AZ Nikolaas

Hemostasis in liver cirrhosis: shifting the balance

Jeoffrey Schouten
AZ Nikolaas, UZGent
DLW , June 2017

Disclosures

No financial disclosures relevant to this presentation

Aims

1. What does prolongation of conventional coagulation tests in patients with liver disease means?

2. Does prolongation of conventional coagulation tests mean that patients with liver disease are auto-anticoagulated?

3. Is there a role for hemostasis in fibrogenesis?

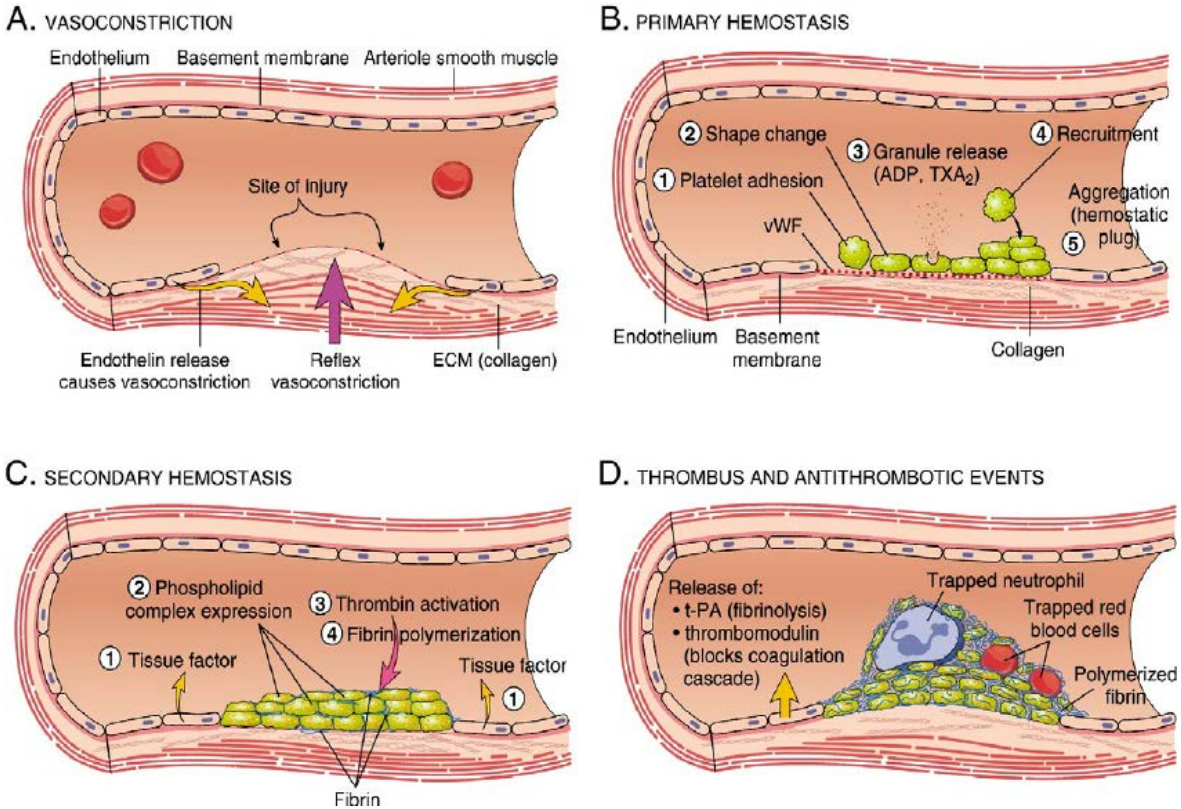
Question 1

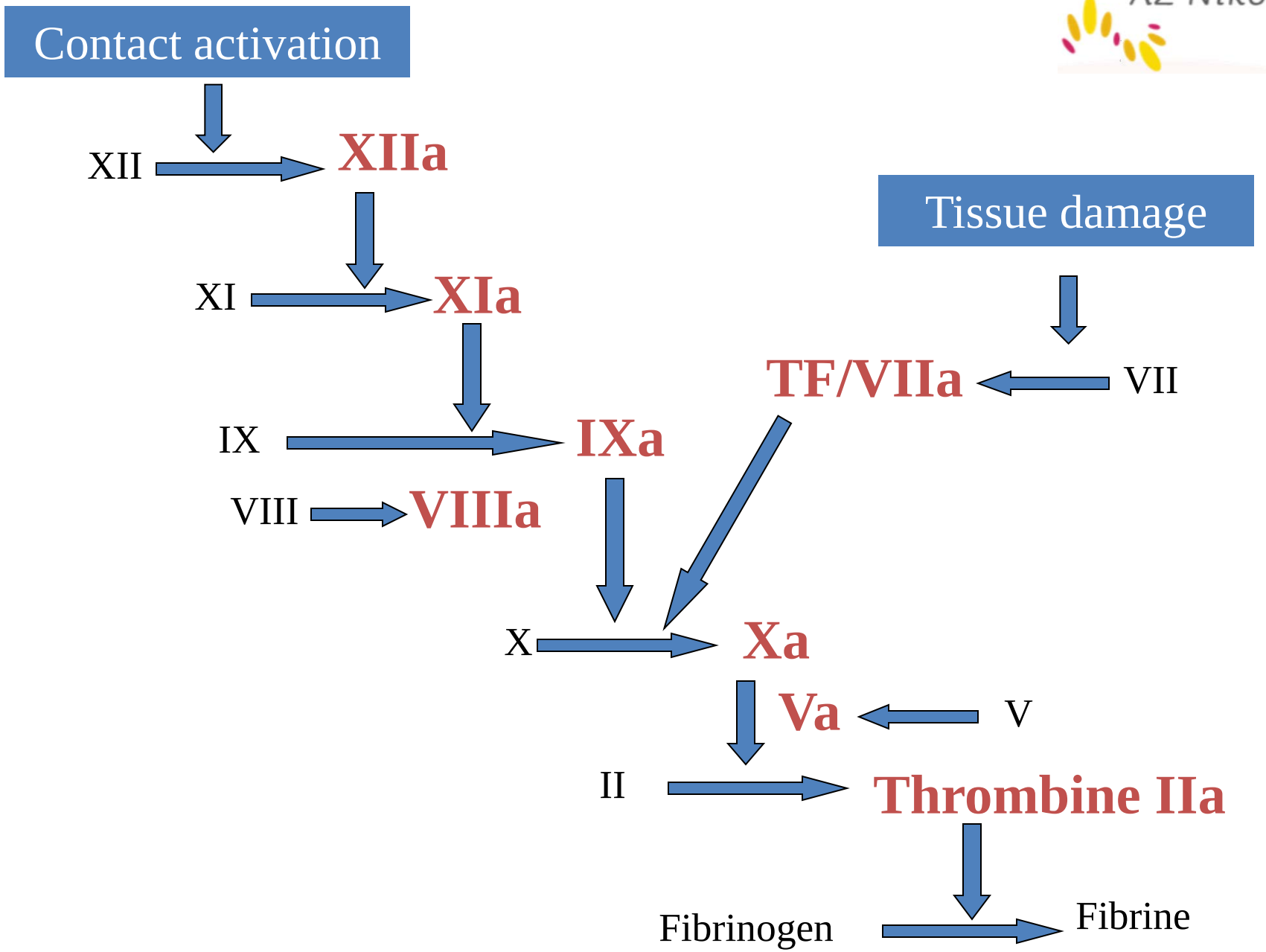
1. Which statement is correct?

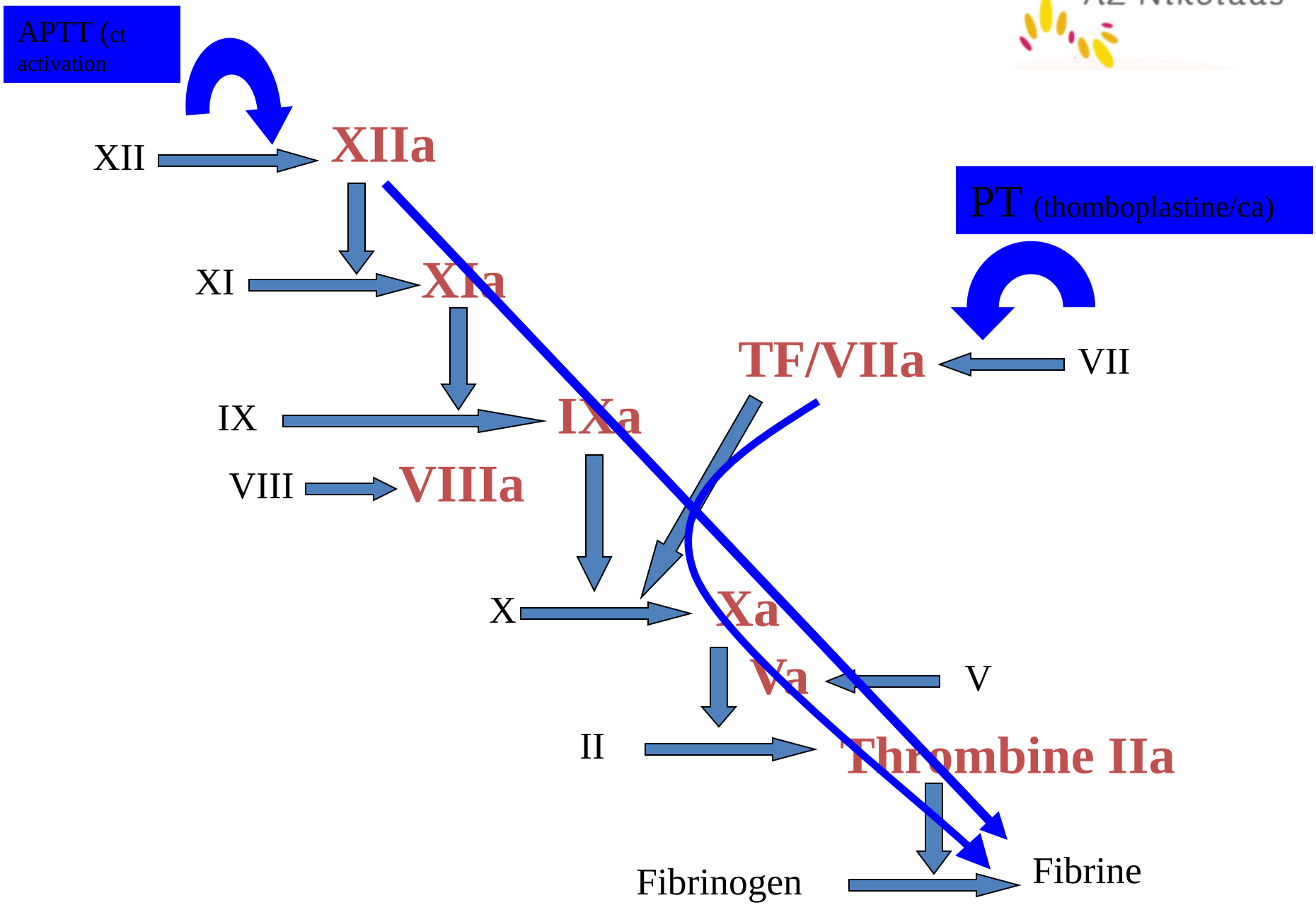
    1. INR is a prognostic test in patient with liver disease
    2. INR elevation is a marker for bleeding tendency in patients with liver disease
    3. All of the above

Introduction

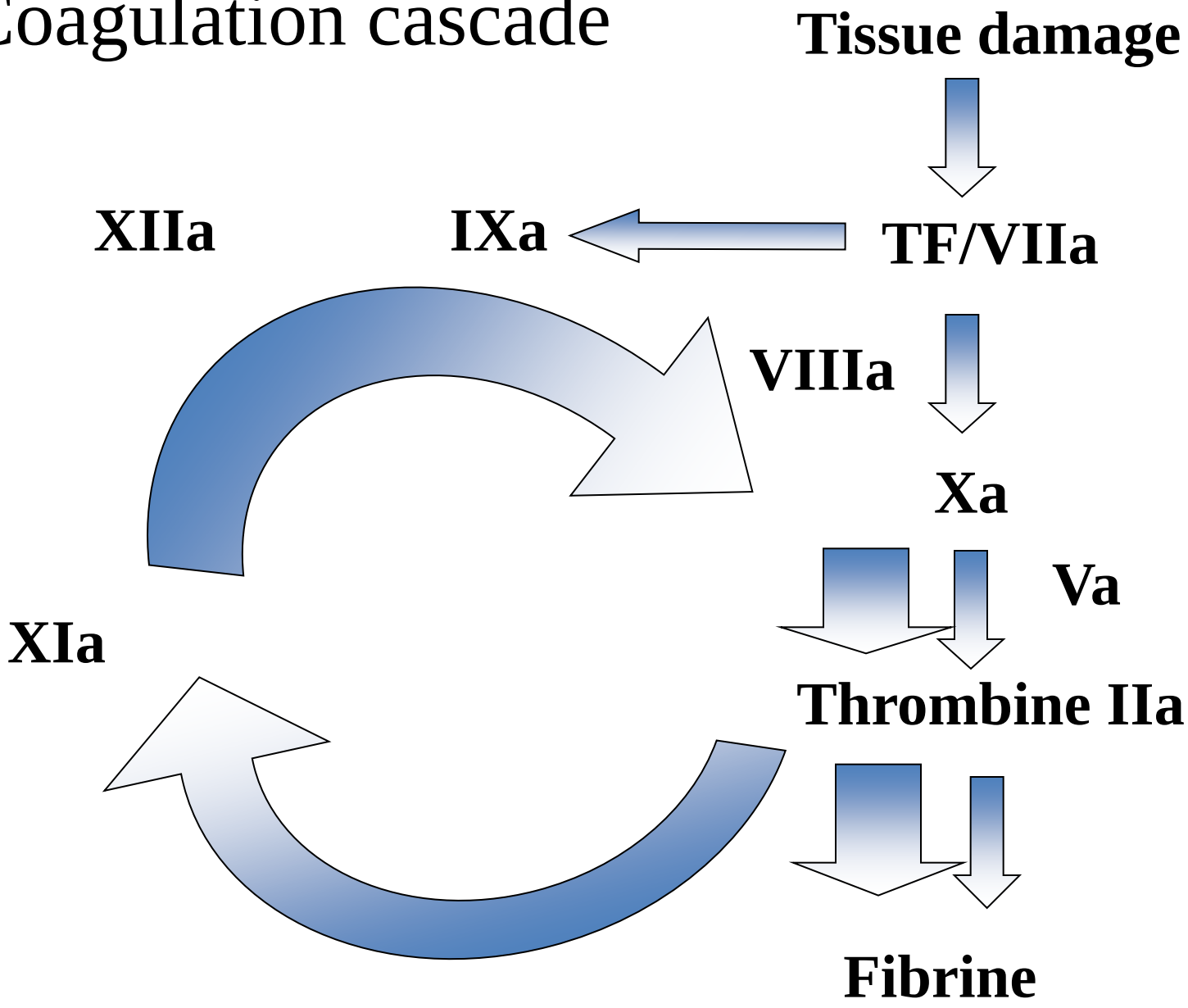
- Hemostasis
  - Primary hemostasis (cellular factors)
    - Platelets
  - Secondary hemostasis (humoral factors)
    - Intrinsic pathway
    - Extrinsic pathway
- Blood coagulation is
  - Balanced by anticoagulant factors
    - Protein S/C
    - ATIII
  - Counteracted by fibrinolysis

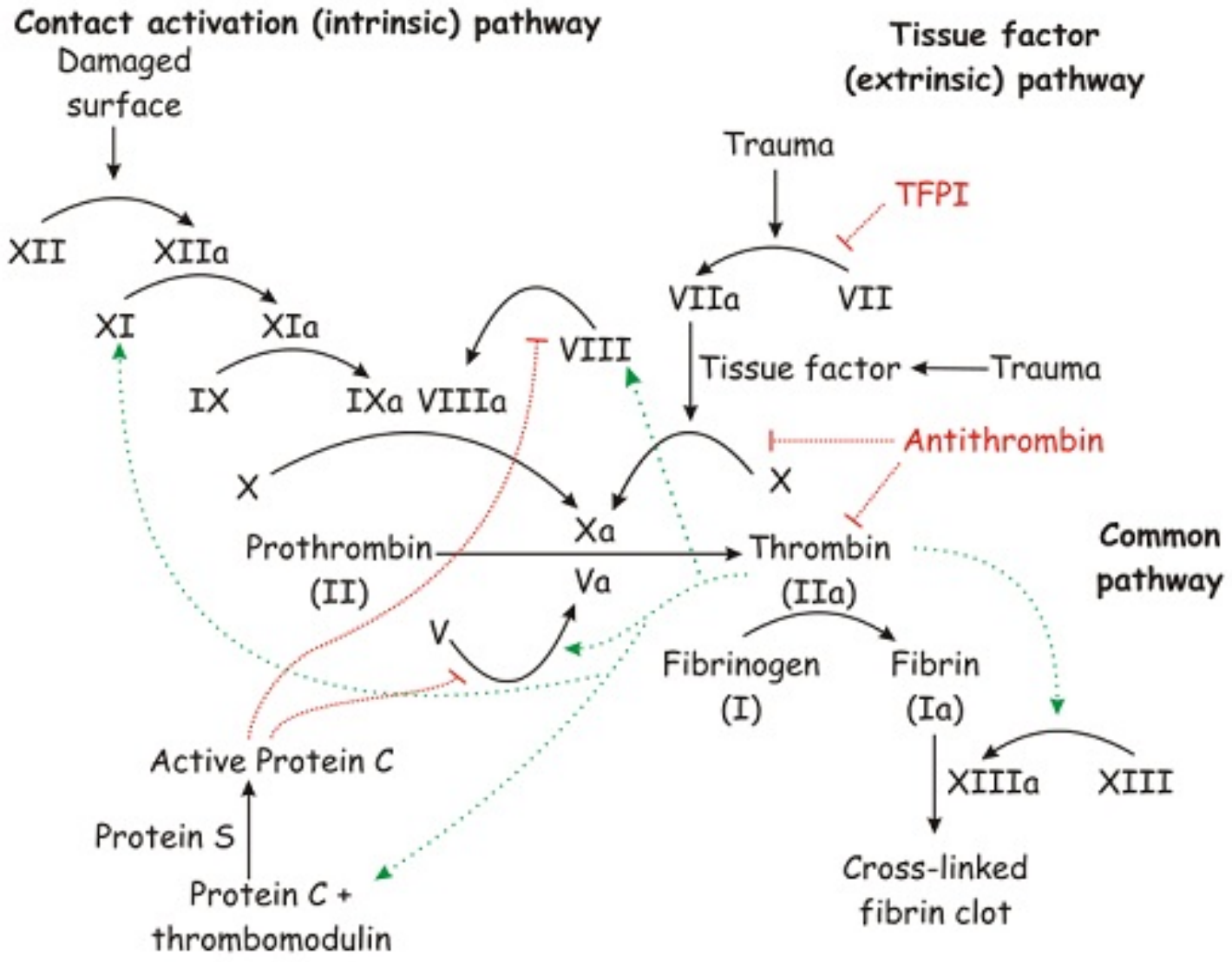

A. VASOCONSTRICTION
Endothelium
Basement membrane
Arteriole smooth muscle
Site of injury
Endothelin release causes vasoconstriction
Reflex vasoconstriction
ECM (collagen)
B. PRIMARY HEMOSTASIS
2 Shape change
3 Granule release (ADP, TXA2)
4 Recruitment
1 Platelet adhesion
vWF
Aggregation (hemostatic plug)
5
Endothelium
Basement membrane
Collagen
C. SECONDARY HEMOSTASIS
2 Phospholipid complex expression
3 Thrombin activation
4 Fibrin polymerization
1 Tissue factor
Tissue factor
1
Fibrin
D. THROMBUS AND ANTITHROMBOTIC EVENTS
Release of:
• t-PA (fibrinolysis)
• thrombomodulin (blocks coagulation cascade)
Trapped neutrophil
Trapped red blood cells
Polymerized fibrin


Contact activation
XII
XIIa
XI
XIa
IX
IXa
VIII
VIIIa
Tissue damage
TF/VIIa
VII
X
Xa
Va
V
II
Thrombine IIa
Fibrinogen
Fibrine


APTT (ct activation
XII
XIIa
XI
XIa
IX
IXa
VIII
VIIIa
PT (thomboplastine/ca)
TF/VIIa
VII
X
Xa
Va
V
II
Thrombine IIa
Fibrinogen
Fibrine

Coagulation cascade




Contact activation (intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa VIIIa
VIII
X
Xa
Va
Prothrombin (II)
Thrombin (IIa)
V
Active Protein C
Protein S
Protein C + thrombomodulin
Tissue factor (extrinsic) pathway
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked fibrin clot
Common pathway

Coagulation/hemostasis in liver disease

AZ Nikolaas

- Liver plays essential role in hemostasis and coagulation
  - Production
    - Pro-coagulant factors
    - Anti-coagulant factors
- Progressive liver failure → factor deficiencies:
  - In patients with liver failure PT/INR are prolonged
- PT and aPTT prolongation = important PROGNOSTIC factor in patients with chronic liver disease
  - Incorporation in different scores:
    - King`s college criteria ALF
    - Child Pugh score
    - MELD score

Early Indicators of Prognosis in Fulminant Hepatic Failure

JOHN G. O'GRADY, GRAEME J. M. ALEXANDER, KAREN M. HAYLLAR, and ROGER WILLIAMS
Liver Unit, King's College School of Medicine and Dentistry, Denmark Hill, London, United Kingdom

GASTROENTEROLOGY 1989;97:439–45

Table 2. Assessment of Prognostic Indicators in 121 Patients With Acetaminophen-Induced Fulminant Hepatic Failure

Prognostic indicator	n	Died	Positive predictive value	Specificity	Sensitivity	Predictive accuracy
pH <7.30	22	21	0.95	0.99	0.49	0.81
Prothrombin time >100 s	60	34	0.72	0.67	0.79	0.71
Serum creatinine >300 μmol/L	54	30	0.56	0.69	0.70	0.69
Nonacidotic patients (n = 99)						
Prothrombin time >100 s	39	17	0.44	0.71	0.77	0.73
Serum creatinine >300 μmol/L	49	17	0.35	0.58	0.77	0.63
Prothrombin time >100 s and serum creatinine >300 μmol/L						
All	22	12	0.55	0.87	0.55	0.80
Grade III-IV encephalopathy	15	10	0.67	0.94	0.45	0.83

Conventional coagulation tests and bleeding

- In patients with unifactorial deficiency and patients on oral anticoagulants:
  - PT prolongation is correlated with risk of bleeding
- Chronic liver disease:
  - Historical dogma: liver disease = acquired bleeding disorder

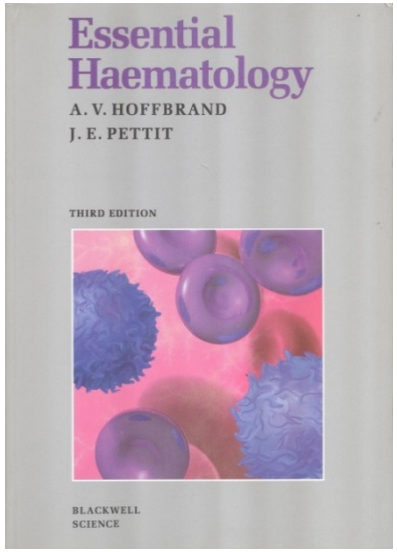
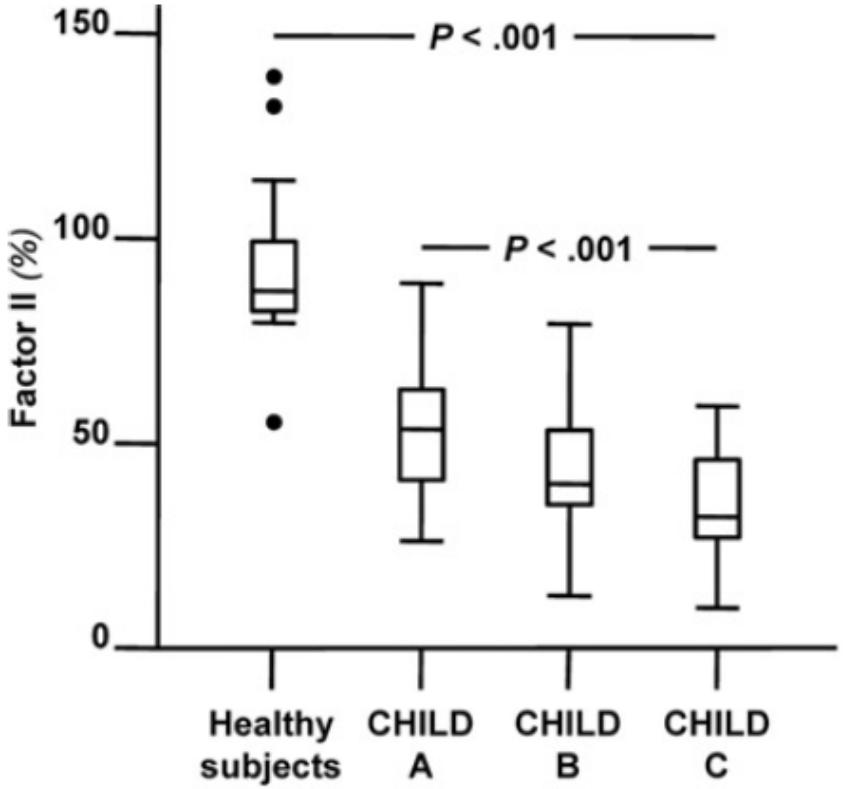
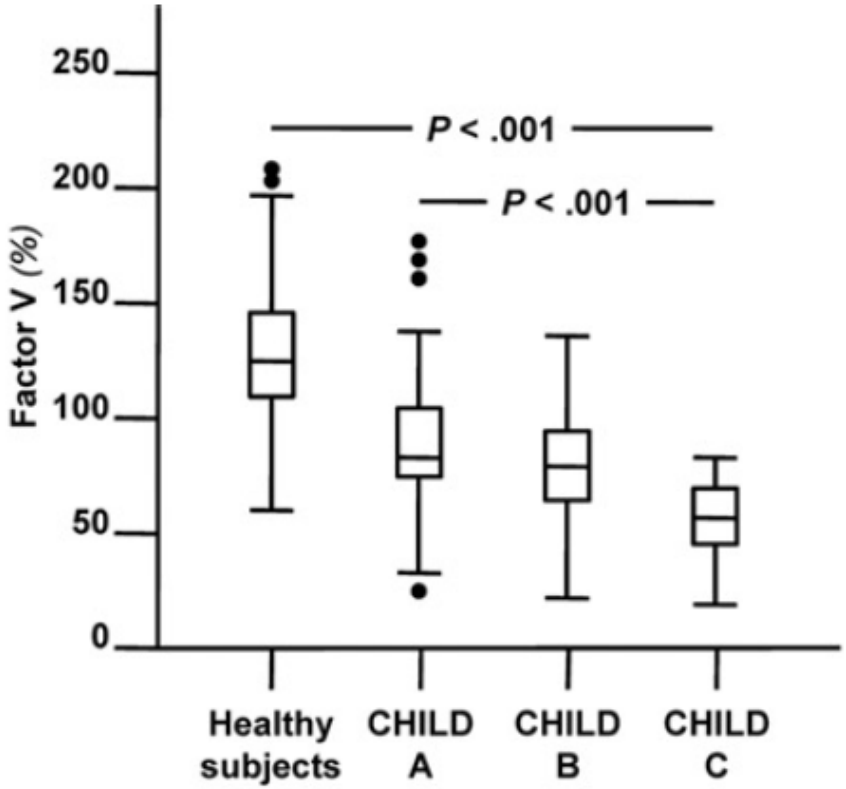


Table 18.3 The acquired coagulation disorders.

Deficiency of vitamin K-dependent factors
Haemorrhagic disease of the newborn
Biliary obstruction
Malabsorption of vitamin K, e.g. sprue, coeliac disease
Vitamin K-antagonist therapy, e.g. coumarins, indanediones
Liver disease
Disseminated intravascular coagulation
Inhibition of coagulation
Specific inhibitors, e.g. antibodies against factor VIII components
Non-specific inhibitors, e.g. antibodies found in systemic lupus erythematosus, rheumatoid arthritis
Miscellaneous
Diseases with M-protein production
L-Asparaginase
Therapy with heparin, defibrinating agents or thrombolytics
Massive transfusion syndrome

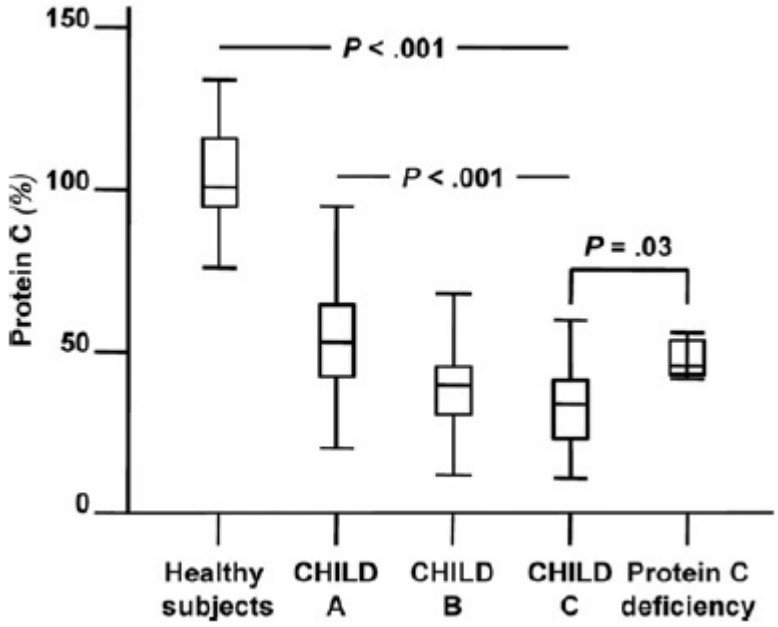
Reduced pro-coagulation factors in cirrhosis

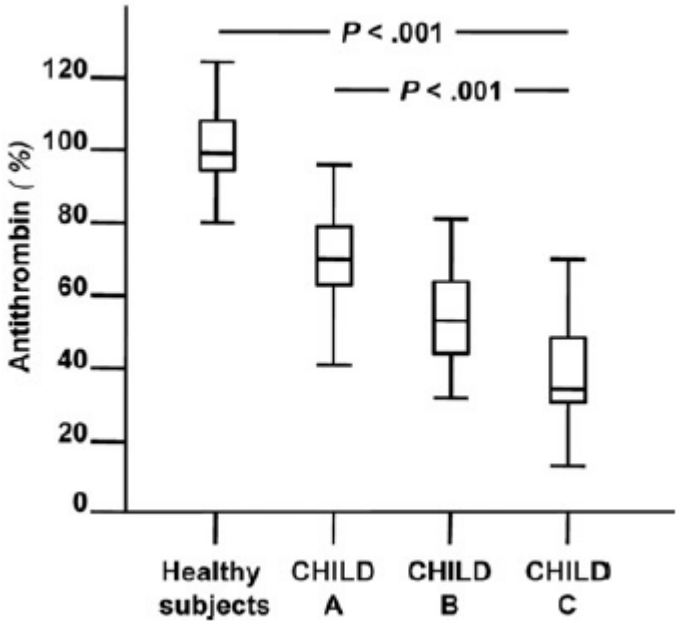




Tripodi A, Gastroenterology 2009.

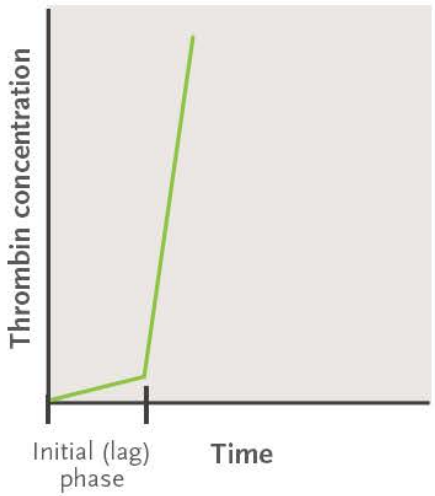
Reduced anti-coagulation factors in cirrhosis

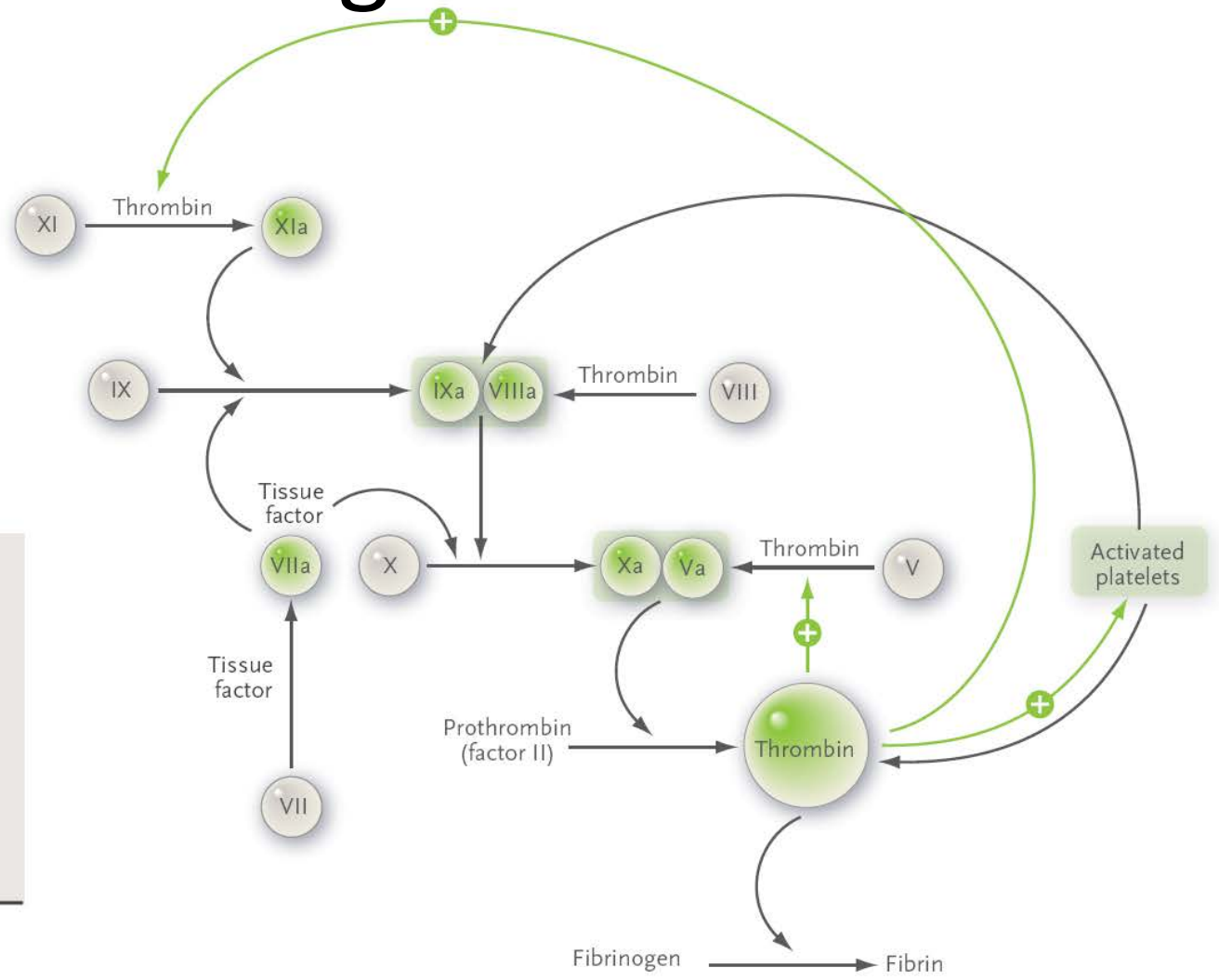




Tripodi A, Gastroenterology 2009.

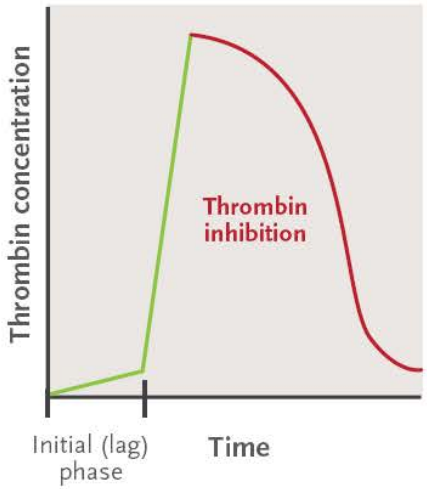
Thrombin generation test

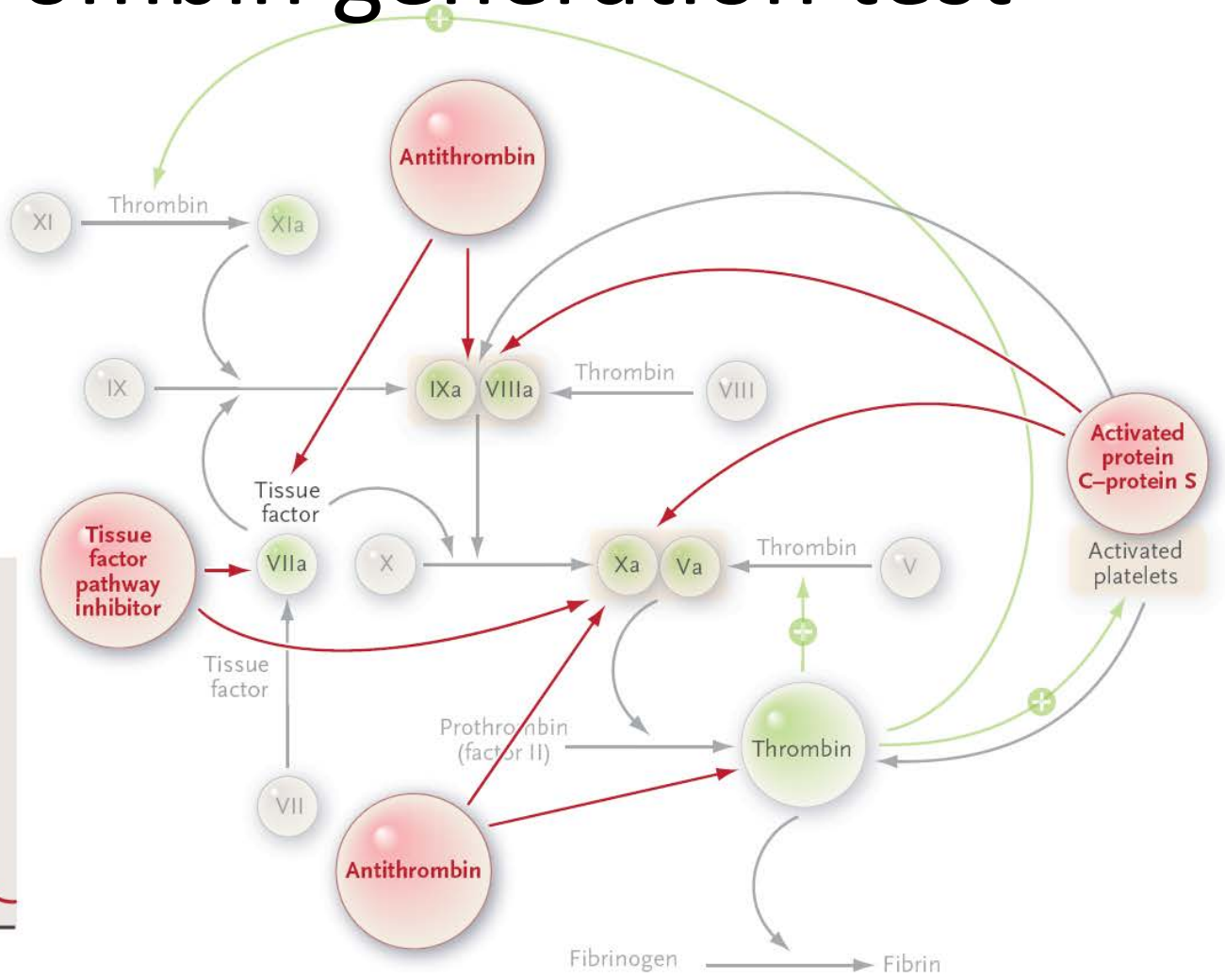




Tripodi, NEJM 2010

Thrombin generation test





Tripodi, NEJM 2010

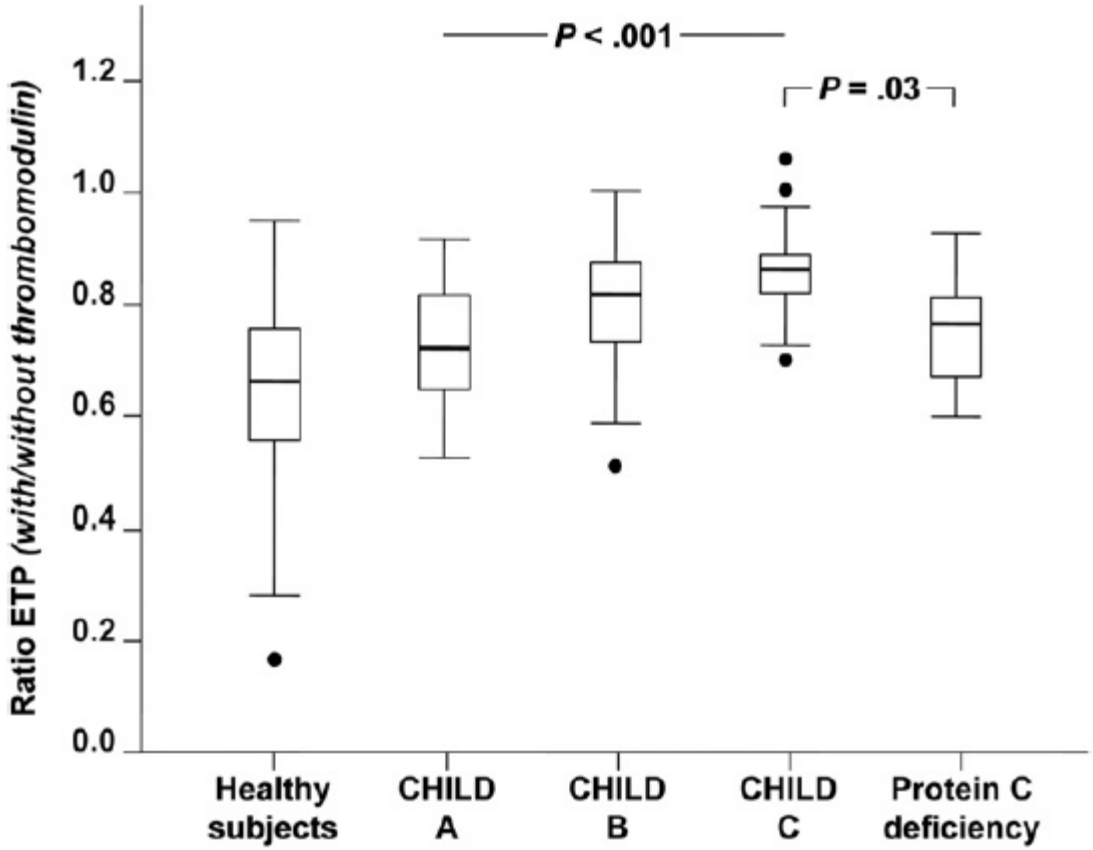
Evidence of Normal Thrombin Generation in Cirrhosis Despite Abnormal Conventional Coagulation Tests

Armando Tripodi, Francesco Salerno, Veena Chantarangkul, Marigrazia Clerici, Massimo Cazzaniga, Massimo Primignani, and Pier Mannuccio Mannucci

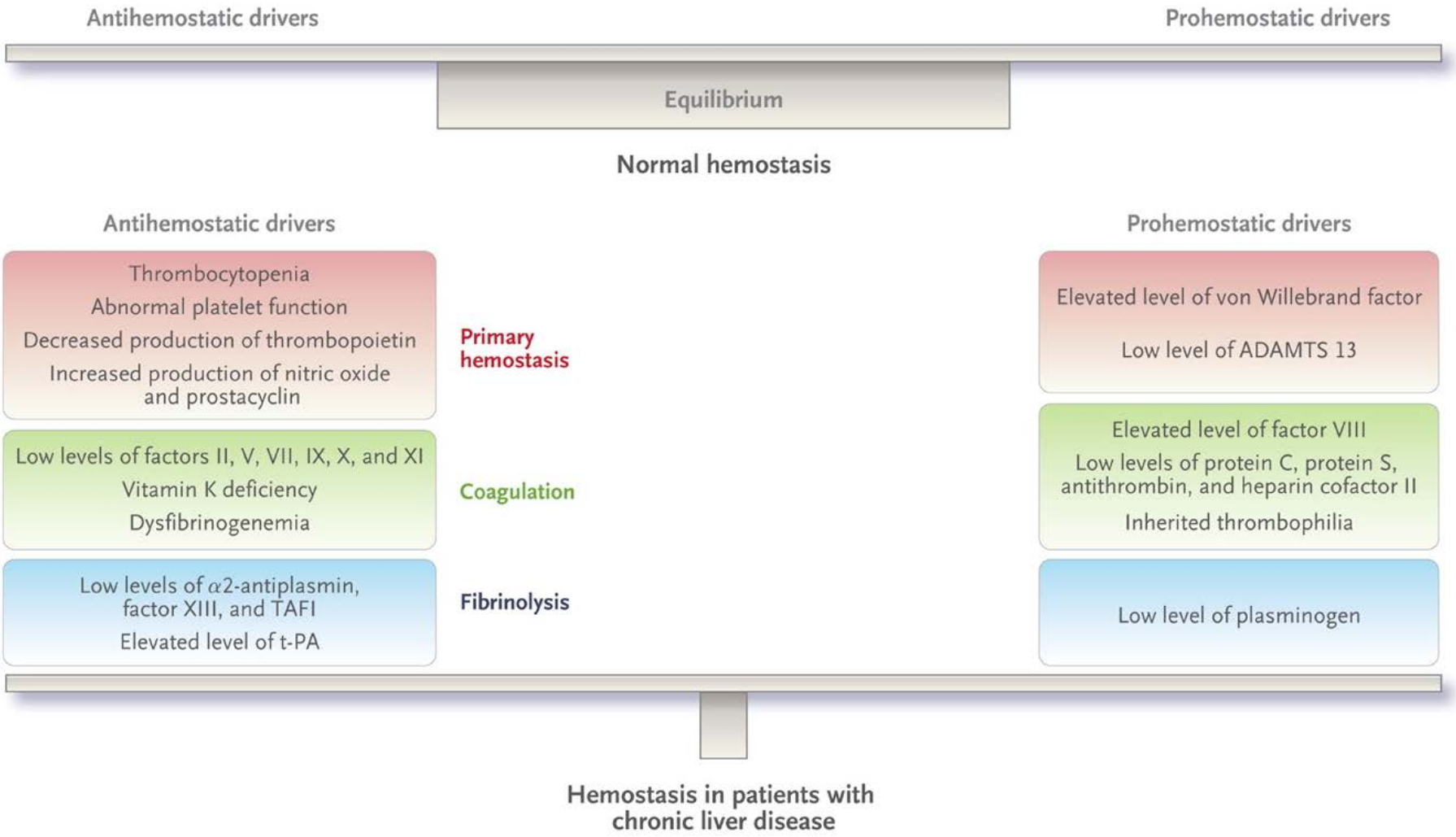
HEPATOLOGY, Vol. 41, No. 3, 2005

The role played by coagulation defects in the occurrence of bleeding in cirrhosis is still unclear. This is partly due to the lack of tests that truly reflect the balance of procoagulant and anticoagulant factors *in vivo*. Conventional coagulation tests such as prothrombin time and activated partial thromboplastin time are inadequate to explore the physiological mechanism regulating thrombin, because they do not allow full activation of the main anticoagulant factor, protein C, whose levels are considerably reduced in cirrhosis. We used a thrombin generation test to investigate the coagulation function in patients with cirrhosis. Thrombin generation measured without thrombomodulin was impaired, which is consistent with the reduced levels of procoagulant factors typically found in cirrhosis. However, when the test was modified by adding thrombomodulin (*i.e.*, the protein C activator operating *in vivo*), patients generated as much thrombin as controls. Hence, the reduction of procoagulant factors in patients with cirrhosis is compensated by the reduction of anticoagulant factors, thus leaving the coagulation balance unaltered. These findings help clarify the pathophysiology of hemostasis in cirrhosis, suggesting that bleeding is mainly due to the presence of hemodynamic alterations and that conventional coagulation tests are unlikely to reflect the coagulation status of these patients. In conclusion, generation of thrombin is normal in cirrhosis. For a clinical validation of these findings, a prospective clinical trial is warranted where the results of thrombin generation in the presence of thrombomodulin are related to the occurrence of bleeding. (HEPATOLOGY 2005;41:553–558.)

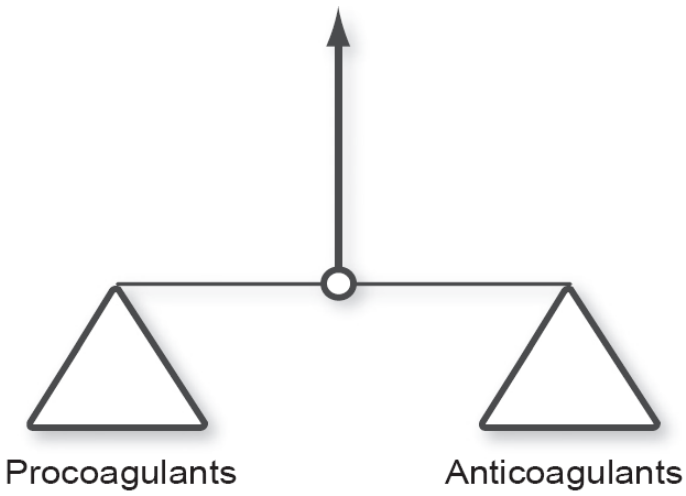
Thrombin generation in cirrhosis



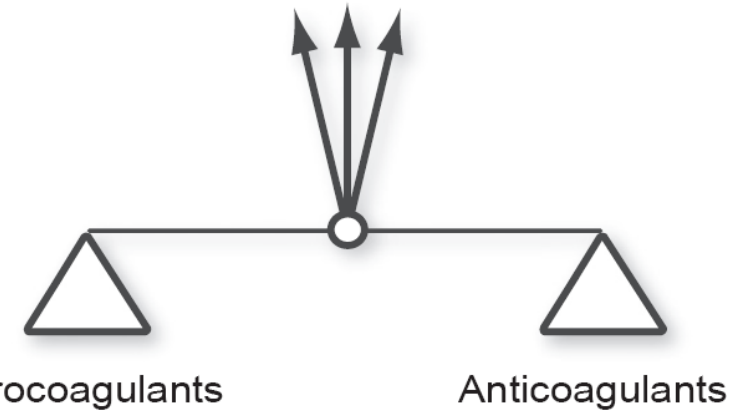
Tripodi A, Gastroenterology 2009.


Antihemostatic drivers
Prohemostatic drivers
Equilibrium
Normal hemostasis
Antihemostatic drivers
Prohemostatic drivers
Thrombocytopenia
Abnormal platelet function
Decreased production of thrombopoietin
Increased production of nitric oxide and prostacyclin
Primary hemostasis
Elevated level of von Willebrand factor
Low level of ADAMTS 13
Low levels of factors II, V, VII, IX, X, and XI
Vitamin K deficiency
Dysfibrinogenemia
Coagulation
Elevated level of factor VIII
Low levels of protein C, protein S, antithrombin, and heparin cofactor II
Inherited thrombophilia
Low levels of α2-antiplasmin, factor XIII, and TAFI
Elevated level of t-PA
Fibrinolysis
Low level of plasminogen
Hemostasis in patients with chronic liver disease

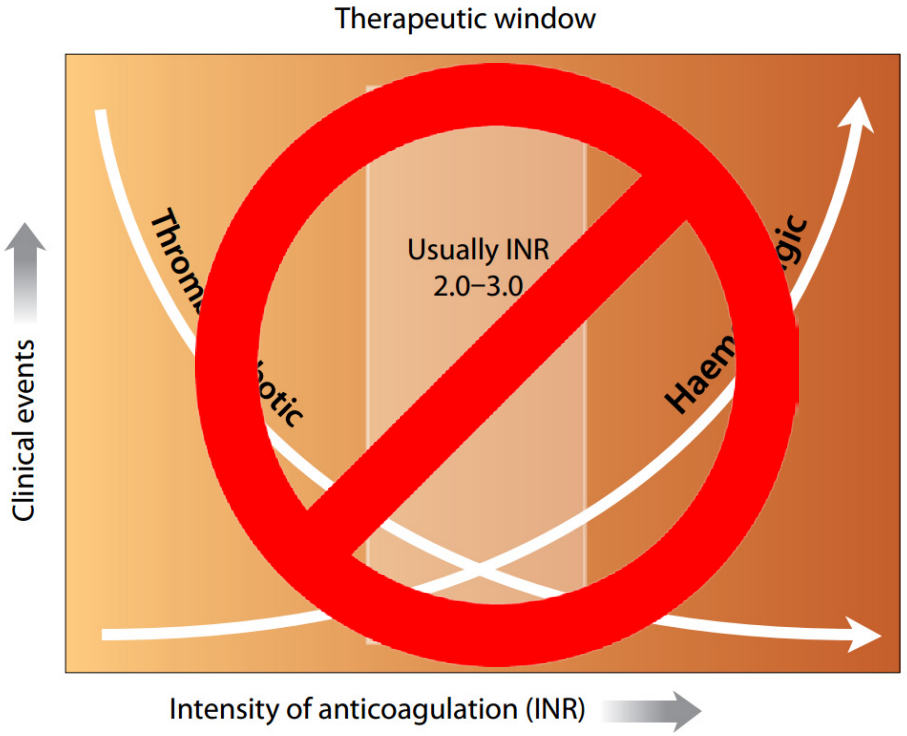
Normal situation – hemostatic balance



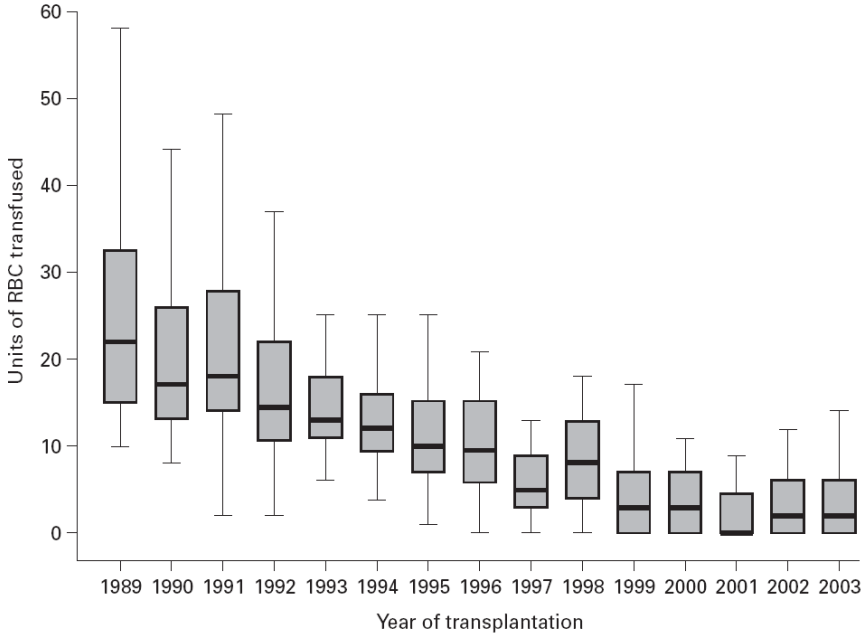
Liver disease – hemostatic rebalance

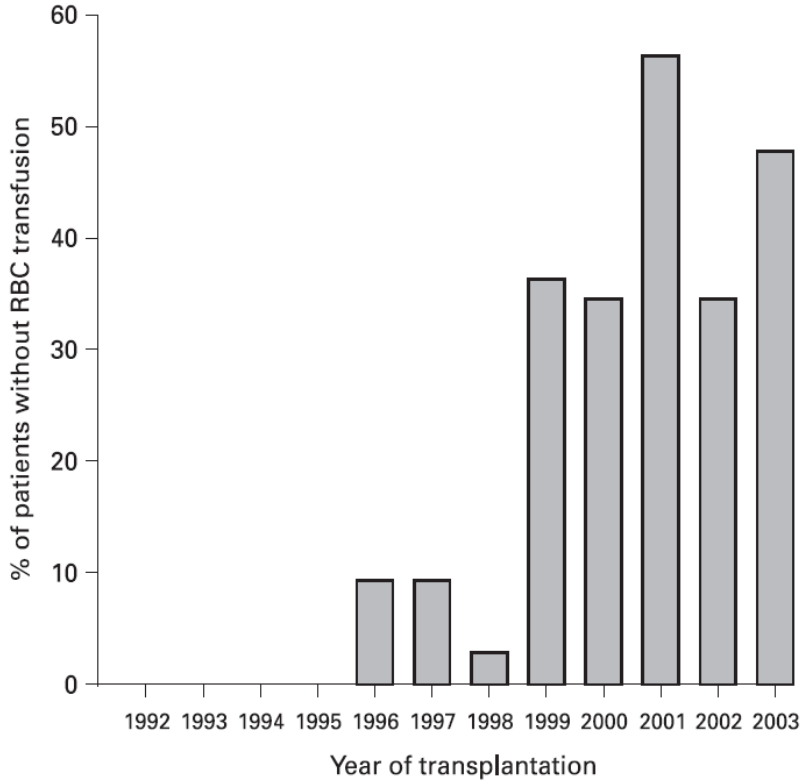


Are there clinical data supporting these data?



LTX blood loss and transfusion over time





De Boer, Dig Surg 2005

Factors associated with bleeding in severe thrombopenia

Table 3. Characteristics of the 32 Patients With Severe Thrombocytopenia Who Underwent Invasive Procedures, Subdivided According to the Occurrence of Procedure-Related Bleeding

	Unit	Bleeders (n = 10)	Nonbleeders (n = 22)	*P*
Age	Years	56 ± 9	58 ± 8	NS
Gender	Male	8 (80%)	14 (64%)	NS
ALT	*IU/L*	44 ± 24	58 ± 62	NS
Albumin	*g/dL*	3.3 ± 0.4	3.4 ± 0.7	NS
Bilirubin	*mg/dL*	1.8 ± 0.8	2.5 ± 1.9	NS
Creatinine	*mg/dL*	0.8 ± 0.2	0.9 ± 0.3	NS
Hemoglobin	*g/dL*	12.3 ± 1.2	11.7 ± 1.9	NS
Hematocrit	*%*	35.5 ± 3.6	33.7 ± 5.6	NS
White blood cells	*n/μL*	4242 ± 2628	3674 ± 1842	NS
Platelet count	*n/μL*	50,200 ± 12,308	50,591 ± 14,895	NS
INR		1.36 ± 0.21	1.49 ± 0.27	NS
αFetoprotein	*ng/mL*	16 ± 16	28 ± 50	NS
MELD score		20 ± 4	23 ± 6	NS
Diabetes	Yes	1 (10%)	5 (23%)	NS
Hepatocellular carcinoma	Yes	5 (50%)	8 (36%)	NS
Esophageal varices	Yes	6 (60%)	19 (86%)	NS
Platelet transfusion	Yes	4 (40%)	3 (14%)	NS

NOTE. Continuous data are shown as mean and standard deviation and categorical data as absolute count and percentage.
ALT, alanine aminotransferase; NS, not significant.

Giannini EG,. Clin Gastroenterol Hepatol 2010;

Factors influencing the bleeding risk in cirrhotics

1. Bacterial infections

TABLE 4. Univariate Logistic Regression Analysis of Possible Risk Factors for Failure to Control Bleeding Among Demographic, Clinical, and Laboratory Characteristics

	Odds Ratio	95% Confidence Interval	*P* Value
Age (per 5 years)	0.97	(0.86-1.10)	.68
Female	1.17	(0.61-2.22)	.64
Etiology of cirrhosis			
Alcoholic	0.78	(0.42-1.46)	.44
Posthepatic	1.99	(0.87-4.57)	.11
Other	0.95	(0.48-1.88)	.88
Child-Pugh score	1.24	(1.11-1.39)	.0002
Hepatomegaly	1.08	(0.58-2.03)	.80
Splenomegaly	0.73	(0.37-1.42)	.35
Ascites	1.68	(0.90-3.13)	.10
Encephalopathy	1.90	(0.93-3.89)	.08
Hemoglobin	0.89	(0.78-1.02)	.10
White cell count (10×10^9/L)	1.03	(0.98-1.08)	.24
Platelets (10×10^9/L)	1.00	(0.96-1.04)	.99
Prothrombin time	1.10	(1.04-1.17)	.002
Creatinine (/10 µmol/L)	1.03	(0.99-1.08)	.14
Bilirubin (/10 µmol/L)	1.00	(0.98-1.02)	.80
Albumin	0.98	(0.94-1.02)	.24
Aspartate aminotransferase (/10 IU/L)	1.01	(0.98-1.03)	.63
Alanine aminotransferase (/10 IU/L)	1.01	(0.97-1.05)	.57
γ-Glutamyltransferase (/10 IU/L)	0.98	(0.96-1.01)	.30
Antibiotic use	5.62	(2.56-12.35)	.0001
Proven bacterial infections	5.97	(2.98-11.94)	.0001

Goulis J. Hepatology. 1998

Factors influencing the bleeding risk in cirrhotics

1. Bacterial infections

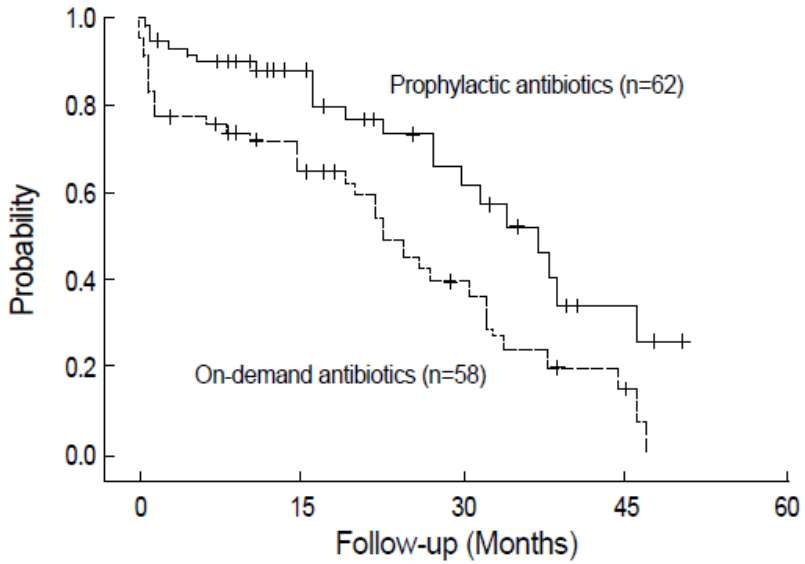


Fig. 1. Actuarial probability of remaining free of rebleeding in the patients in terms of prophylactic and on-demand antibiotics use. The difference between the groups was statistically significant (p=0.0035 by log-rank test).

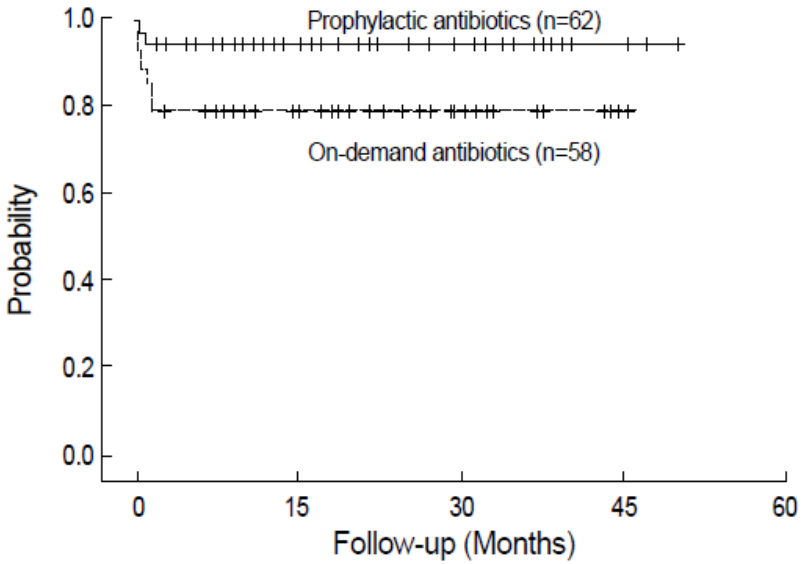


Fig. 2. Actuarial probability of remaining free of early rebleeding in the patients in terms of prophylactic and on-demand antibiotics use. The difference between the groups was statistically significant (p=0.0085 by log-rank test).

Goulis J. Hepatology. 1998

Factors inducing the bleeding risk in cirrhotics

2. Thrombopenia

Table 2. Type of Invasive Procedures Subdivided According to the Degree of Thrombocytopenia

	Platelet count	
	<75,000/μL (n = 32)	>75,000/μL (n = 18)
Endoscopic variceal ligation	9	9
TACE	8	3
TIPS	3	2
Dental extraction	4	0
Large volume paracentesis	3	1
Endoscopic polypectomy	2	1
RFTA	1	1
Thyroid biopsy	1	0
Endoscopic gastric biopsies	1	0
Liver biopsy	0	1

RFTA, radiofrequency thermal ablation; TACE, transcatheter arterial chemoembolization; TIPS, transjugular intrahepatic portosystemic shunt.

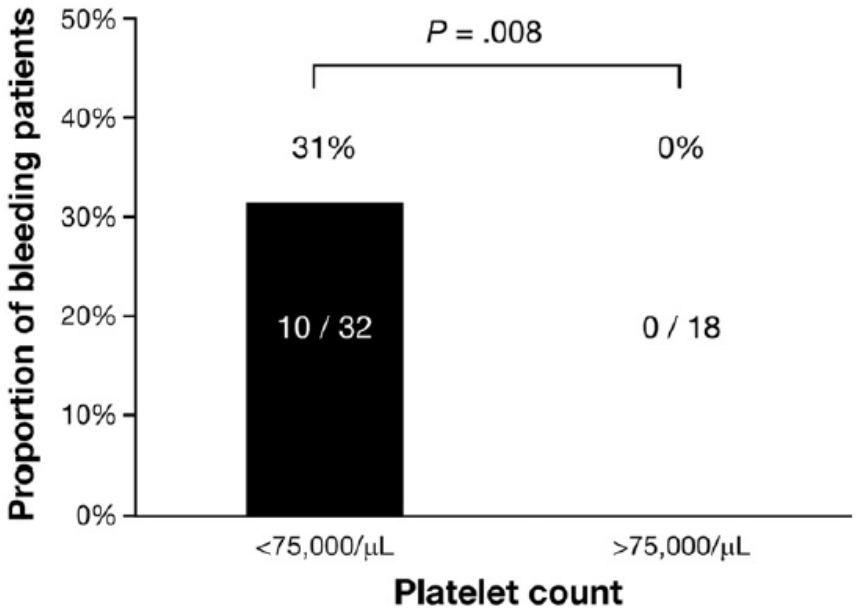
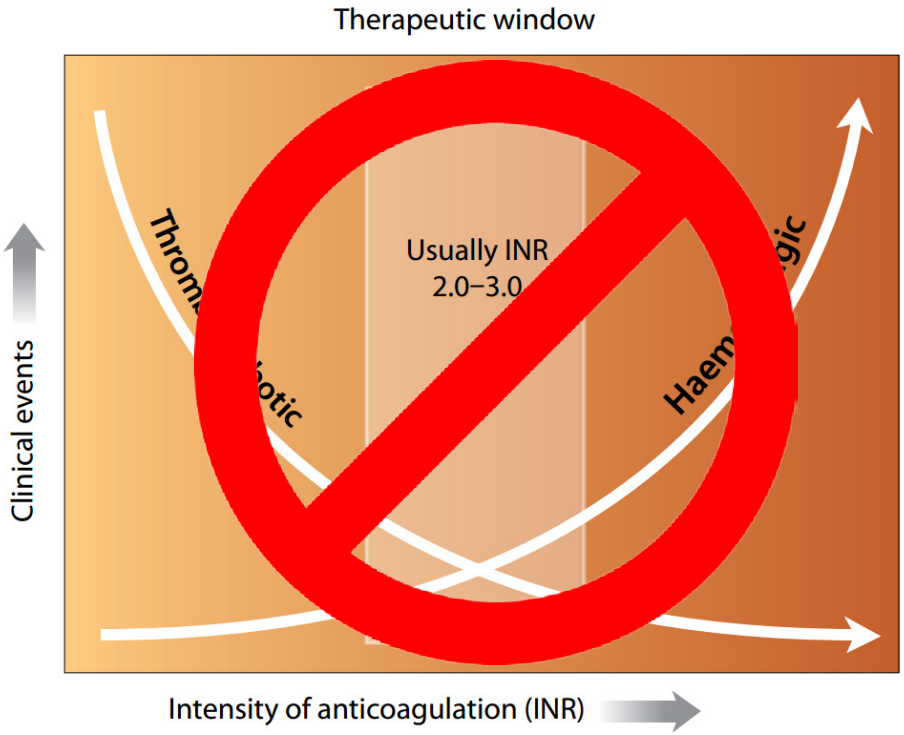


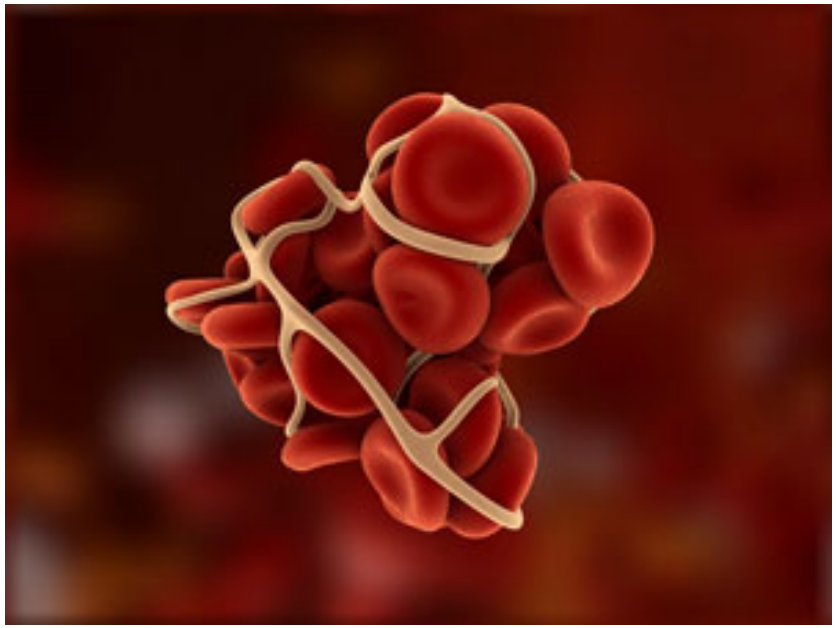
Figure 1. Number and proportion of thrombocytopenic patients who had procedure-related bleeding subdivided according to the degree of thrombocytopenia.

Giannini EG. Clin Gastroenterol Hepatol 2010.


Therapeutic window
Usually INR
2.0–3.0
Clinical events
Intensity of anticoagulation (INR)

Auto-anticoagulation in chronic liver disease?

AZ Nikolaas



Auto-anticoagulation in chronic liver disease?

AZ Nikolaas

1. Clinical evidence
    1. Patients with liver dysfunction are not protected from
        1. Deep venous thrombosis:
            1. Incidence of thrombosis increases with severity of liver failure
        2. Portal vein thrombosis
        3. Pulmonary embolism

2. Short life of renal replacements circuits in patients with liver failure

Tripodi, Gastro 2009

Deep venous thrombosis in liver disease

- Population-based case-control study of 99 444 with venous thrombosis versus 496 872 controls:
  - High relative risk for venous thrombosis for cirrhosis

- Despite prolonged conventional coagulation tests these patients should be treated with anticoagulation!!!

Table 4. Relative risks[a] (odds ratios) and 95% CIs for VTE

Variable	All venous thromboembolism		Unprovoked venous thromboembolism	
	Crude RR	Adjusted[b] RR	Crude RR	Adjusted[c] RR
Liver cirrhosis	2.60 (2.34–2.88)	1.74 (1.54–1.95)	2.88 (2.52–3.29)	2.06 (1.79–2.38)
Non-cirrhotic liver disease	2.54 (2.36–2.73)	1.87 (1.73–2.03)	2.84 (2.59–3.11)	2.10 (1.91–2.31)
Liver cirrhosis and HCC	2.64 (2.38–2.93)	1.75 (1.56–1.97)	2.90 (2.54–3.32)	2.08 (1.81–2.40)

HCC, hepatocellular carcinoma.
[a]Computed with conditional logistic regression. [b]Adjusted for cancer, fractures, trauma, surgery, pregnancy, Charlson Index, psychiatric diseases, and obesity. [c]Adjusted for Charlson Index, psychiatric diseases, and obesity.

Sogaard, AJG 2009

Portal vein thrombosis

- The prevalence of PVT is associated with the severity of cirrhosis
  - 1% compensated cirrhosis
  - 8-25% candidates for LTX

Table 2 Prevalence and relative risk (odds ratio) of PVT in relation to disease condition with major risk of PVT

Patient category	*n* (%)	PVT (%)	O.R. (95% C.I.)[1]	*P* value	O.R. (95% C.I.)	*P* value
Cirrhosis	1193 (5.0)	72 (6.0)	7.9 (6.0 - 10.5)	<0.001		
with primary hepatic cancer	182	26 (14.3)	17.1 (11.1 - 26.4)	<0.001	3.5 (2.1 - 5.8)	<0.001
without primary hepatic cancer	1011	46 (4.5)	5.2 (3.7 - 7.2)	<0.001	1[2]	
Primary hepatobiliary cancer	698 (2.9)	59 (8.5)	10.8 (8.0 - 14.7)	<0.001		
hepatic carcinoma	392	38 (9.7)	11.5 (8.0 - 16.5)	<0.001		
with cirrhosis	182	26 (14.3)	17.1 (11.1 - 26.4)	<0.001	2.8 (1.3 - 5.6)	0.004
without cirrhosis	210	12 (5.7)	5.8 (3.2 - 10.6)	<0.001	1[2]	
extrahepatic biliary / gall bladder carcinoma	313	21 (6.7)	7.2 (4.5 - 11.4)	<0.001		
Secondary hepatic malignancy						
from all tumours	3446 (14.5)	113 (3.3)	4.9 (3.8 - 6.2)	<0.001		
from pancreatic carcinoma	312	36 (11.5)	13.9 (9.6 - 20.2)	<0.001	5.2 (3.4 - 7.8)[3]	<0.001[3]
gastric carcinoma	316	18 (5.7)	5.9 (3.6 - 9.7)	<0.001	1.9 (1.2 - 3.2)[3]	0.019[3]
colorectal carcinoma	637	13 (2.0)	2.0 (1.1 - 3.5)	0.028	0.5 (0.3 - 1.0)[3]	0.063[3]
Myeloproliferative disorders	231 (1.0)	7 (3.0)	3.0 (1.4 - 6.3)	0.012		
All patients	23796 (100)	254 (1.0)				

Ogren. World J Hepatol 2006.

Thrombotic problems with extracorporeal circuits

- Circuit life is longer in hematology patients in comparison to patients with liver disease
  - Anticoagulation improved circuit life
- Thrombosis of liver assist devices is pertinent issue

Duration of continuous renal replacement (CRRT) circuits.

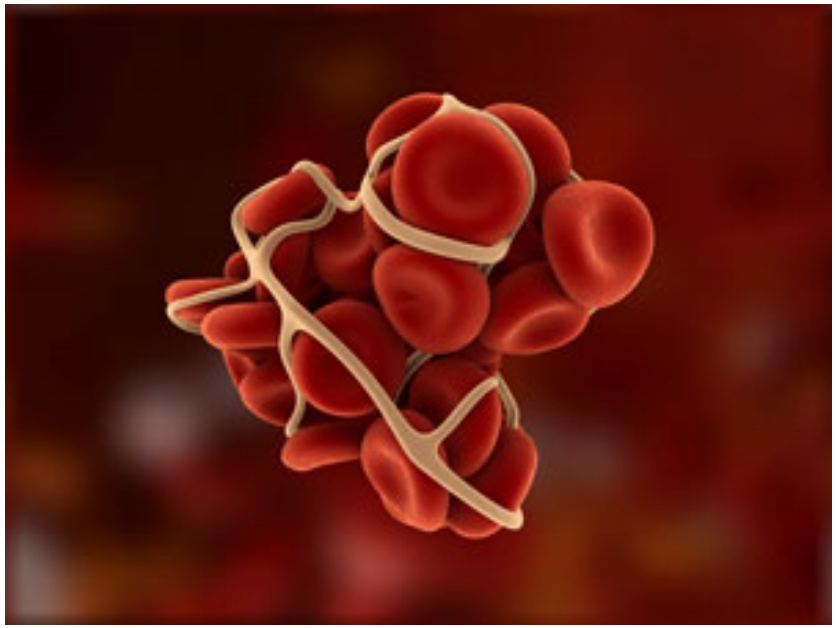
Parameter	ALF	ACLD	Post-LTx	Sepsis	Haematological
Filter life in hours – 1st filter	11 (10.5)	11.6 (6.6)	7.4 (5.1)	9.2 (6.4)	24.3 (22.9)
Filter life in hours – 2nd filter	9 (7.6)	11.9 (6.41)	7.7 (5.3)	12.0 (9.0)	21.1 (19.7)
Filter life in hours – 3rd filter	11.7 (8)	8.8 (9.5)	9.2 (8.2)	11.5 (11.4)	16.3 (6.3)
Mean filter life in hours – 1st–3rd filter	10.4 (8.6)	11.1 (7.8)	8.1 (6.2)	11.6 (11.4)	21.7 (19.7)*
Number of filters used/48 h	4.3 (1.3)	4.2 (2.1)	5.3 (1.5)	4.6 (1.5)	2.4 (1.1)**
Number of filter clots the 1st 3 CRRT circuit	2.1 (0.7)	1.9 (1.1)	1.9 (1.1)	2.1 (1.1)	1.8 (1)
Number of PRBC transfusion	4.8 (4.2)	4.2 (4.16)	2.2 (2.1)	3.0 (1.6)	1.2 (1.3)

Agarwal, J Hep 2009

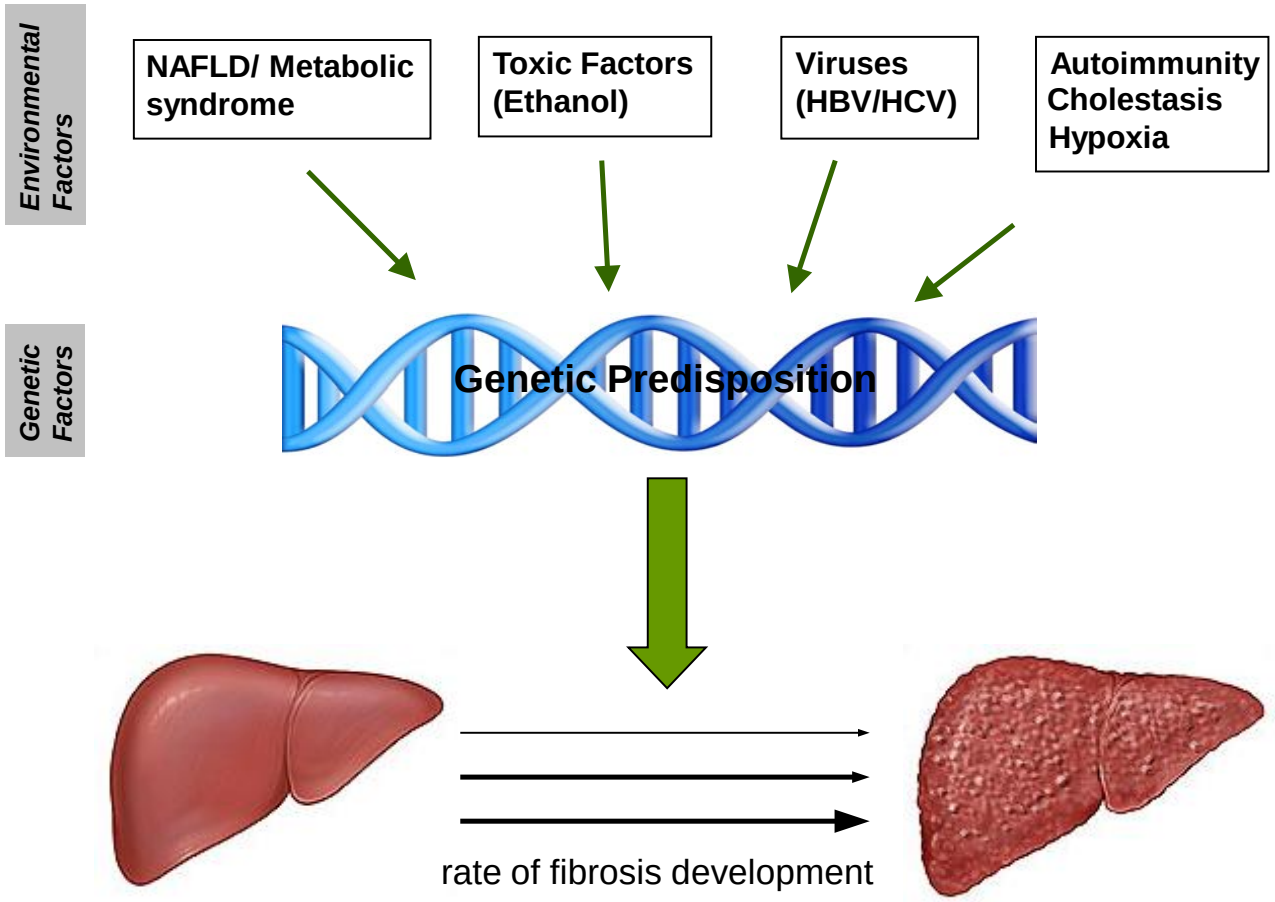
Laleman, Crit Care 2006

AZ Nikolaas

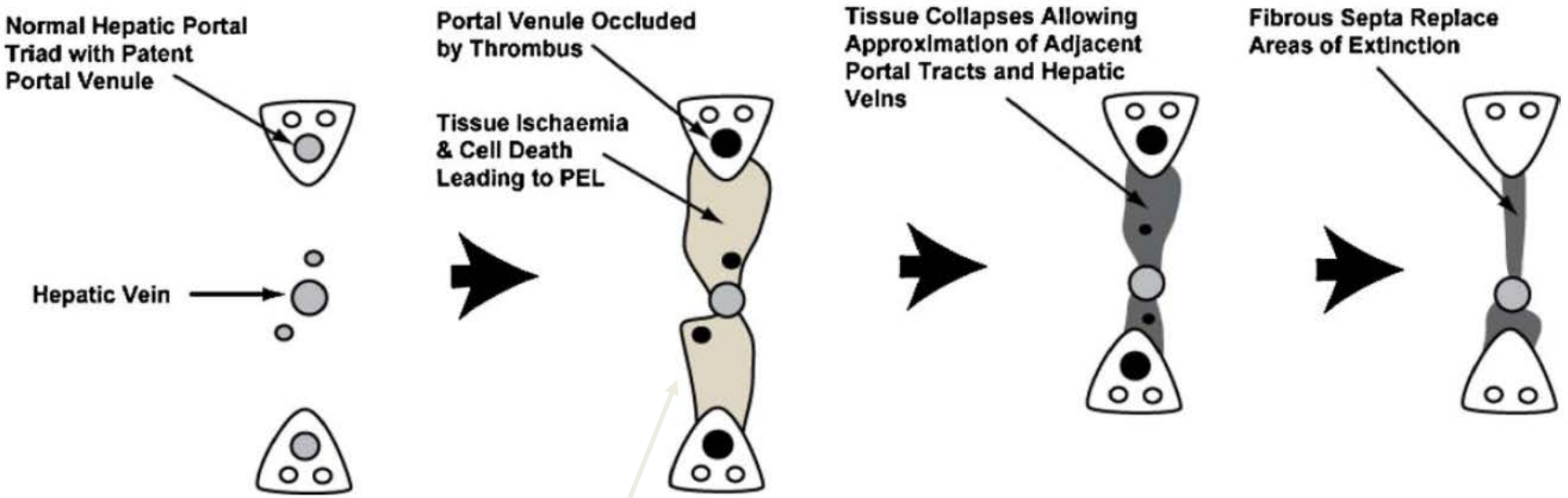
Patients with liver disease have a higher prevalence of thrombotic events!!



Pathophysiological role of hemostasis



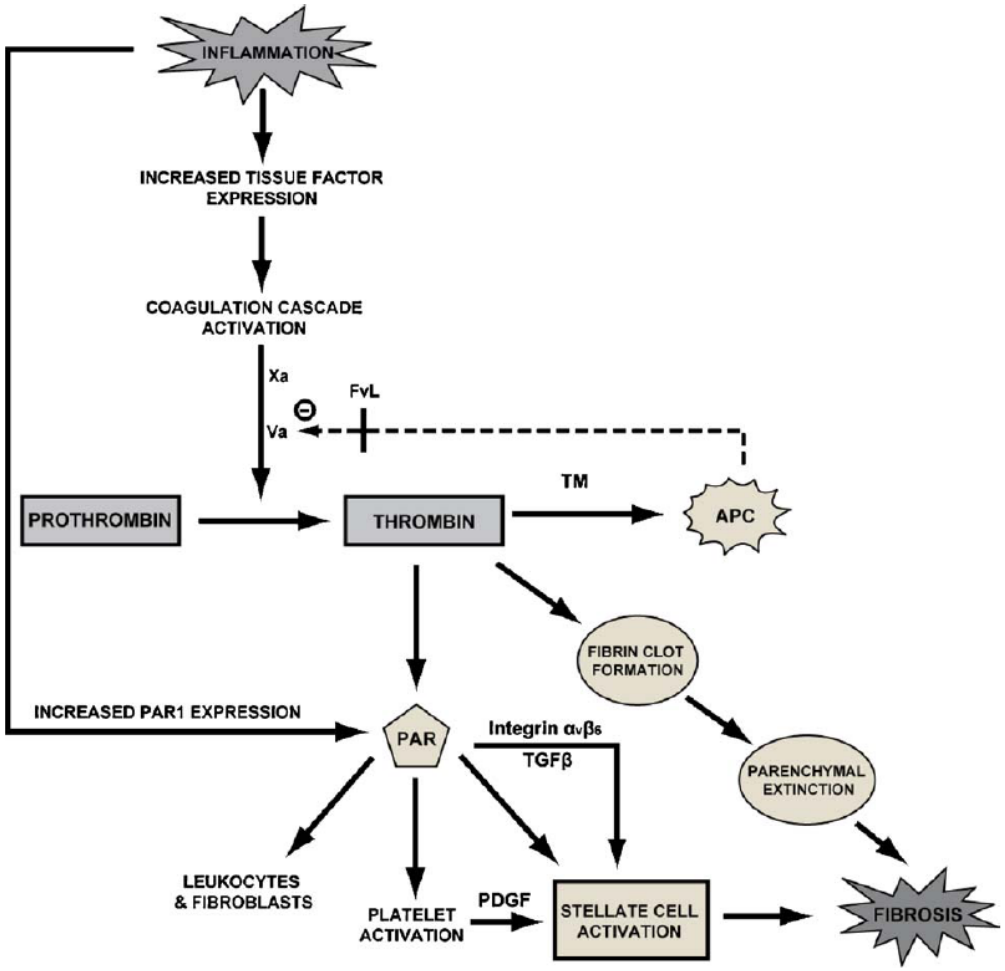
Correlation between grade of fibrosis and microvascular thrombi



Parenchymal extinction lesions

Anstee, 2011

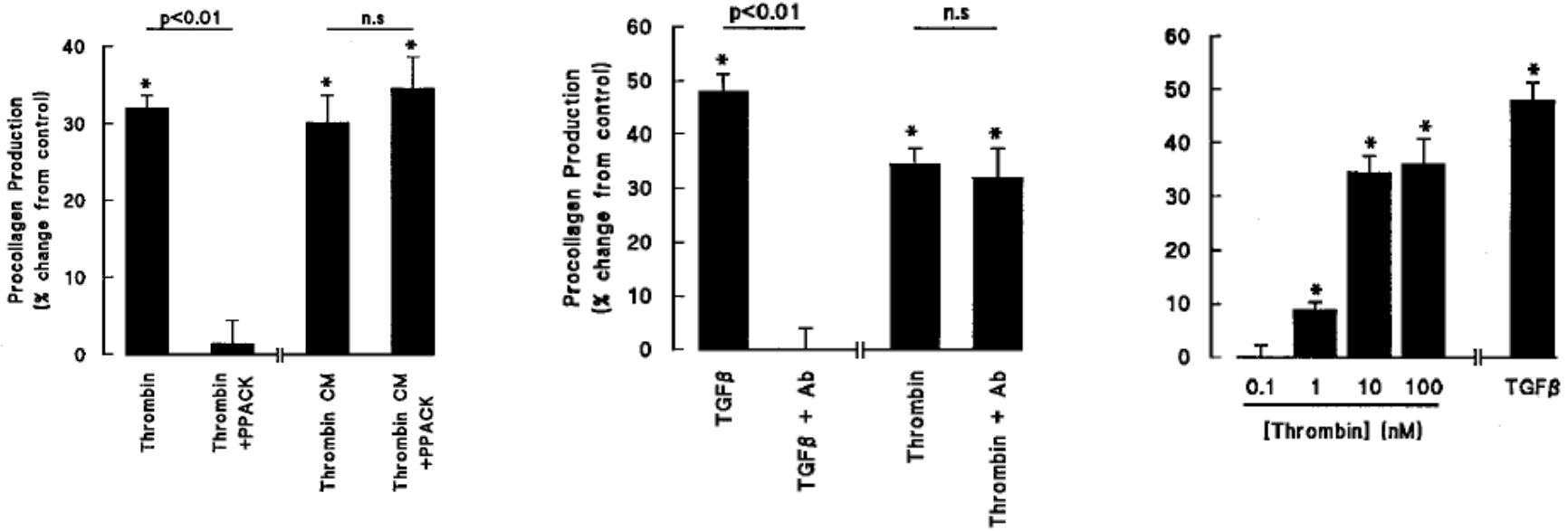
Direct stellate cell activation hypothesis



Thrombin Stimulates Smooth Muscle Cell Procollagen Synthesis and mRNA Levels via a PAR-1 Mediated Mechanism

K. Dabbagh, G. J. Laurent, R. J. McAnulty, R. C. Chambers

From the Centre for Cardiopulmonary Biochemistry and Respiratory Medicine, University College, London Medical School, The Rayne Institute, London, United Kingdom



Dabbagh, 1998

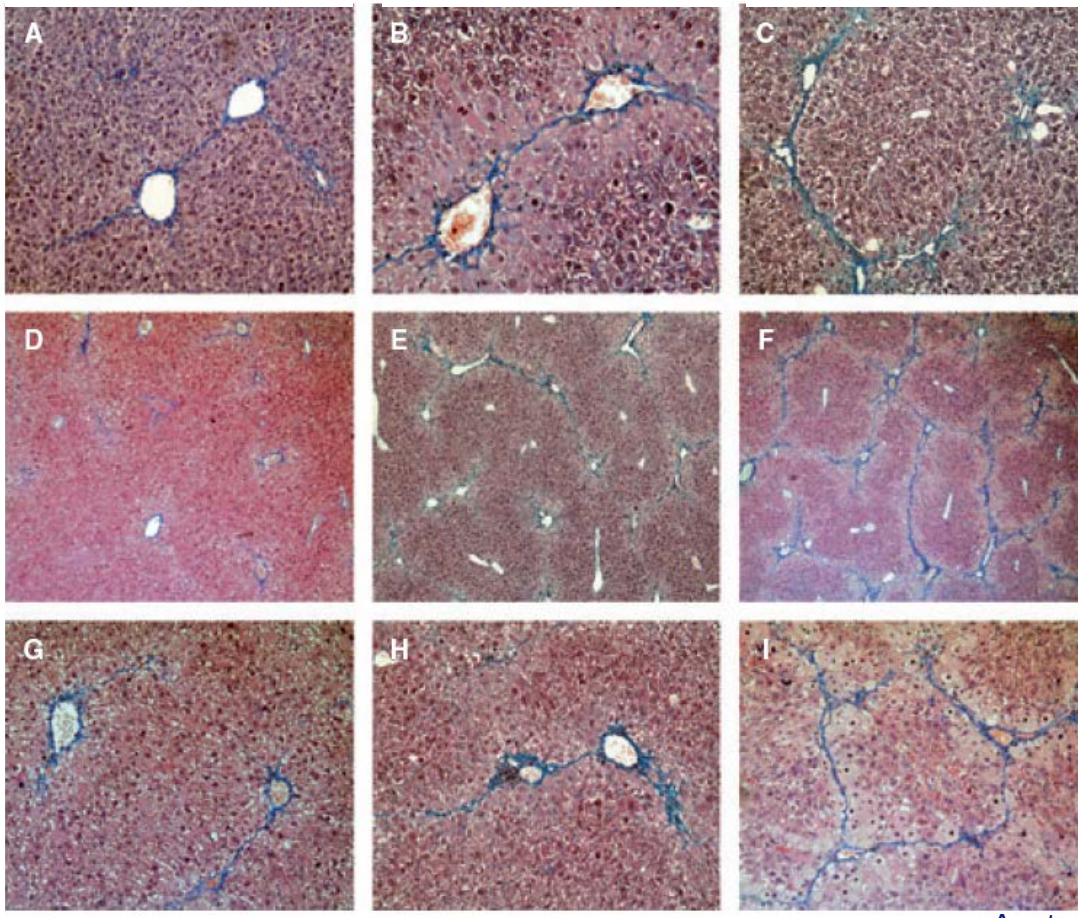
Warfarin treated animals | **Control animals** | **Transgenic Factor V Leiden**

CCL_4 CCL_4

2 weeks

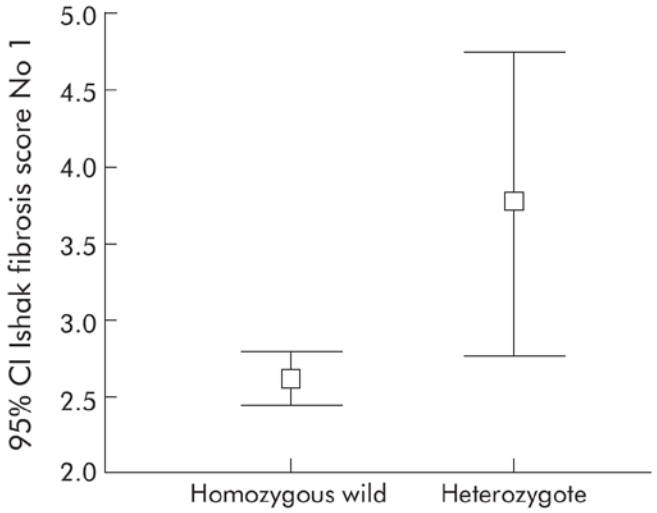
4 weeks (low)

4 weeks (high)



Anstee, J Throm Haemost 2008

Factor V Leiden polymorphisms and rate of fibrosis



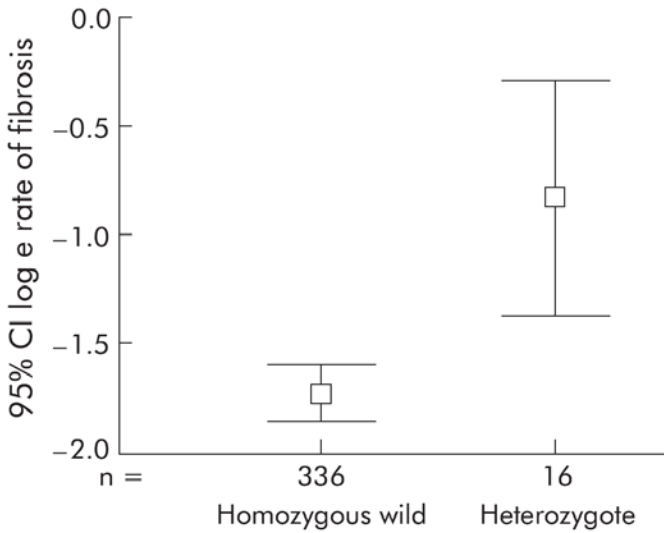


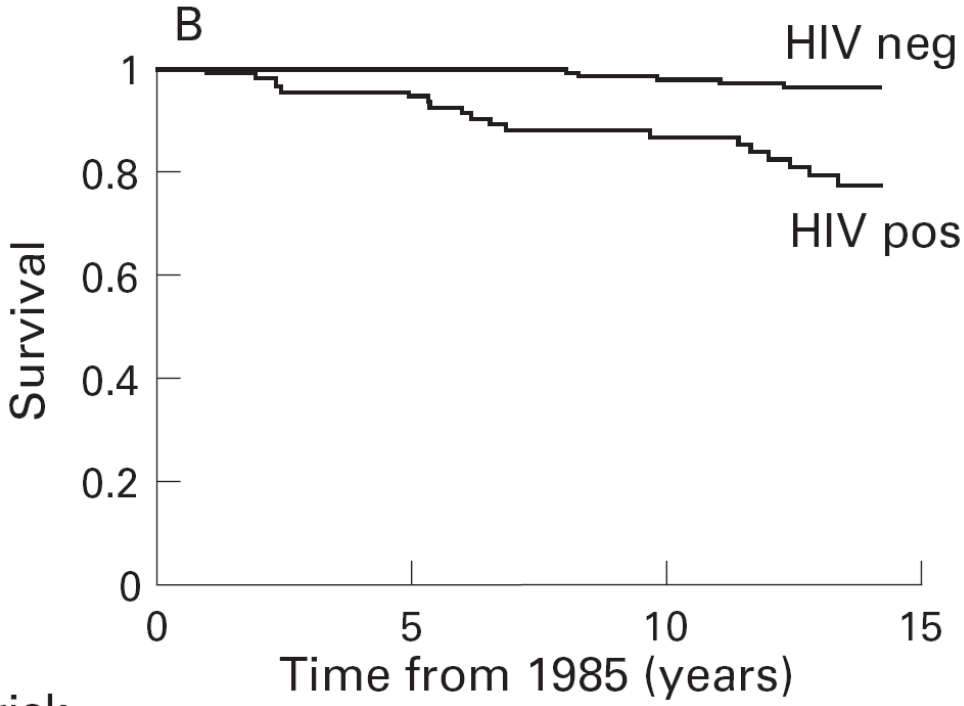
Table 2 Summary of disease association and ANOVA results for factor V Leiden

	Study population	Wild-type factor 5	Factor V Leiden heterozygotes	
Total population 352		336	16	ANOVA, p=0.004
	Fast 170	158	12	Fisher's exact, p=0.029; OR 3.38 (95% CI 1–12.7)
	Slow 182	178	4	

OR, odds ratio; 95% CI, 95% confidence interval.

Wright, Gut 2003

Liver related death in Hep C infected haemophilics



No. at risk			
HIV neg	183	173	158
HIV pos	121	98	67

Yee, Gut 2000

Prothrombotic genetica risk factors and liver fibrosis

AZ Nikolaas

Table 2. Association of the Factor V Leiden mutation, prothrombin G20210A gene variant, ABO blood group type and presence of LS ⩾8.0 kPa.

	Total cohort (n = 1055)	LS <8.0 kPa (n = 954)	LS ≥8.0 kPa (n = 101)	OR (95%CI)*	*p* value*
FVL mutation†	49 (4.6%)	41 (4.3%)	8 (7.9%)	2.00 (0.90-4.46)	0.09
Prothrombin G20210A gene variant‡	20 (1.9%)	16 (1.7%)	4 (4.0%)	2.04 (0.66-6.28)	0.2
FVL mutation or Prothrombin G20210A gene variant◊	68 (6.4%)	56 (5.9%)	12 (11.9%)	2.09 (1.07-4.07)	0.03
Blood group type non-O¥	568 (55.0%)	513 (54.9%)	55 (55.6%)	0.92 (0.60-1.40)	0.7

Plompen E, J Hepatol 2015

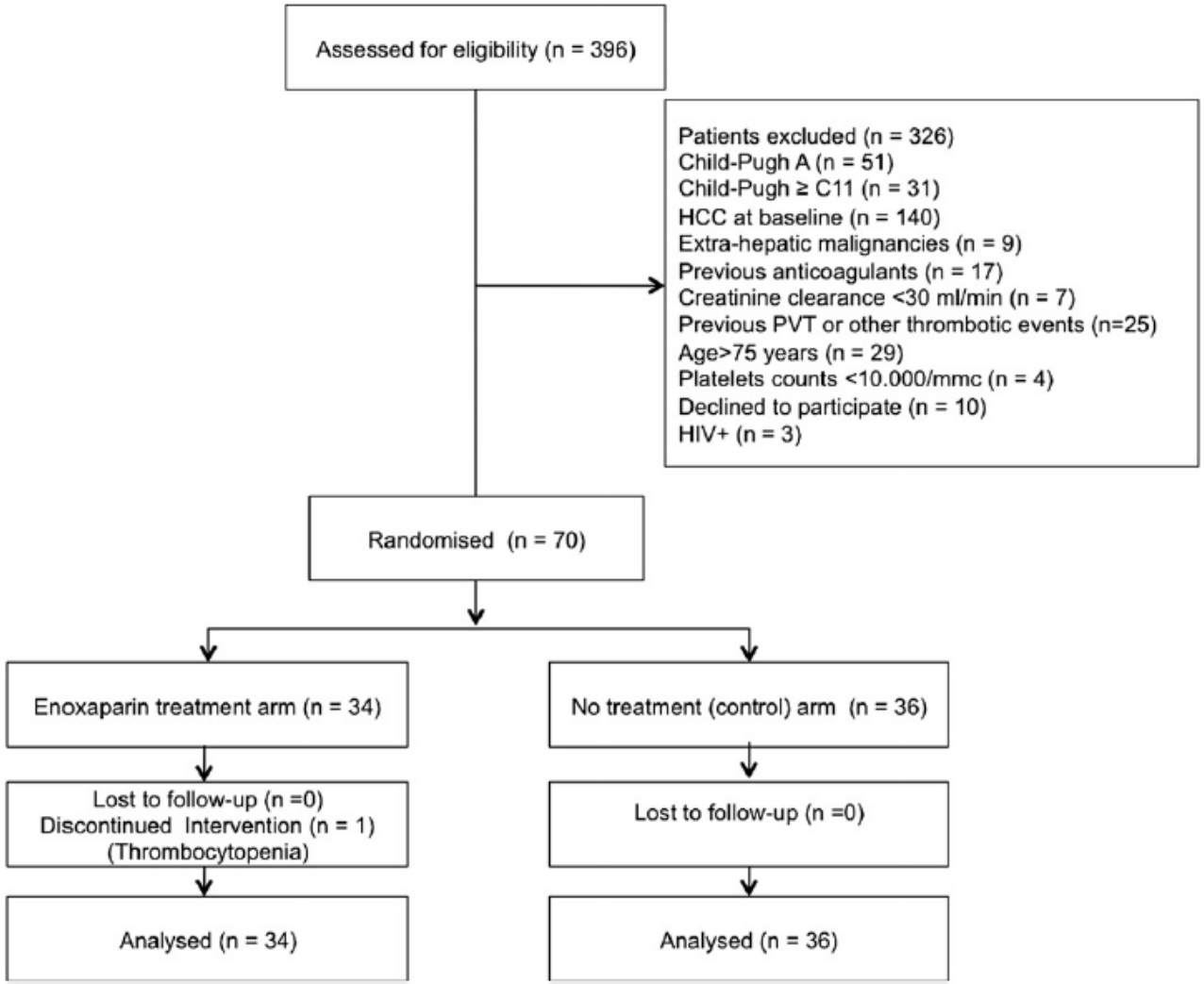
Clinical consequences of the etiological role of hemostasis in fibrogenesis

1. Questions the unrestricted use of plasma infusion to correct the conventional coagulation tests in patients undergoing invasive procedures
    1. Progression of liver disease
    2. Induce thrombosis

2. Prevention of fibrosis progression in post LTX Hep C
    - WAFT-C trial (London Imperial College)
    - Coumarin based anticoagulation post LTX
    - First year results were promising (2015)
    - Stellate cells activation on biopsy

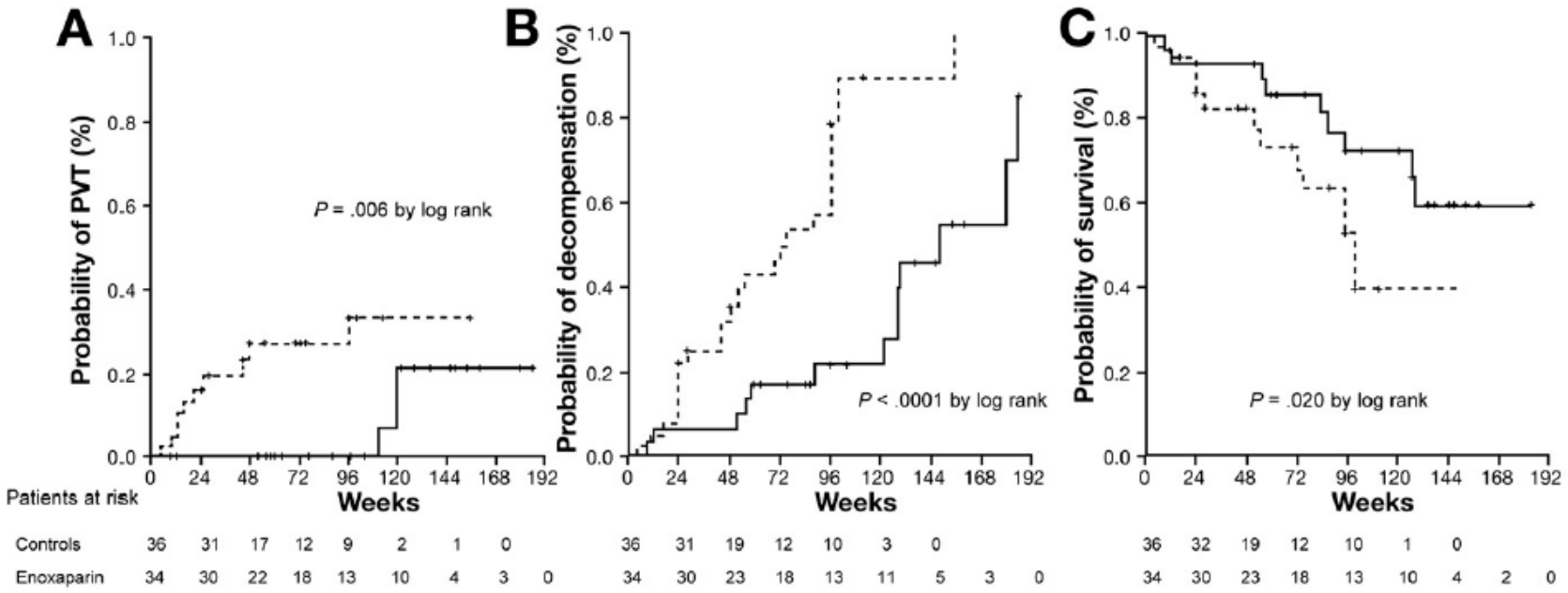
3. Prevention of progression of liver disease

LMWH in liver disease



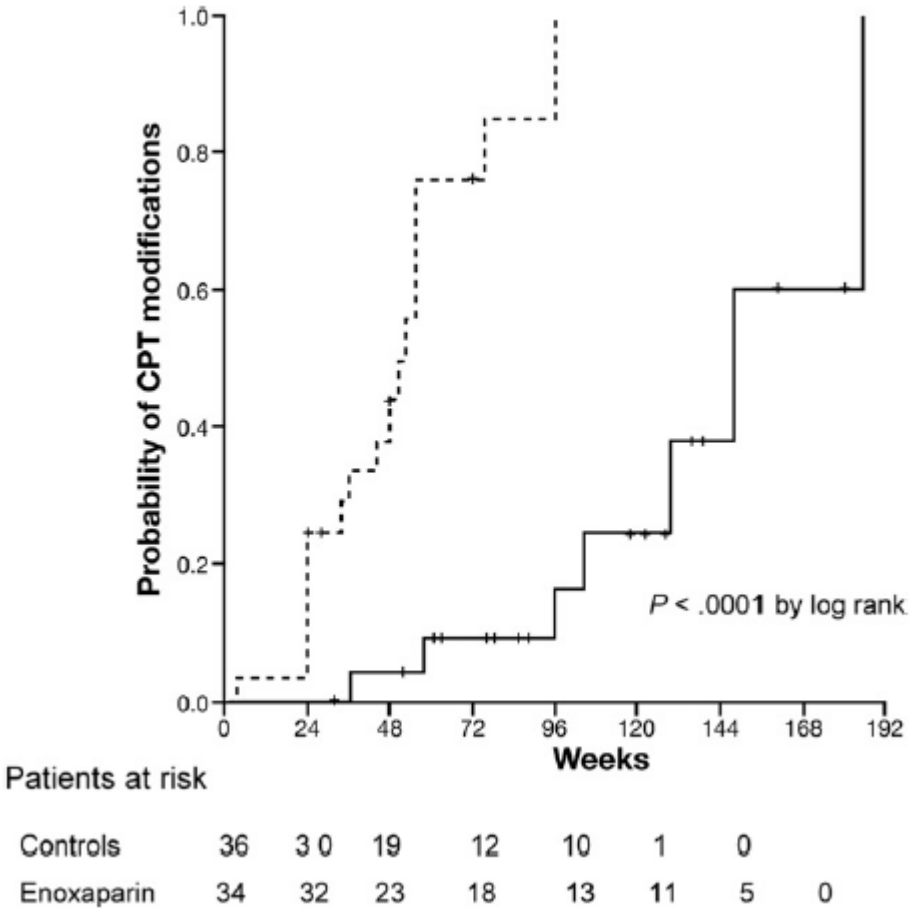
Villa, Gastro enterology2012

LMWH in liver disease



Villa, Gastro enterology2012

LMWH in liver disease



Villa, Gastro enterology2012

NOAC's and liver disease

AZ Nikolaas

Table 3 Summary of new oral anti-coagulants

Name	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Clearance	80% renal clearance	73% hepatic 27% renal clearance	50% hepatic 50% renal clearance	65% hepatic 35% renal clearance
CYP3A4 interaction?	No	Yes (minor)	Minimal	Yes
Absorption with food?	No effect	No effect	Up to 20% more	40% more therefore intake with food
Elimination half life	12-17 h	12 h	9-11 h	8-9 h young 11-13 h elderly

Conclusion

AZ Nikolaas

- Conventional coagulation tests in patients with liver disease
  - Are prognostic factors of survival
- Historical paradigm on hemostasis in liver disease are incorrect
  - Chronic liver disease in NO acquired bleeding disorder
  - Patients with cirrhosis are NOT auto-anticoagulated
    - Despite PT/INR prolongation DVT and LE
- There is an important pathophysiological role for thrombophilia in the development of fibosis
  - New treatment options?

Question 1

1. Which statement is correct?

    1. INR is a prognostic test in patient with liver disease
    2. INR elevation is a marker for bleeding tendency in patients with liver disease
    3. All of the above