CHU CLERMONT FERRAND

CENTRE HOSPITALIER UNIVERSITAIRE

Génération de thrombine et cirrhose

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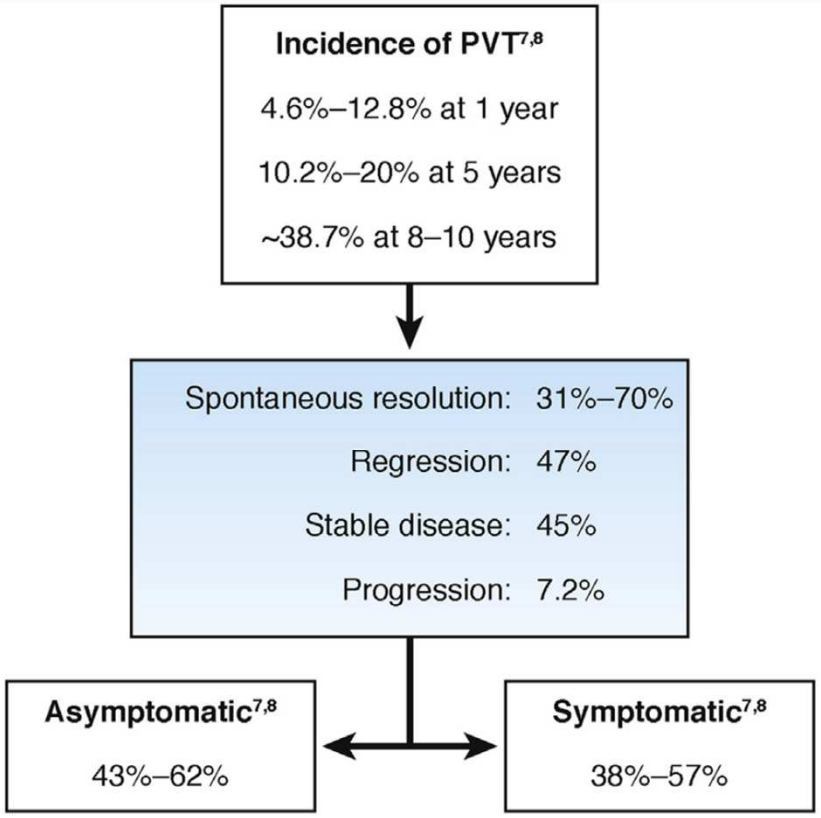
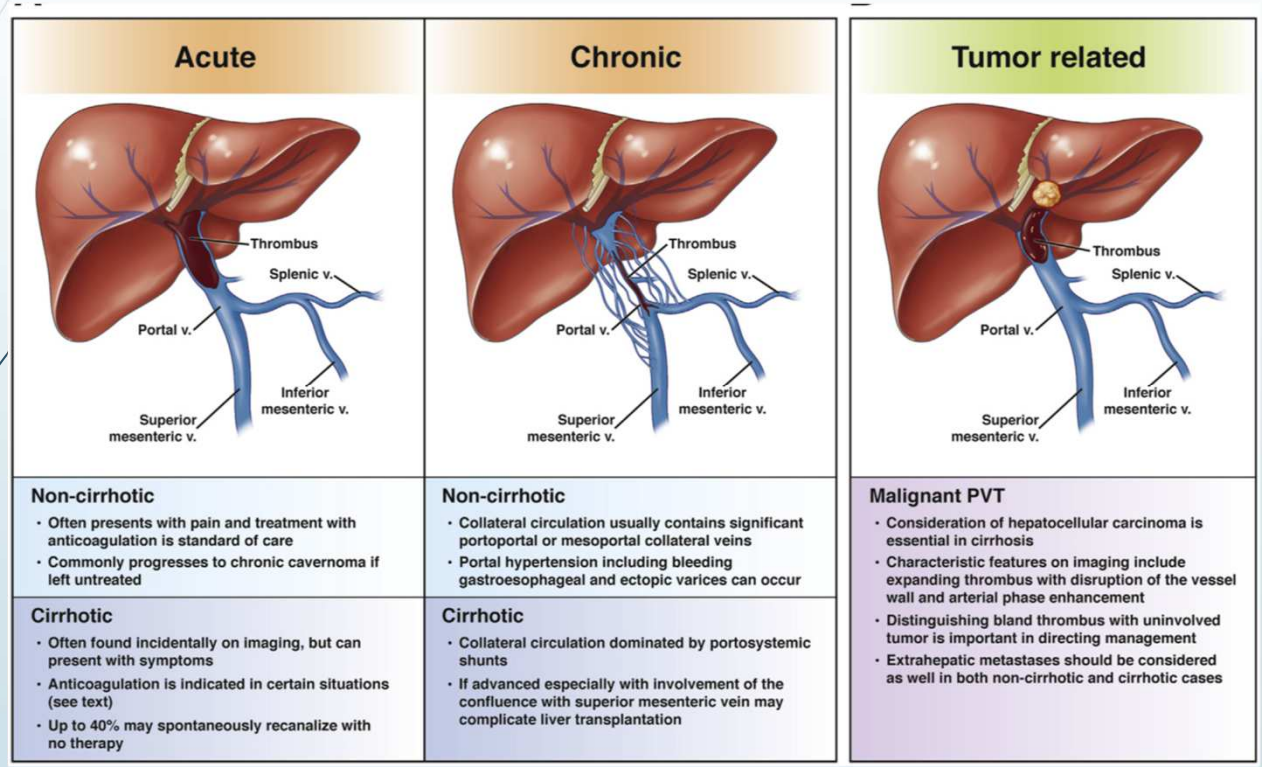
23/05/2019

TVP et cirrhose : épidémiologie et clinique



Sarin et al. Gastroenterology 2016

TVP et cirrhose



Intagliata et al. Gastroenterology 2019

TVP et cirrhose
Classification de Yerdel

Grade 1: minimally or partially thrombosed PV where in thrombus is mild or confined to <50% of lumen with or without extension into SMV

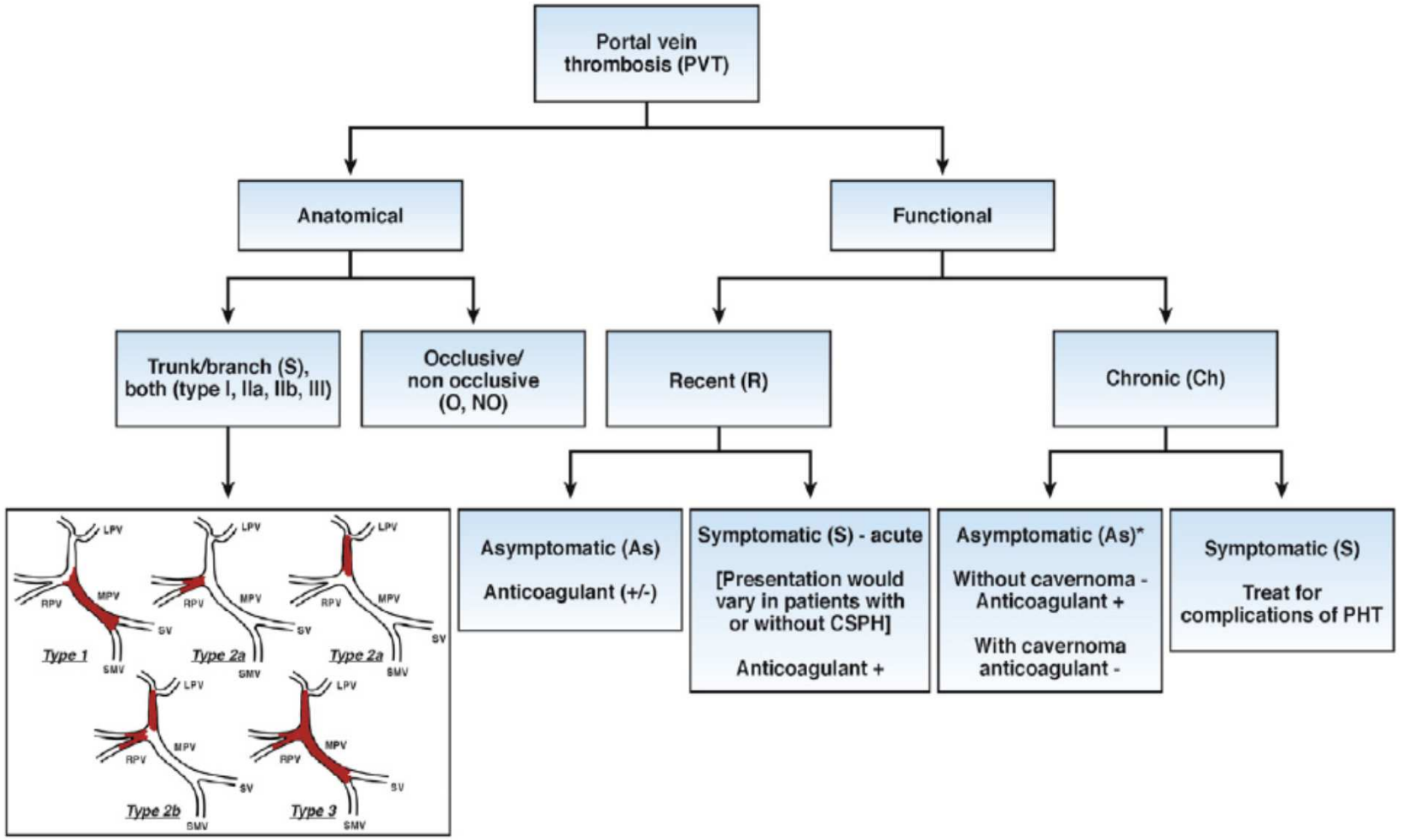
Grade 2: >50% occlusion including total occlusion with or without minimal extension into SMV

Grade 3: complete thrombosis of both PV and proximal SMV

Grade 4: complete thrombosis of PV and both proximal and distal SMV

Yerdel et al. Transplantation 2000

TVP et cirrhose
Classification de Sarin



*In patients with procoagulant states, antigoagulation is recommended to prevent extension of PVT.[7]

Sarin et al. Gastroenterology 2016

TVP et cirrhose : facteurs de risque

Major Characteristic
Child's class B or C cirrhosis
Prior history of resolved PVT
Associated prothrombotic risk factors – factor V LM, prothrombin gene mutation, MTHFR mutation.

Sarin et al. Gastroenterology 2016

TVP et cirrhose : facteurs de risque

Minor Characteristic
Evidence of a largacte portosystemic shunt, large IGV1
Active hepatocellular malignancy
History of/or active systemic venous thrombotic events or abortions
Clinical symptoms and signs of acute abdomen
New onset or worsening portal hypertension complications
Recent abdominal interventions – endoscopic, radiological or surgical
Portal flow velocity < 15 cm per second at any time during prior Doppler evaluations

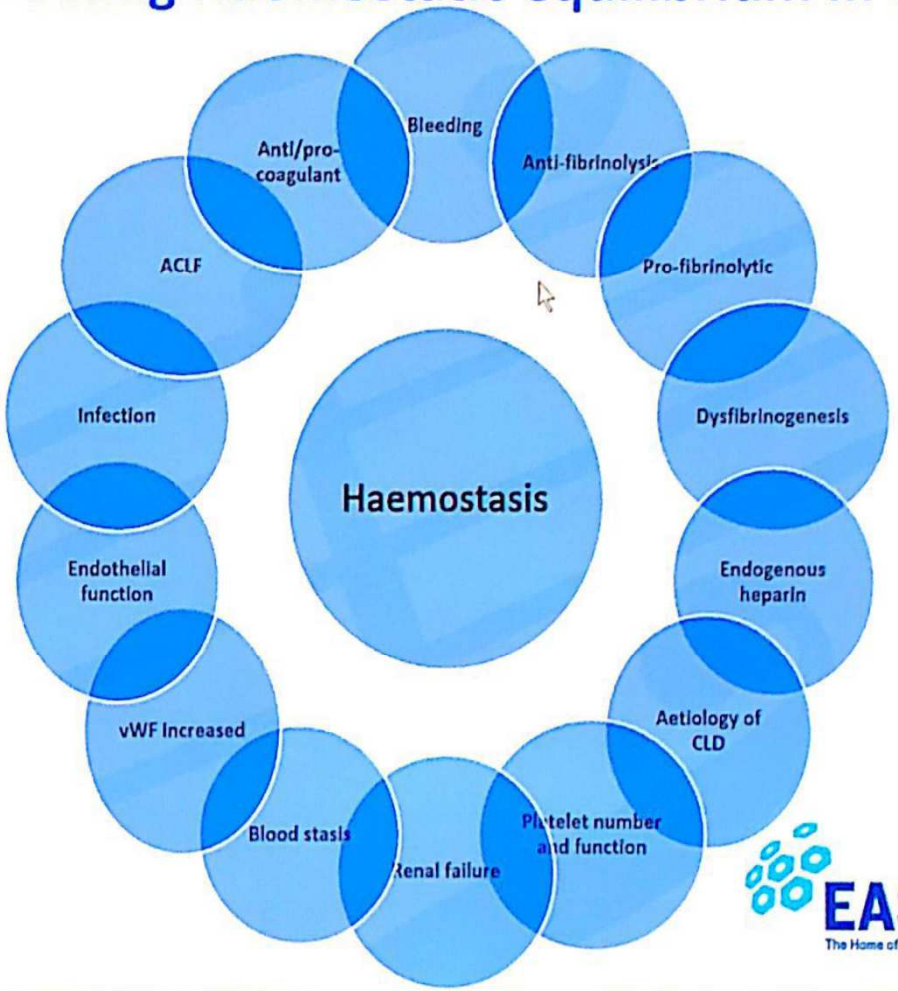
Sarin et al. Gastroenterology 2016

TVP et cirrhose : facteurs de risque

- Systemic disorder
  - Advanced portal hypertension with reduced portal flow velocity
  - Steal syndrome from large spontaneous portosystemic shunts
  - Malignancy
- Inherited thrombophilia[b]
  - Factor V Leiden
  - Prothrombin gene G20210A mutation
- Acquired thrombophilia
  - Increased Factor VIII
  - Protein C and S deficiency, antithrombin deficiency
- Other systemic risk factors
  - Non-alcohol steatohepatitis
  - Other extrinsic factors
- Local
  - Abdominal malignancy (HCC)
  - Intrabdominal surgery (hepatectomy, surgical shunt)
  - Local regional therapy for HCC (TACE, radioembolization)
  - TIPS

Intagliata et al. Gastroenterology 2019

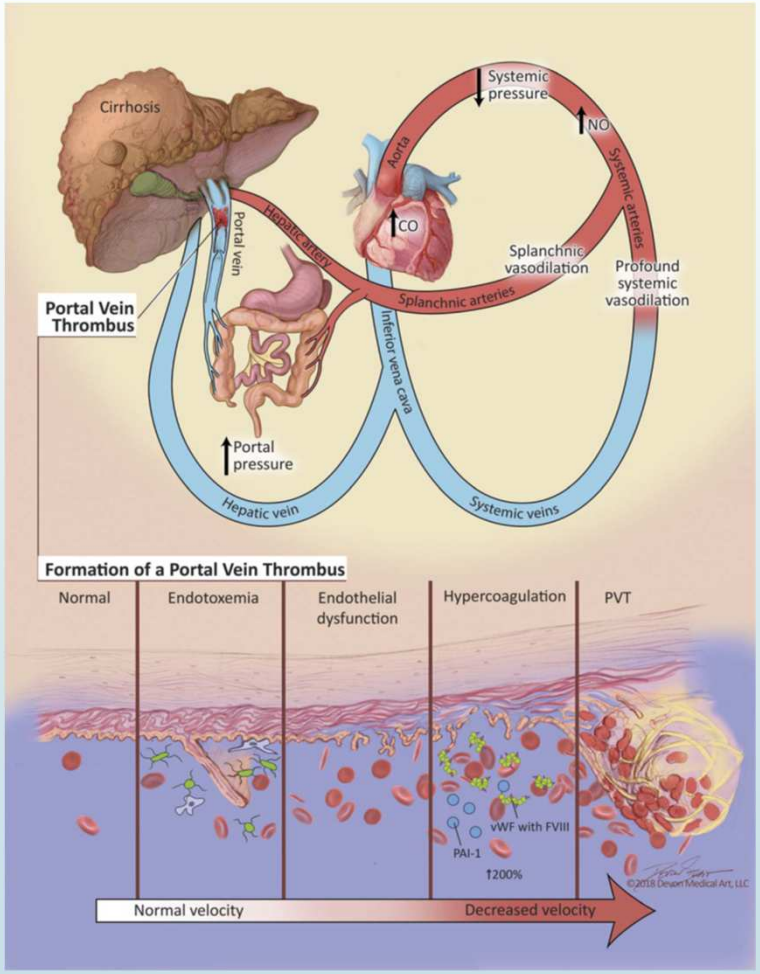
Factors Affecting Haemostatic equilibrium In Cirrhosis



EASL The Home of Hepatology | THE INTERNATIONAL LIVER CONGRESS™ 2019

Senzolo M. EASL 2019

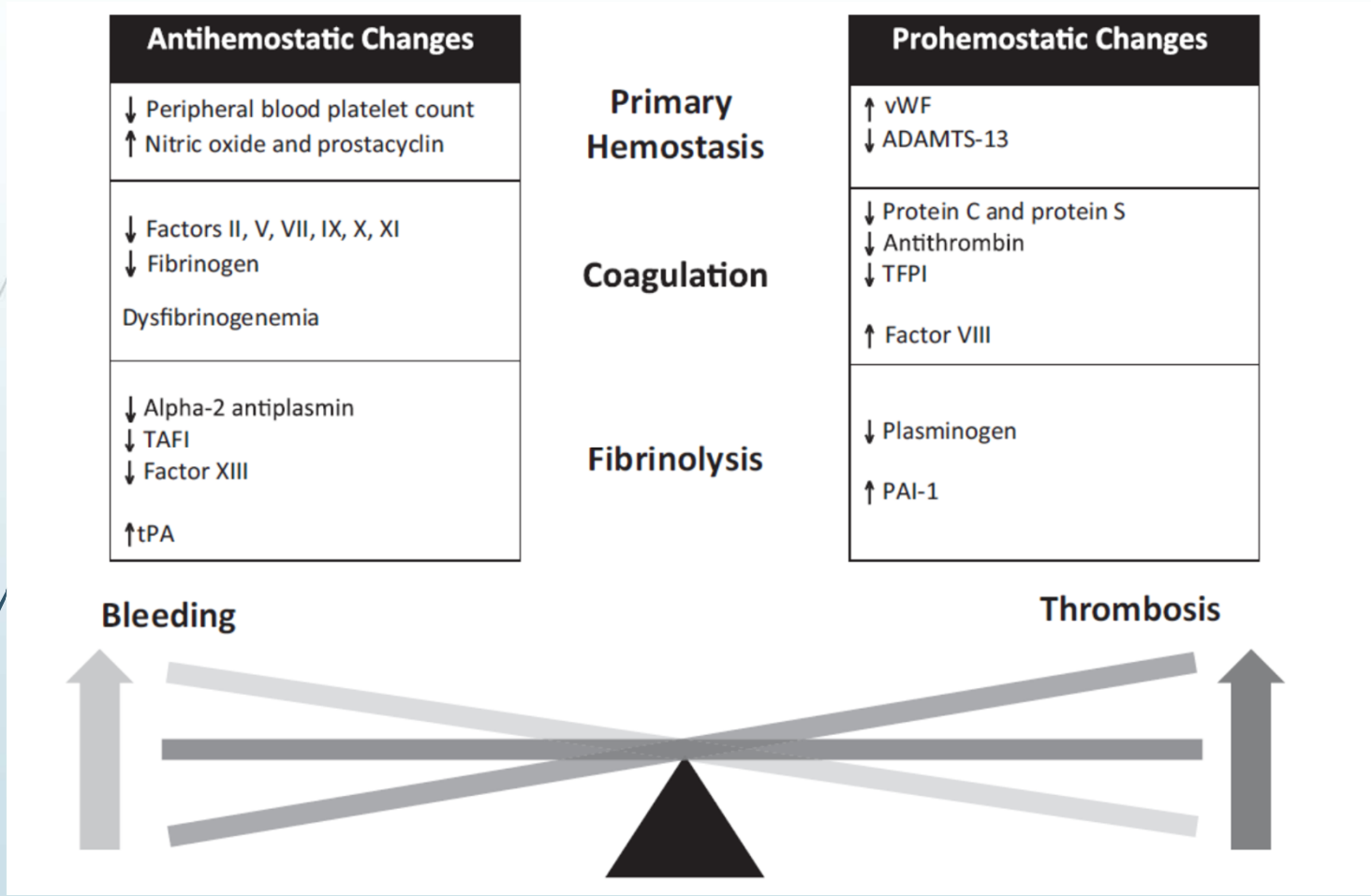
TVP et cirrhose : facteurs de risque
Triade de Virchow



Verbeek et al. Transplantation Direct 2018

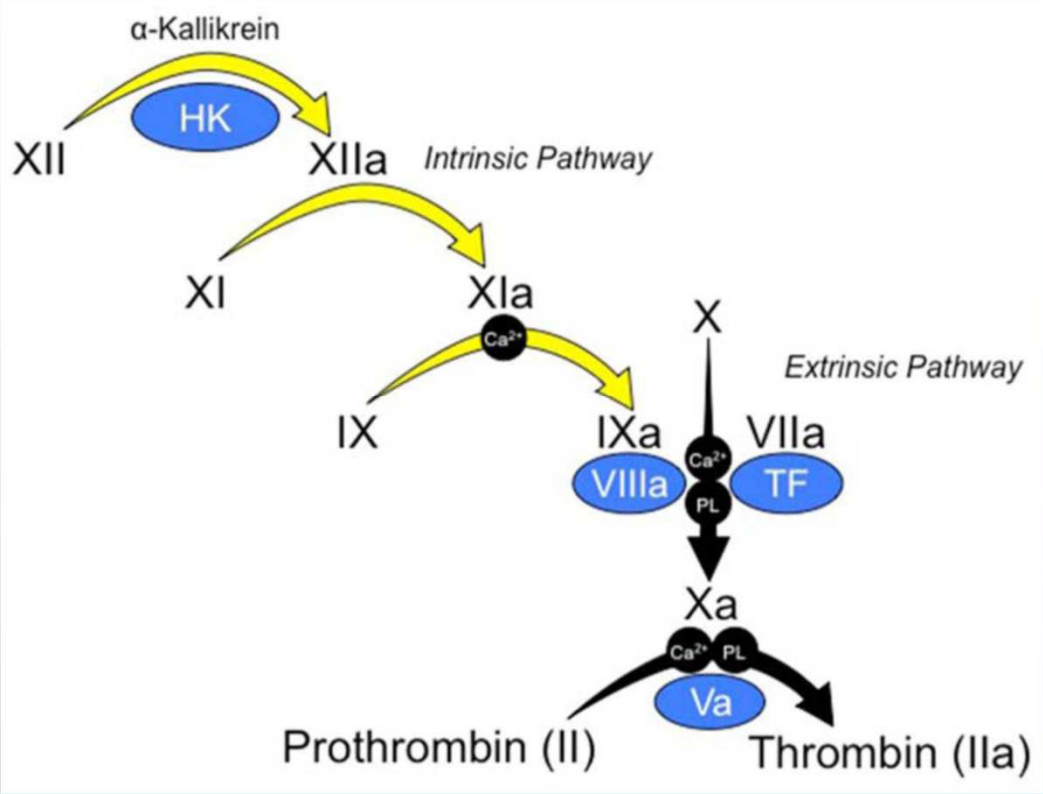
Coagulation : rappels

Hémostase et cirrhose



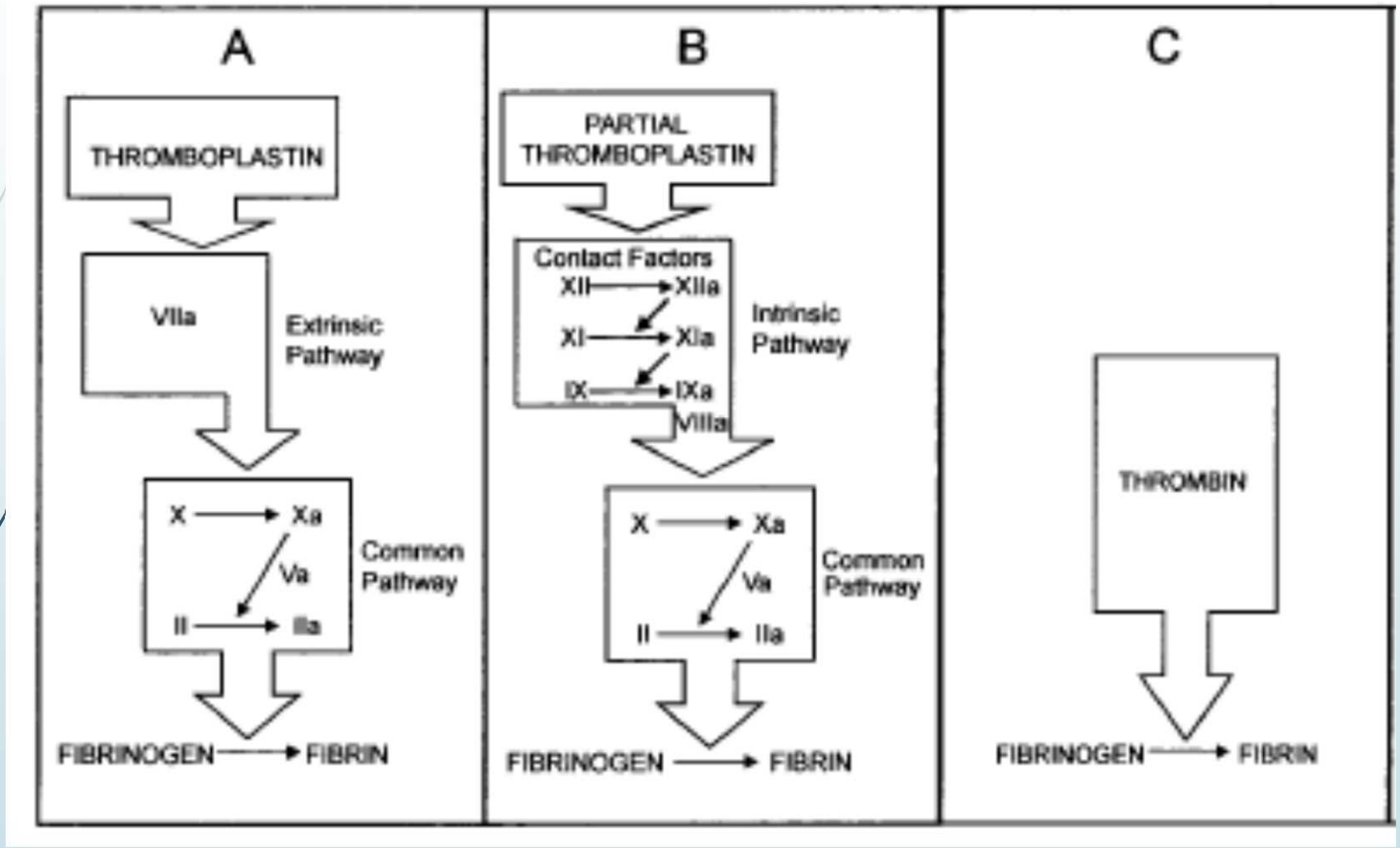
Northup et Reutemann. Liver Transplant 2018

Schéma classique de la coagulation
Voie extrinsèque et voie intrinsèque



Weeler et al. Expert Rev Hematol 2017

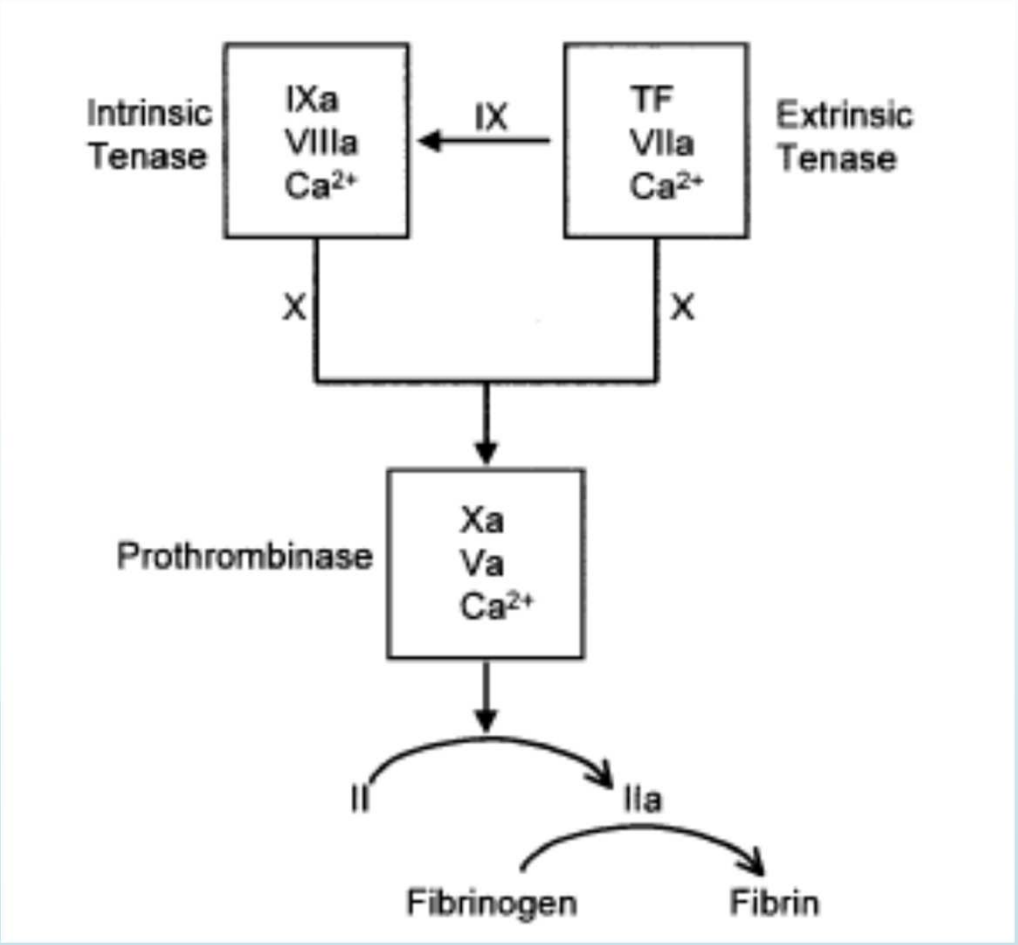
La cascade
Intérêt pour la compréhension des tests de coagulation



TP **TCA** **TT**

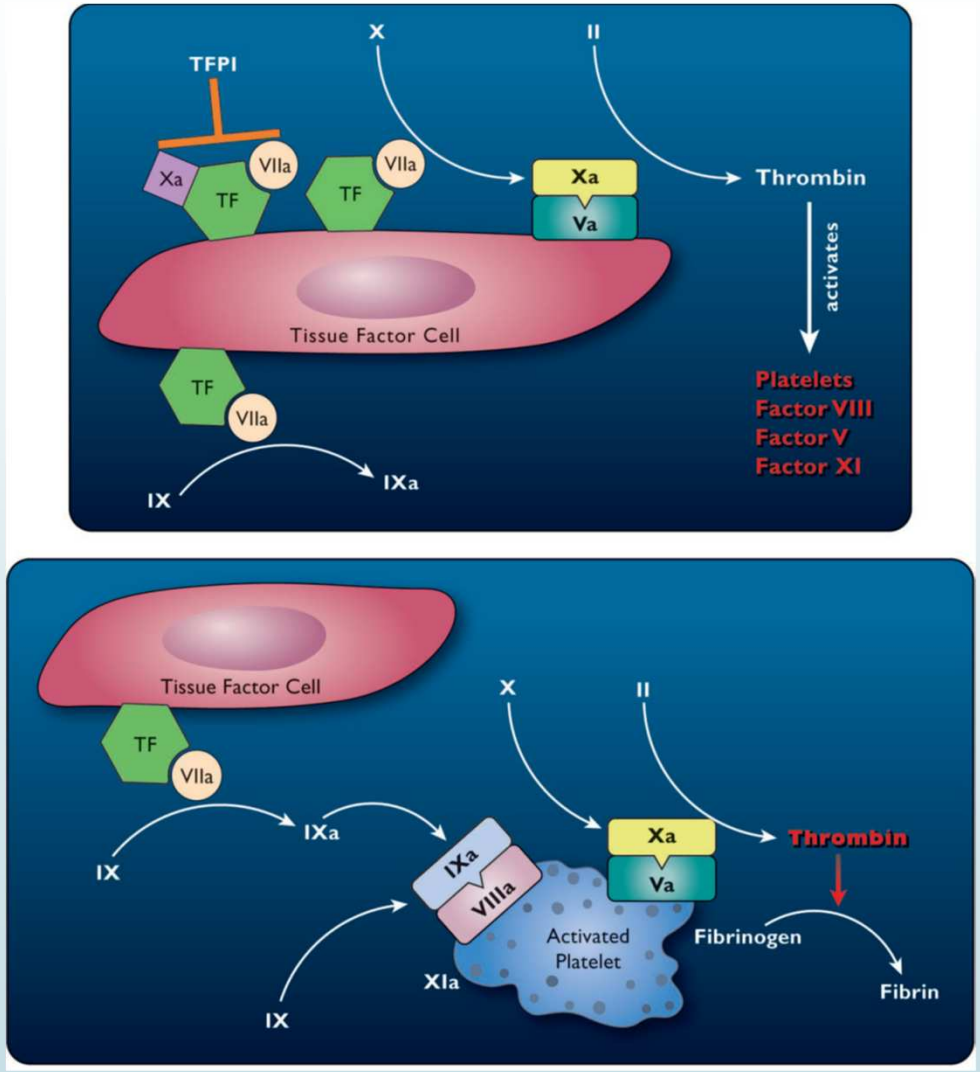
Bates and Weitz. Circulation 2005

Rôle du facteur tissulaire dans les 2 voies (voie extrinsèque et voie intrinsèque)



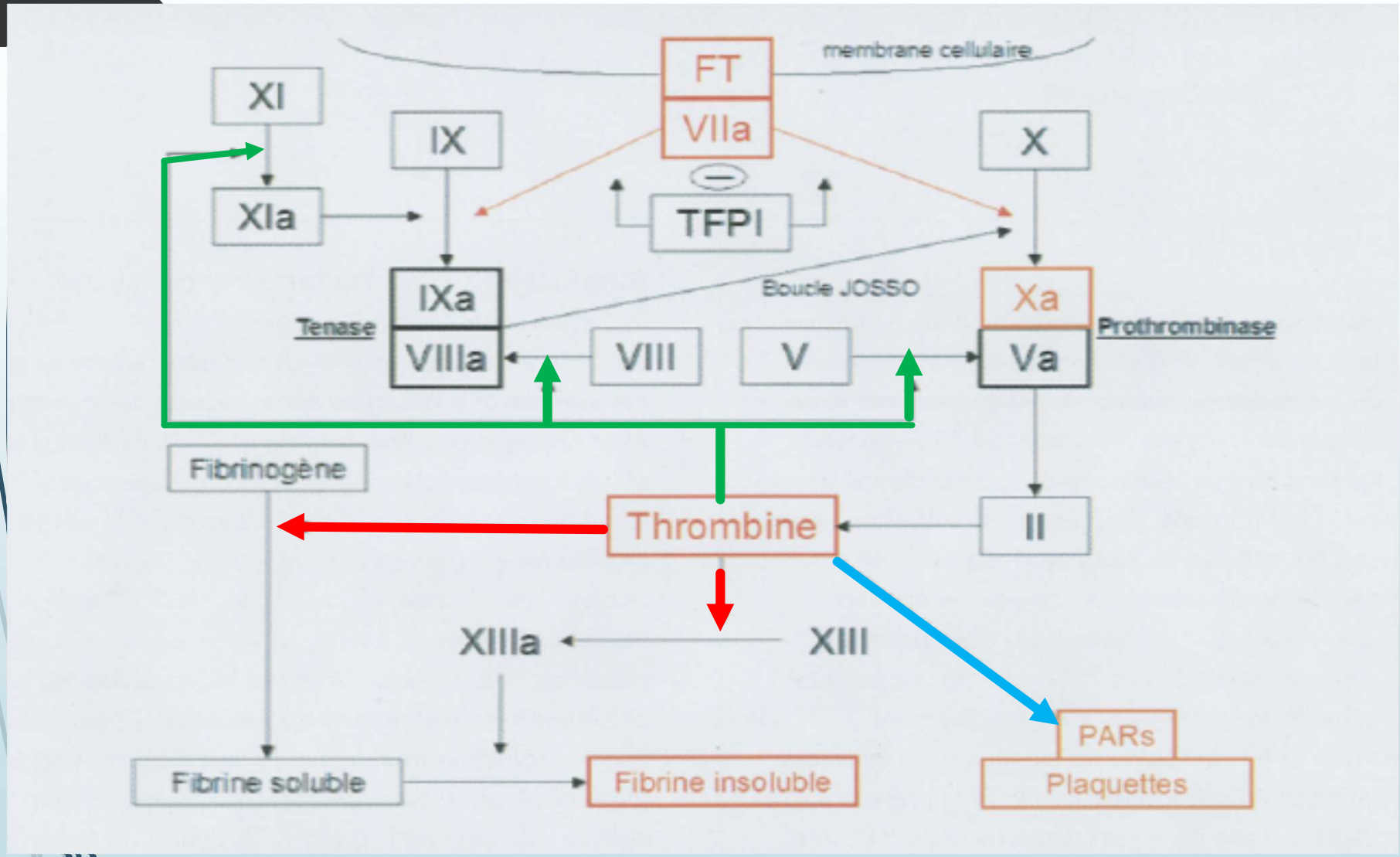
Bates and Weitz. Circulation 2005

Rôles des cellules : cellules porteuses de FT et plaquettes



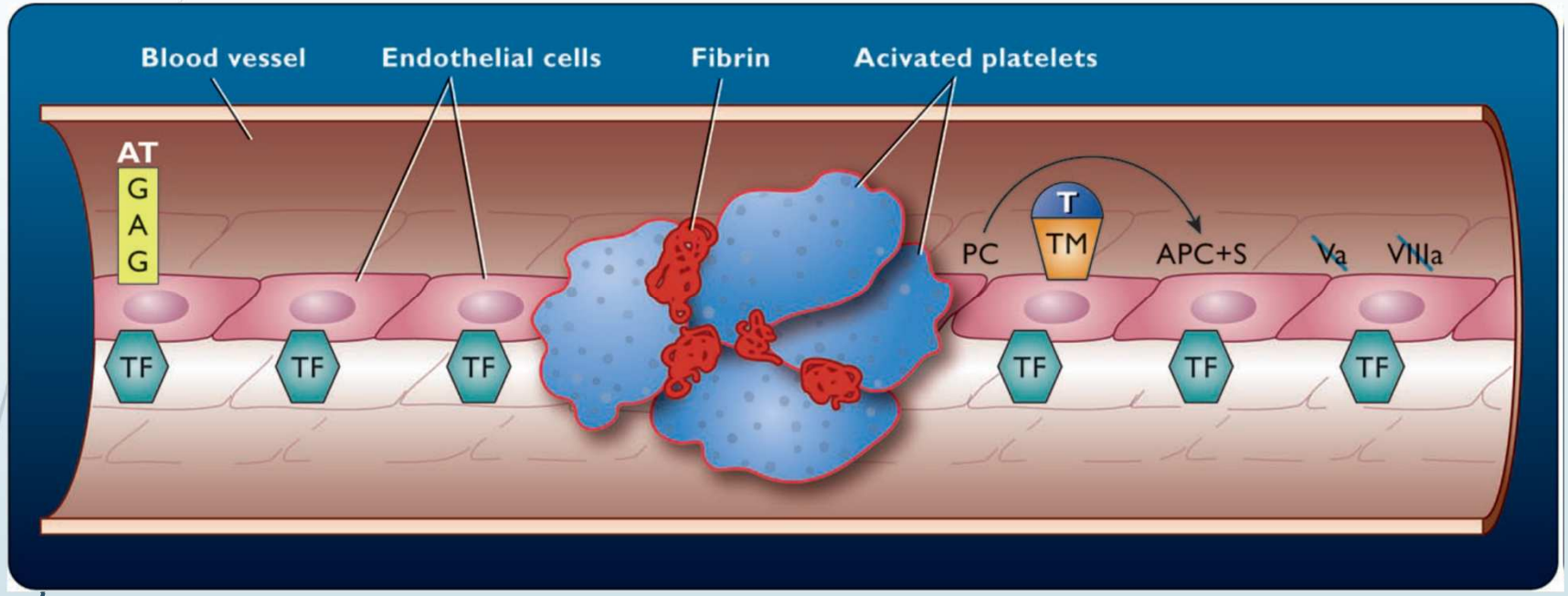
Roberts et al. Anesthesiology 2004

Rôle de la thrombine



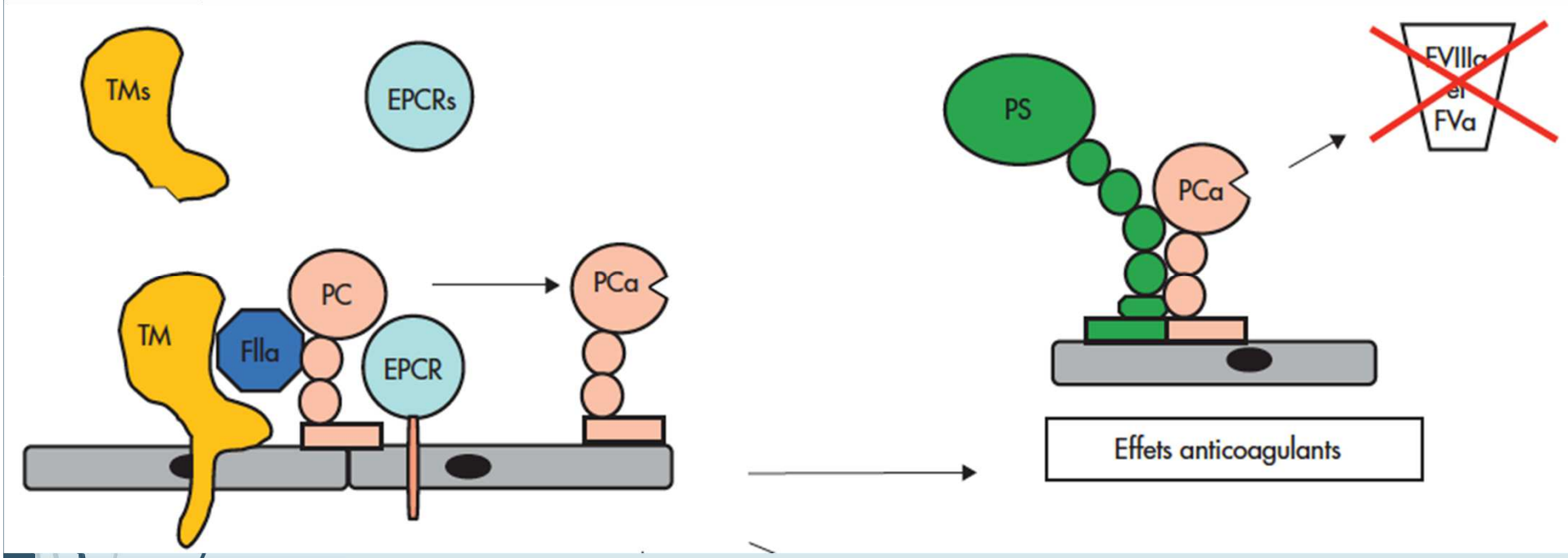
De Prost et al. Revue Francophone des Laboratoires 2006

Mécanismes de contrôle des effets de la thrombine l'antithrombine et la protéine C activée



Roberts et al. Anesthesiology 2004

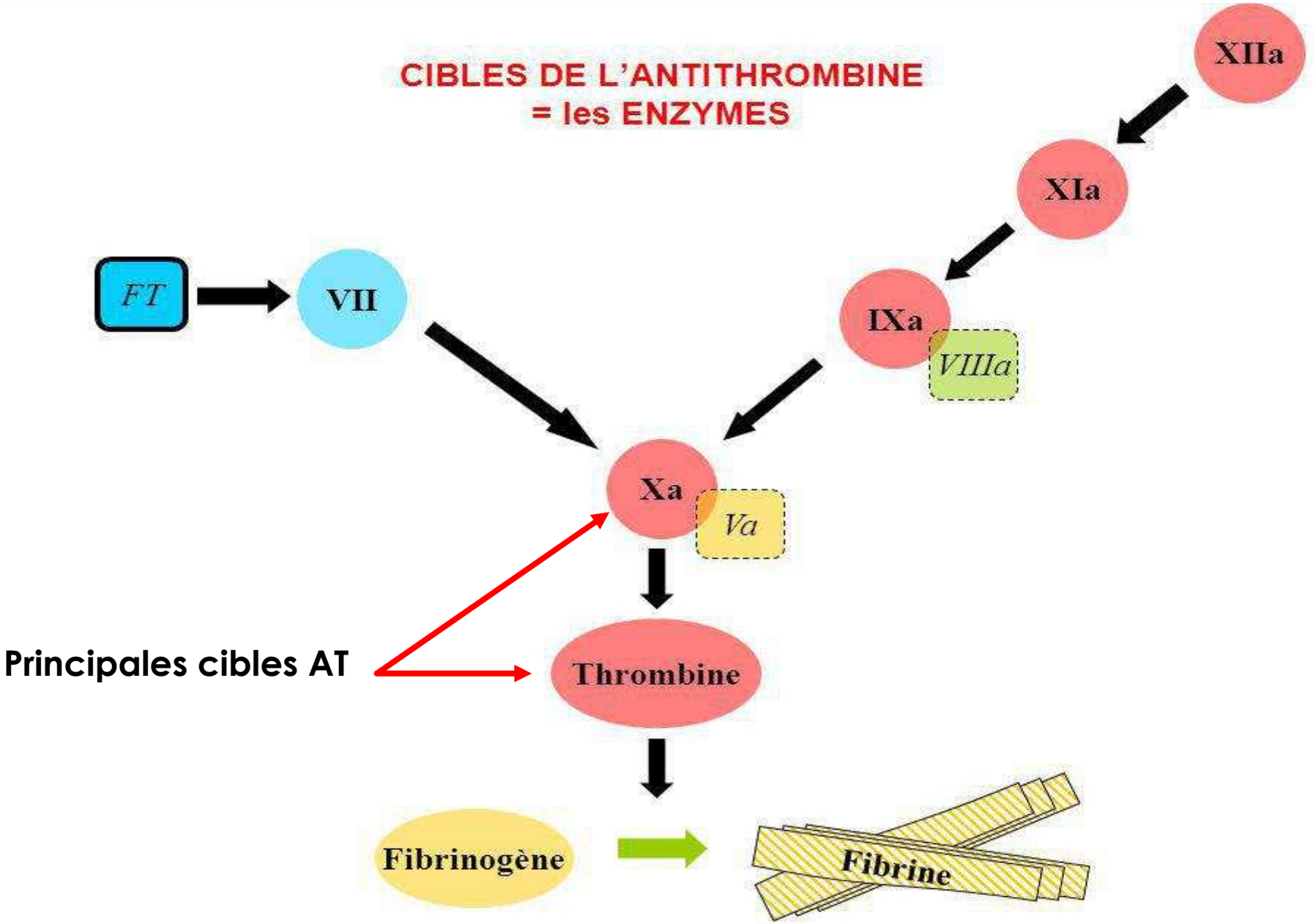
Voie de la protéine C



- **Thrombomoduline est un cofacteur de la thrombine**
- **EPCR (Endothelial Protein C Receptor) : récepteur de la protéine C**

Borgel et al, Hématologie, 2005

Cibles de l'antithrombine



La thrombinographie

Mesure dynamique de la génération et l'inactivation de la thrombine au cours de la coagulation in vitro.

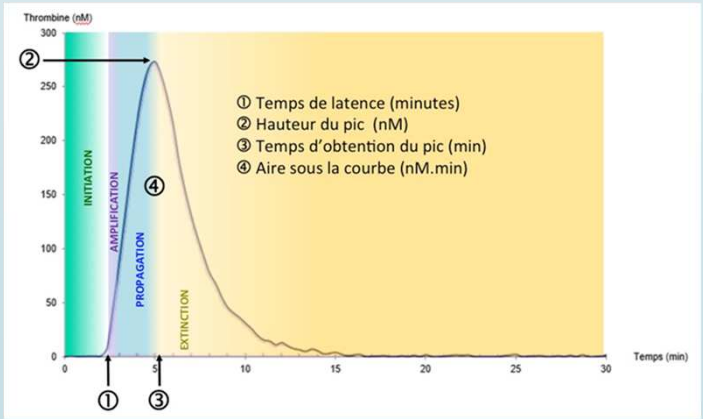
Modalités de mesures possibles :

-PRP vs PPP

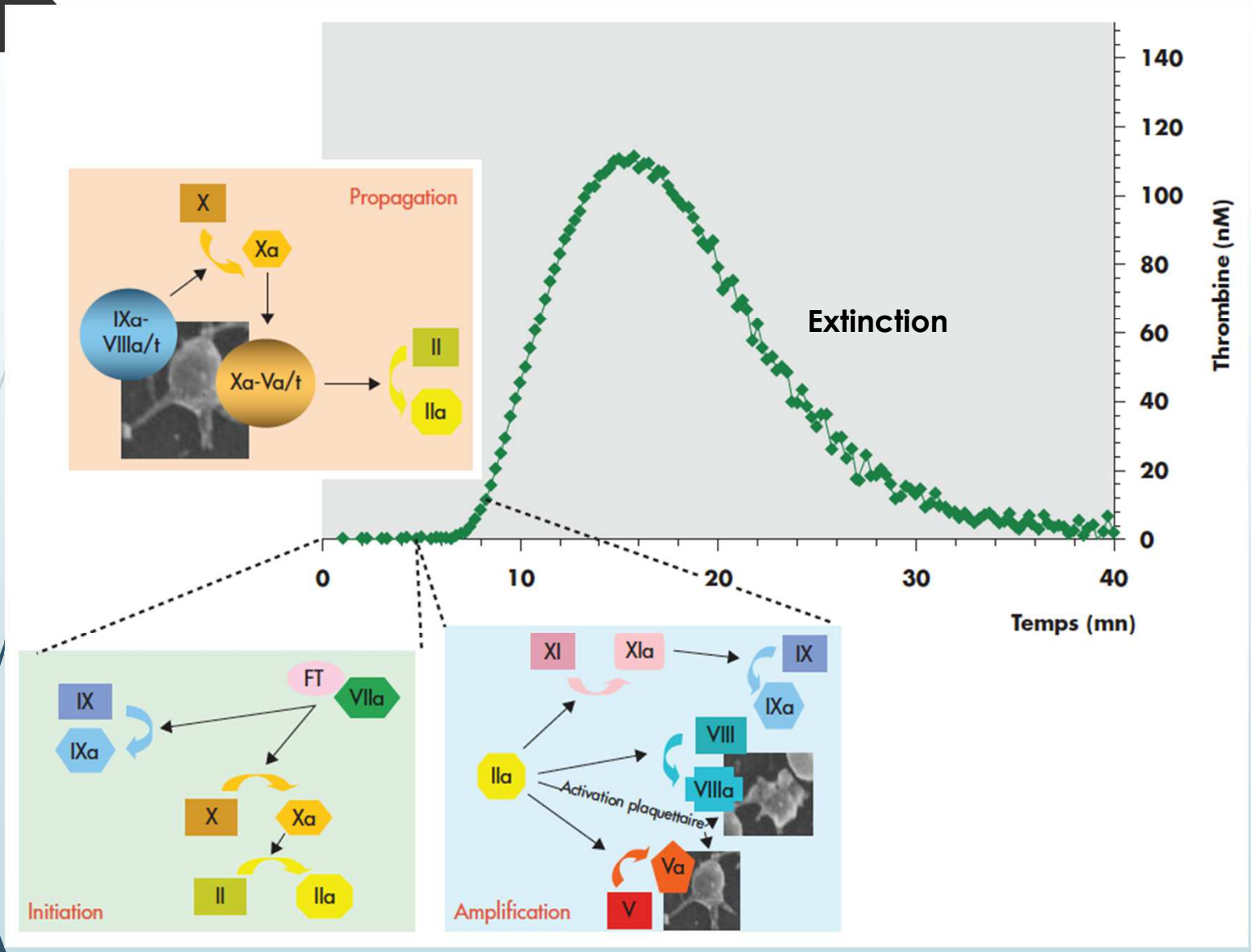
-Avec ou sans activateur de la voie de la protéine C (thrombomoduline = TM)

-Différentes doses de PL (phospholipides)

-Différentes concentrations de FT



Génération de thrombine

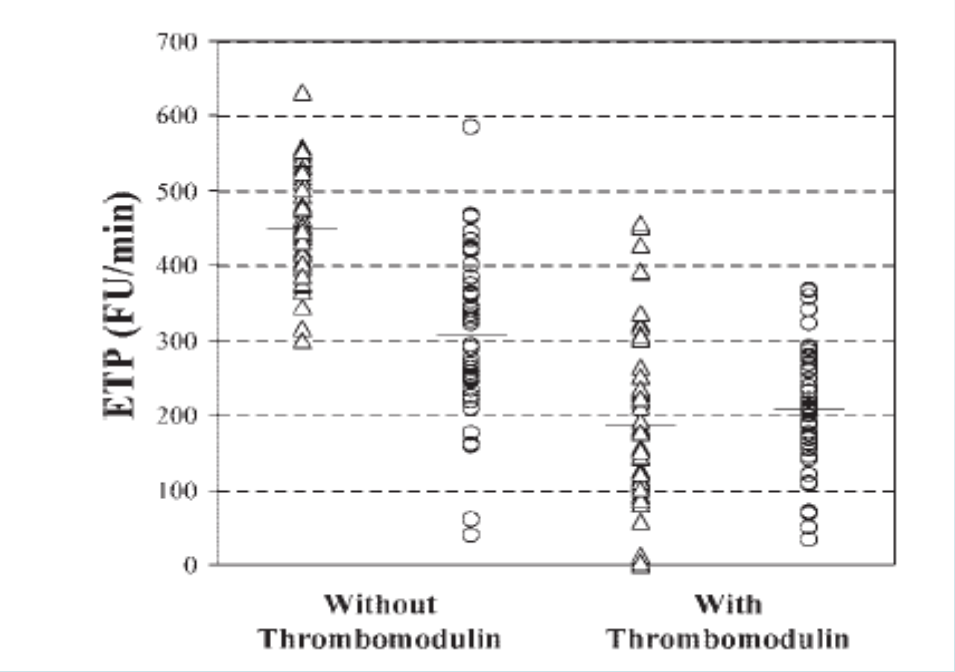


Lecompte et al, Hématologie, 2006

TGT et cirrhose

Etude de la génération de thrombine chez les patients cirrhotiques

Génération de la thrombine en présence et en l'absence de thrombomodulline

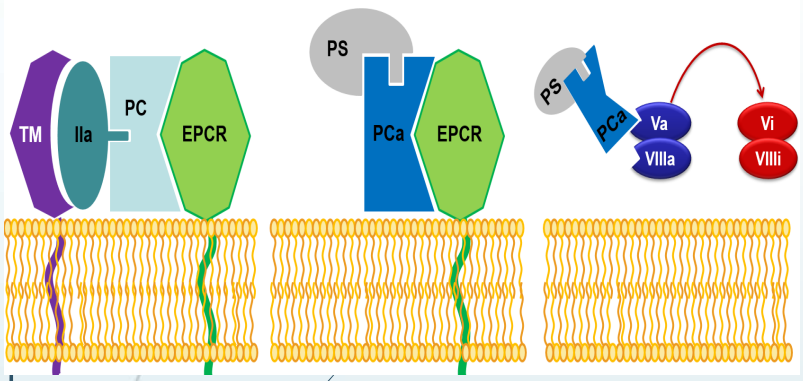


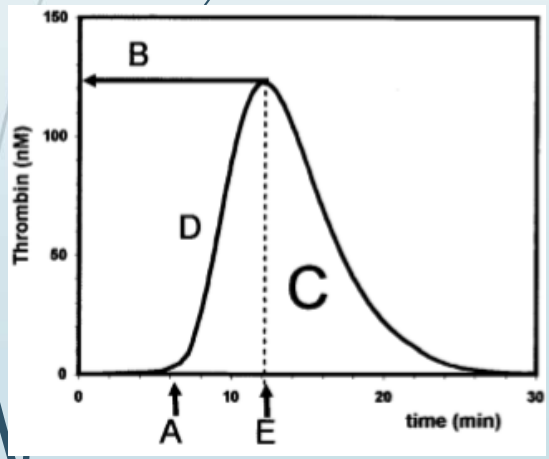
Contrôles Cirrhose **Contrôles Cirrhose**

Plasma Pauvre en Plaquettes (PPP)

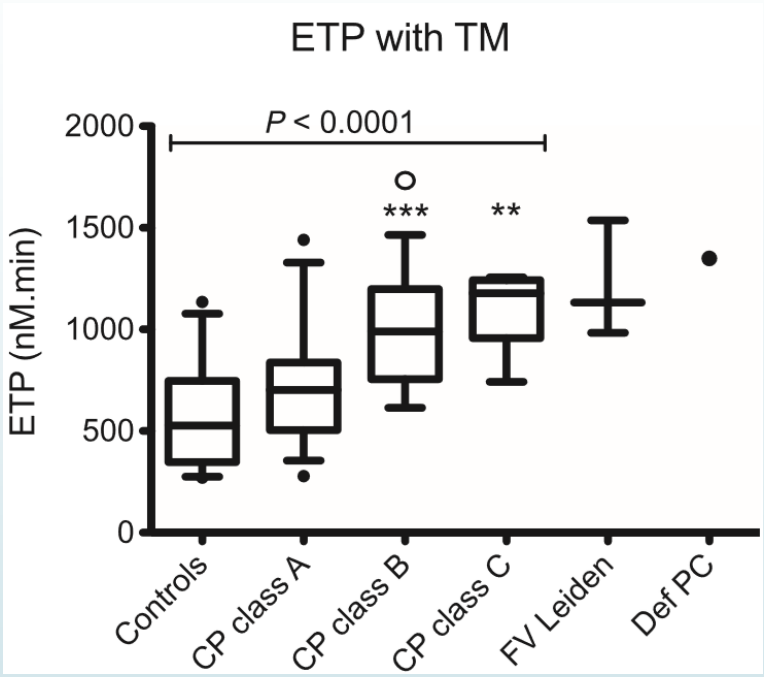
Tripodi et al. Hepatology 2005

Thrombin genration: ETP with TM, a marker of hypercoagulability



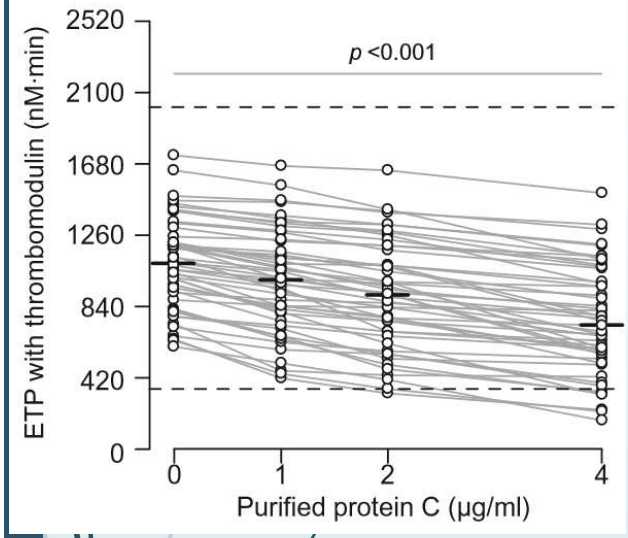


Hemker et al. TH 2006

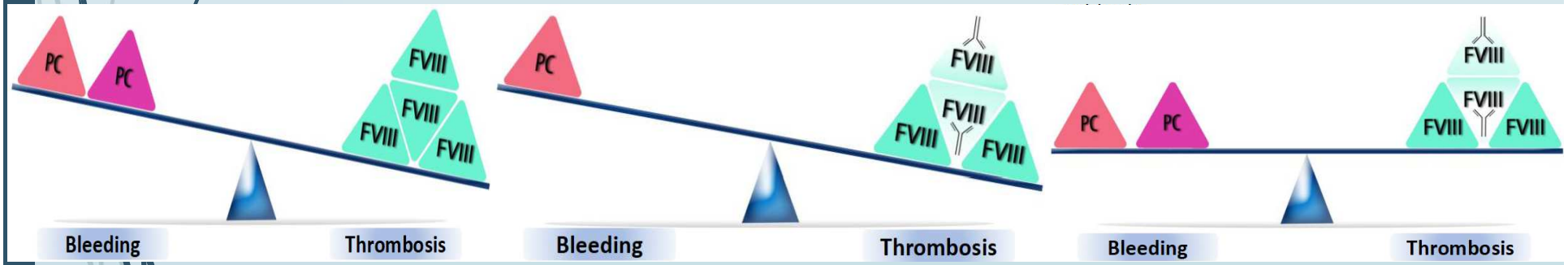


Lebreton et al. JGH, 2017

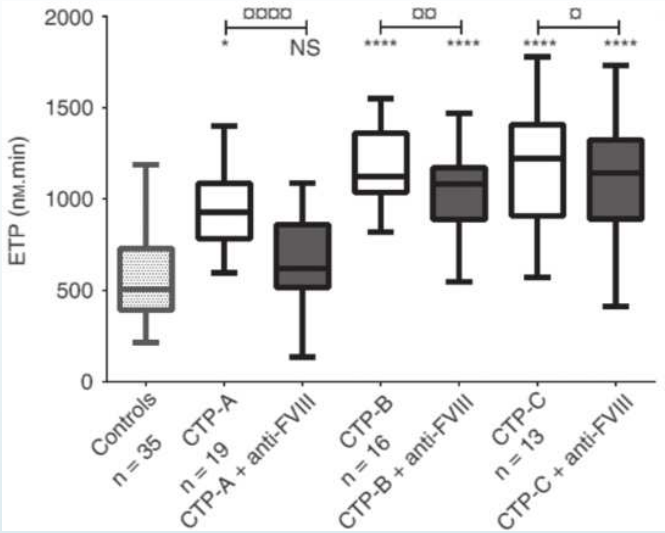
Cirrhosis-induced hypercoagulability explained by low PC and high FVIII



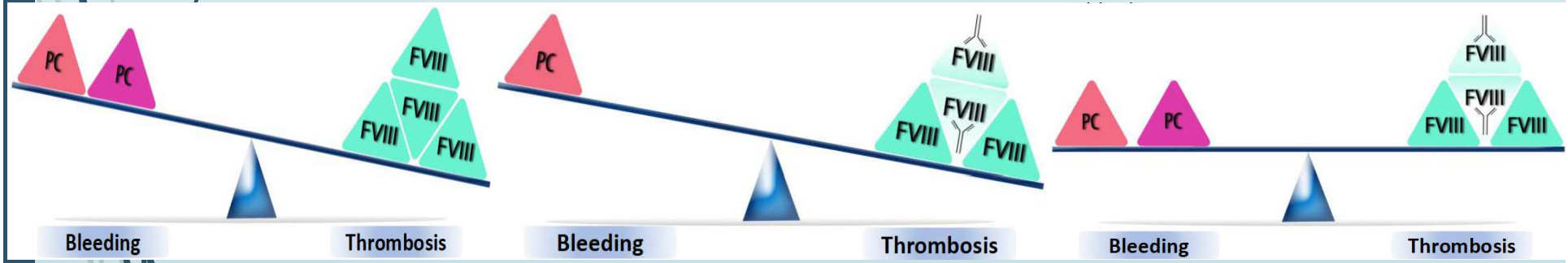
Tripodi et al. J Hepatol, 2013



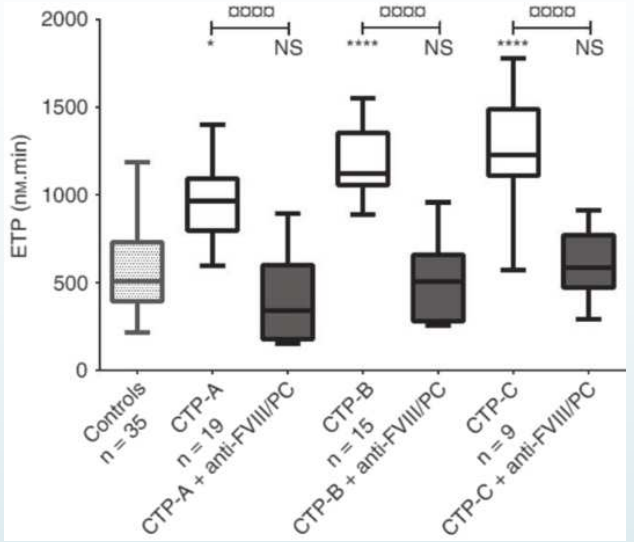
Cirrhosis-induced hypercoagulability explained by low PC and high FVIII



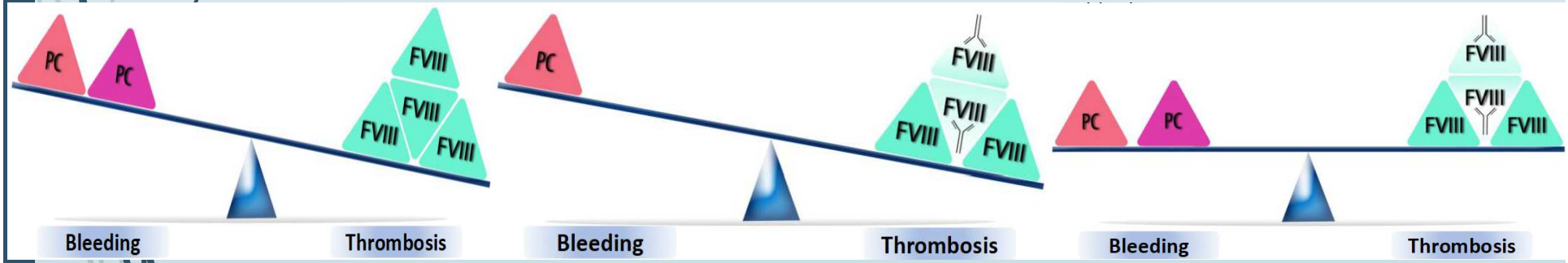
Sinegre et al. JTH 2018



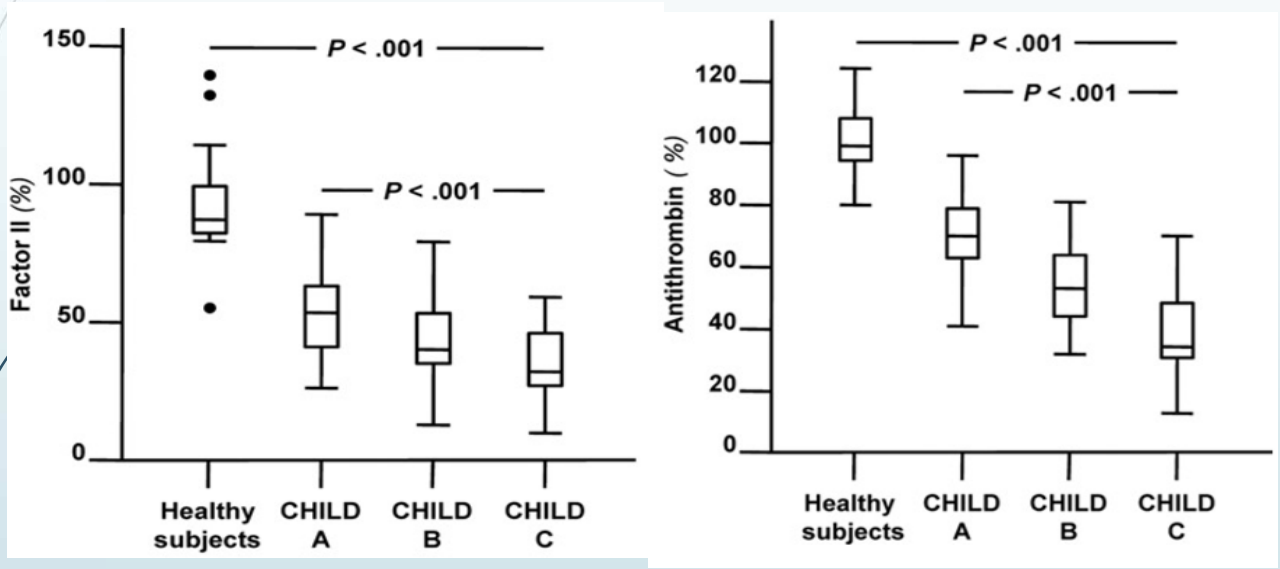
Cirrhosis-induced hypercoagulability explained by low PC and high FVIII



Sinegre et al. JTH 2018

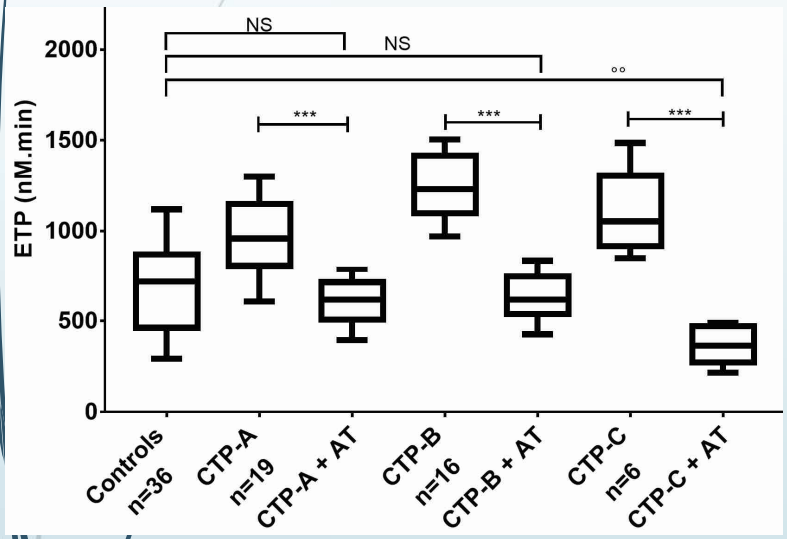


Cirrhosis-induced hypercoagulability: What about the antithrombin-prothrombin system ?

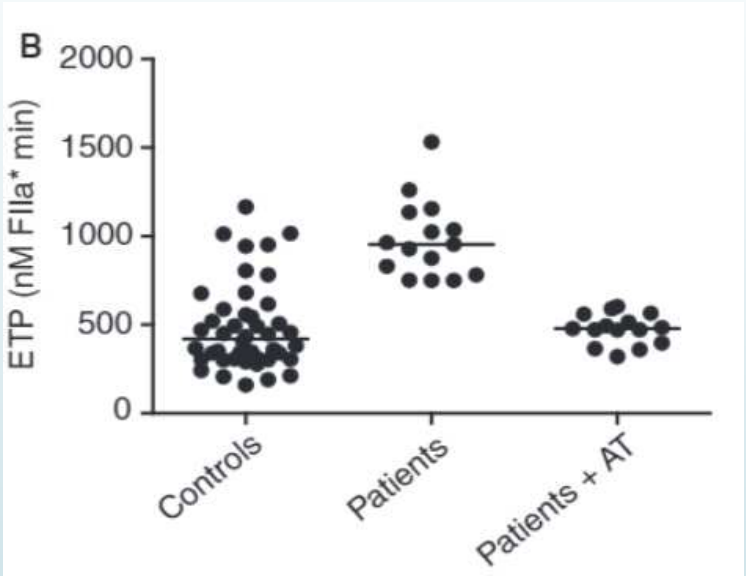


Tripodi et al. Gastroenterology, 2009

Results: Impact of normalization of AT on TG-TM



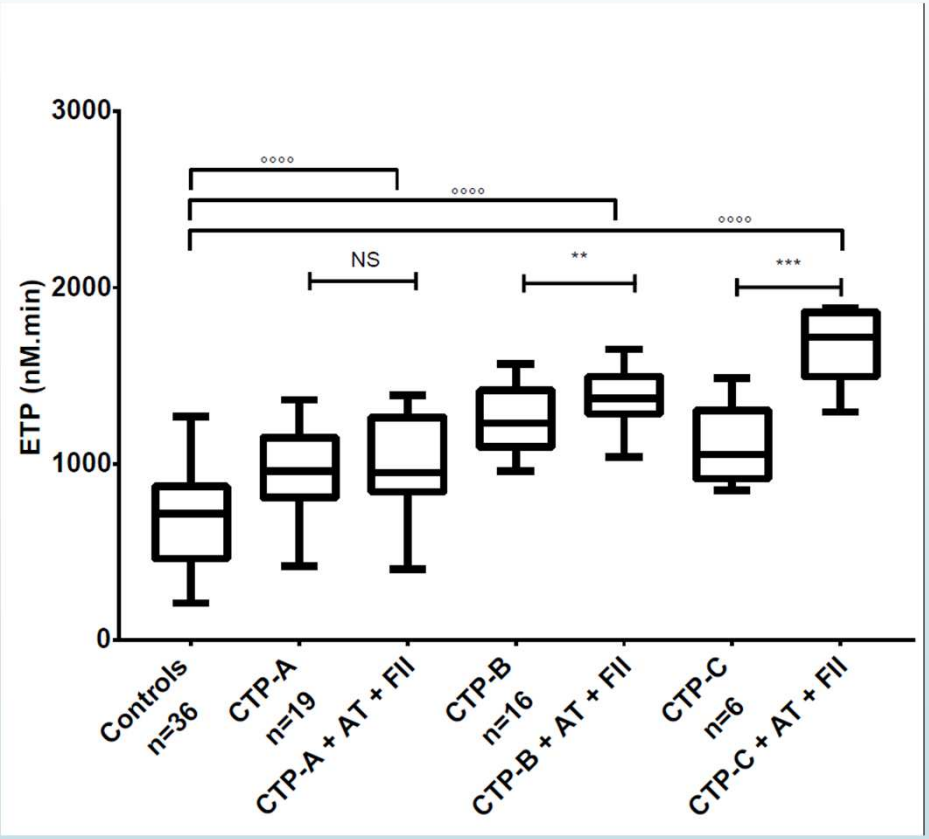
Sinegre et al. JFHOD 2019



Lisman et al. JTH 2018

Cirrhosis-induced hypercoagulability: What about the antithrombin-prothrombin system ?

Results: Impact of normalization of AT and FII on TG-TM



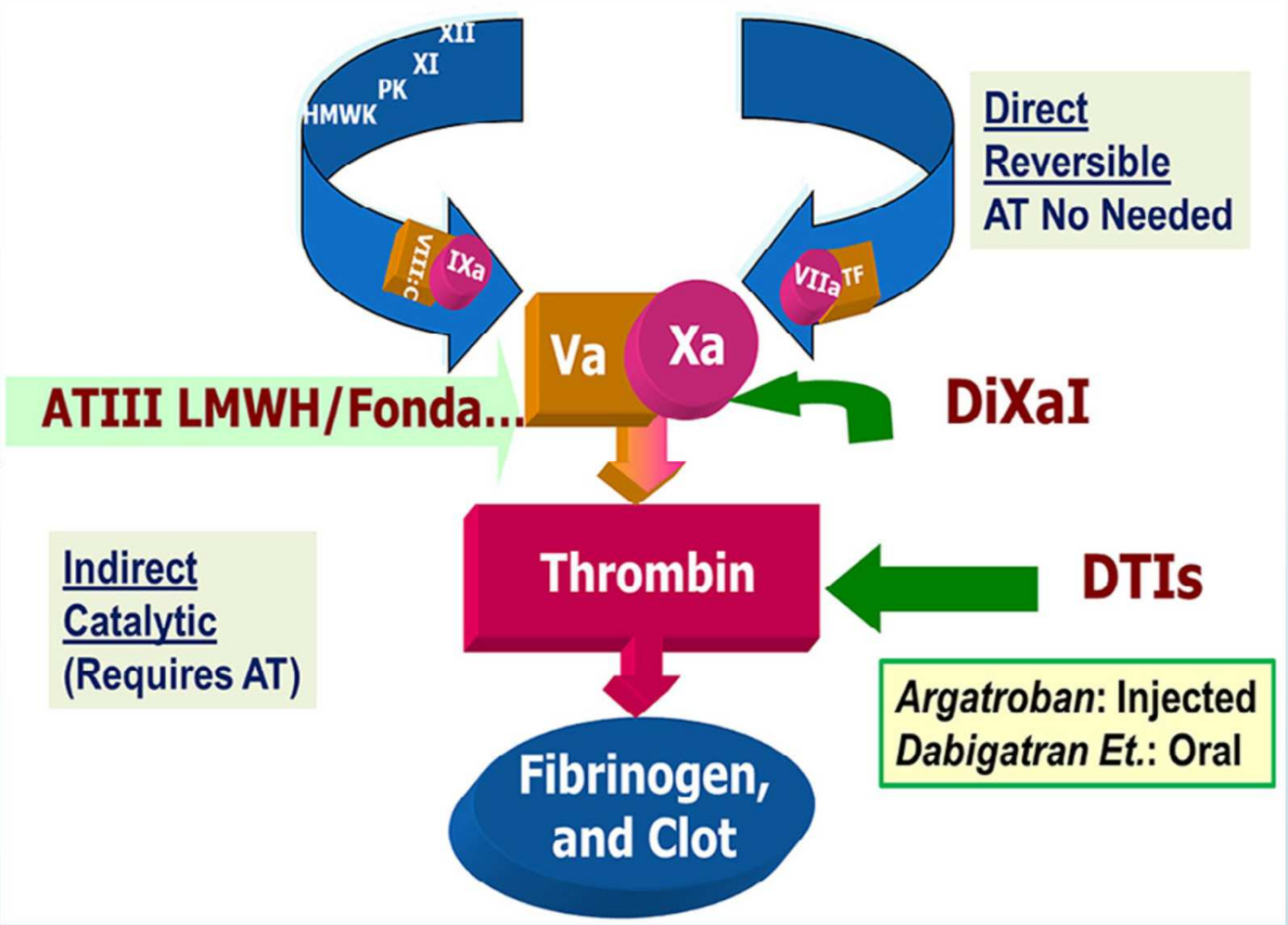
Sinegre et al. JFHOD 2019

Conclusions
TGT et cirrhose

- Dans la cirrhose, **il existe un état d'hypercoagulabilité** : en présence de thrombomoduline
- Il s'agit donc d'un état d'hypercoagulabilité lié essentiellement à un **déficit acquis en protéine C** et à une **élévation de la concentration du facteur VIII**
- **Baisese plus importante du facteur II par rapport à la baisse de l'AT : rôle protecteur ?**
- **La génération de thrombine est un examen qui met en évidence l'hypercoagulabilité du cirrhotique**
- **Le TGT est-il un bon test pour prédire la survenue d'une TVP ?**

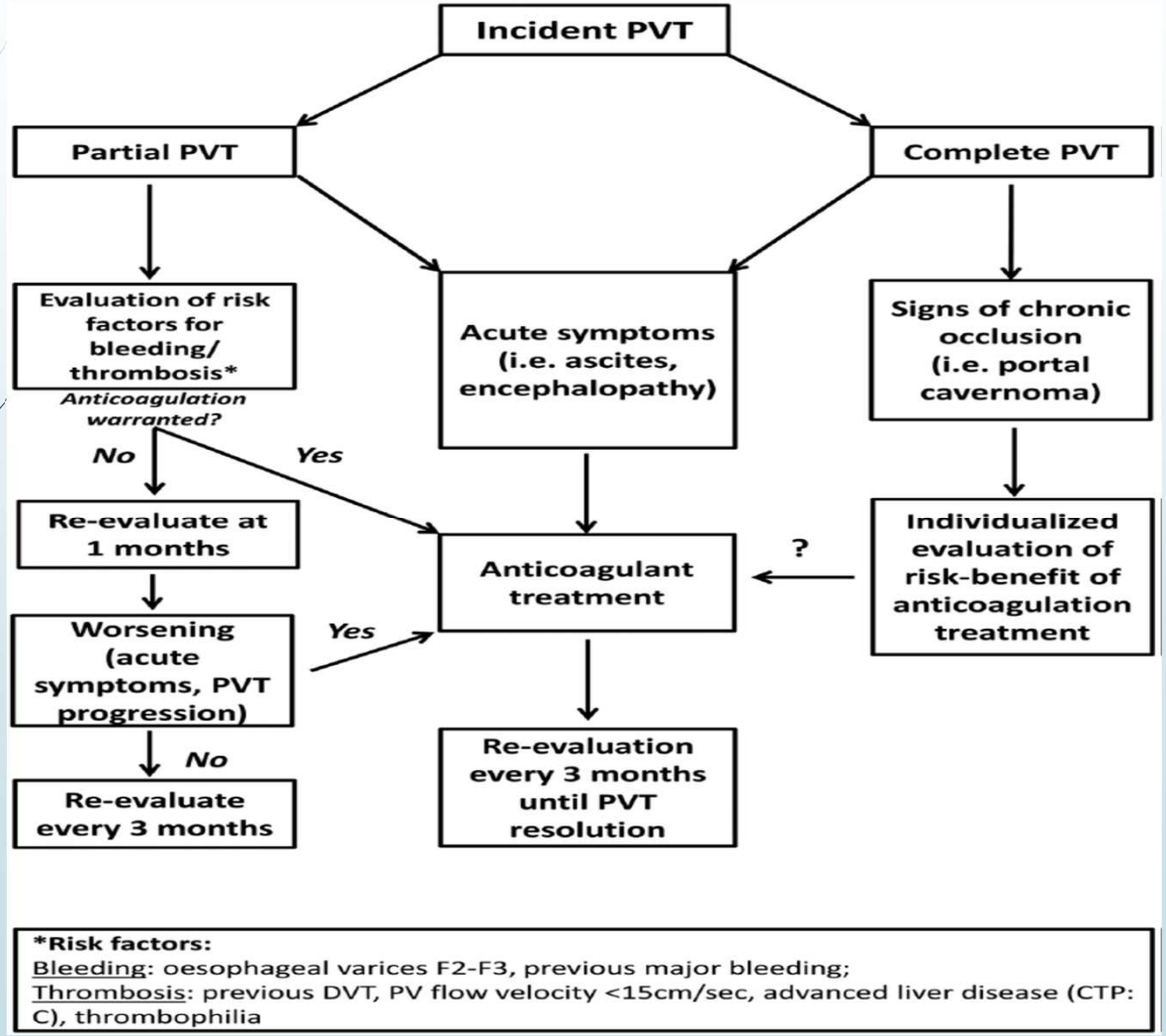
Anticoagulants et cirrhose

Traitements anticoagulants
Mécanismes d'action



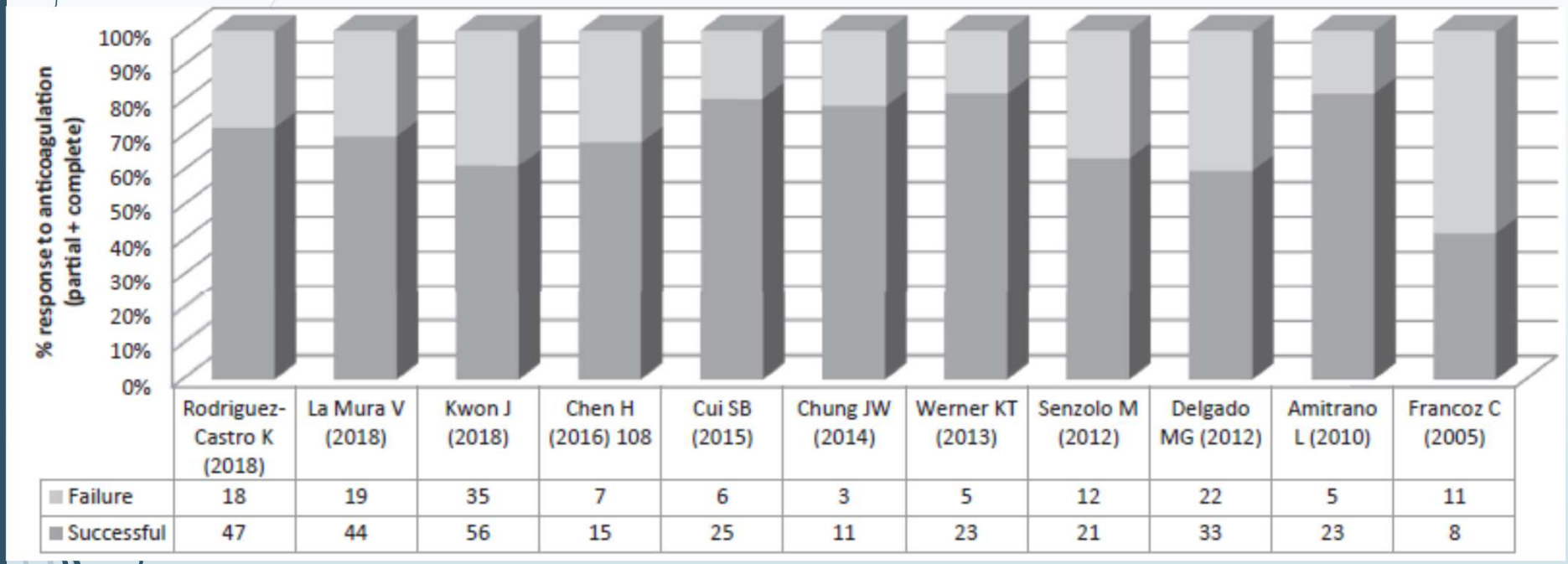
Amiral et al. Transfusion and Apheresis Science 2016

Indication des anticoagulants chez les patients ayant une TVP sur cirrhose



Basili et al. Ther Adv Gastroenterol 2018

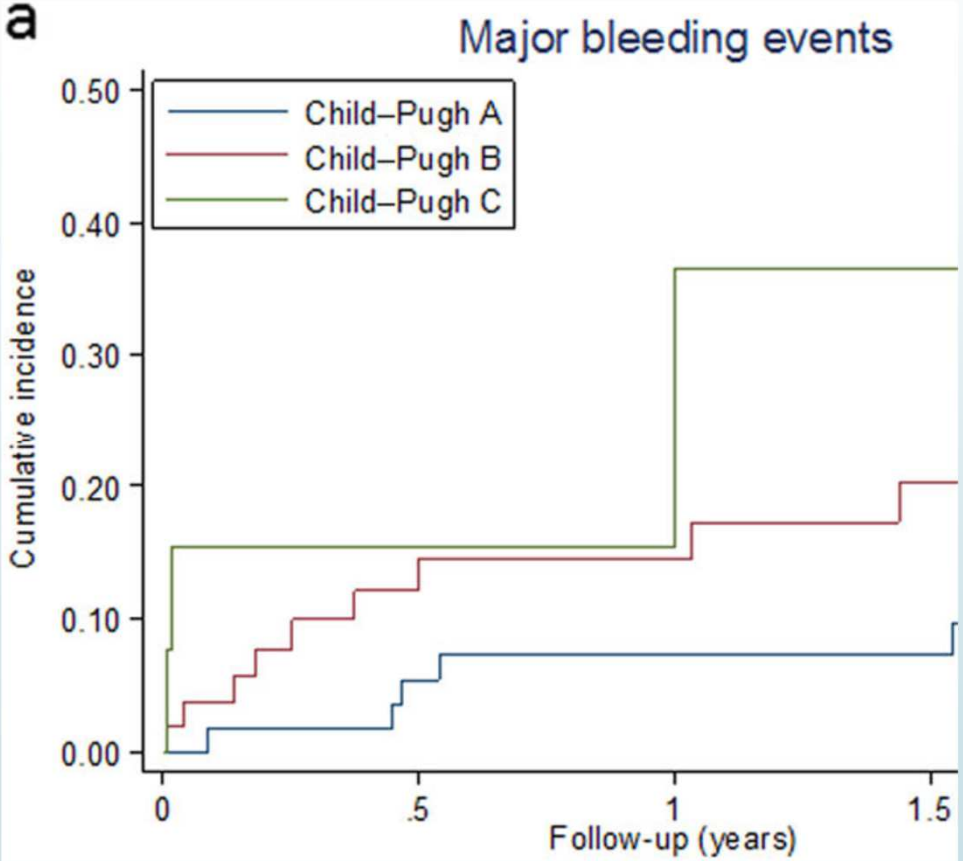
Efficacité des HBPM et/ou des AVK chez les patients ayant une TVP sur cirrhose



	Rodriguez-Castro K (2018)	La Mura V (2018)	Kwon J (2018)	Chen H (2016) 108	Cui SB (2015)	Chung JW (2014)	Werner KT (2013)	Senzolo M (2012)	Delgado MG (2012)	Amitrano L (2010)	Francoz C (2005)
Failure	18	19	35	7	6	3	5	12	22	5	11
Successful	47	44	56	15	25	11	23	21	33	23	8

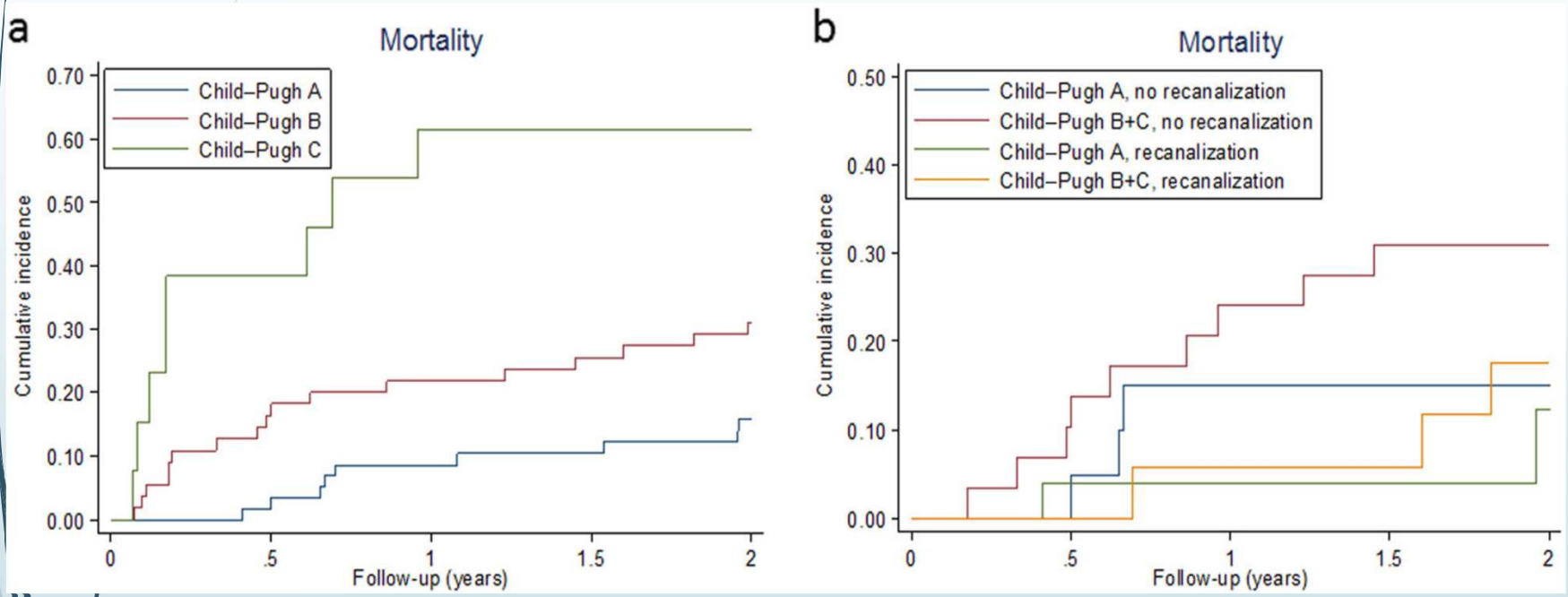
Intagliata et al. Gastroenterology 2019

Tolérance au traitement par HBPM et/ou AVK en fonction de la sévérité de l'hépatopathie



Senzolo et al. Clinical and Translational Gastroenterology 2018

Mortalité en fonction de la sévérité de l'hépatopathie et la réponse au traitement par HBPM et/ou AVK

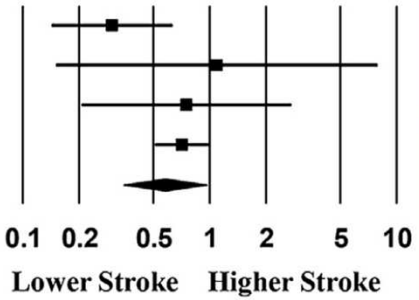


Senzolo et al. Clinical and Translational Gastroenterology 2018

Efficacité et tolérance chez près de 20.000 patients cirrhotiques traités par NACO pour fibrillation auriculaire
Méta-analyse de 7 études rétrospectives

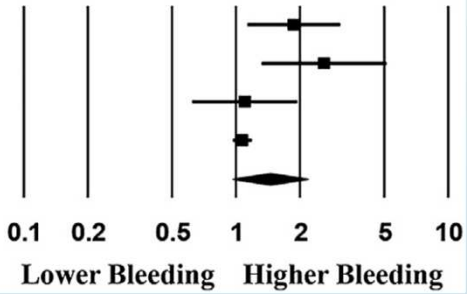
A) Risk of Stroke in Patients with AF and Cirrhosis

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Lee et al	0.300	0.143	0.631	-3.172	0.002
Lai et al	1.090	0.151	7.890	0.085	0.932
Choi et al	0.750	0.206	2.729	-0.437	0.662
Kuo et al	0.710	0.510	0.989	-2.024	0.043
	0.577	0.346	0.962	-2.109	0.035



B) Risk of Bleeding in Patients with AF and Cirrhosis

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Lee et al	1.870	1.131	3.092	2.439	0.015
Choi et al	2.600	1.320	5.121	2.763	0.006
Kuo et al	1.100	0.622	1.946	0.328	0.743
Grewal et al	1.070	0.966	1.185	1.297	0.194
	1.446	0.963	2.172	1.777	0.076



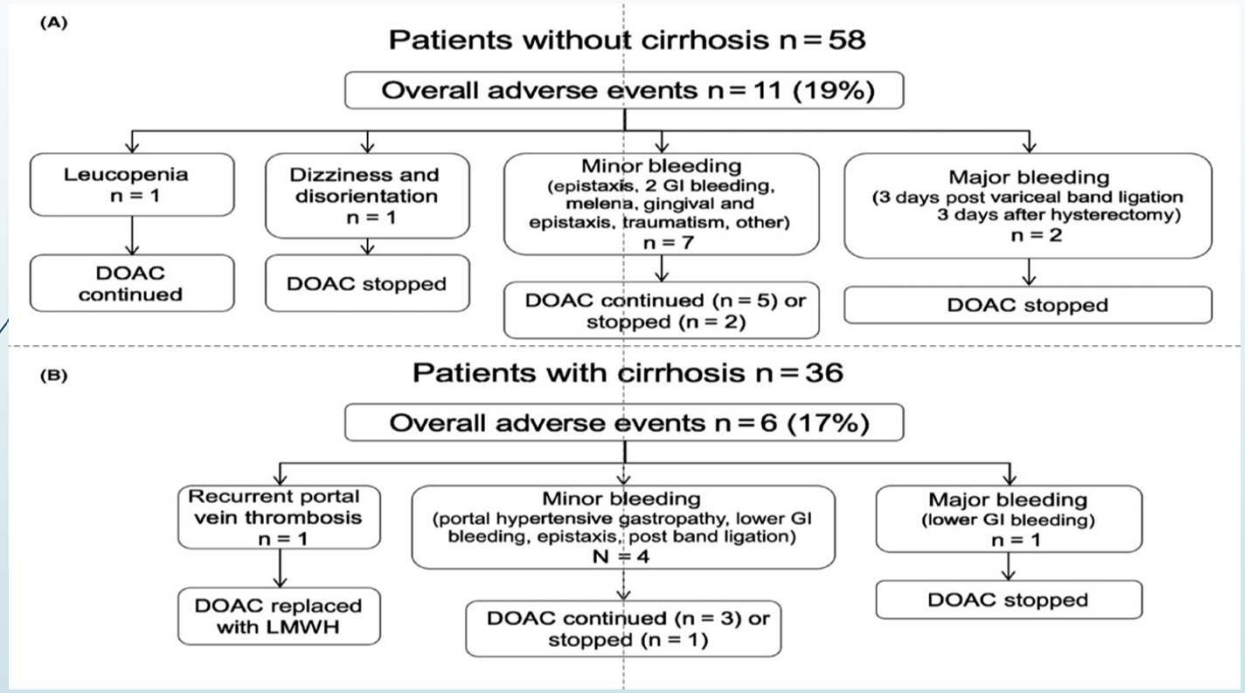
Chokesuwattanaskul et al. Dig Liv Dis 2019

Tolérance des NACO vs AVK chez les patients cirrhotiques traités pour fibrillation auriculaire

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Bleeding / Total Warfarin	Bleeding / Total DOAC
Pastori et al	2.459	1.915	3.158	7.051	0.000	261 / 1297	96 / 1033
Goriacko et al	1.222	0.554	2.695	0.496	0.620	25 / 158	10 / 75
	1.925	1.001	3.702	1.963	0.050		

Chokesuwattanaskul et al. Dig Liv Dis 2019

Tolérance des NACO chez les patients cirrhotiques



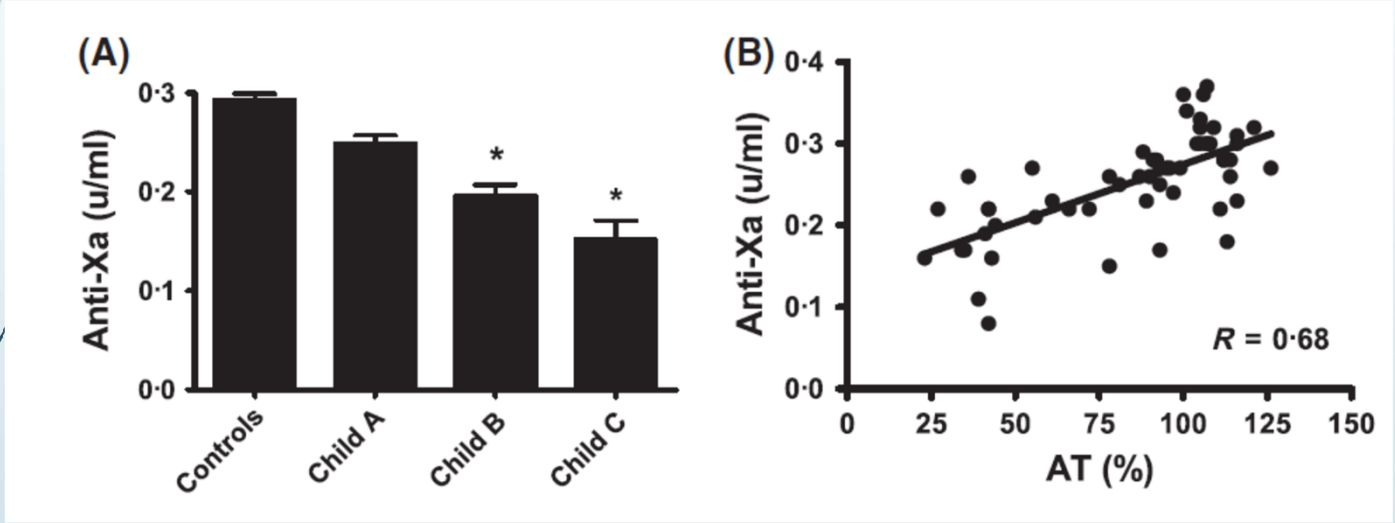
De Gottardi et al. Liver Int 2017

Variation de l'INR
en fonction de la thromboplastine utilisée

Thromboplastin	INR	
	Mean (SD)	Range
1	2.3 (0.9)	1.5-5.2
2	2.5 (1.0)	1.6-5.8
3	3.0 (1.4)	1.7-6.7
4	3.2 (2.0)	1.7-11.1
5	3.6 (2.2)	1.8-11.8
6	3.1 (1.5)	1.8-8.5
7	4.1 (2.8)	1.9-14.3

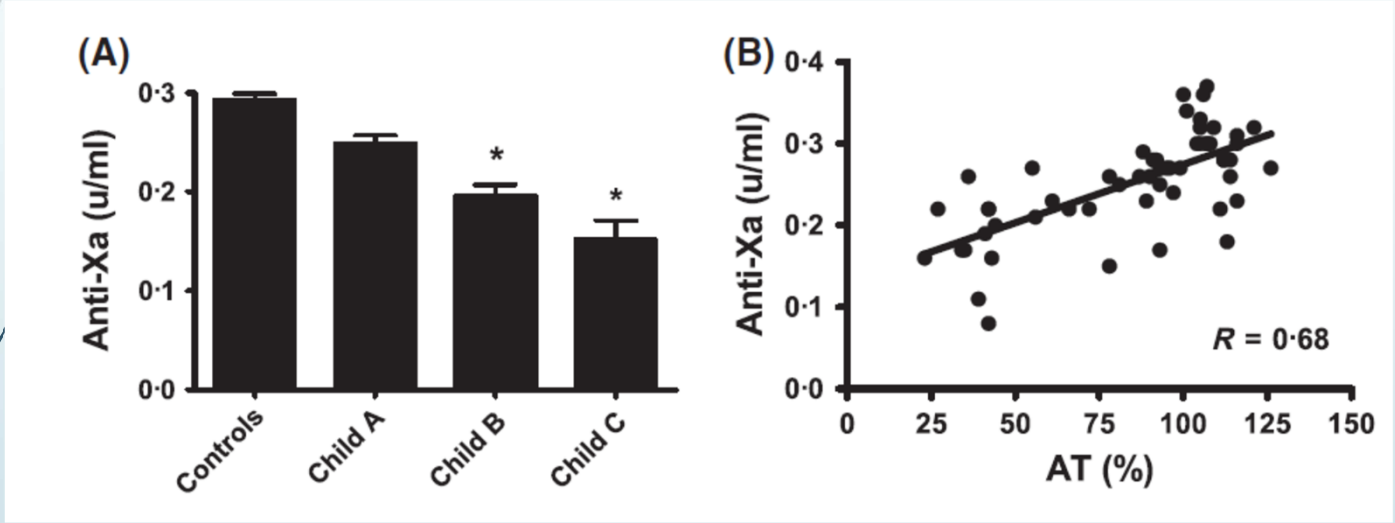
Robert et al. Hepatology 2004

Activité anti-Xa in vitro de l'héparine à la dose de 0.3 UI/mL chez les patients cirrhotiques



Potze et al. Br J Hematol 2013

Activité anti-Xa in vitro de l'héparine à la dose de 0.3 UI/mL chez les patients cirrhotiques



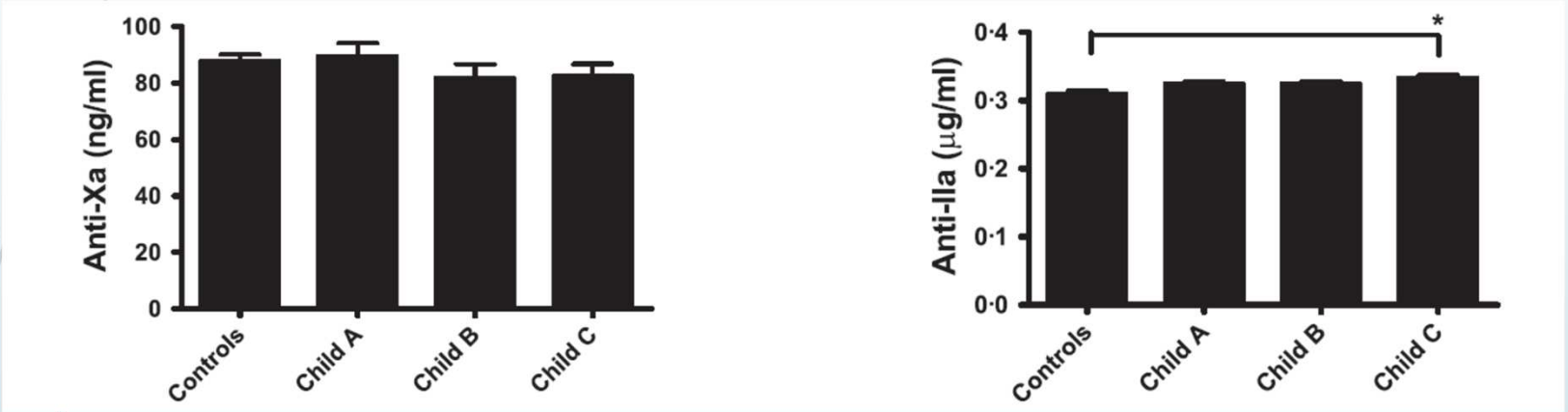
Potze et al. Br J Hematol 2013

Les nouveaux anticoagulants oraux (NACO)

DCI	SPECIALITE	DOSE PAR CP	NOMBRE DE PRISES	BIO DISPO	LIAISON PROT	ADAPTATION DOSE	CONTRE INDICATIONS
Apixaban	Eliquis	2.5 et 5 mg	2	66%	87%	IRC	IH SEVERE SAIGNEMENT
Rivaroxaban	Xarelto	10, 15, 20 mg	1	80% 66%	90-95%	IRC	CPB, CPC SAIGNEMENT
Dabigatran	Pradaxa	75, 110, 150 mg	2	6.5%	35%	IRC	IH SAIGNEMENT INH OU IND CYP3A4

Données Vidal

Activité anti-Xa des NACO

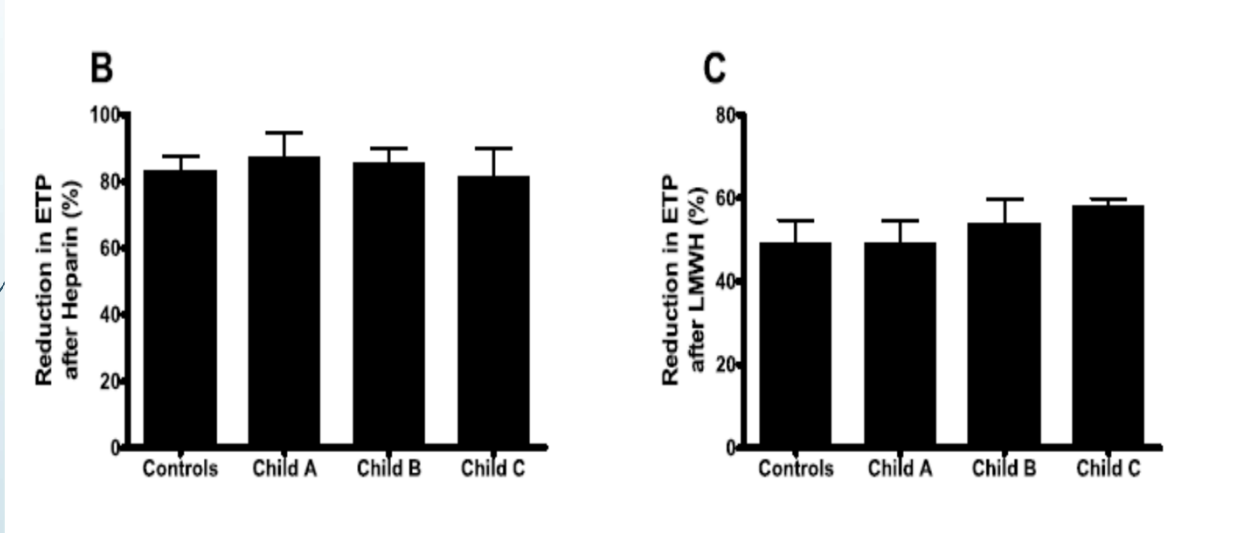


Rivaraxaban 100 ng/mL

Dabigatranan 0.3 µg/mL

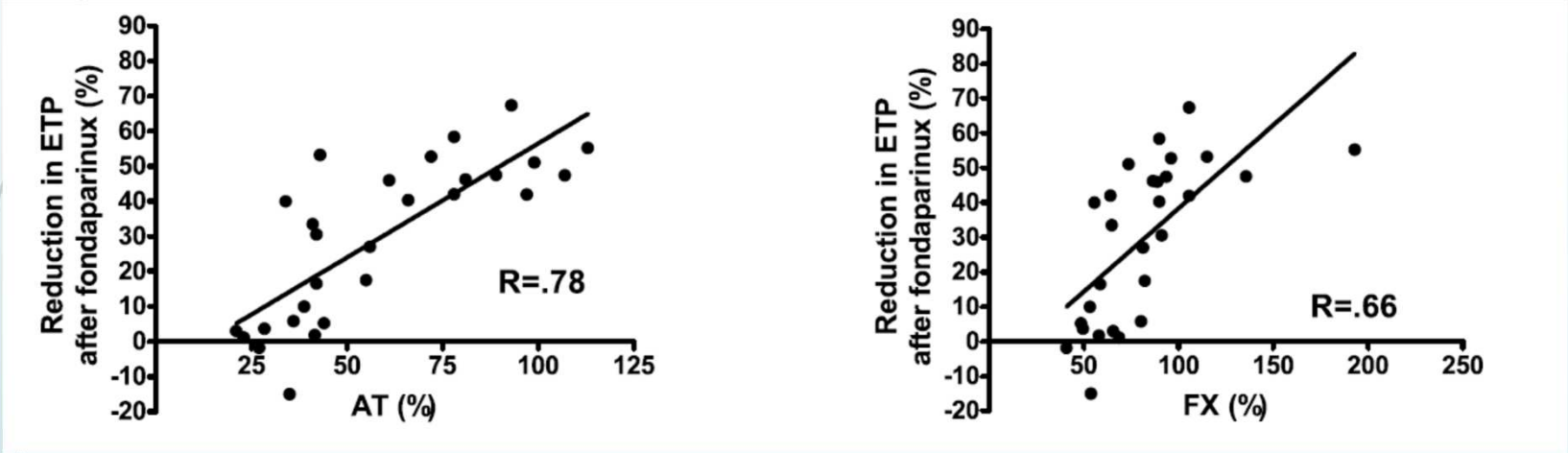
Potze et al. Br J Hematol 2013

Effet des héparines sur le TGT



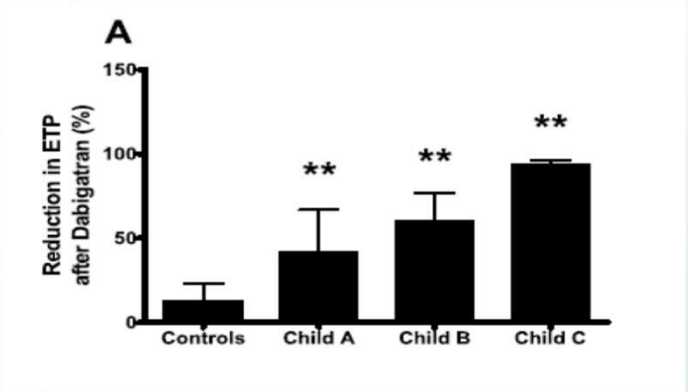
Potze et al. Plos One 2014

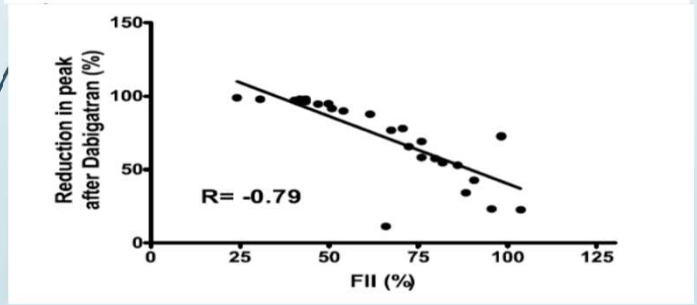
Corrélation entre l'effet sur la TGT du fondaparinux et la valeur des facteurs II et X

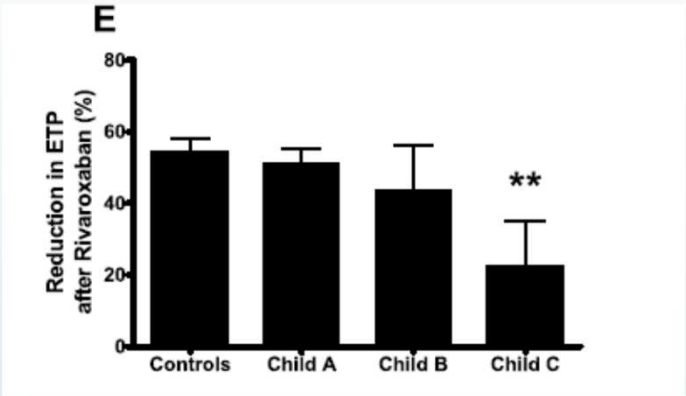


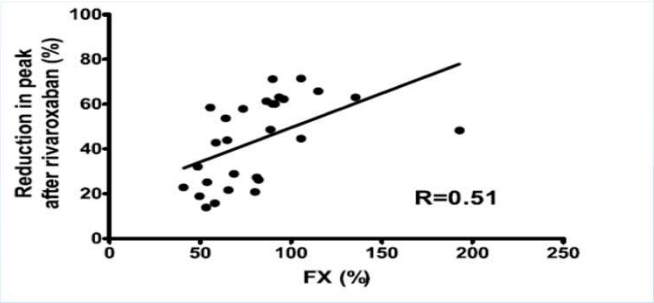
Potze et al. Plos One 2014

Effet des NACO sur le TGT
Rôle des facteurs II et V



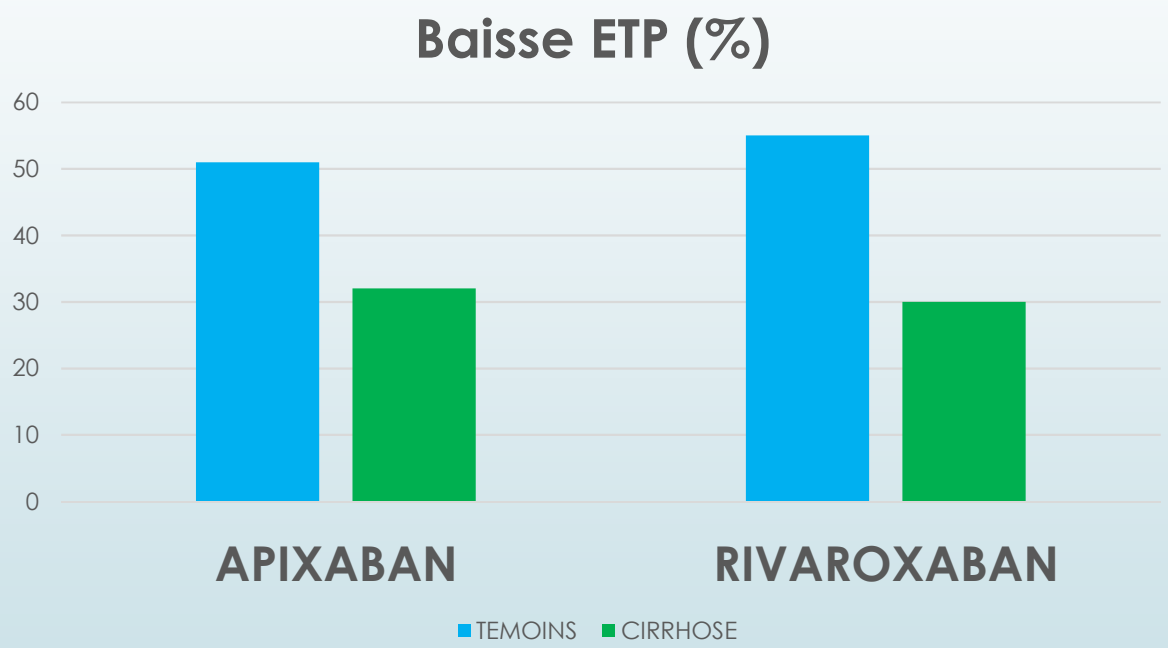






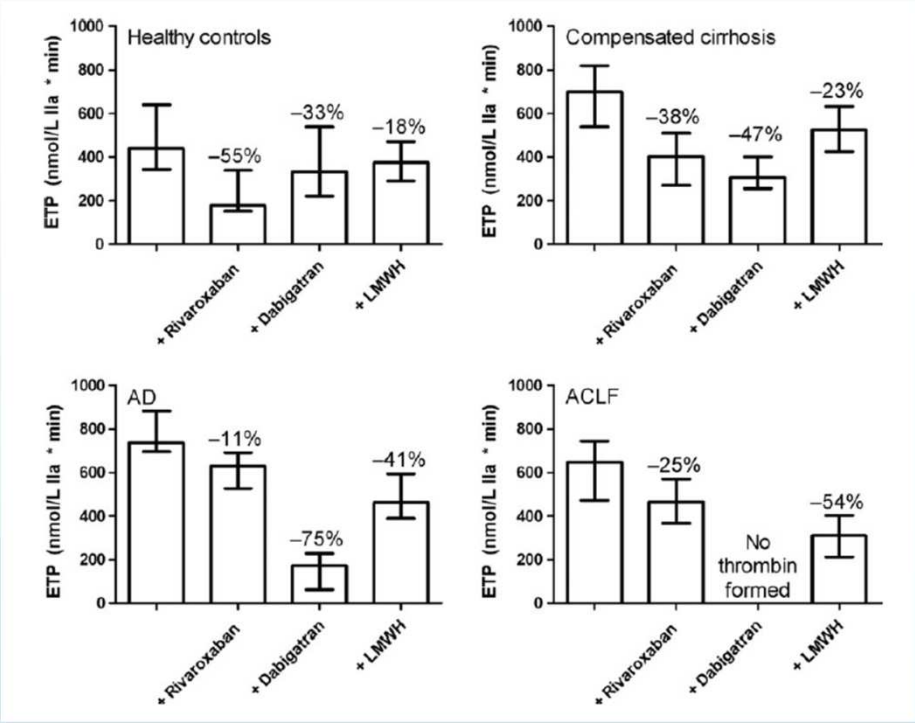
Potze et al. Plos One 2014

TGT et NACO
chez les patients cirrhotiques



Potze et al. Hepatology 2015

TGT et anticoagulants chez les patients cirrhotiques compensés, décompensés avec ACLF



Lisman et al. Liver Int 2018

Peut-on utiliser la génération de thrombine en pratique quotidienne chez les patients cirrhotiques?
Nécessité d'une standardisation

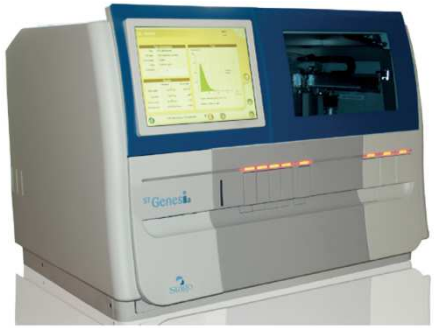
480 µL plasma

320 µL plasma

800 µL plasma

CAT/Réactifs CAT **CAT/Réactifs Genesia**

Genesia/Réactifs Genesia



Conclusions
Anticoagulants et cirrhose

- **Les anticoagulants sont efficaces et bien tolérés chez les patients ayant une TVP sur cirrhose. Précautions chez les patients Child C.**
- **L'INR et le TCA ne sont pas de bons examens pour suivre l'efficacité des héparines et AVK**
- **L'activité anti-Xa ne permet de suivre l'efficacité des héparines chez les patients cirrhotiques**
- **La génération de la thrombine serait un bon examen in vitro pour évaluer l'efficacité des anticoagulants**
- **La mesure de l'activité anti-Xa permettrait de mesurer l'activité des NACO**