic state

- Coagulation imbalance in plasma
- Increased risk of venous thrombosis
- Bleeding related to mechanical factors or associated diseases
- Not reflected by usual screening tests


Tissue
Extracellular Matrix
Endothelium
Blood


Tissue
Platelets
FvW
FVIII
Blood


Tissue
Cell
Tissue Factor
FVIIa
Thrombin
Blood


Tissue
Cell
Tissue Factor
FVIIa
Platelets
FvW
FVIII
Fibrin
Thrombin
FDP
Blood

Thrombocytopenia and Cirrhosis

- Splenic sequestration
- Decreased survival (platelet bound IgG)
- Inappropriate thrombopoiesis/thrombopoietin
- Altered platelet function

Lisman, Hepatology 2006

Thrombocytopenia and Cirrhosis

- Splenic sequestration
- Decreased survival (platelet bound IgG)
- Inappropriate thrombopoiesis/thrombopoietin
- Altered platelet function

Increased factor VIII and vW factor
No impairment in hemostasis when > 50,000/µL

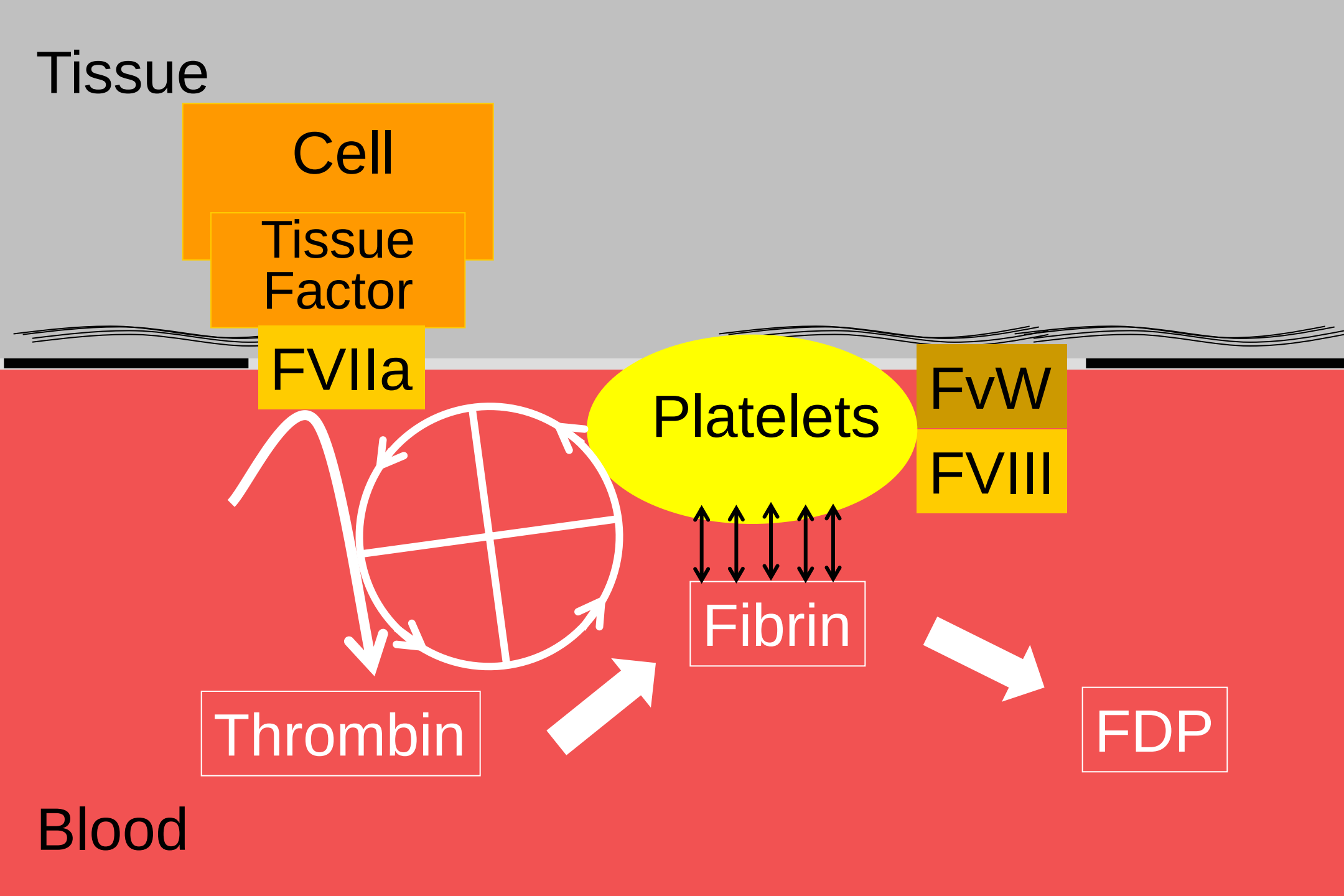
Lisman, Hepatology 2006

Thrombocytopenia and Cirrhosis

When Platelets > 30,000/μL

- Not a risk factor for gastrointestinal bleeding
- In index of the severity of liver disease
- Increased risk of portal vein thrombosis with Eltrombopag (ELEVATE study)

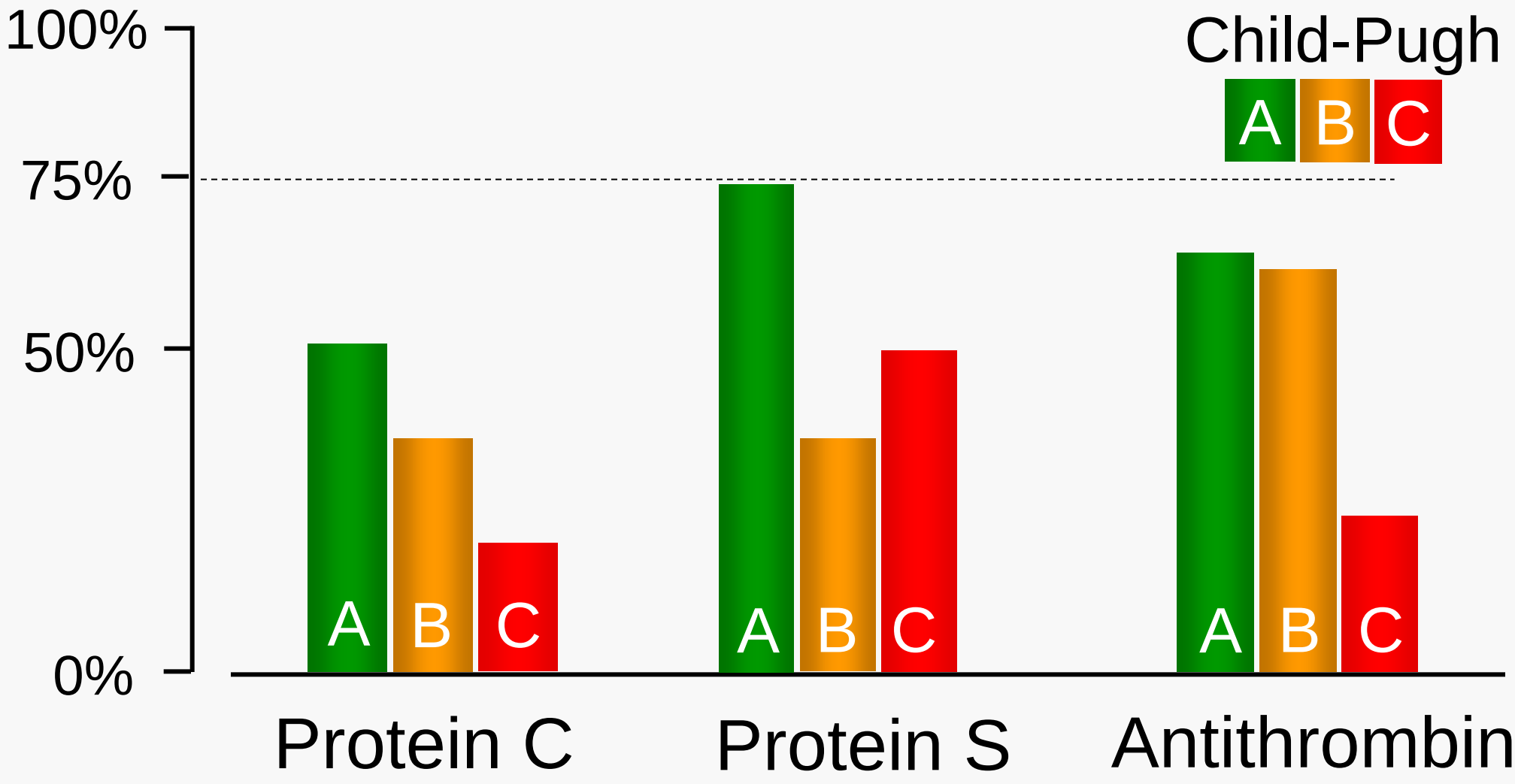
Lisman, J Hepatol 2002. Caldwell, Hepatology 2006.
Senzolo, Worls J Gastroenterol 2006


Tissue
Cell
Tissue Factor
FVIIa
Platelets
FvW
FVIII
Fibrin
Thrombin
FDP
Blood

Coagulation in Cirrhosis

- Tissue factor increased
- Coagulation factor VIII increased
- Other coagulation factors decreased
- Clearance of activated factors decreased
- Coagulation inhibitors decreased

Coagulation Inhibitors in Cirrhosis



Romero-Gomez. J Clin Gastroenterol 2000

Coagulation in Cirrhosis

- Tissue factor increased
- Coagulation factor VIII increased
- Other coagulation factors decreased
- Clearance of activated factors decreased
- Coagulation inhibitors decreased

Increased thrombin generation potential in plasma
Increased resistance to thrombomodulin in plasma

Tripodi Hepatology 2005 & 2006, Tripodi Gastroenterology 2009

Cirrhosis could be prothrombotic state

- Coagulation imbalance in plasma
- Increased risk of venous thrombosis
- Bleeding related to mechanical factors or associated diseases
- Not reflected by usual screening tests

Northup AJG 2006. Soogard AJ 2009.

Coagulation in Cirrhosis

No benefit from recombinant activated Factor VII in patients with bleeding esophageal varices

Bosch, Gastroenterology 2004. Bosch J Hepatol 2007

Cirrhosis could be a prothrombotic state

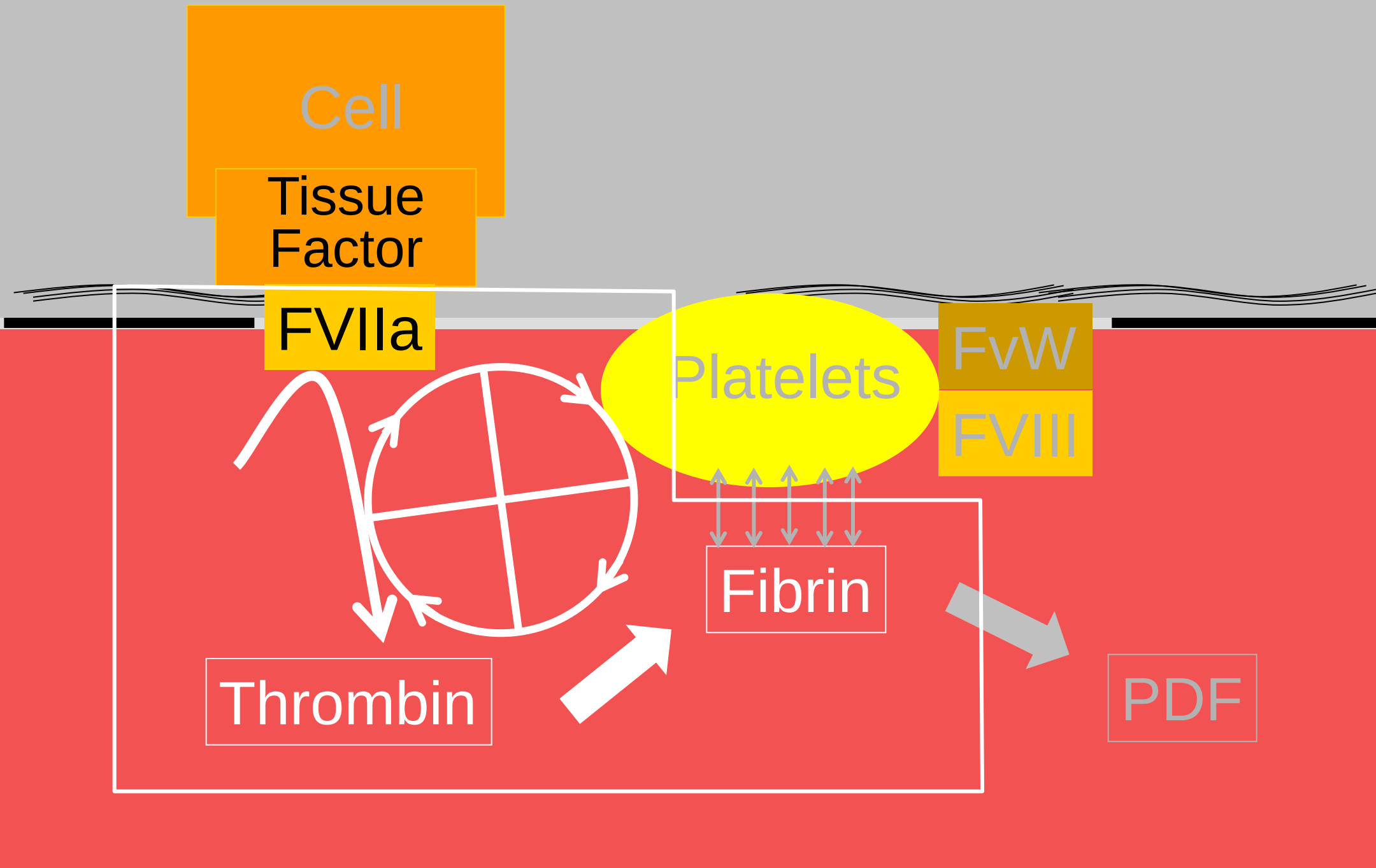
- Coagulation imbalance in plasma
- Increased risk of venous thrombosis
- Bleeding related to mechanical factors or associated diseases
- Not reflected by usual screening tests

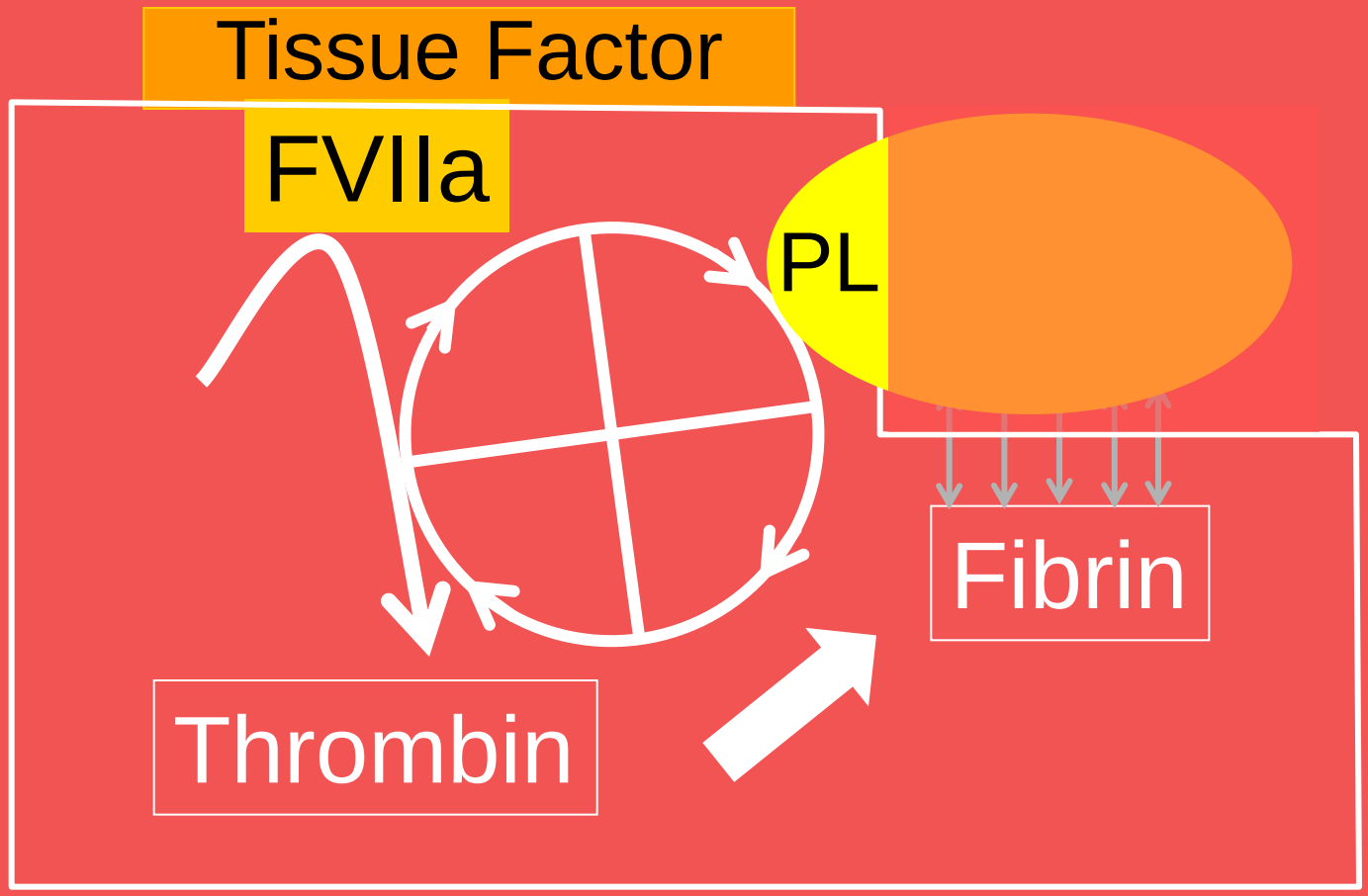
The exception of hyperfibrinolysis !

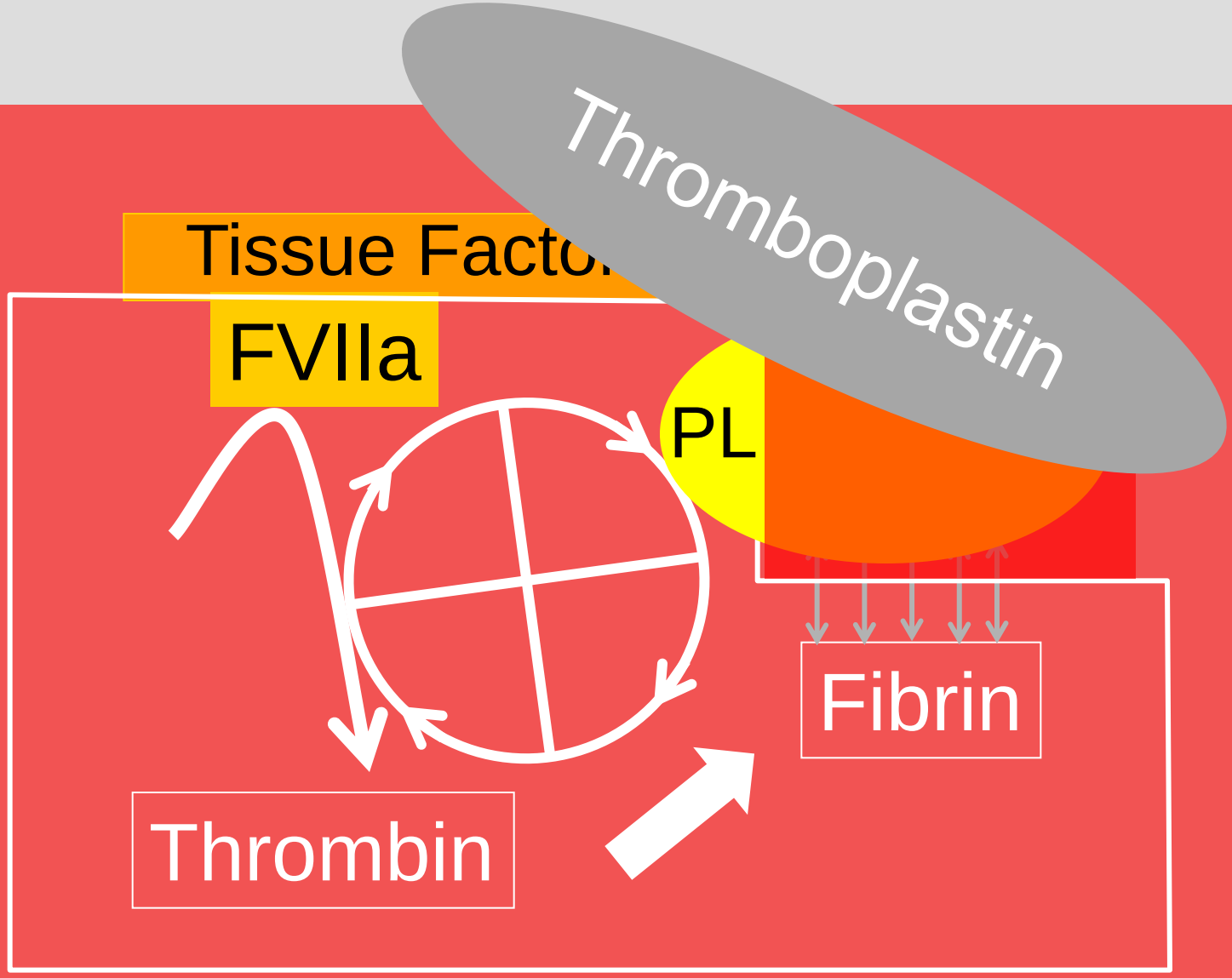
Cirrhosis could be a prothrombotic state

- Coagulation imbalance in plasma
- Increased risk of venous thrombosis
- Bleeding related to mechanical factors or associated diseases
- Not reflected by usual screening tests

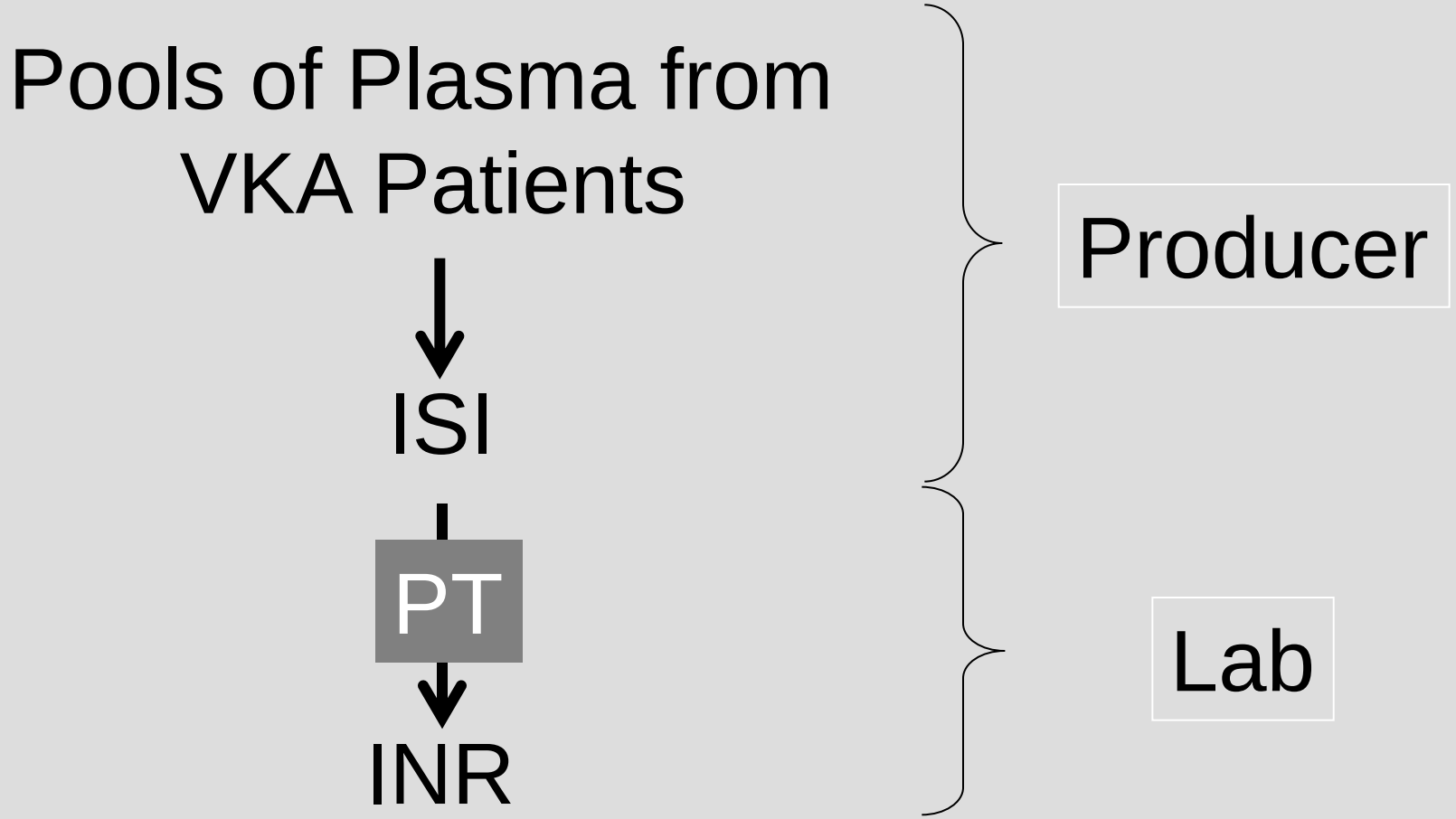
Northup AJG 2006. Soogard AJ 2009.


Cell
Tissue Factor
FVIIa
Platelets
FvW
FVIII
Fibrin
Thrombin
PDF

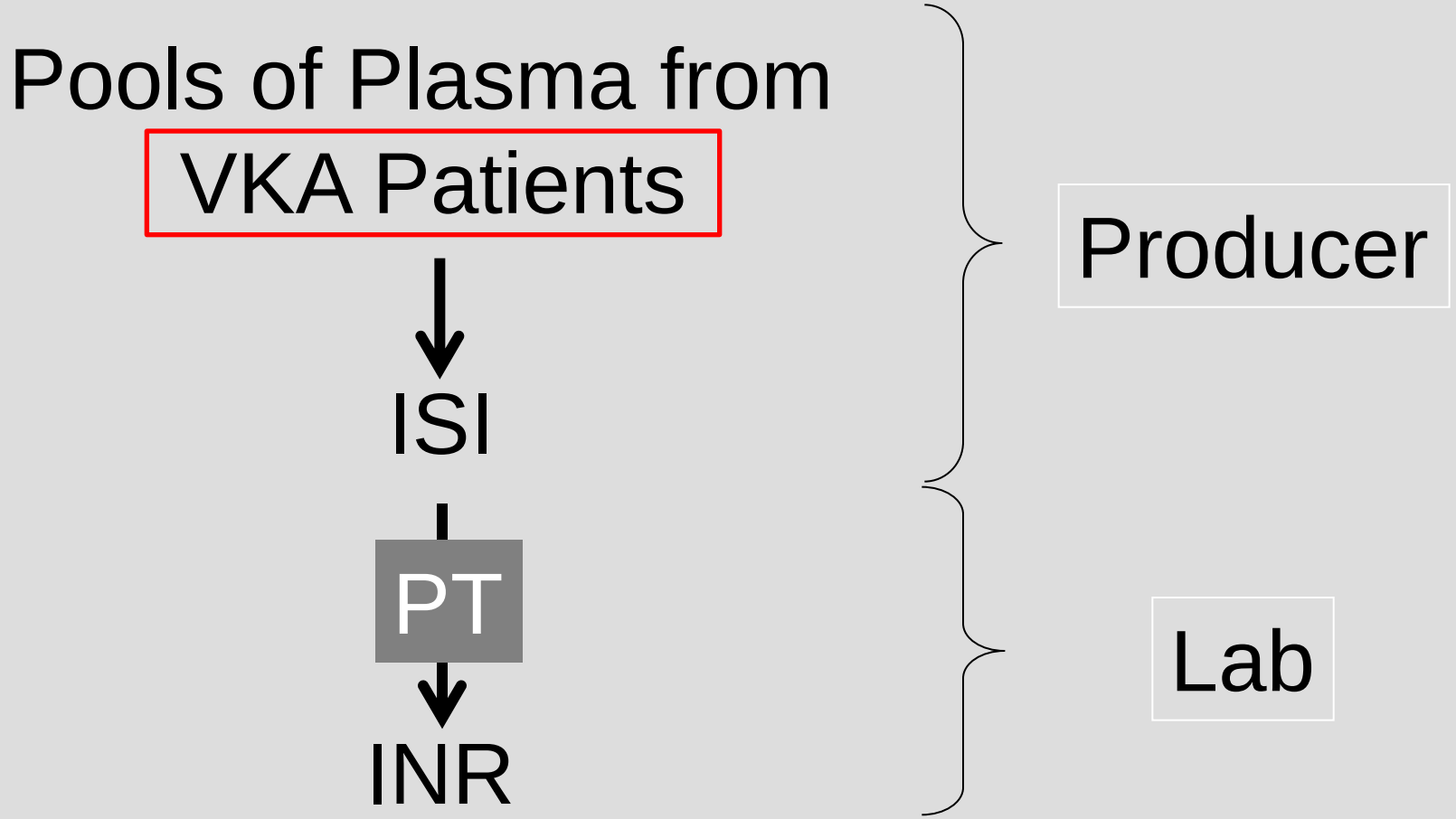

Tissue Factor
FVIIa
PL
Fibrin
Thrombin


Thromboplastin
Tissue Factor
FVIIa
PL
Fibrin
Thrombin

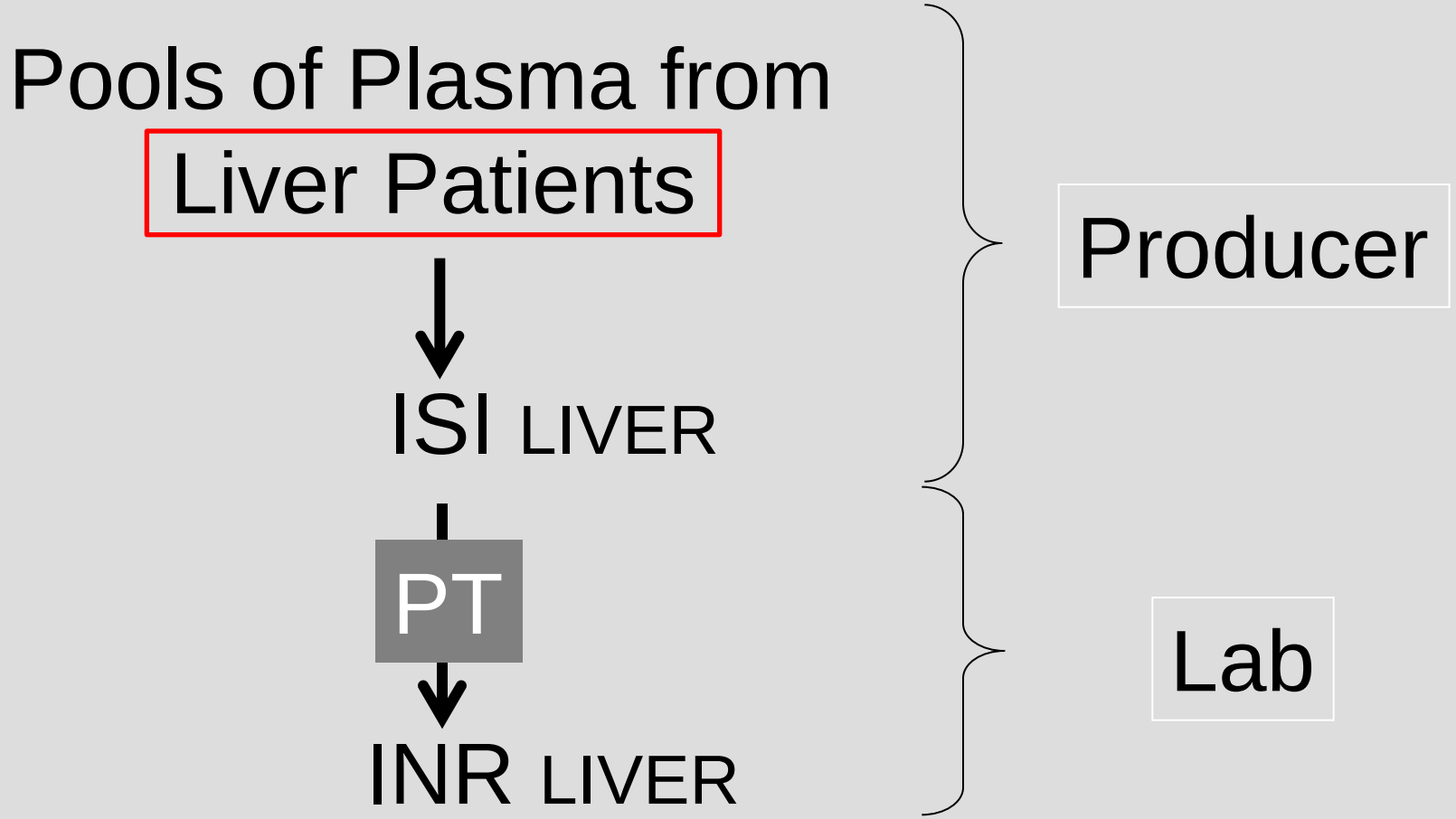
From PT to INR



From PT to INR



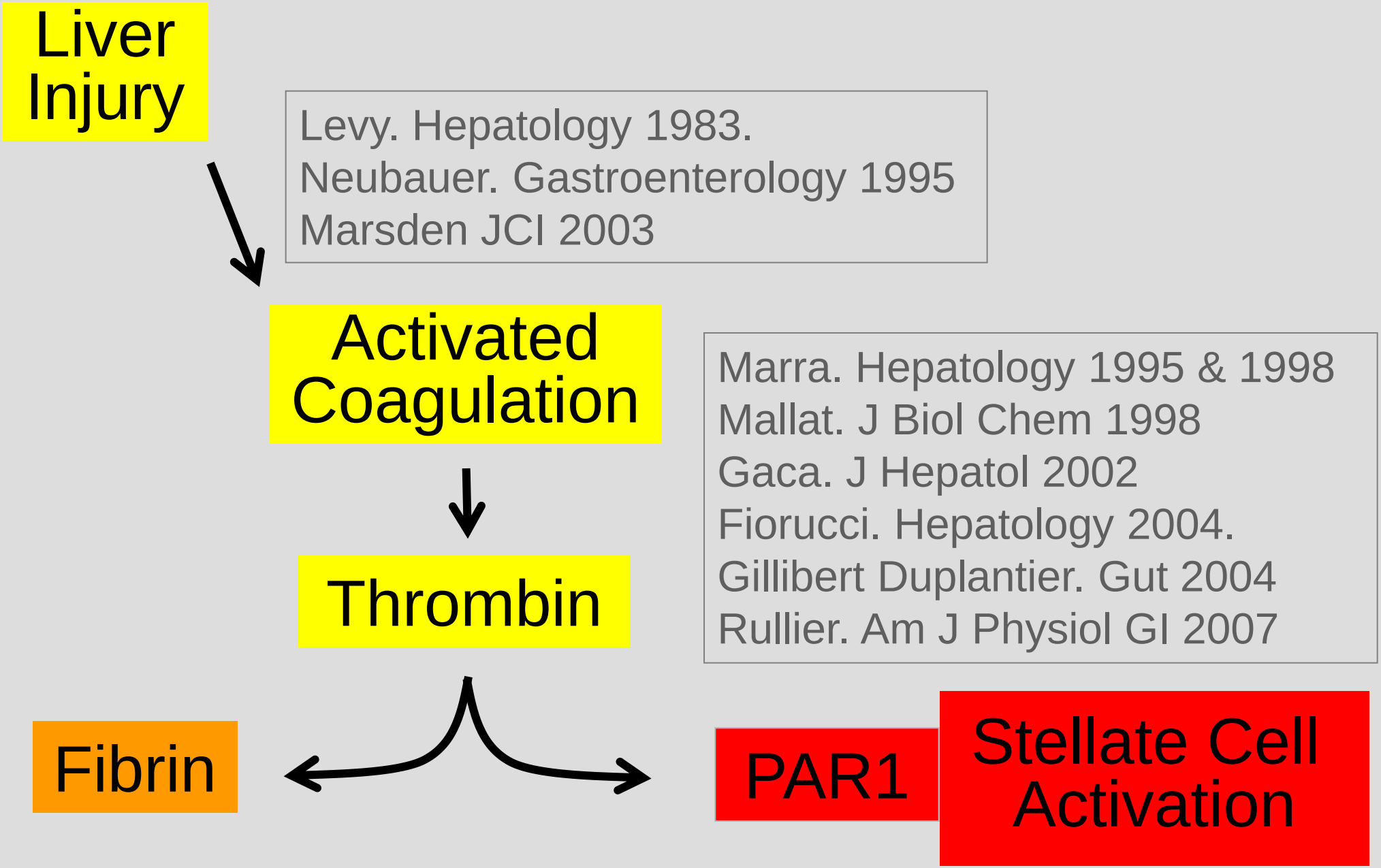
From PT to INR

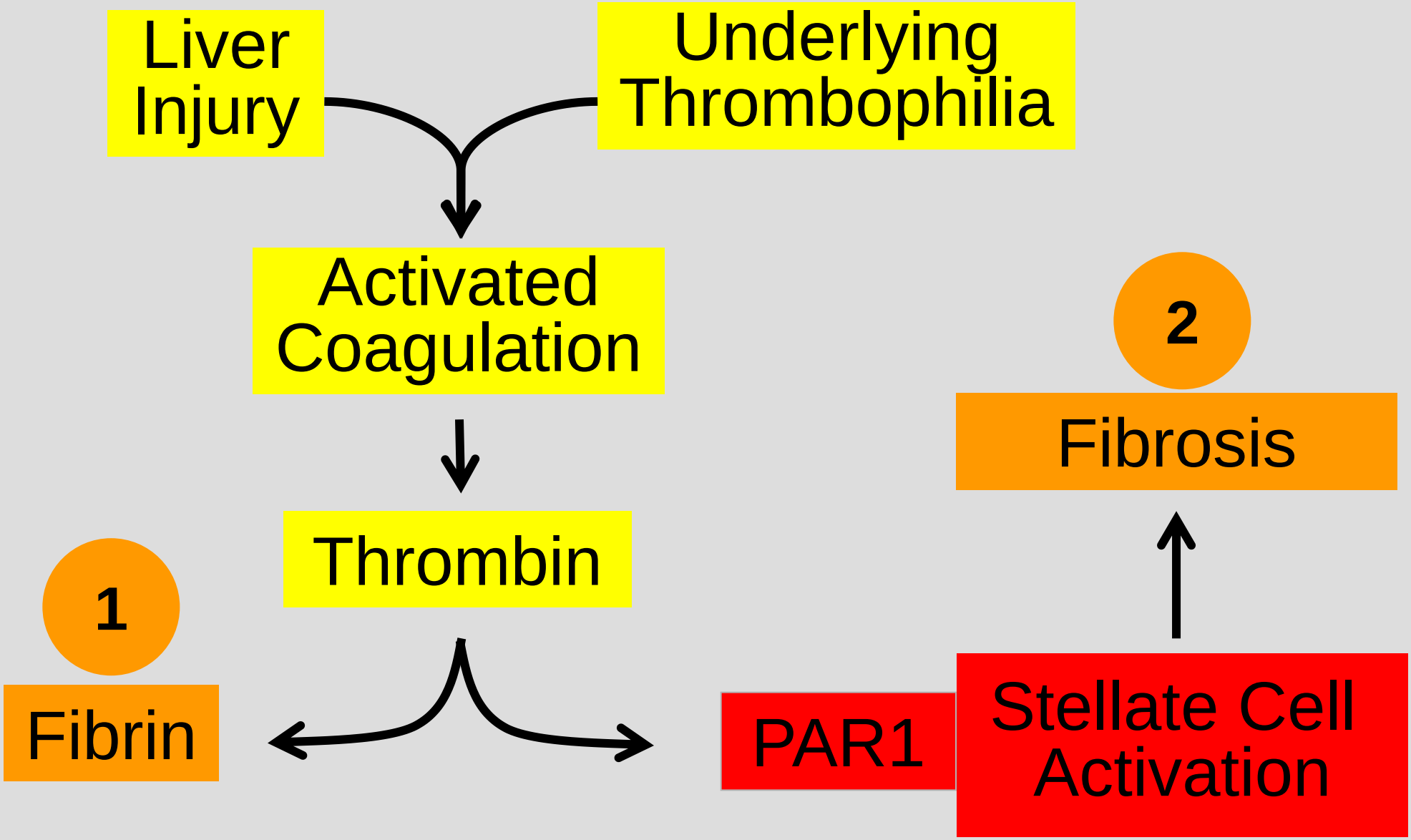


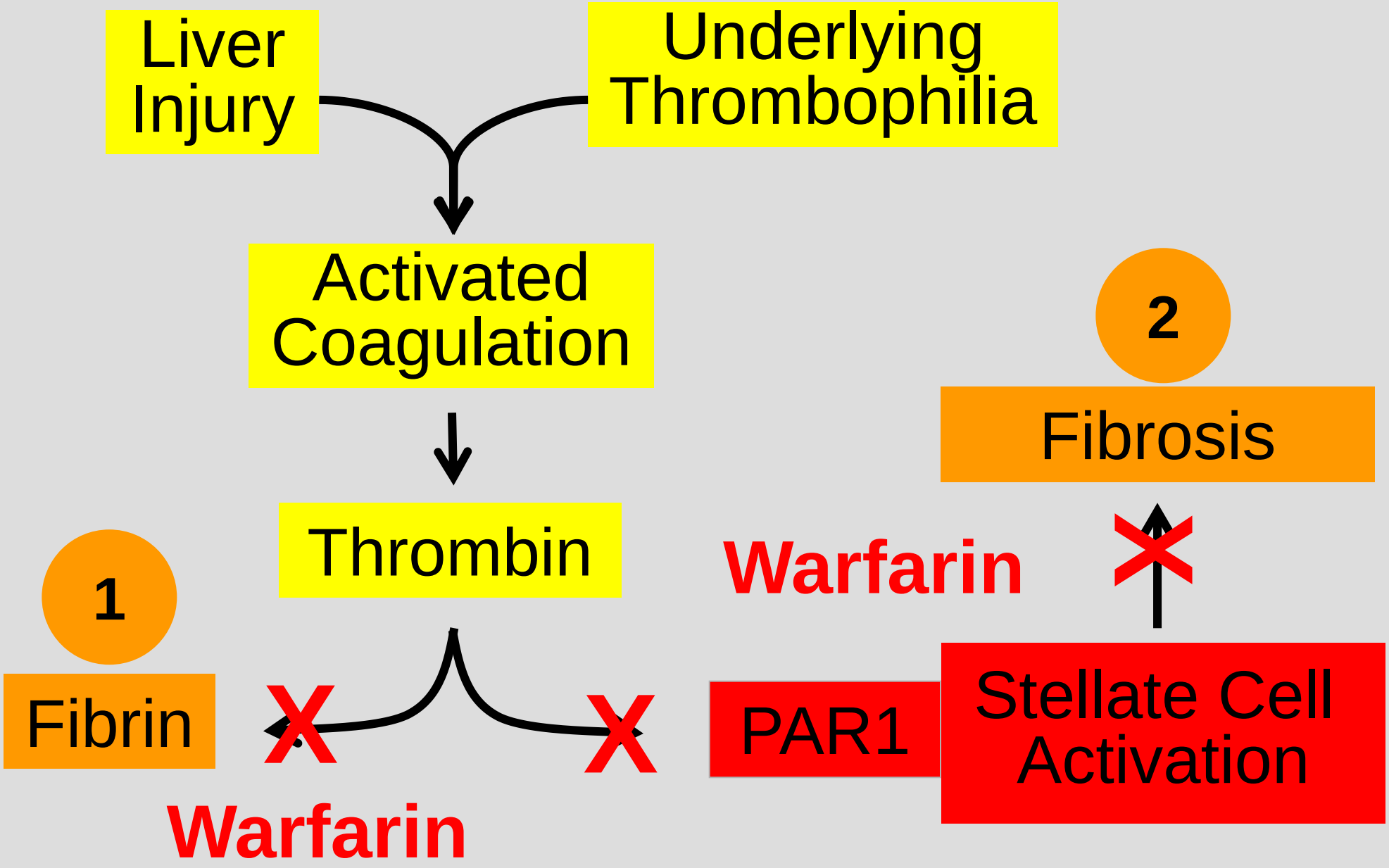
Hemostasis and Thrombosis in Cirrhotic Patients

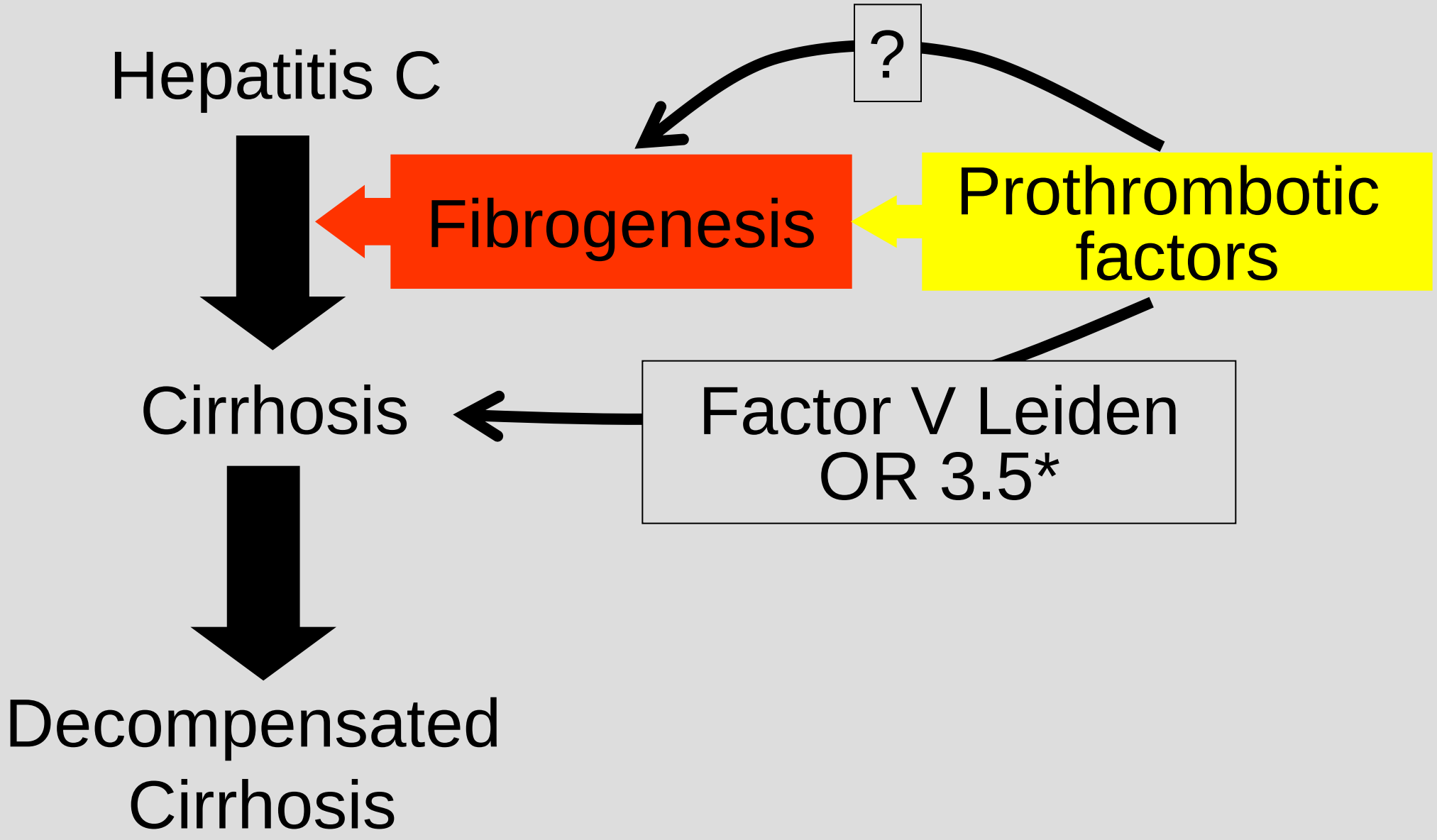
1. Cirrhosis is a prothrombotic state
2. Coagulation activation is a fibrogenic factor
3. HVT & PVT associated with cirrhosis severity
4. PVT constitutes a limitation to LTx
5. A strengthening rationale for anticoagulation

HVT, hepatic vein thrombosis. PVT, Portal vein thrombosis

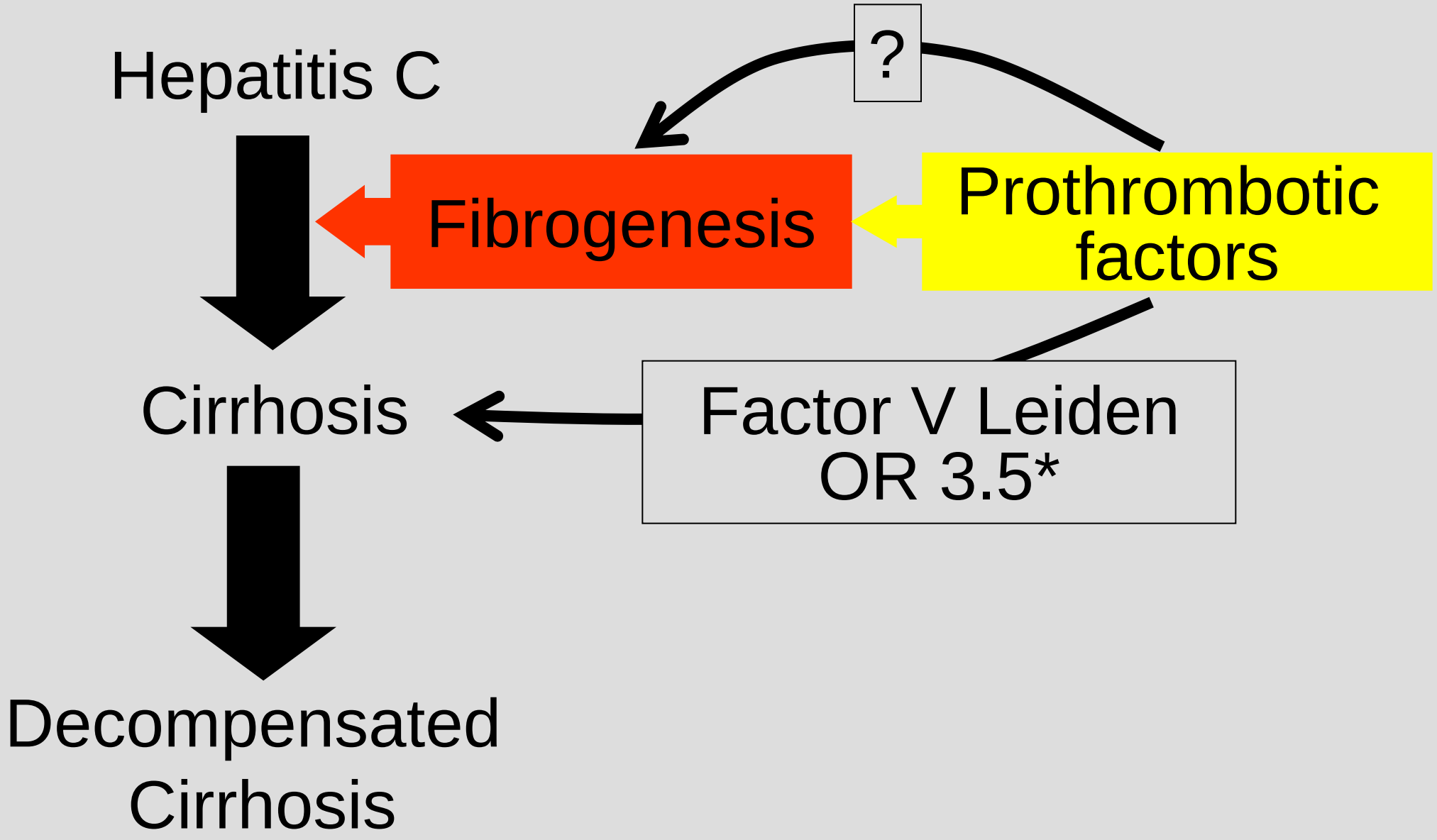

Liver Injury
Levy. Hepatology 1983.
Neubauer. Gastroenterology 1995
Marsden JCI 2003
Activated Coagulation
Marra. Hepatology 1995 & 1998
Mallat. J Biol Chem 1998
Gaca. J Hepatol 2002
Fiorucci. Hepatology 2004.
Gillibert Duplantier. Gut 2004
Rullier. Am J Physiol GI 2007
Thrombin
Fibrin
PAR1
Stellate Cell Activation


Liver Injury
Underlying Thrombophilia
Activated Coagulation
Thrombin
1
Fibrin
PAR1
Stellate Cell Activation
2
Fibrosis


Liver Injury
Underlying Thrombophilia
Activated Coagulation
Thrombin
1
Fibrin
Warfarin
2
Fibrosis
Warfarin
PAR1
Stellate Cell Activation



*Wright, Gut 2003. Papatheodoridis. Gut 2003. Poujol-Robert. *Hepatology 2004, AJG 2004. Goulding J Viral



*Wright, Gut 2003. Papatheodoridis. Gut 2003. Poujol-Robert. *Hepatology 2004, AJG 2004. Goulding J Viral

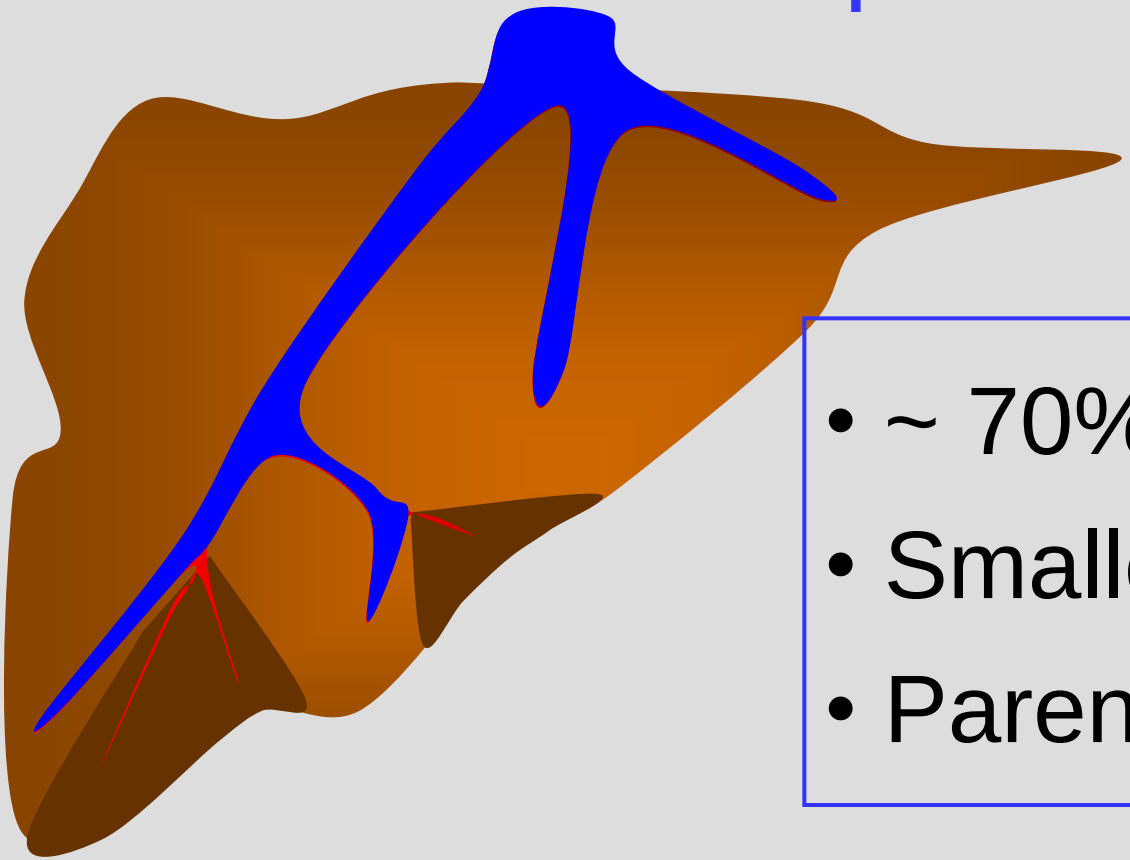
Hemostasis and Thrombosis in Cirrhotic Patients

1. Cirrhosis is a prothrombotic state
2. Coagulation activation is a fibrogenic factor
3. HVT & PVT associated with cirrhosis severity
4. PVT constitutes a limitation to LTx
5. A strengthening rationale for anticoagulation

HVT, hepatic vein thrombosis. PVT, Portal vein thrombosis

Explanted Cirrhotic Livers

Hepatic vein thromboses

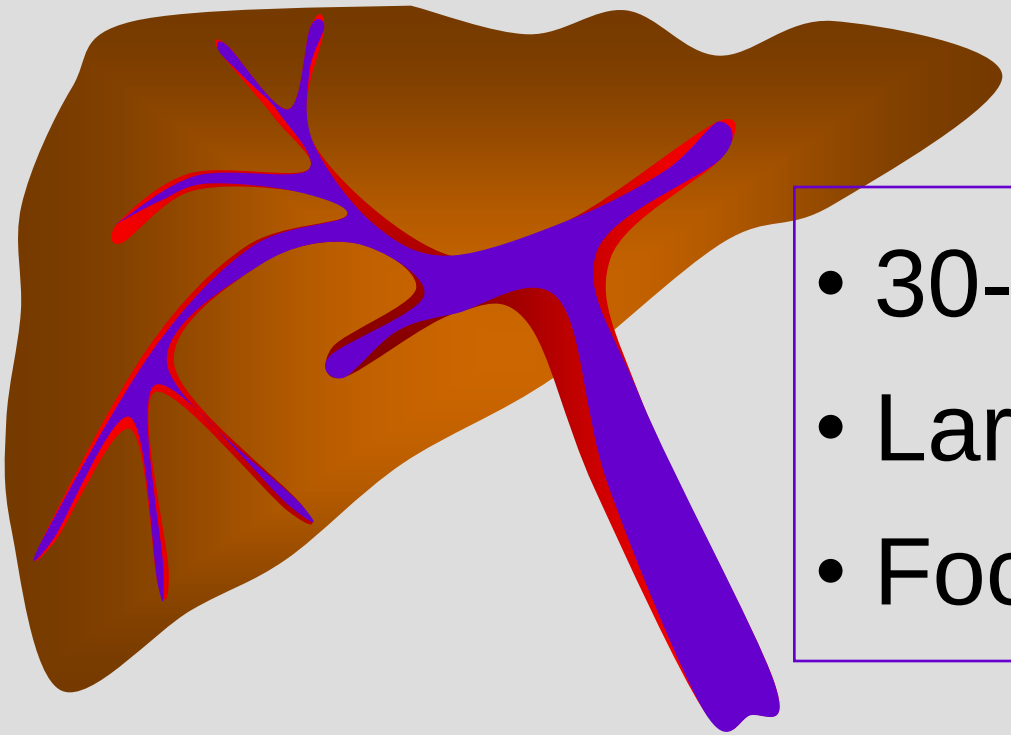


- ~ 70% of veins involved
- Smallest first
- Parenchymal extinction

Wanless, Hepatology 1995. Shimamatsu, Hepatology 1997

Explanted Cirrhotic Livers

Portal vein thromboses



- 30-50% of veins involved
- Largest first
- Focal atrophy/regeneration

Wanless, Hepatology 1995. Shimamatsu, Hepatology 1997

Association of PVT with a Small Liver

At LTx	N	Liver weight	*P*
PVT	63	17 g/Kg	< *.02*
No PVT	401	21 g/Kg	

Nonami et al. Hepatology 1992;16:1195-8

PVT and Complications of Cirrhosis

- Portal hypertensive bleeding
- Failure to control bleeding
- Ascites
- Hepatic encephalopathy

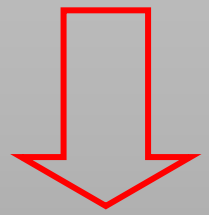
Nonami Hepatology 1992. Orloff J Gastrointest Surg 1997. D'Amico Hepatology 2003. Amitrano J Hepatol 2004.

Extrahepatic PVT in Cirrhosis

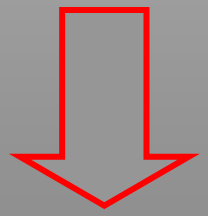
	Prevalence
Screening for HCC	0.6 %
In-Hospital	7.0 %
Necropsy	8.0 %
Before LTx or PSS	15.0 %

Okuda et al. Gastroenterology 1985;89:279-86.
Chang et al. J Pathol Bacteriol 1965;89:473-80.

Advanced
Liver Disease

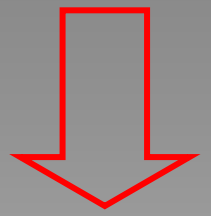


Blood stasis
Wall changes (PHT)

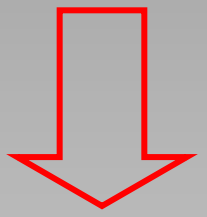


Thrombosis

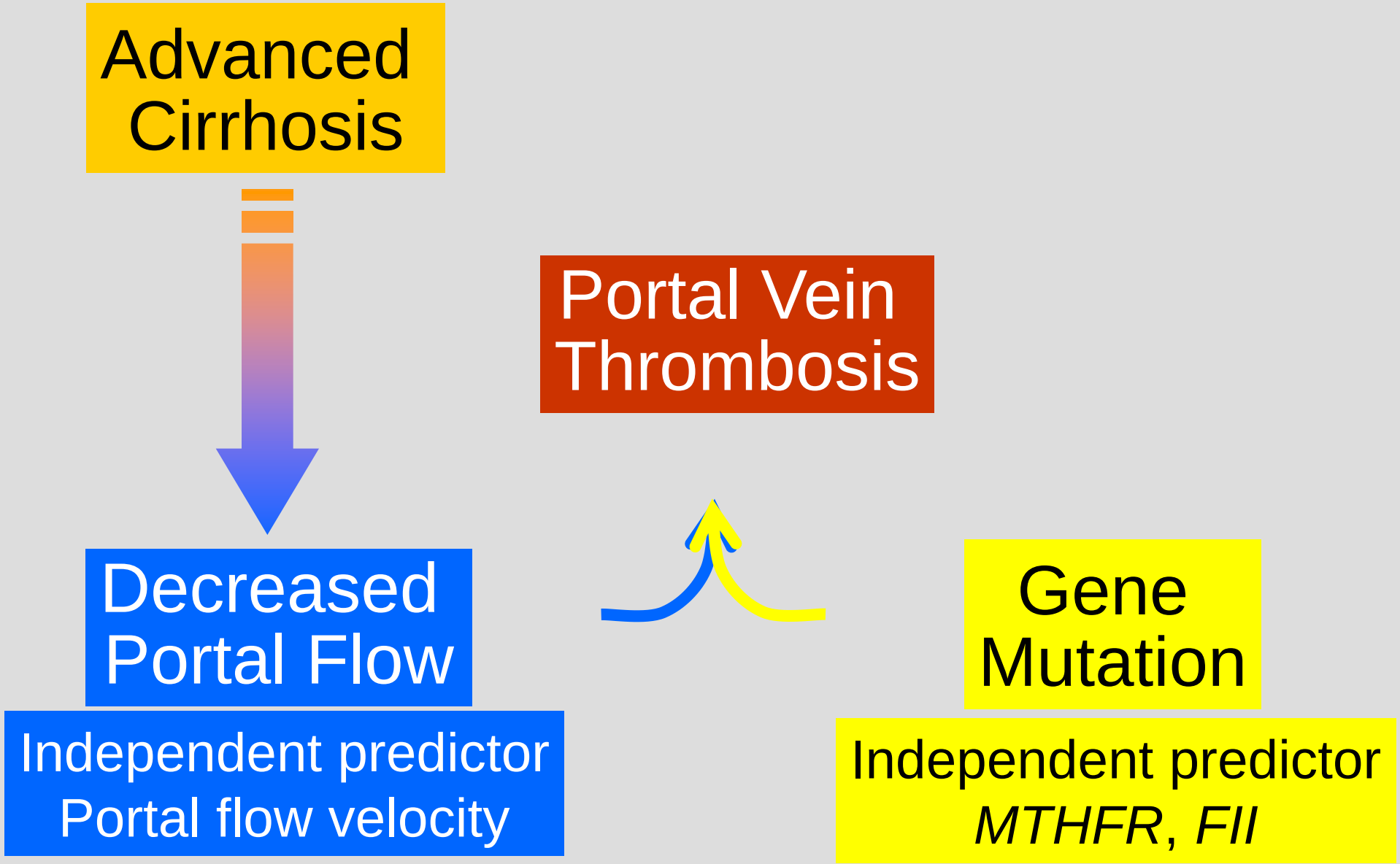
Thrombosis



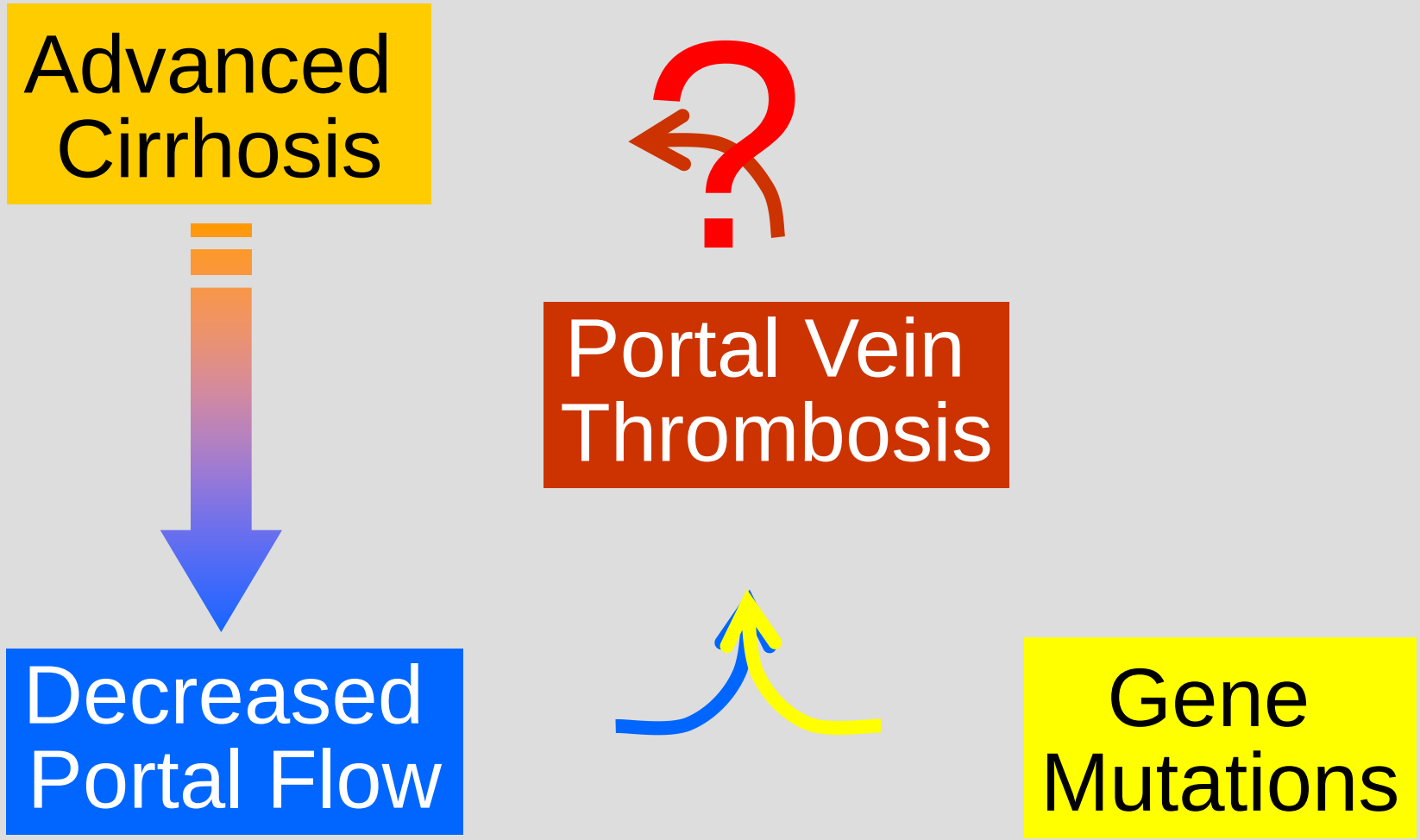
Decreased Portal
Blood Inflow



Advanced
Liver Disease



Pellicelli. ILC 2011, P.180. Zocco, J HEP 2009. Amitrano, J HEP 2004

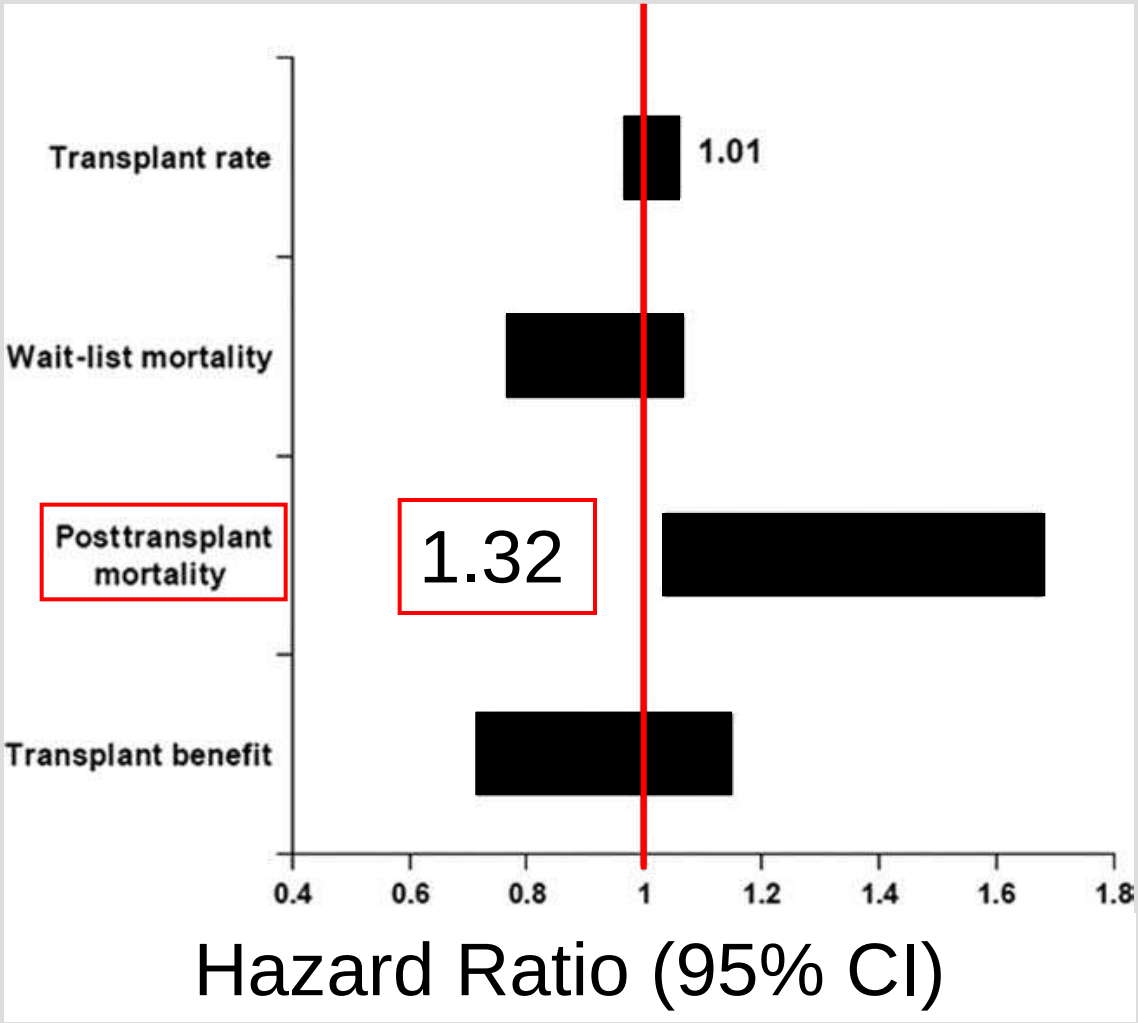

Advanced Cirrhosis
Portal Vein Thrombosis
Decreased Portal Flow
Gene Mutations

Hemostasis and Thrombosis in Cirrhotic Patients

1. Cirrhosis is a prothrombotic state
2. Coagulation activation is a fibrogenic factor
3. HVT & PVT associated with cirrhosis severity
4. PVT constitutes a limitation to LTx
5. A strengthening rationale for anticoagulation

HVT, hepatic vein thrombosis. PVT, Portal vein thrombosis

Pre and post LTx impact of PVT



Englesbe. Liver Transplant 2010. SRTR 22,291 recipients. PVT 4.02%

Hemostasis and Thrombosis in Cirrhotic Patients

1. Cirrhosis is a prothrombotic state
2. Coagulation activation is a fibrogenic factor
3. HVT & PVT associated with cirrhosis severity
4. PVT constitutes a limitation to LTx
5. A strengthening rationale for anticoagulation

HVT, hepatic vein thrombosis. PVT, Portal vein thrombosis

Anticoagulation in Patients with Cirrhosis

Anticoagulation therapy targeting PVT

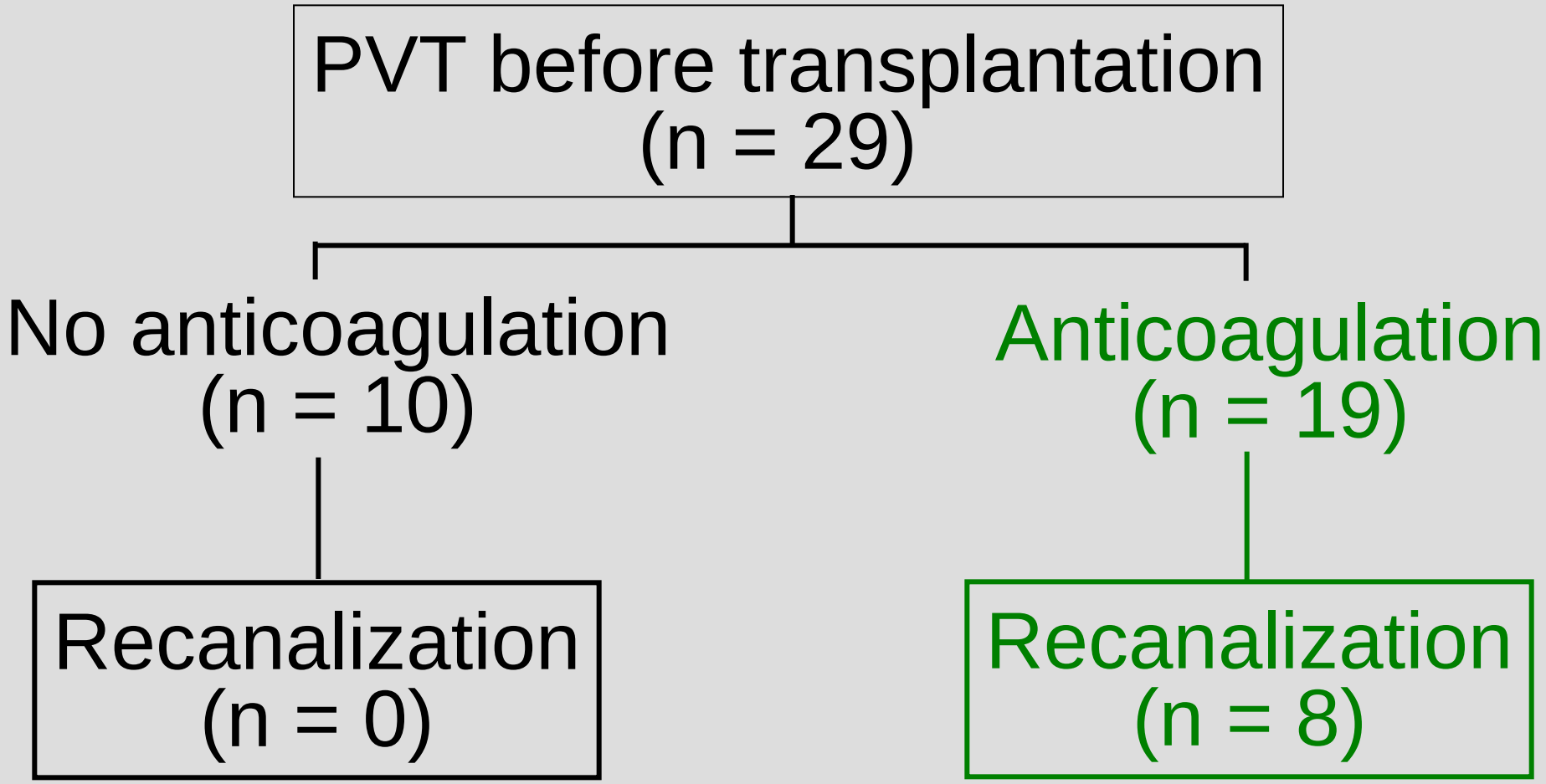
- Recanalization
- Prophylaxis

Anticoagulation for PVT and Cirrhosis

- <150 patients reported
- Various anticoagulation protocols
- Partial occlusion in 80-88% of patients
- Recanalization 60-80% (3-12 months).
  More likely when occlusion is partial and anticoagulation therapy is prolonged
- Bleeding apparently not a problem

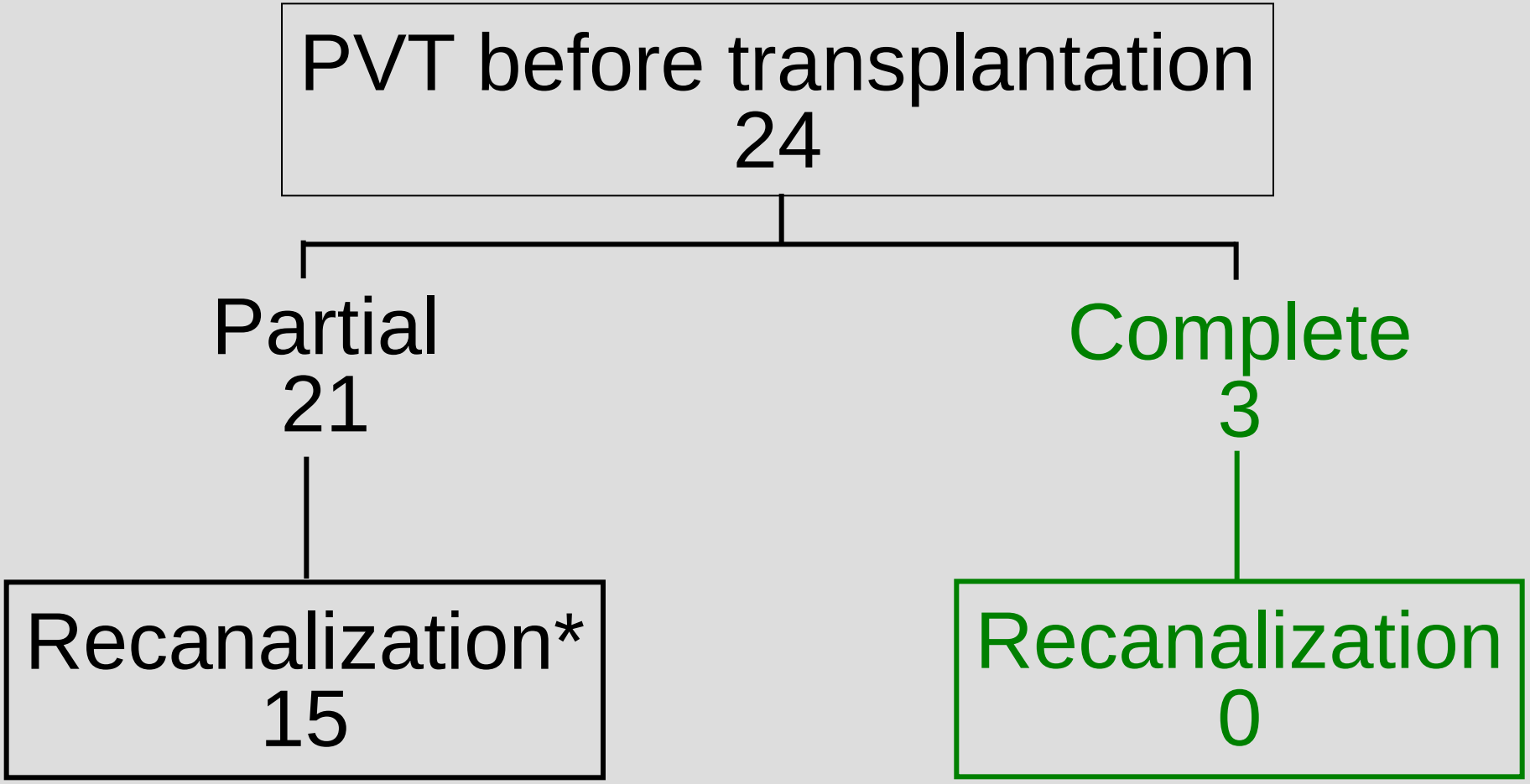
Romero-Gomez Gastroenterology 2002. Amitrano J Clin Gastro 2010. Francoz Gut 2005. Francoz ILTS 2008. Pellicelli EASL 2009. Senzolo Intern Emerg Med 2009

Patients on the Waiting List for LTx



Francoz, Gut 2005

Anticoagulation on the Waiting List for LTx



* No PVT post-OLT

Francoz, ILTS 2008

Treatment of PVT in Patients with Cirrhosis

Anticoagulation or TIPS for recanalization ?

TIPS in Cirrhosis with PVT

- Several case series. N = 13 - 100 patients
- Only retrospective uncontrolled studies
- Anticoagulation frequently added after TIPS
- Cavernoma, Total/Partial obstruction merged

Senzolo, AP&T 2006. Van Ha, Cardiovasc Intervent Radiol 2006. Perarnaud, Eur J Gastro Hepato 2010. Han, J Hepatol 2010. Luca, Gut 2011

TIPS in Cirrhosis with PVT

- 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

Anticoagulation in Patients with Cirrhosis

Anticoagulation for PVT

- Recanalization
- Prophylaxis

Prophylaxis of PVT in Cirrhosis

Child B7-C10 patients

	Enoxaparin	Placebo
Number of Pt	26	25
Partial PVT	0	3
Complete PVT	0	2

Zechini. EASL ILC 2010. Enoxaparin 4 000 UI/day 24 months

Hemostasis, Thrombosis and Cirrhosis

1. Cirrhosis certainly not a hemophilia-like state. Beware of hyperfibinolysis.
2. Cirrhosis certainly a prothrombotic state for splanchnic veins due to reduced flow velocity.
3. Hepatic or portal venous thromboses common in advanced cirrhosis.
4. Mounting evidence for an aggravating role of splanchnic venous thromboses in cirrhosis.
5. PT/current INR not satisfactory tests for investigating the coagulopathy of cirrhosis.

Anticoagulation in Cirrhosis

Mainly studied in a context of extrahepatic PVT

- The risk of bleeding appears to be acceptable.
- Recanal<u>ization</u> of a partial thrombus is usual.
- Recanal<u>ization</u> of complete occlusion less clear.
- The benefit of recanal<u>ization</u> is to be established.
- The places of TIPS and AC are to be clarified.

Treatment for PVT in Patients with Cirrhosis

- Complication refractory to medical/endoscopic therapy and visible intrahepatic portal veins :

  → TIPS feasible, PVT not a contraindication

- In candidates to liver transplantation and partial occlusion due to PVT:

  → Anticoagulation feasible & usually effective

Anticoagulation in Cirrhosis

In the absence of overt PVT, there might be a role for anticoagulation to prevent aggravation.

Anticoagulation in Cirrhosis

A practical issue :
How to monitor anticoagulation

- Vitamine K antagonists:
  which INR? INR_{VKA} or INR_{LIVER}?
- LMWH:
  antithrombin deficiency
  renal dysfunction
  antiXa level?

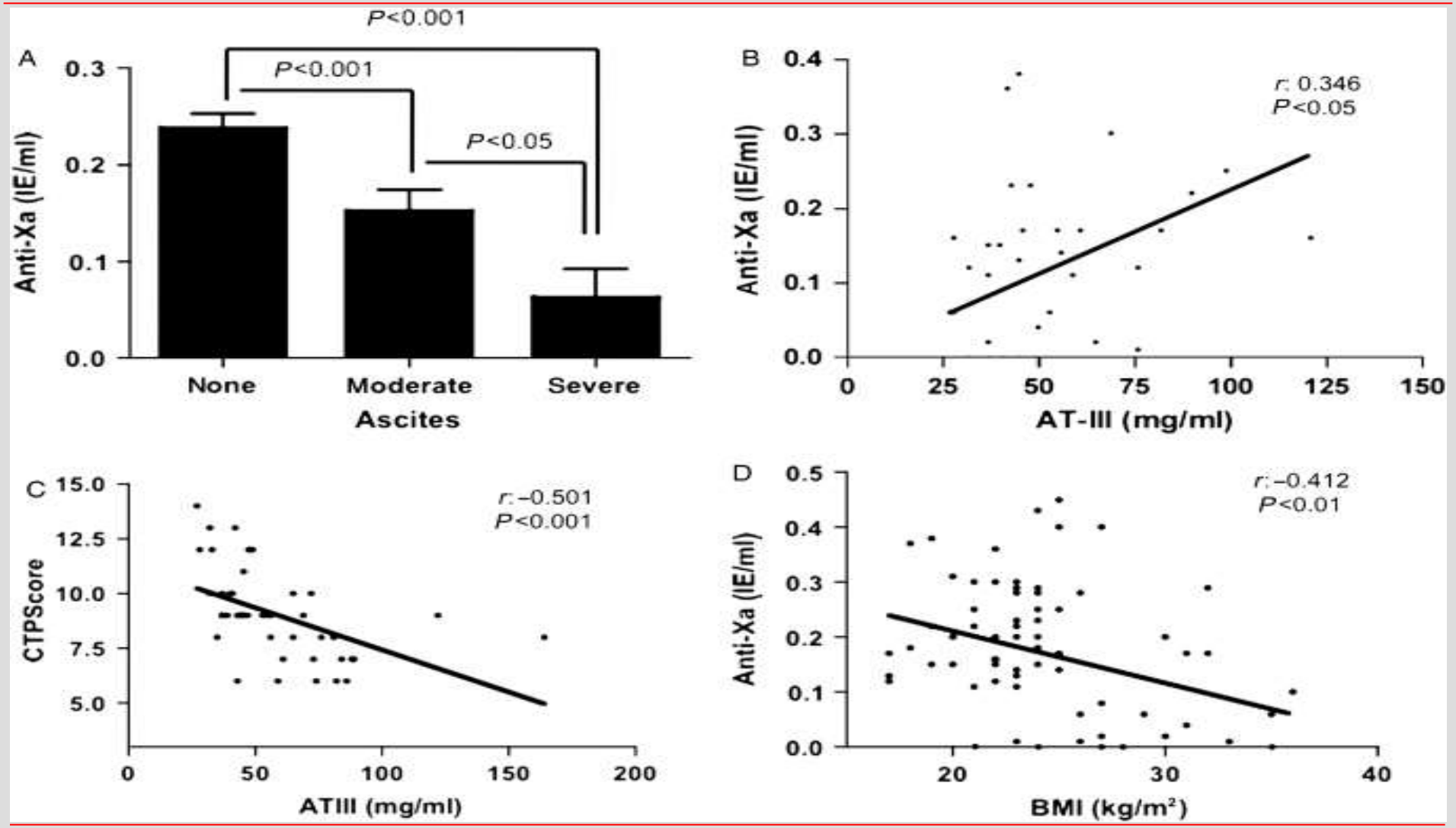
INR in Patients with Cirrhosis

- Not related to prothrombin levels along the same regression line as for Vitamin K antagonists.
- Due to uncarboxylated metabolites of coagulation factors
- Interlaboratory variability.

→ Adjustment based on Factor II level 25-35%?

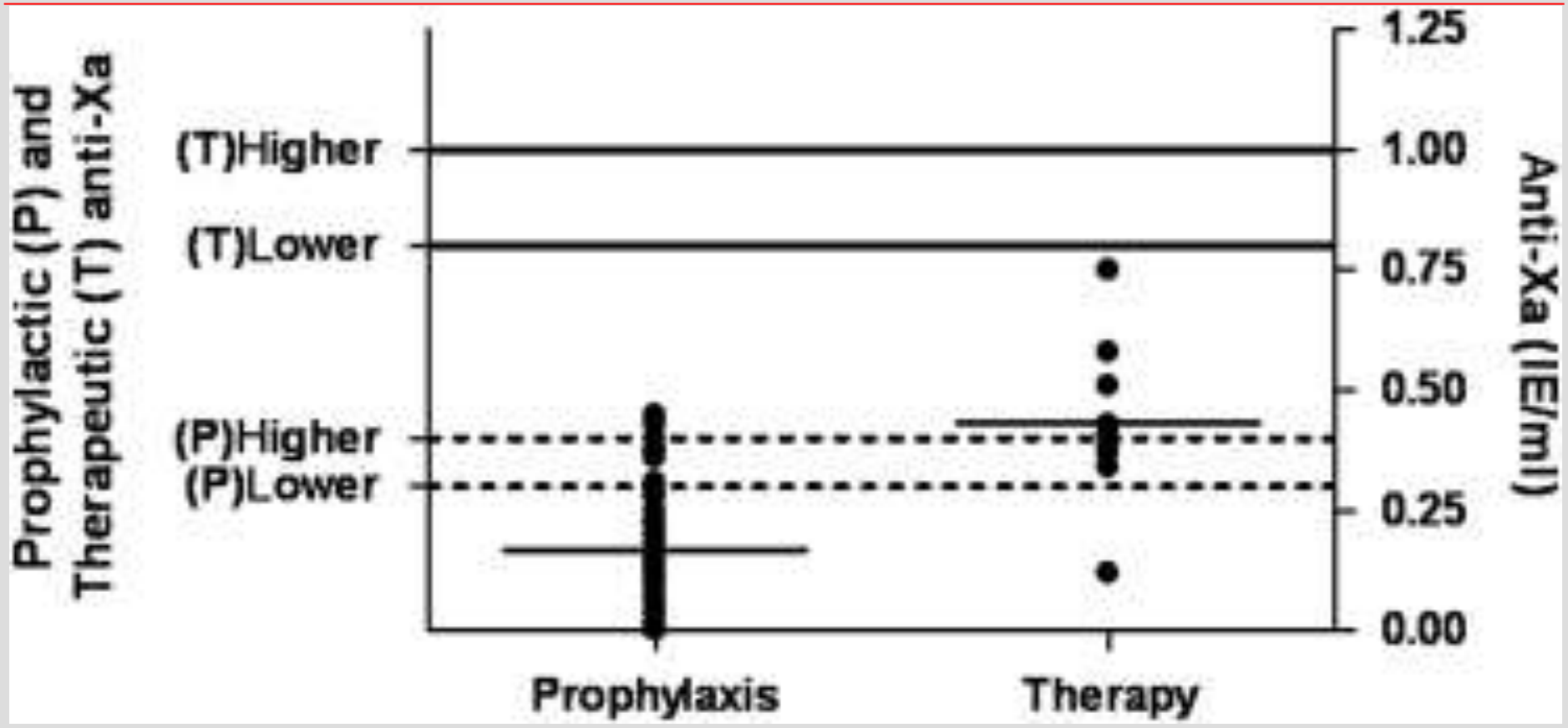
Robert, Hepatology 1996. Bellest, Hepatology 2007. Tripodi, Hepatology 2007

LMWH in Cirrhosis



Bechmann. Liver Int 2010. 75 patients with prophylactic doses

LMWH in Cirrhosis



Bechmann. Liver Int 2010.
84 patients with prophylactic (75) or therapeutic (9) doses

Risk Factors for Portal Vein Thrombosis. Cirrhosis without HCC

Univariate: Age,
Child-Pugh class,
Surgery for portal hypertension
Endoscopic sclerotherapy
Prothrombotic features

Multivariate*: G20210A FII (OR 5.94)

Mangia, Am J Gastroenterol 1999. Nonami, Hepatology 1992.
Davidson, Transplantation 1994. *Amitrano, J Hepatol 2004.

Risk Factors for Portal Vein Thrombosis. Cirrhosis without HCC

Univariate: MELD > 13
Platelets
Antithrombin
Protein C
Protein S
Portal flow velocity < 15 cm/sec

Multivariate: Portal flow velocity < 15 cm/sec

Zocco. J Hepatol 2009

Anticoagulation in Patients with Cirrhosis

Rationale

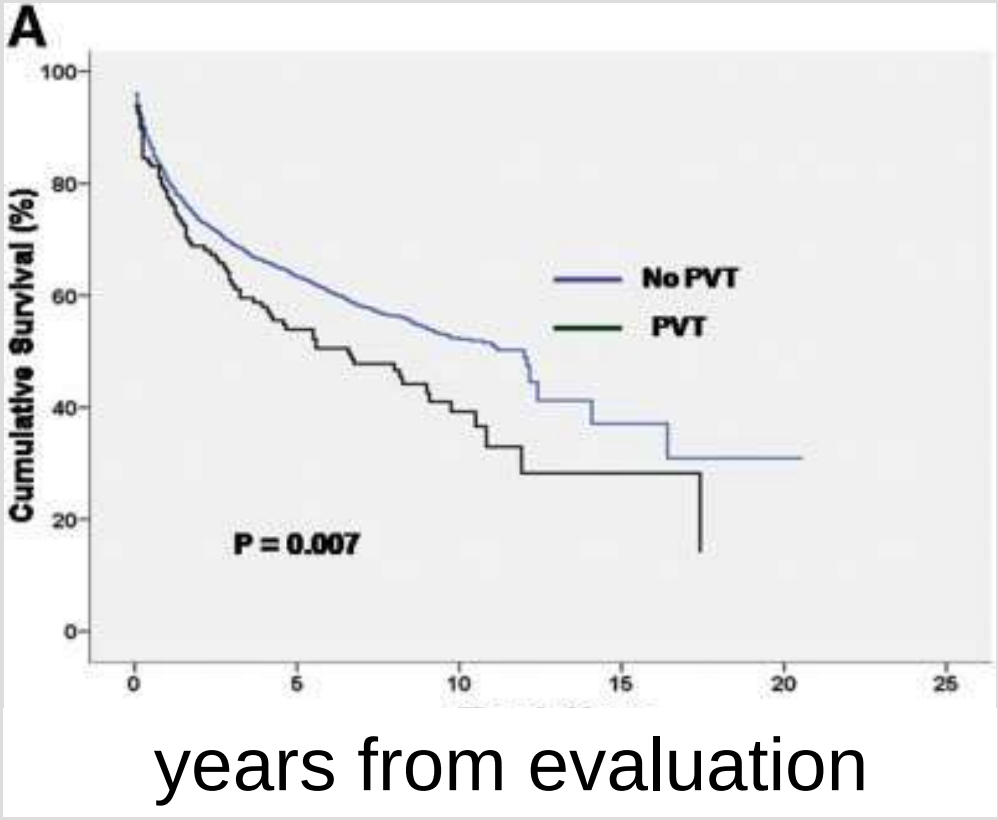
- Cirrhosis as a prothrombotic state
- Coagulation as a fibrogenic factor
- Anticoagulation in BCS and PVT
- PVT and cirrhosis severity
- PVT as a limitation to LTx

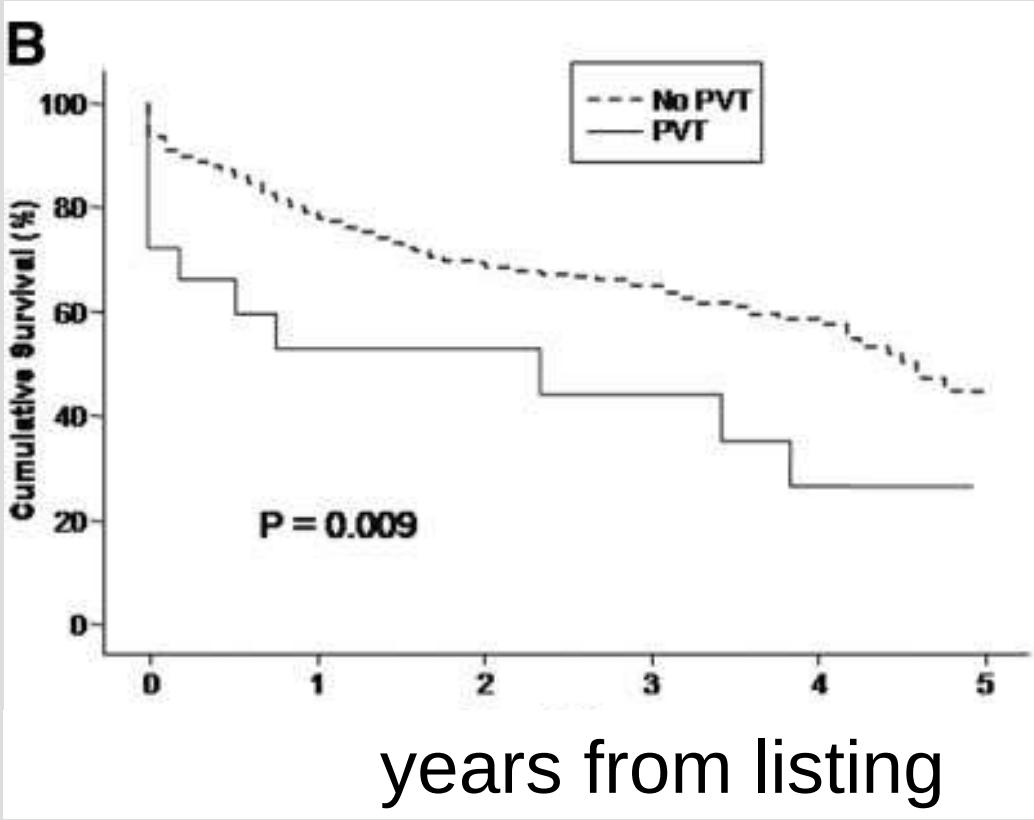
Occult PVT in Explanted Cirrhotic Livers

	Frequency
Small mural thrombus (all veins)	64 %
Intimal fibrosis (large veins)	25 %
Intimal fibrosis (small veins)	36 %

Wanless et al. Hepatology 1995;21:1238-47.

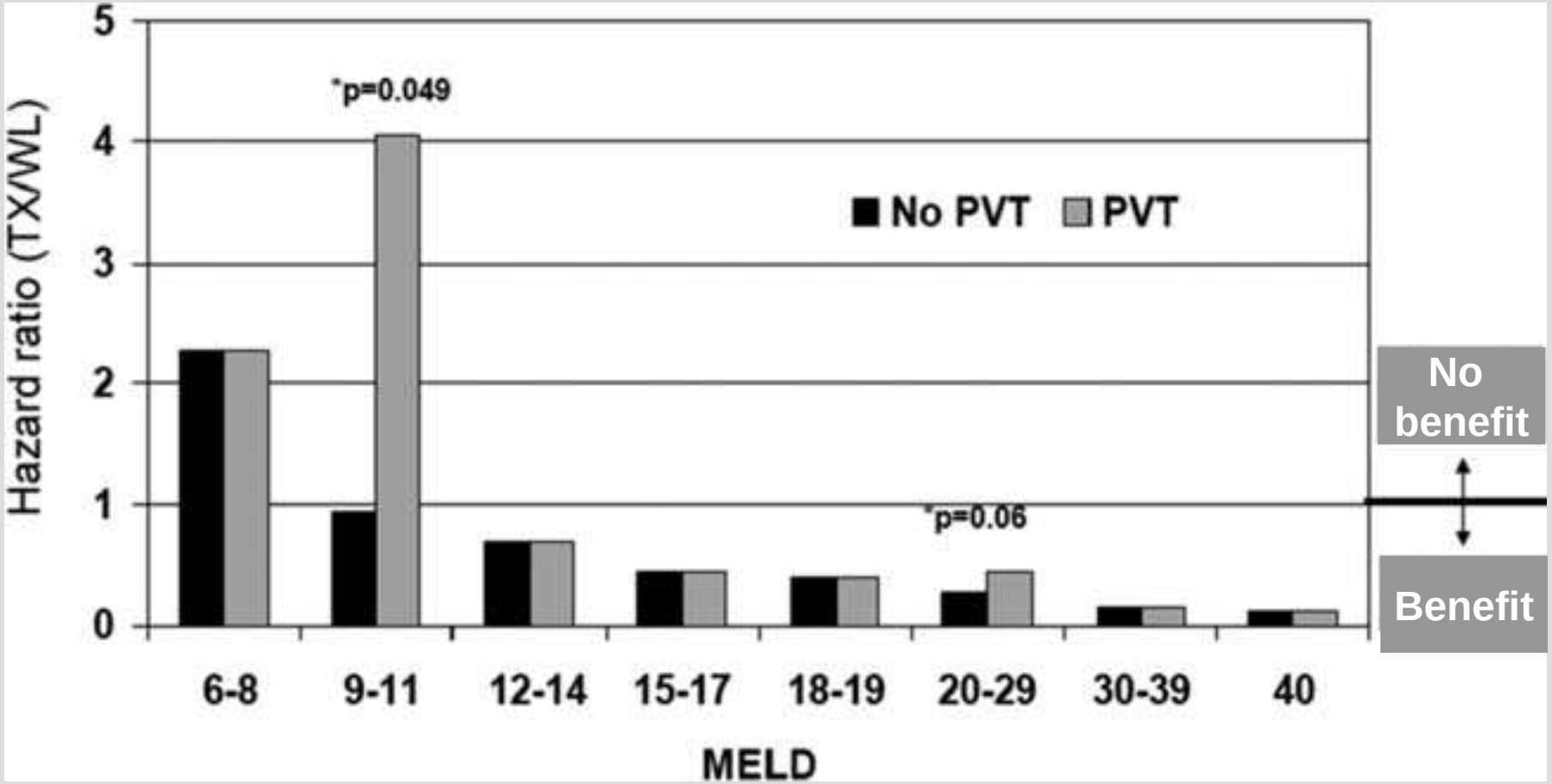
PVT and Survival in Patients with Cirrhosis





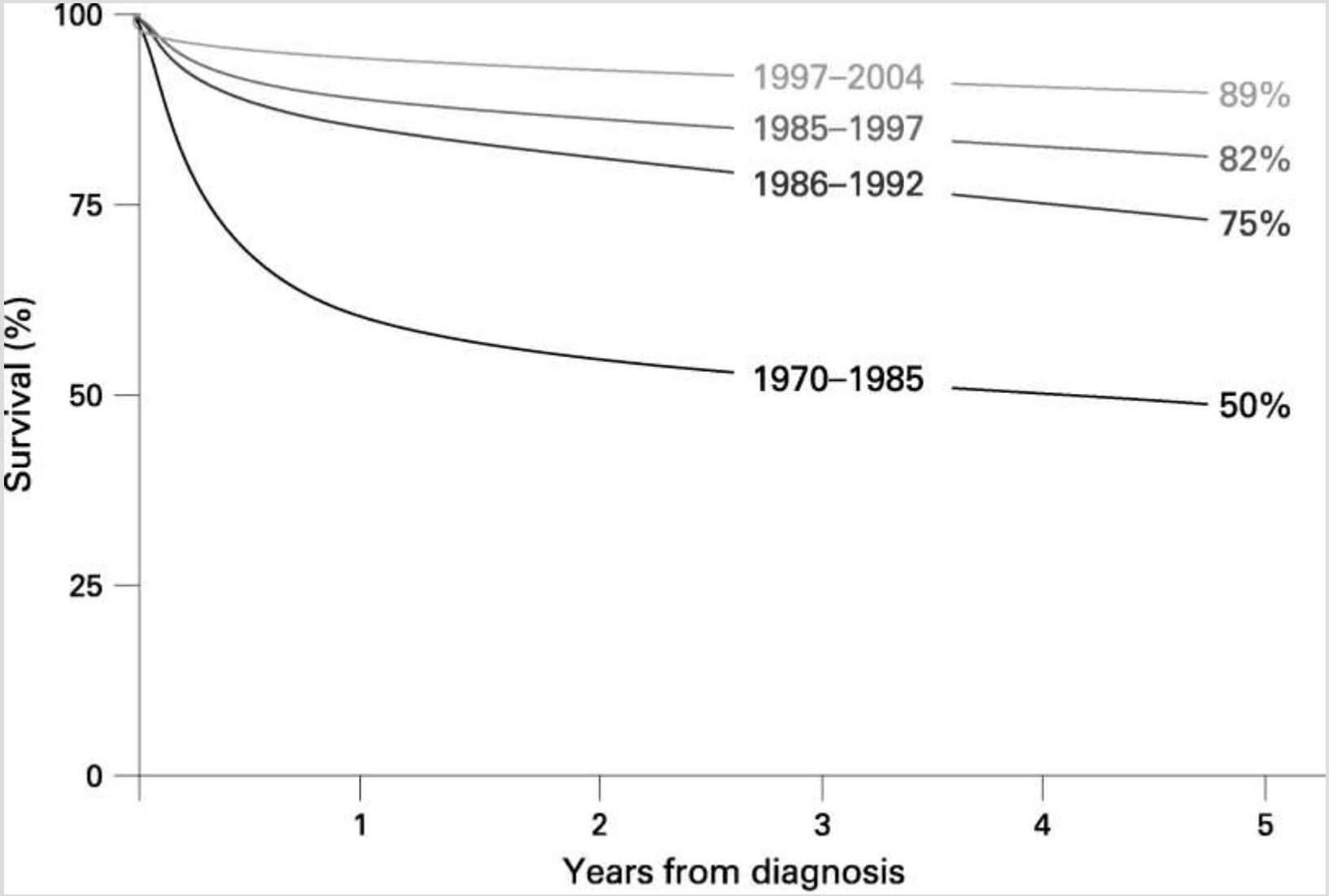
Englesbe Liver Transplant 2010a. 3295 patients with cirrhosis, 148 with occlusive PVT

PVT and LTx: Survival Benefit from LTx



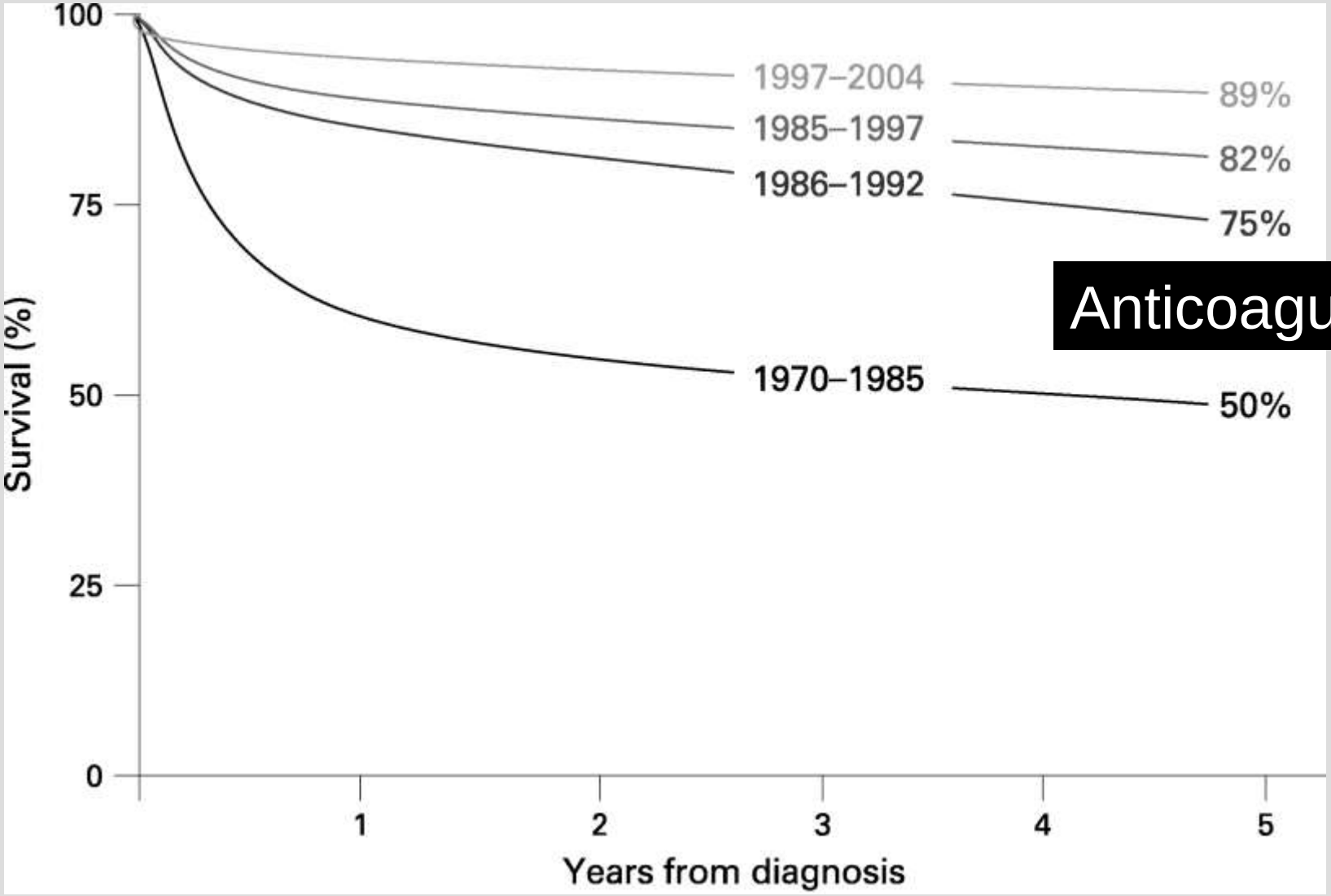
Englesbe. Liver Transplant 2010. 22,291 recipients. PVT 4.02%

HVT – Improvement in Survival



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

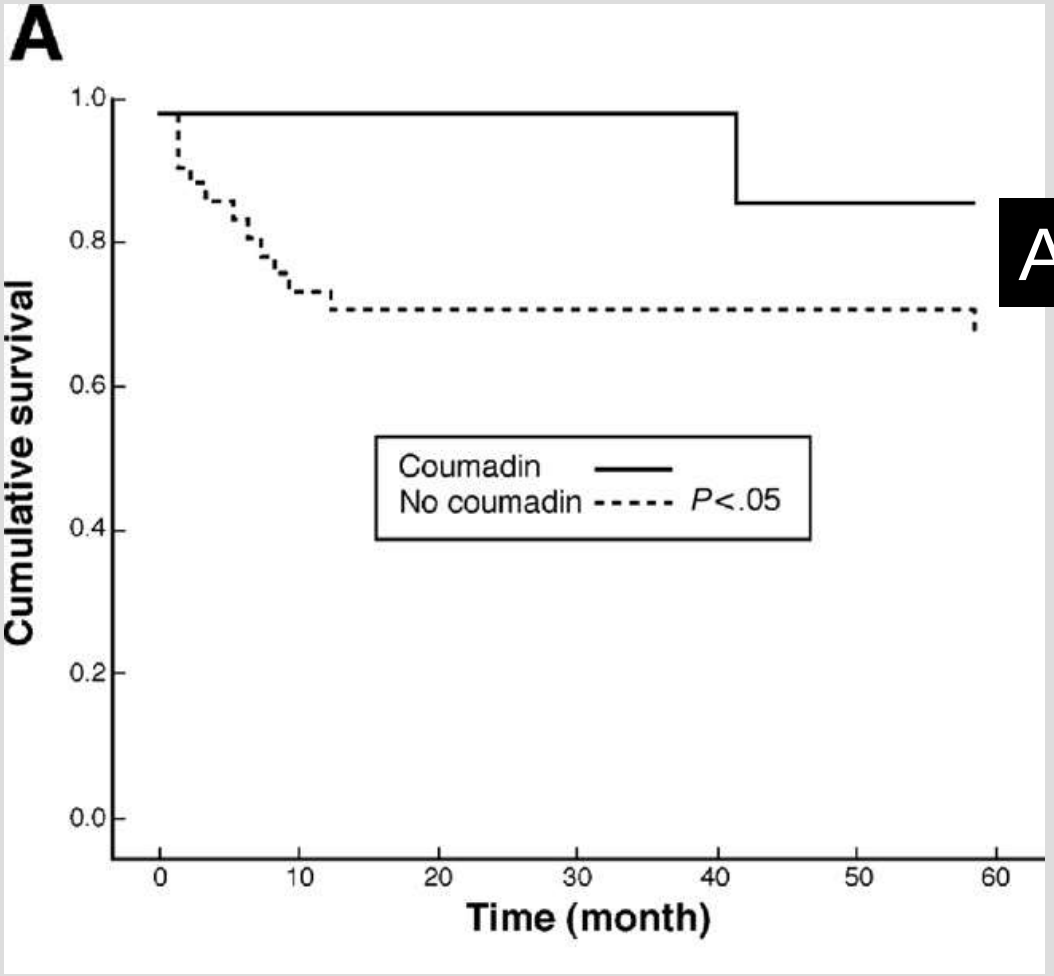
HVT: Improvement in Survival



Anticoagulation

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

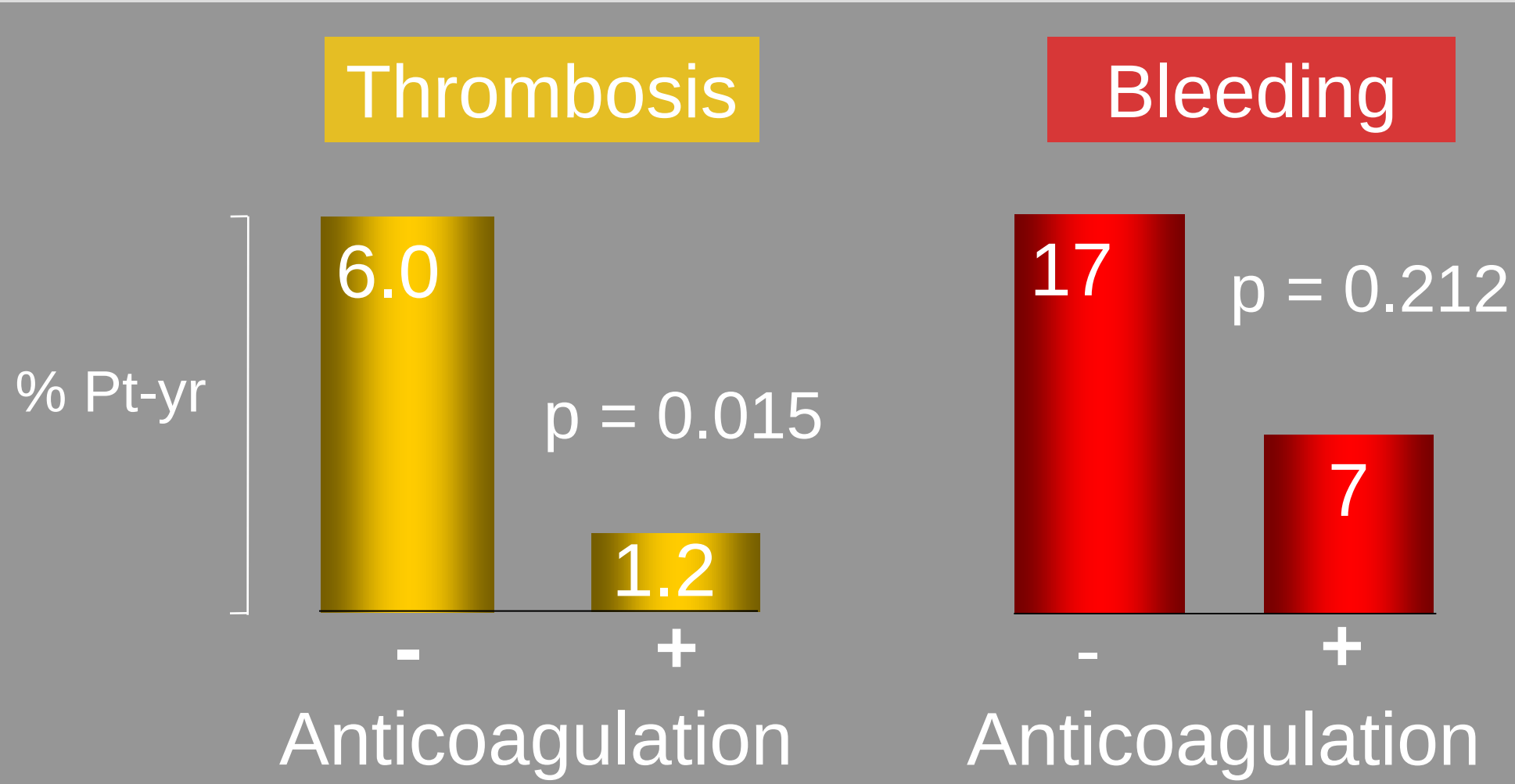
Portomesenteric venous thrombosis



Anticoagulation

Orr DW et al. Clin Gastroenterol Hepatol 2007

Portal vein thrombosis – Anticoagulation



Condat et al. Gastroenterology 2001; 120:490

Feasibility of TIPS in Cirrhosis with PVT

- Related to the type of obstruction
  - Thrombus, partial obstruction ~100%
  - Thrombus, complete obstruction ~ 90%
  - Cavernoma ~ 65%
- Predictive factors for successful insertion: Visible intrahepatic portal veins

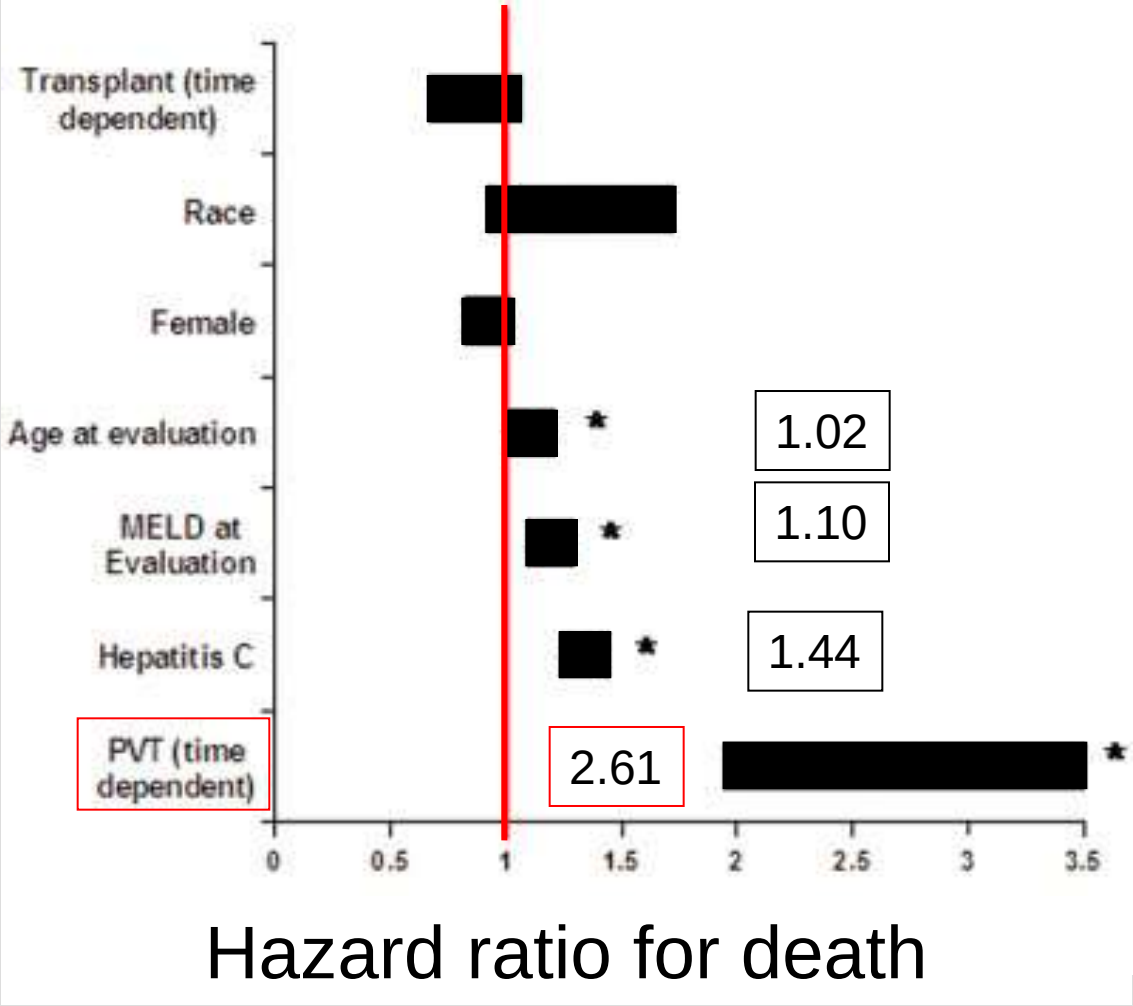
Senzolo, AP&T 2006. Van Ha, Cardiovasc Intervent Radiol 2006. Perarnaud, Eur J Gastro Hepato 2010. Han, J Hepatol 2010

Results of TIPS in Cirrhosis with PVT

- Dysfunction ~ 25-30% at 1 yr
  Similar to patients without PVT
- Encephalopathy ~ 20-25% at 1 yr
- Impact on complications of cirrhosis
  Limited data.
  Mortality similar to patients without PVT

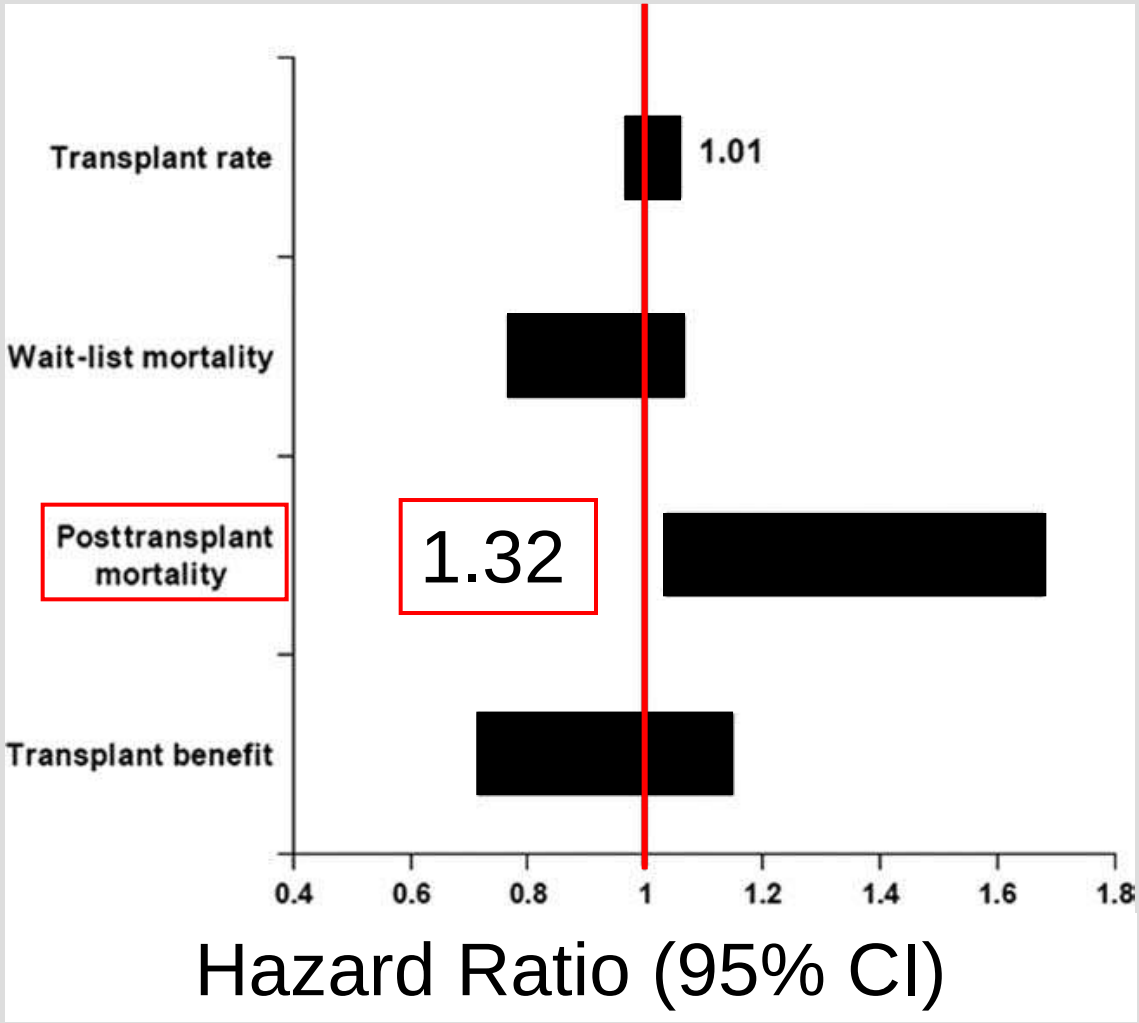
Senzolo, AP&T 2006. Van Ha, Cardiovasc Intervent Radiol 2006. Perarnaud, Eur J Gastro Hepato 2010. Han, J Hepatol 2010

PVT and Survival in Patients with Cirrhosis



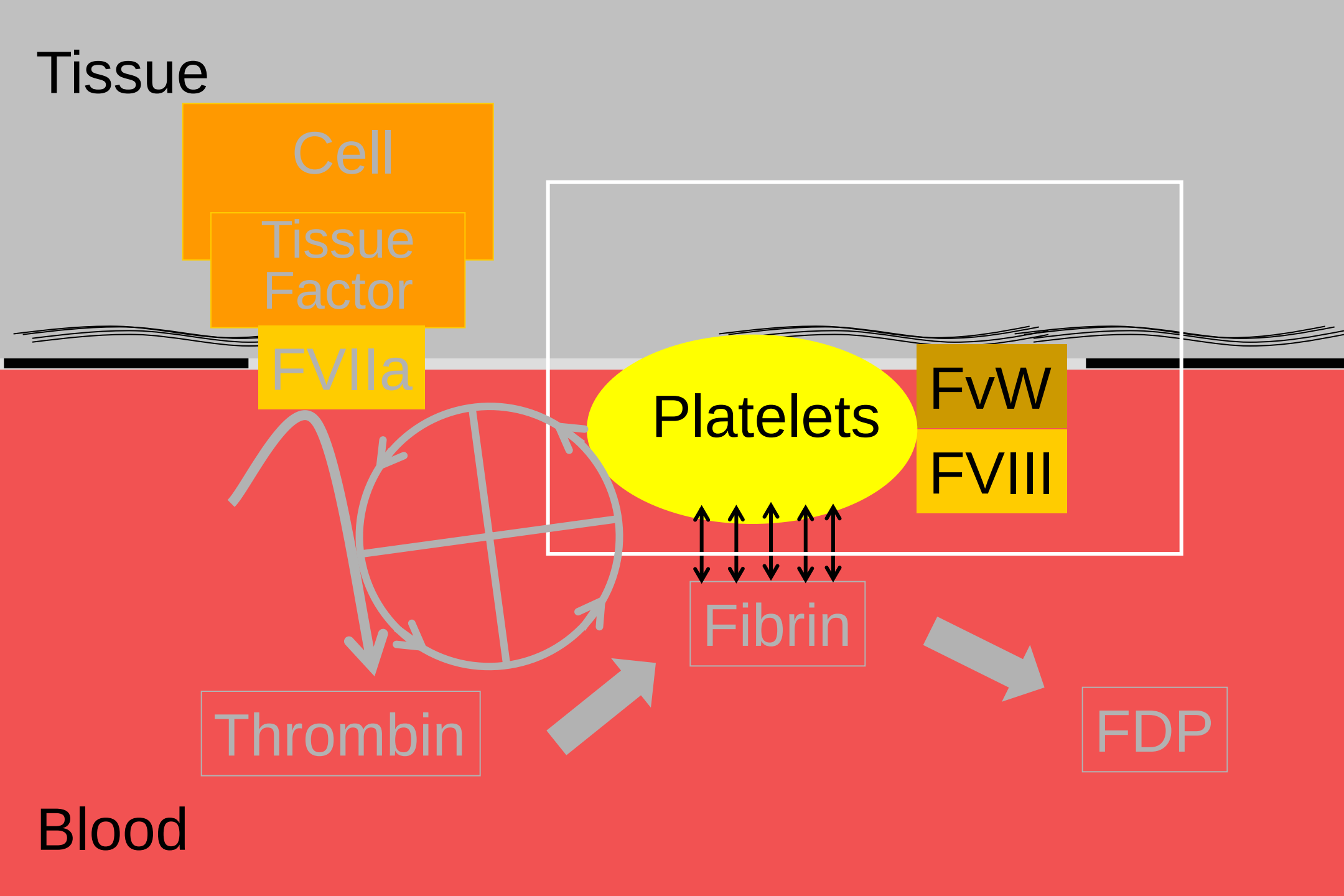
Englesbe Liver Transplant 2010. 3295 patients with cirrhosis, 148 with occlusive PVT

Impact of PVT on pre and post LTx survival



MELD 9-11

Englesbe. Liver Transplant 2010. 22,291 recipients. PVT 4.02%


Tissue
Cell
Tissue Factor
FVIIa
Platelets
FvW
FVIII
Fibrin
Thrombin
FDP
Blood

Maladies du Foie

	Variabilité due à la thromboplastine
• Temps de Quick	++++
• Ratio de Temps de Quick M/T	++
• % activité M/T (Taux de Quick)	+
• INR	+++

Robert, Hepatology 1996

Maladies du Foie

	Variabilité due à la thromboplastine
• Temps de Quick	++++
• Ratio de Temps de Quick M/T	++
• % activité M/T (Taux de Quick)	+
• INR	+++
• Child-Pugh ou MELD	+++

Trotter Liver Transpl 2004

De l'INR à l'INR_{AVK} et à l'INR_{FOIE}

Plasma de Patients
AVK
↓
ISI_{AVK}
↓
INR_{AVK}

Plasma de Patients
FOIE
↓
ISI_{FOIE}
↓
INR_{FOIE}

Bellest Hepatology 2007. Tripodi Hepatology 2007

De l'INR_{AVK} à l'INR_{FOIE}

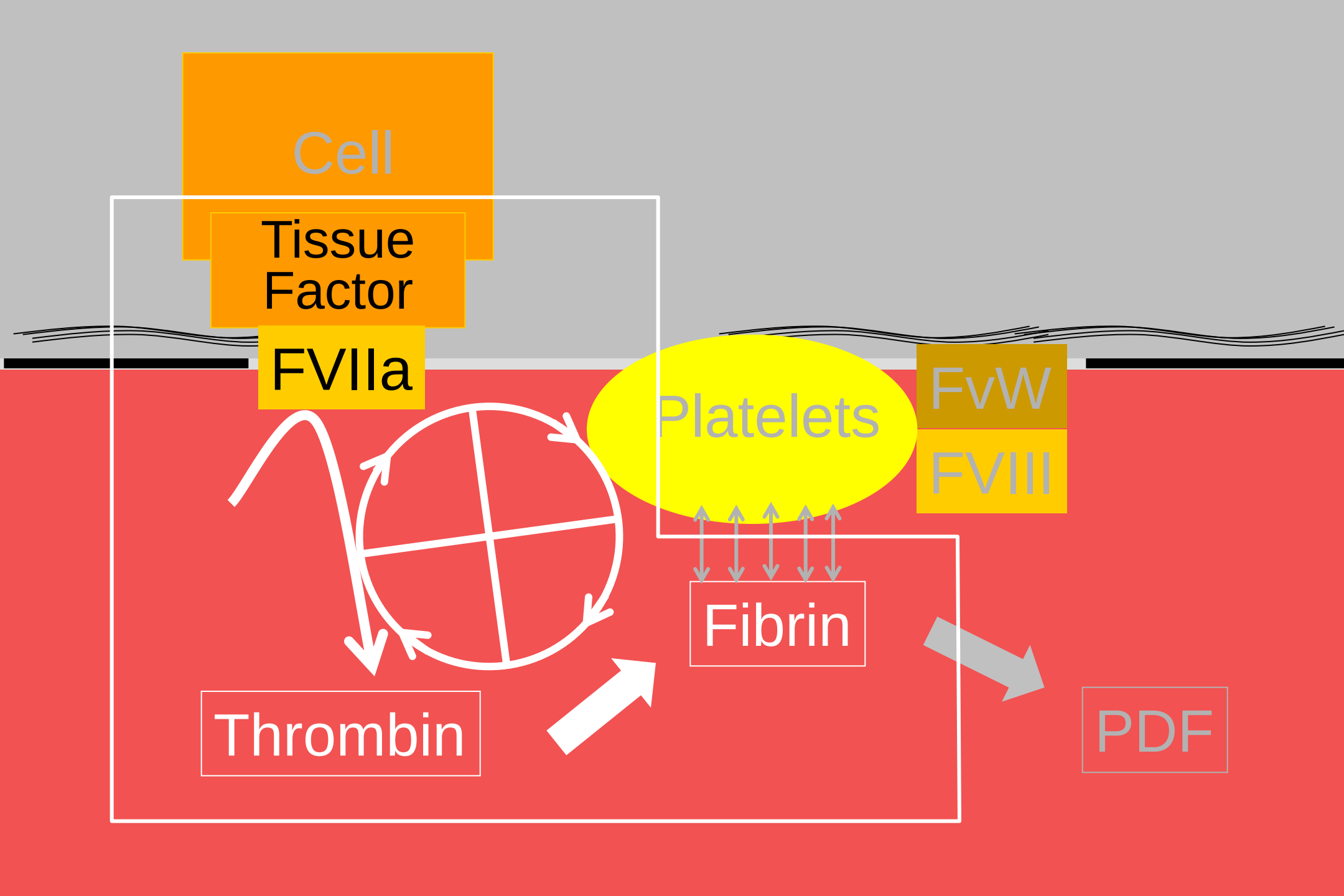
	Influence de la Thromboplastine
• Temps de Quick	++++
• Ratio de Temps de Quick M/T	++
• % activité M/T (Taux de Quick)	+
• INR_{AVK}	+++
• INR_{FOIE}	0

Bellest Hepatology 2007. Tripodi Hepatology 2007

Extrahepatic PVT in Cirrhosis

	Incidence
Sclerotherapy	12 per 100 pt-yr
Listed for LTx	18 per 100 pt-yr

Amitrano, Endoscopy 2002. Francoz, Gut 2005


Cell
Tissue Factor
FVIIa
Platelets
FvW
FVIII
Fibrin
Thrombin
PDF