

Cirrhosis and Coagulation A Paradigm of Awareness

2014

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Disclosures:

- None relevant

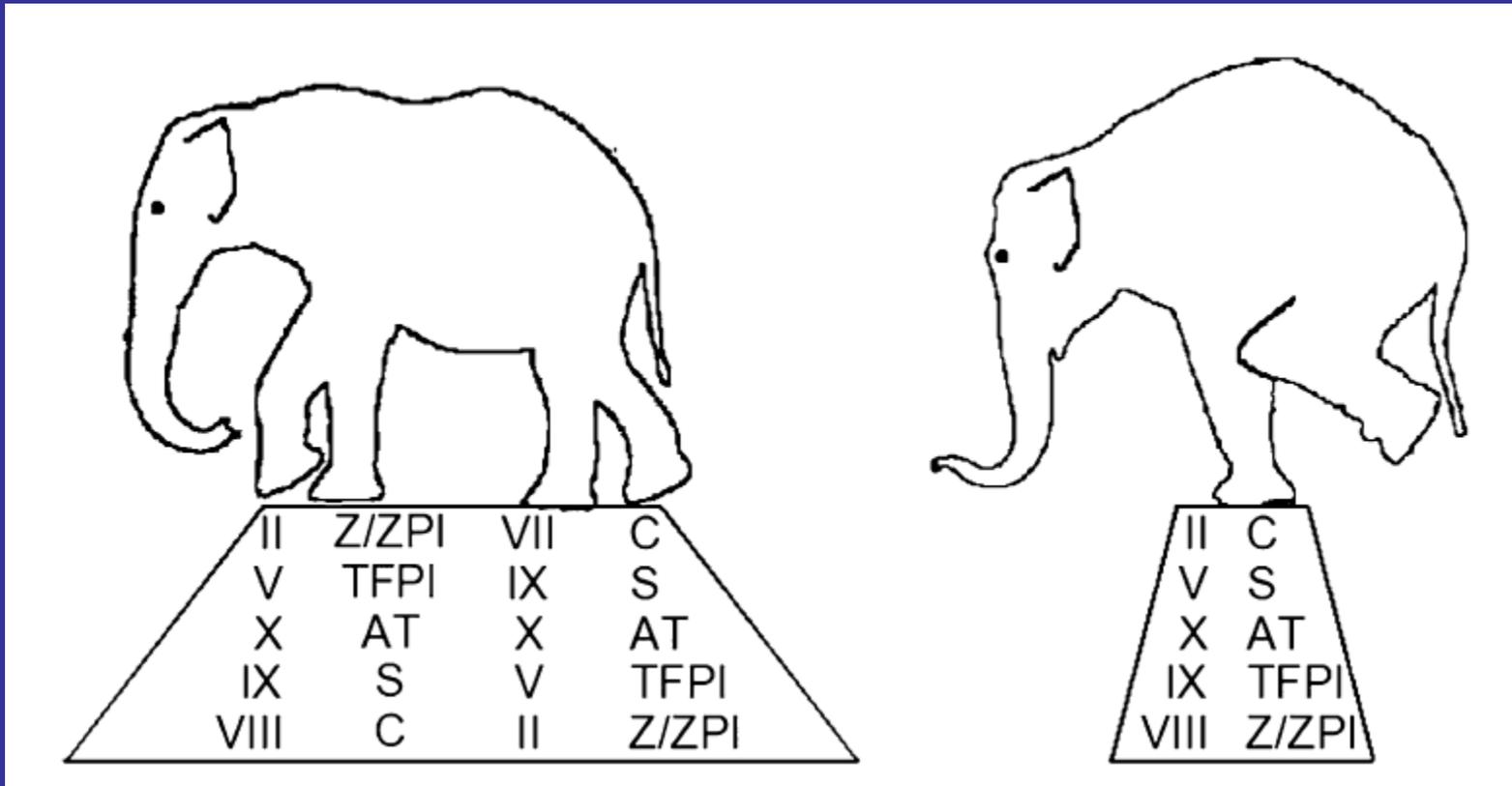
The Clotting Process

- Initiation and formation of the platelet plug
- Propagation of the clotting process by the coagulation cascade
- Termination of clotting by antithrombotic control mechanisms
- Removal of the clot by fibrinolysis

Coagulation Factors: comments relevant to liver disease patients

- All coagulation factors except von Willebrand's factor/VIII, and Calcium are produced in liver
 - Vitamin K dependant factors: II, VII, IX, X
- Decreased vitamin K: liver disease
 - Dietary deficiency, lack of absorption in cirrhosis
 - Lack of bile salts – obstructive jaundice
 - Decrease utilization of Vit K via liver dysfunction
- Decreased degradation of activated coagulation factors
- Synthesis of abnormal coagulation factors
 - Abnormal fibrinogen

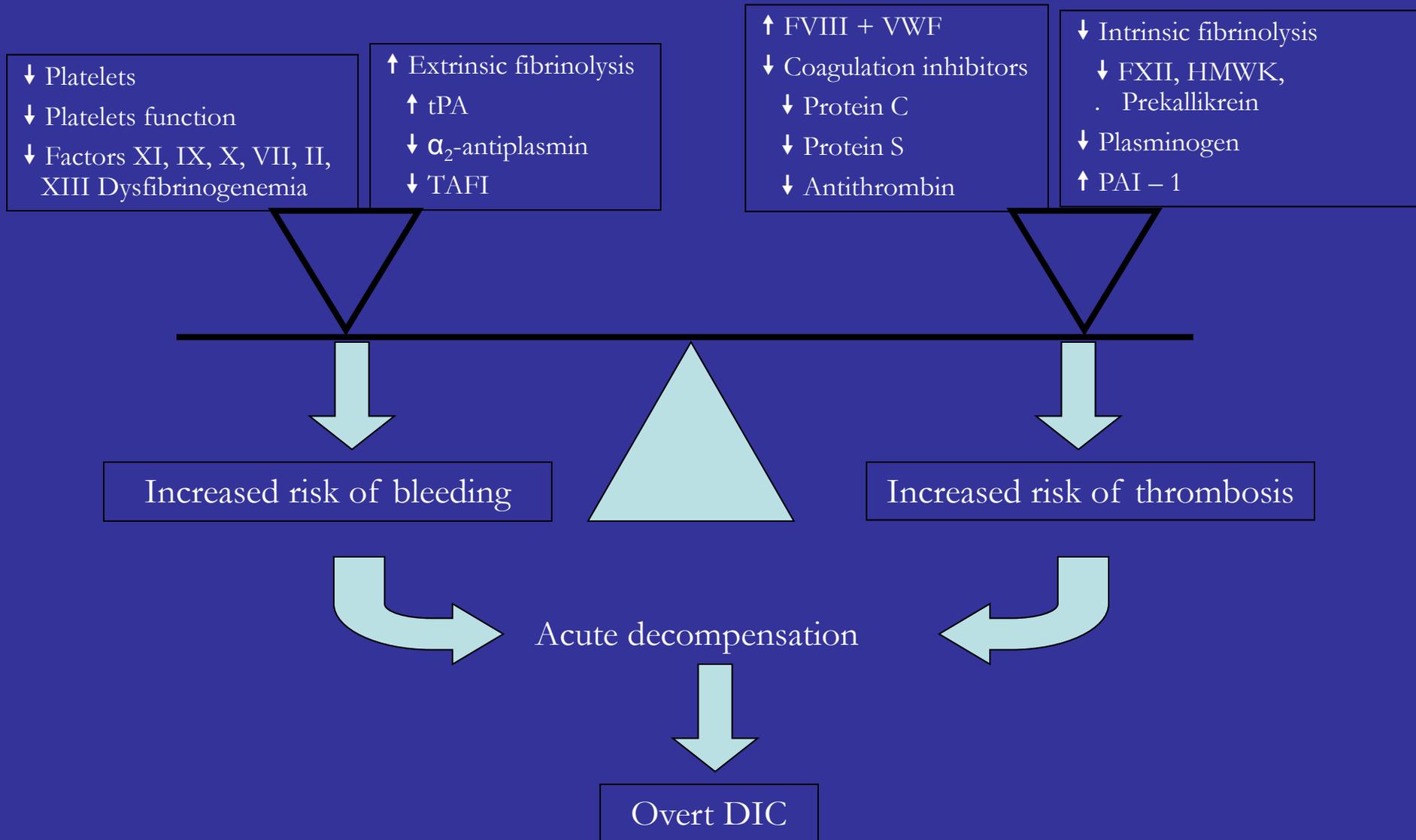
Coagulation is a Precarious Balance



Normal Patient

Cirrhotic Patient

Hemostatic Rebalance in Liver Disease



Thrombotic Complications are common in patients with Acute and CLD

- **Macro-thrombotic:**
 - Portal vein thrombosis seen in 10-20% of cirrhotics
 - Lower in Child's A, increases with worsening liver dysfunction
 - DVT/PE can occur in 5% of hospitalized patients with Acute and CLD
- **Micro-thrombotic:**
 - Intrahepatic microthrombi “parenchymal extinction”
 - Portopulmonary hypertension
 - Cirrhosis as an ischemic/reinjury process

So can we predict bleeding risk with our laboratory tests? NO

Study	PT	INR	BT	PLT	TEG	Result
Ewe 1981 Liver bleeding time at Bx	•			•		No relation of parameters to liver bleeding time
Boks et al 1986 bleeding in cirrhosis patients	•		•	•		Limited: only if fibrinolysis was measured
Segal and Dzik 2005 composite report on liver biopsy studies	•	•		•		Poor predictive value of conventional indices
Da Rocha et al 2009 Post banding ulcer bleeding in cirrhotic varices	•	•		•	•	No predictive value of any of the measured parameters

Paracentesis and Coagulopathy

- Mayo Clinic
- GI assistants performed 1,100 LVP in 628 pts
 - Median:
 - INR 1.7 ± 0.46 (0.9-8.7)
 - Platelet 50.4×10^3 (19-341)
 - No blood product used
- No significant procedure related complications, bleeding or otherwise

What are the detailed
changes we encounter in
cirrhosis?

The Yin and the Yang

Platelet abnormalities

- Decreased amount
 - Splenic sequestration
 - Decreased thrombopoietin levels
 - Bone marrow suppression
 - Auto-antibody destruction
- Increased function
 - New platelets: Old platelets are selectively destroyed/sequestered in the spleen
- Poor function
 - Uremia
 - Changes to vessel wall phospholipid composition

Hyperfibrinolysis

- AICF: Accelerated intravascular coagulation and fibrinolysis
 - Resembles DIC
- Mild systemic fibrinolysis found in 30-45% of cirrhotics
 - Parallels degree of liver dysfunction
- Clinically evident fibrinolysis seen in 5-10%
- Ascites associated with increased fibrinolytic activity

Increased Thrombotic Risk

- Decreased protein C and S
- Decreased anti-thrombin levels
- Decreased plasminogen
- Elevated levels of vWF/Factor VIII

***There is no “auto-anticoagulation” in cirrhosis!

Other Risk Factors for clotting a case series of DVTs

- 2074 patients admitted with liver cirrhosis
- 17 had deep vein thromboses
- Risk factors were also **low albumin and high PTT**
- 5 patients had anti-phospholipid antibodies all with decreased levels of AT III, Prot C/S
 - Gupta V. A rare association of primary biliary cirrhosis with antiphospholipid antibody syndrome. *Dig Dis Sci* 2007; 52: 3530-1
- 5 patients had **surgery** in the previous week (4 had ortho)

García-Fuster MJ, Venous thromboembolism and liver cirrhosis. *Rev Esp Enferm Dig* 2008; 100: 259-262.

Other Risk Factors for clotting a case series of DVTs

- Eleven treated with LMWH only, 6 transitioned to Coumadin
 - 14 (83%) had hemorrhagic complications, 6 (35%) required blood transfusions (5 on Coumadin, 1 on LMWH)
 - Only 3 finished 6 months of therapy
- Conclusion: “It would be advisable that experiences be pooled together in order to develop prophylactic and therapeutic guidelines for this type of patient.”

Effect of Infection: on clotting events

- Infection reported in up to 47% of hospitalized cirrhotic patients
- Overt sepsis or low levels of endotoxemia affects platelet function, production, and adhesion through release of nitric oxide and prostacyclin
- Infection associated with endogenous heparinoid production as a result of endothelial dysfunction

Effect of Renal Failure

- Abnormalities seen of platelet structure
 - Lower than normal ADP and serotonin in granules: decreased thromboxane A2 generation
 - Dysfunction of glycoprotein GpIIb-IIIa: membrane glycoprotein important in aggregation and adhesion
- Platelet NO synthesis increased: inhibits platelet aggregation and adhesion
- Worsens anemia: metabolically reduces platelet function and reduce platelet physical interactions with vessel wall

Serologic Markers of Clotting

- PTT: intrinsic pathway
 - Sensitive to levels <25-35%
 - A very poor liver function test and poor predictor or risk of bleeding
- PT/INR: extrinsic pathway
 - Sensitive to levels <35-45%
- Platelet count
- TEG: thromboelastography
- Individual factor levels

Increased PT/INR

- Developed to assess dysfunction in vitamin K dependent coagulation factors during warfarin therapy
 - Wide inter-laboratory variation in patients with liver disease
 - Can be different by as much as 0.8 depending on which reagent is used
 - Has been validated as prognostic marker for liver disease mortality, but not for bleeding risk
- To fully correct INR in liver patients may take up to 7 L of FFP

Factor Levels

- Factor VIII: can help distinguish DIC from liver failure: decreased in DIC, increased in cirrhosis
- Factor V and VII:
 - A greater reduction in factor VII than factor V favors vitamin K deficiency
 - Factor VII half life ~6 hours
 - Factor V half life ~36 hours
- Fibrinogen levels: levels below 120 mg/dL associated with diminished clot formation
 - Treat with fibrinogen-rich cryoprecipitate

The balance: Thromboelastography (TEG)

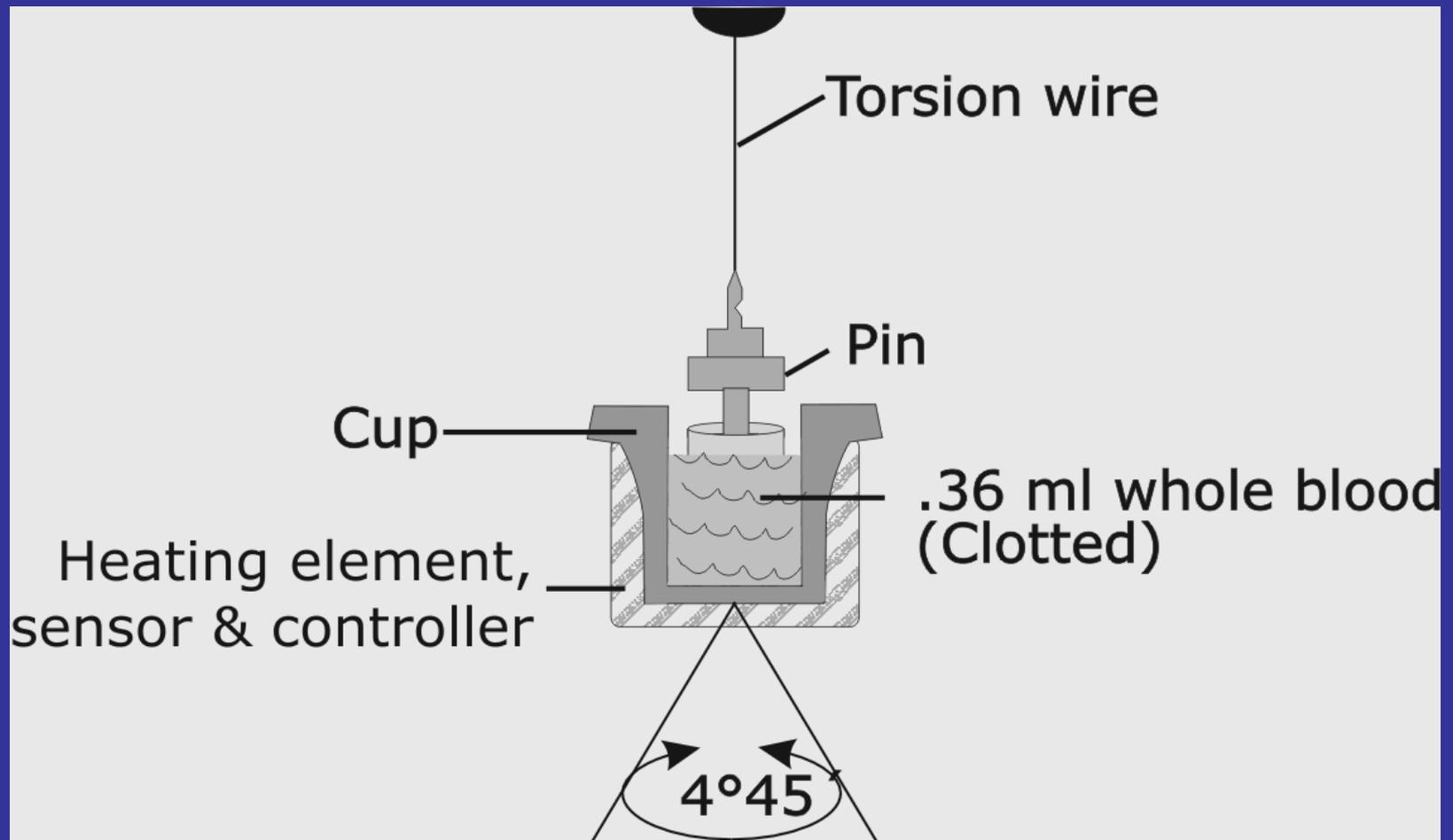
- Measures
 - Time to initial fibrin formation
 - Rate of clot formation
 - Clot quality/strength
 - Platelet function
 - Clot lysis

Thromboelastography (TEG)



- Time to initial fibrin formation
- Rate of clot formation
- Clot quality/strength
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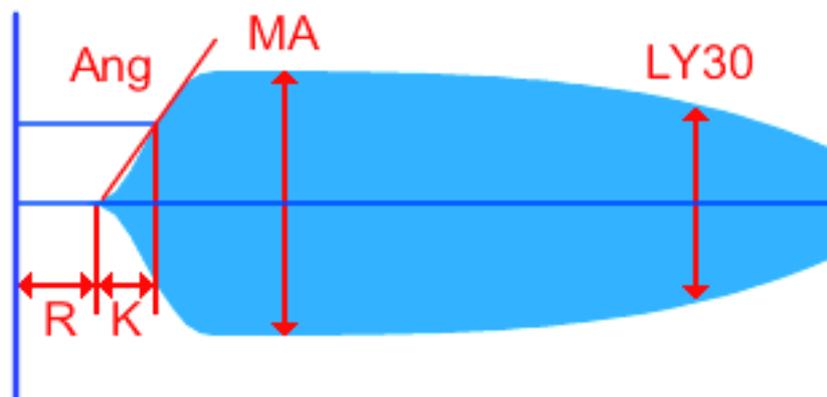
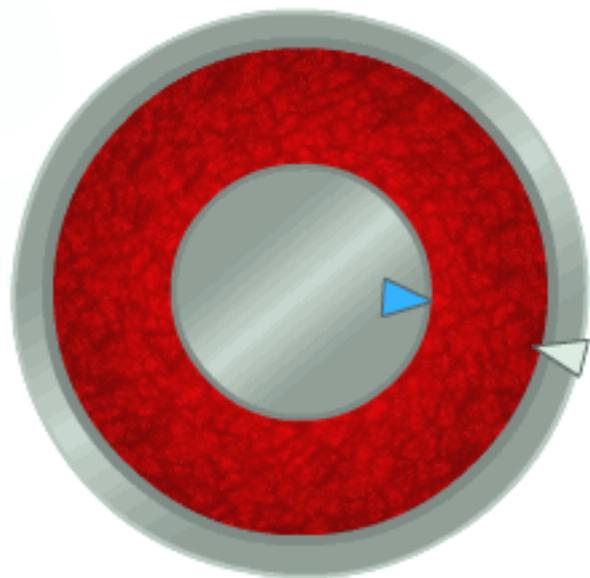
TEG: How it works



Thromboelastograph

Thromboelastogram

Available at <http://vam.anest.ufl.edu/wip.html>



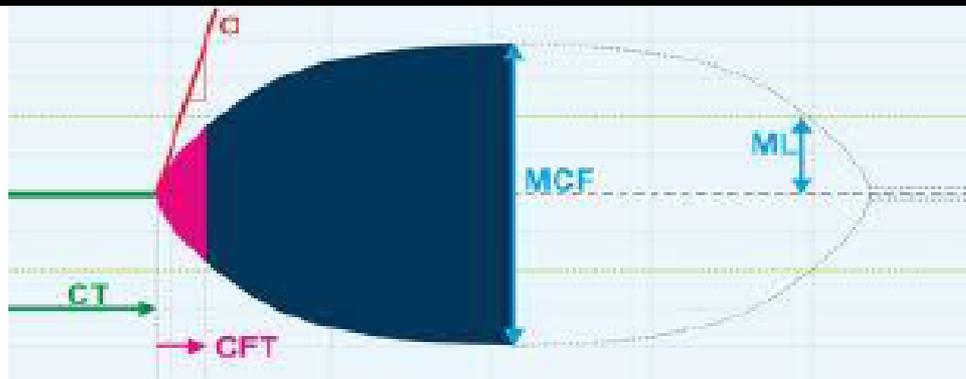
60:00

Time (mm:ss)

R(min)	K(min)	Ang(deg)	MA(mm)	LY30(%)
14	10	55	51	28

Rotem analysis

<u>ROTEM</u>	<u>CT secs</u>	<u>CFT secs</u>	<u>α angle</u>	<u>MCF mm</u>
INTEM	122-208	45-110	70-81	51-72
EXTEM	43-82	48-127	65-80	52-70
FIBTEM	n/a	n/a	n/a	7-24
HEPTEM	122-208	45-110	70-81	51-72



CT= Coagulation Time - to generate thrombin and assemble protofibrils

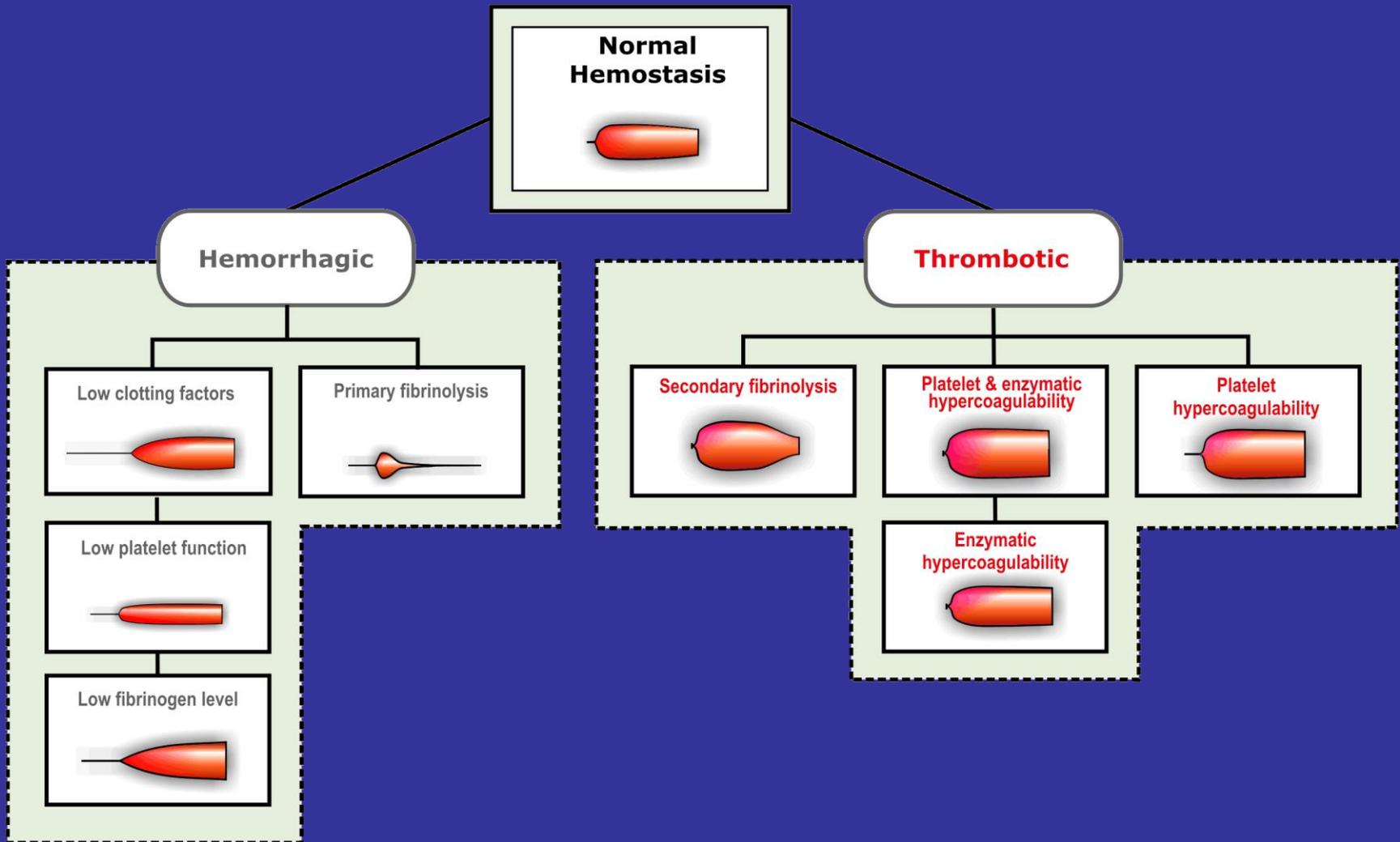
CFT= Clot Formation Time - to generate fibrin gel; **α angle=** polymerization rate

MCF= Maximum Clot Firmness/clot amplitude (mm) – gauges clot strength & stability

LI30: How much stable clot is left at 30 minutes (lysis) –normally LI30 is 94-100%

In addition to ROTEM, do mixing test, & measure fibrinogen, and Factors V and VII

TEG decision tree



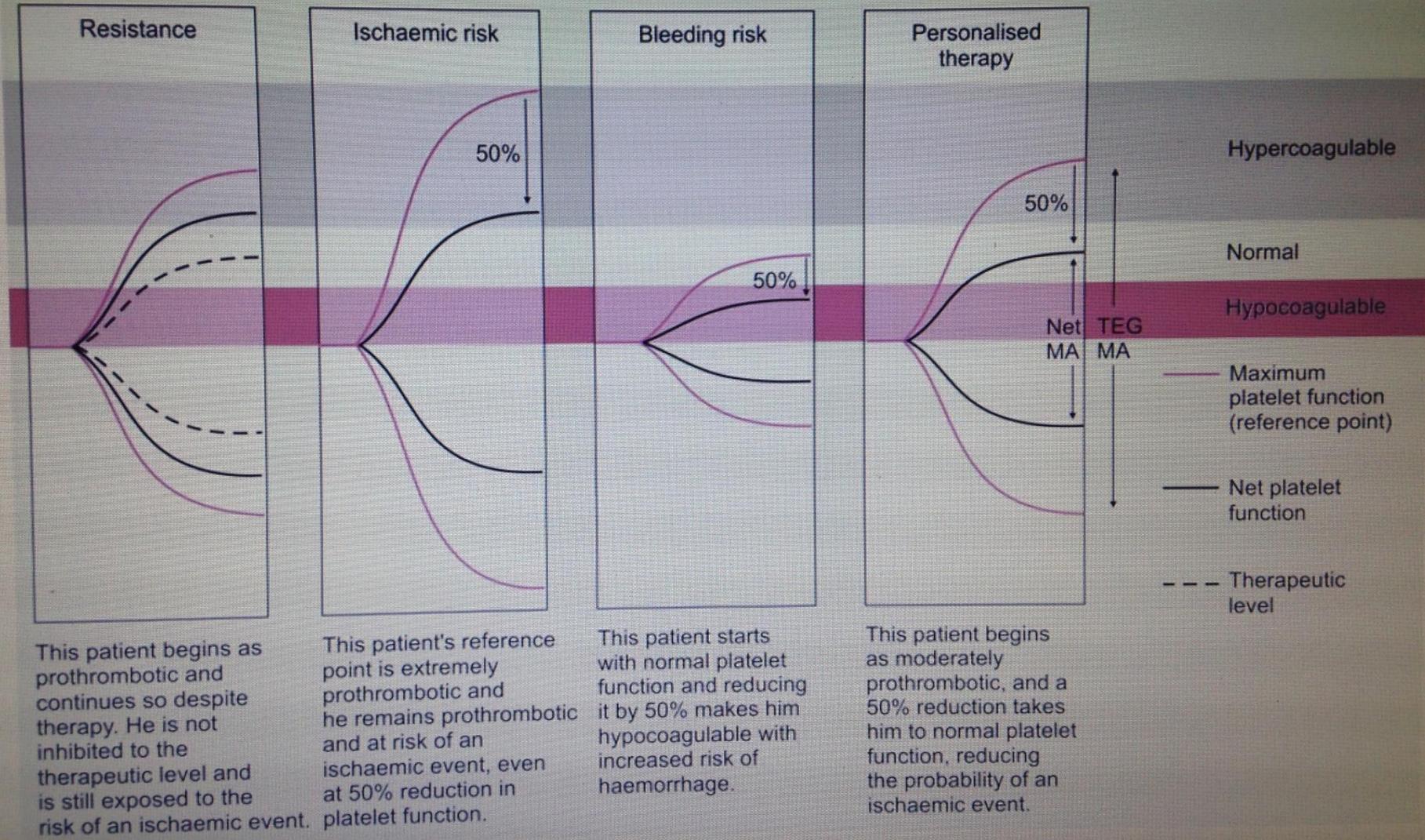


Fig. 5: Interpretation of TEG and platelet function analysis traces (Source: Haemonetics UK)

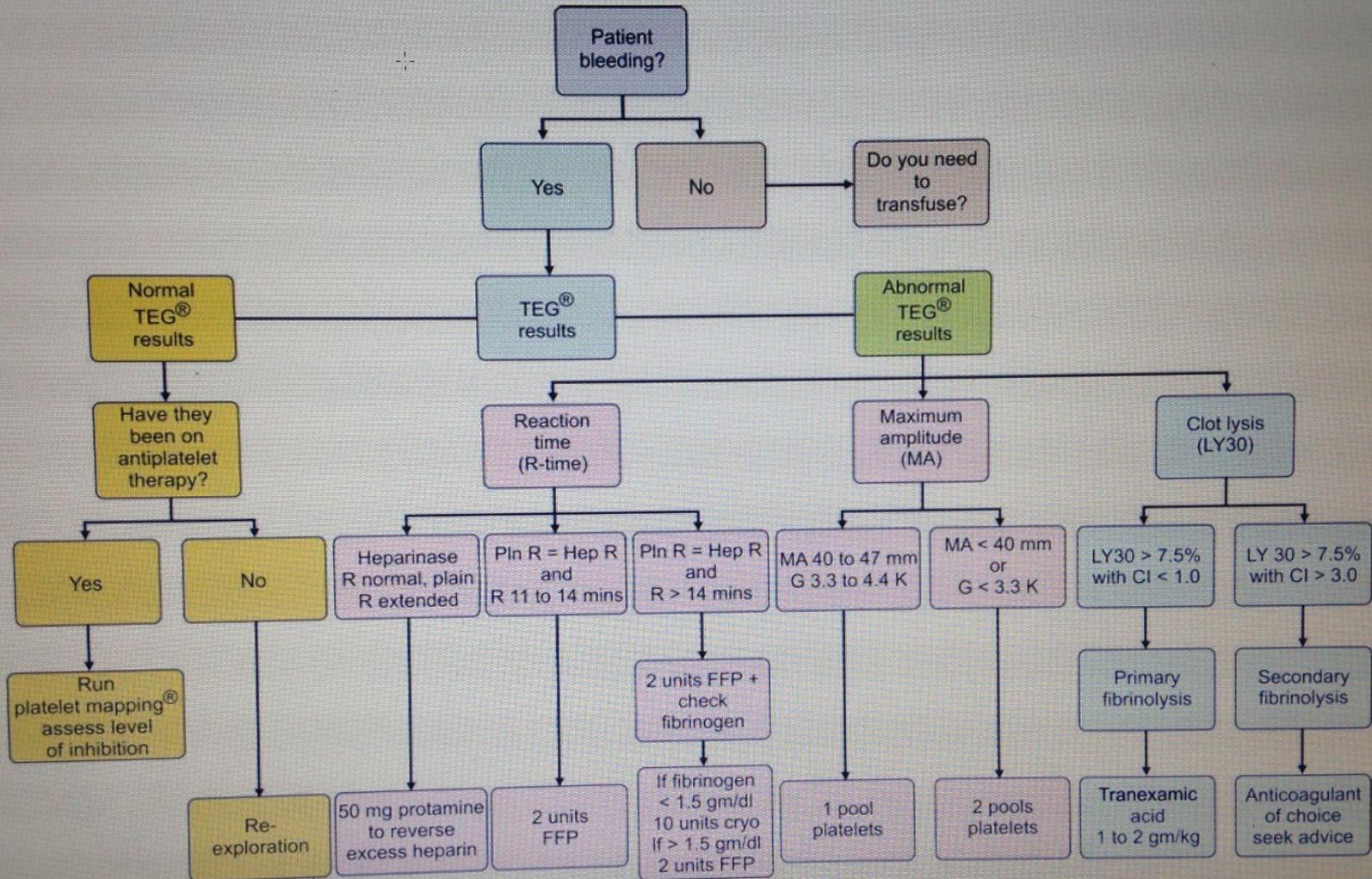


Fig. 6: Suggested guidance for haemostasis management using a TEG-based protocol (Source: Modified Leicester protocol and Haemonetics UK)

Fig. 3: Examples of qualitative TEG traces for interpretation

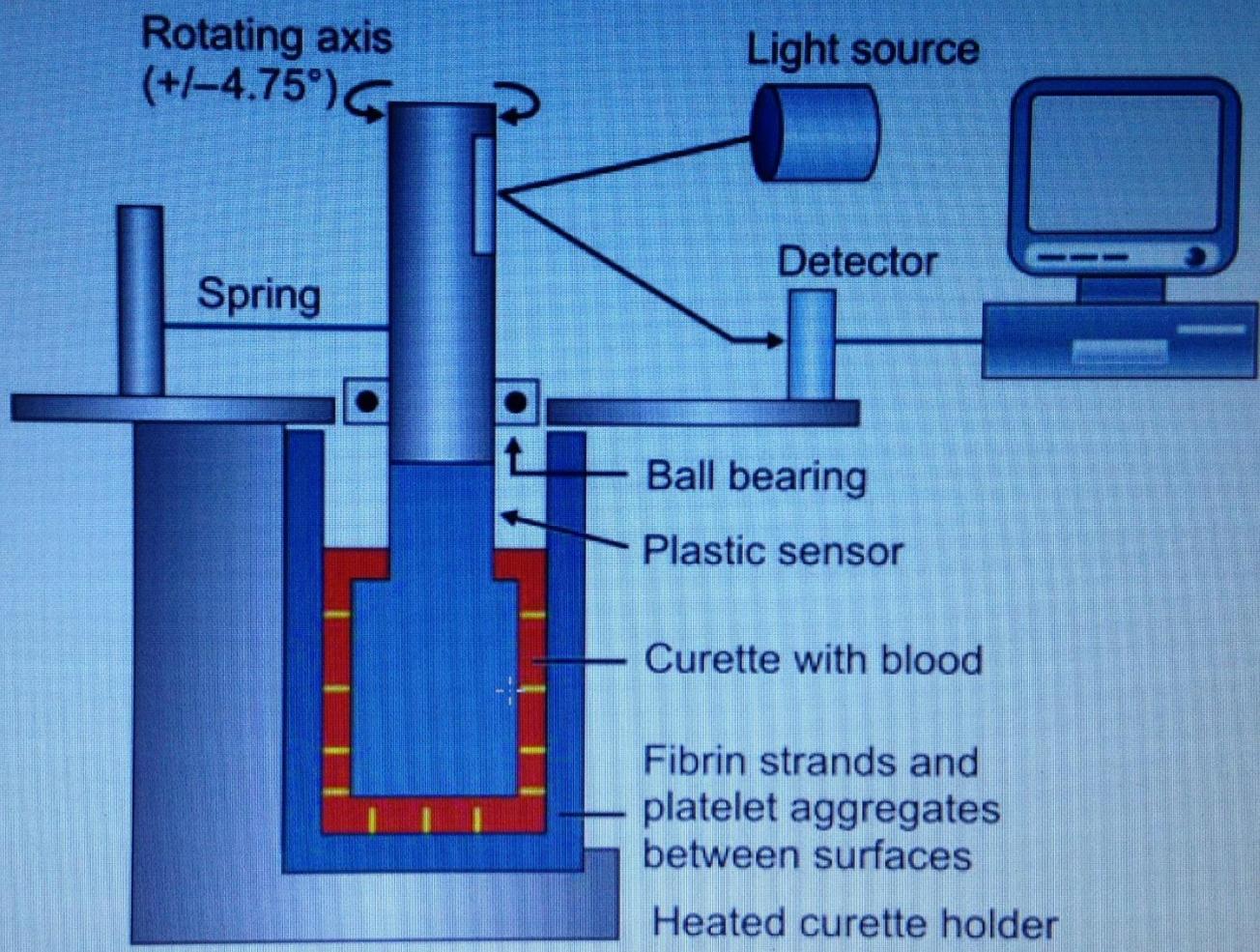


Fig. 4: Basis of ROTEM (Rotational thromboelastometry)

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Thrombelastographic changes and early rebleeding in cirrhotic patients with variceal bleeding

T N Chau, Y W Chan, D Patch, S Tokunaga, L Greenslade, A K Burroughs

Table 3 Difference in thromboelastographic variables and routine coagulation tests on the day of rebleeding in those who rebled and the mean of daily results in the non-rebleeding group assessed by analysis of covariance

	<i>Difference between rebleeding and non-rebleeding group</i>	<i>p Value</i>	<i>Variables used for adjustment*</i>
log [r]	0.65 (0.37 to 0.94)	0.001	Age
log [k]	1.11 (0.66 to 1.56)	0.001	Sex, Child's class, number of units of blood transfused
MA	5.53 (5.85 to 16.9)	0.32	
<i>a</i>	-17.9 (-27.3 to -8.4)	0.001	Child's class
log [platelet]	-0.18 (-0.71 to 0.34)	0.47	
log [PT]	-0.16 (-0.01 to 0.33)	0.07	
log [APTT]	0.004 (-0.14 to 0.14)	0.45	
WBCLI	2.5 (-1.1 to 3.4)	0.88	

Results are given with 95% confidence intervals in parentheses.

*Variables were selected by the model using backward elimination of baseline characteristics.

PT, prothrombin time; APTT, activated partial thromboplastin time; WBCLI, whole blood clot lysis index.

- 20 patients studied x 7 days
- No difference in baseline characteristics
- No difference in any TEG variable within 24 hours of admission
- 5/6 with early rebleeding had evidence of sepsis

GI bleeding and infection is a major driving force in tipping rebalanced hemostasis of cirrhosis

TEG provides a more accurate assessment of bleeding risk versus PT/PTT

Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography

R. Todd Stravitz^{1,*}, Ton Lisman³, Velimir A. Luketic¹, Richard K. Sterling¹, Puneet Puri¹, Michael Fuchs¹, Ashraf Ibrahim², William M. Lee⁴, Arun J. Sanyal¹

Feature	Normal	Entire group (n=51)	Spont Survivors (n=29)	Death or OLT (n=22)
INR		3.4 ± 1.7	3.0 ± 1.3	4.0 ± 1.9
aPTT	25-36	49 ± 17	41 ± 10	59 ± 19
R-time	2.5-7.5	4.7 ± 1.9	4.1 ± 1.5*	5.5 ± 2.2*
K-time	0.8-2.8	1.7	1.9	1.7
α-Angle	55.2-78.4	63.7 ± 12.2	63.6 ± 12.7	63.7 ± 11.8
MA	50.6-69.4	55.0 ± 10.9	55.0 ± 11.2	55.1 ± 10.6
Lysis 30 (%)	0.0-7.5	0.0	0.0	0.0

63% had Zero abnormalities
16% had 1 abnormality
10% had 2 abnormalities
8% had 3 abnormalities
4% had 4 abnormalities

TEG guided transfusion decreases intraoperative blood transfusion during OLT

- 28 pts undergoing OLT
- Randomized into
 - Monitored by TEG during surgery
 - Monitored standard coag tests
- FFP use less in TEG: 12.8 (± 7.0) vs 21.5 (± 12.7)
- Blood loss was not significantly different (less in TEG group)
- No differences in total fluid administration and 3 yr survival

TEG guided transfusion decreases intraoperative blood transfusion during OLT

- Use of blood product: Control group
 - PRBC: Hgb <8g/dL
 - Platelet: plt <50 x10⁹/L
 - FFP: to maintain PT and PTT <1.5 times ctrl
 - Cryoprecipitate: fibrinogen <1g/L

TEG guided transfusion decreases intraoperative blood transfusion during OLT

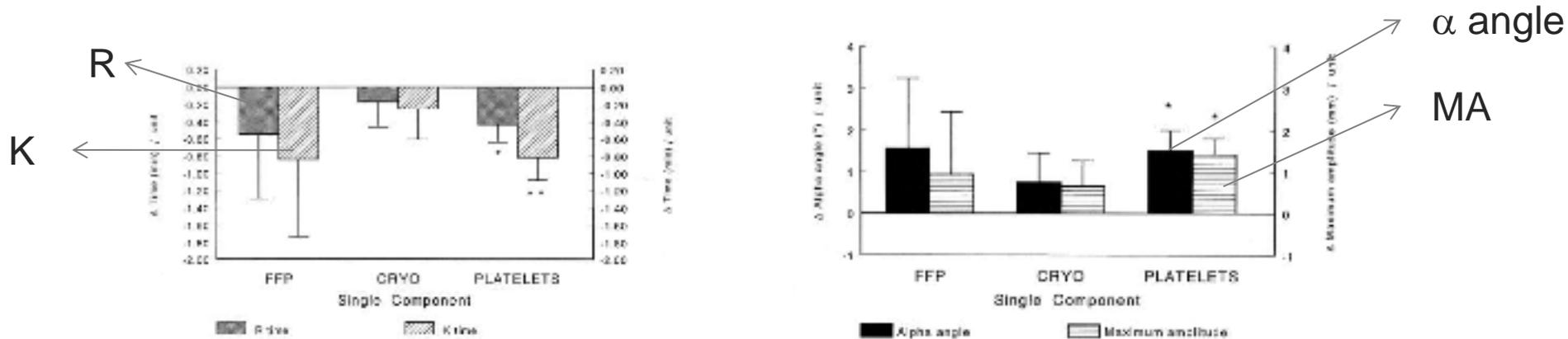
- Use of blood product: TEG group
 - Single plasmapheresis unit (~6-8 pooled units) of platelets when MA<55mm
 - Cryoprecipitate (5 pooled units) when alpha angle <43 degree
 - FFP to keep reaction time to <10min
 - Fibrinolysis (LY 30) checked

Coagulation management in multiple trauma: systemic review

- Review of 230 articles
- “TEG”
 - Coagulation monitoring in trauma patients by TEG has been increasingly analyzed
 - A number of TEG based algorithms published, enabling faster therapeutic decisions

What products have the greatest impact on clot strength as measured by TEG?

- Platelet count > fibrinogen > procoagulant factor levels
- Study of TEG after 74 blood component transfusions in 60 critically ill patients with liver disease
 - Platelets had the most dramatic effect on TEG parameters



Potential Interventions: (If abnormal TEG)

- Platelets
 - For low risk procedures: no transfusion
 - For moderate risk procedures: >50k
 - For high risk procedures: >100k
- Fresh Frozen Plasma
 - Lack of predictable effect: conventional doses correct cirrhotics in only 10-12%
 - Risk of volume overload
 - Risk of TRALI
- Cryoppt if low fibrinogen (K or angle)

Central Venous Catheterization in Patients with Coagulopathy

- 202 percutaneous central venous catheterization in liver transplant recipients with prolonged PT, PTT, & thrombocytopenia
- No medications & no infusion of blood products
- Results: no serious bleeding complications
 - mean plt 47,000 /ul (8000 to 79,000)
 - PTT 97 secs (78 to 100 secs)
 - INR of 2.0 (1.5 to 8.0)

Foster PF et al. Archives of surgery 1992 Mar; 127(3): 273-

Paracentesis & Thoracentesis in Patients With Mild Coagulation Abnormalities

- 608 consecutive paracentesis and thoracentesis procedures in pts with untreated mild coagulopathy
 - PT & PTT up to twice the midnormal range or platelet count of 50 to 99/ul
- No increased bleeding in pts with mild coagulopathy
- Pts with elevated serum Cr (6 to 14 mg/dl) had a significantly greater average hemoglobin loss

Does FFP use prevent bleeding complications?

- Review of 57 RCT investigating the efficacy of FFP to prevent hemorrhagic complications over wide variety of indications and clinical settings
- Data insufficient to recommend or refute the prophylactic use of FFP

Does abnormal PT/INR predicts bleeding during invasive diagnostic procedures?

- Analysis of 25 studies of the ability of abnormal coagulation parameters to predict bleeding associated with invasive bedside or image-guided procedures
- Elevated coagulation parameters provide little or no predictive value for bleeding complications from image-guided interventions
- Mild to moderate elevation of coagulation times should neither assumed to represent an increased risk for preprocedural bleeding nor be used as an indication for transfusion of FFP or clotting factor concentrates

Potential Interventions, cont

- Cryoprecipitate
 - Less volume than FFP
 - Useful in patients with fibrinogen <120 mg/dL
- rFVIIa
 - Can quickly reverse INR
 - Expensive
 - Can result in severe clotting problems

Potential Interventions, cont

- Vitamin K: 10 mg parenterally x3 days
 - Orally may not be absorbed well
- DDAVP: analogue to ADH
 - Increases levels of factor VIII/vWF
 - Most useful in uremia
- Maintain Hct >25%
 - Allows platelets to circulate nearer to endothelial cells where they can be activated if necessary

PPC and Factor VIIa

- **Prothrombin Complex Concentrate (PCC) and Recombinant Factor VIIa (FVIIa) Guidelines**
- Optimize platelet count to 30-50K
- Fibrinogen > 100, ideally at 200
- Profilnine 25units/kg x1 and/or FVIIa 20-40 mcg/kg (1-3 mg)
 - Consider starting with a single agent and then alternating agents for continued bleeding
- Daily or BID TEGs
- Consult Hematology

When using blood products

- Consent patient for transfusion reactions including the risk of TRALI
- Consent patient for risk of infectious diseases
 - HCV < 1 : 1 M transfusions
 - HBV < 1 : 400 000 transfusions

AE from FFP and Plt infusion – EUROPE-

Events per 10,000 Transfusions	Plasma	Platelet
Non-haemolytic transfusion reactions	0,22 [†]	0 [†]
(urticaria, allergic and anaphylaxis symptom)	0,35 [‡]	1,04 [‡]
	2,35 [§]	5,42 [§]
Congestive heart failure/volume overload	0,1 [†]	0,13 [†]
	2,06 [§]	4,82 [§]
Sepsis due to inadvertent bacterial contamination	0,02 [‡]	0,28 [†]
	0 [‡]	0,29 [‡]
		2,41 [§]
Transfusion-related acute lung injury*	0,18 [†]	0,46 [†]
	0 [§]	1,81 [§]
Posttransfusion purpura	0,04 [†]	0
Viral transmission	0	0,03 [‡]
Severe anaphylaxis with Ig A deficiency and anti IgA	0	0
Transfusion-associated graft-versus host disease	0	0
Citrate toxicity	NR	NR
Transmission of other pathogens not tested for or recognised	NR	NR
Alloimmunisation against HLA-antigens	NR	NR

Question

- Should we anti-coagulate patients with cirrhosis?

Enoxaparin Prevents Portal Vein Thrombosis and Liver Decompensation in Patients With Advanced Cirrhosis

GASTROENTEROLOGY 2012

Liver Journal Club

Shireena Desai

Nov 27, 2012

aims

- To evaluate the safety and efficacy of enoxaparin in preventing PVT in patients with advanced cirrhosis

Assessed for eligibility (n = 396)

Patients excluded (n = 326)
Child-Pugh A (n = 51)
Child-Pugh \geq C11 (n = 31)
HCC at baseline (n = 140)
Extra-hepatic malignancies (n = 9)
Previous anticoagulants (n = 17)
Creatinine clearance <30 ml/min (n = 7)
Previous PVT or other thrombotic events (n=25)
Age>75 years (n = 29)
Platelets counts <10.000/mm³ (n = 4)
Declined to participate (n = 10)
HIV+ (n = 3)

Randomised (n = 70)

Enoxaparin treatment arm (n = 34)

No treatment (control) arm (n = 36)

Lost to follow-up (n = 0)
Discontinued Intervention (n = 1)
(Thrombocytopenia)

Lost to follow-up (n = 0)

Analysed (n = 34)

Analysed (n = 36)

Events

- Hepatic decompensation at 48 weeks:
 - Control group: 21 of 36 [59.4%]
 - Enoxaparin group: 4 of 34 [11.7%]; **P .0001**
- Hepatic decompensation during follow-up period:
 - Control group: 9 of 31 (29.0%)
 - Enoxaparin group: 9 of 32 (28.0%); **P .890**
- Overall decompensation:

Probability of developing PVT

Probability of developing hepatic decompensation

Probability of survival

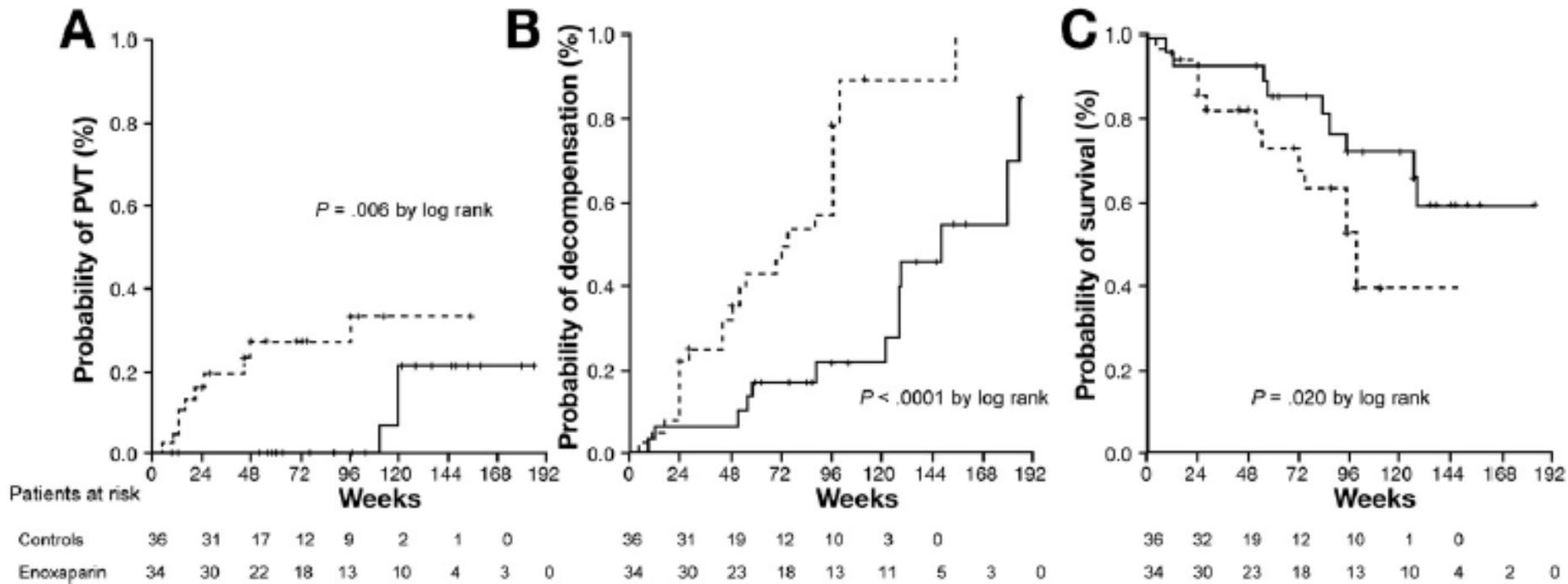
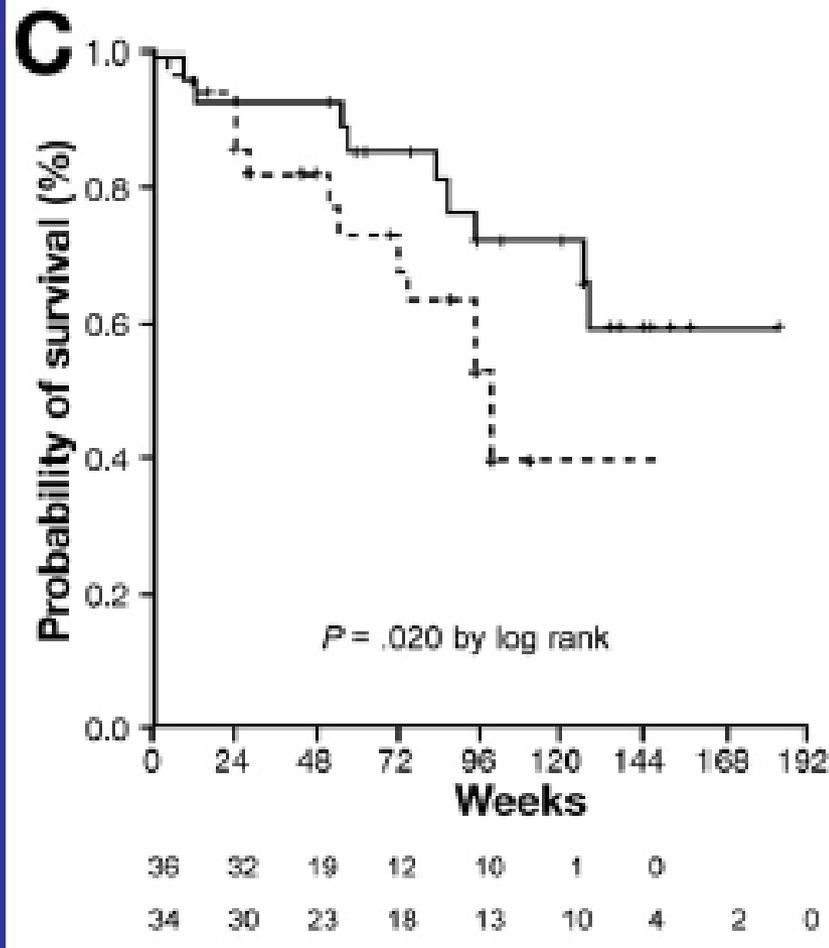


Figure 1. Actuarial probability of developing PVT or hepatic decompensation, and probability of survival according to treatment group. Probability of remaining free from (A) PVT, (B) hepatic decompensation, and (C) probability of survival. *Dashed line:* controls; *continuous line:* enoxaparin-treated patients.



- Thirteen controls and 8 enoxaparin-treated patients died
- Kaplan–Meier curve analysis revealed a higher survival rate in the enoxaparin treated group than in controls ($P = .020$)

Conclusions: enoxaparin

- A 12-month course of enoxaparin was safe and effective in preventing PVT in patients with cirrhosis and a Child-Pugh score of B7–C10.
- Enoxaparin appeared to significantly reduce the risk of PVT development and liver decompensation, improve liver function and Child-Pugh score, and increase overall survival.

Portal Vein Thrombosis

- Check first for cirrhosis, cancer of the abdominal organs, or an inflammatory focus in the abdomen.
- Nontumorous and noncirrhotic patients: 30%-40% of patients with PVT are affected with myeloproliferative diseases:
 - polycythemia vera
 - essential thrombocythemia
- Iron deficiency or portal hypertension can mask the expected elevated Hgb or platelet count. Do not rule out a diagnosis of myeloproliferative disease solely on the basis of normal/low blood cell counts.
- Point mutation of the tyrosine kinase JAK2 is a marker for myeloproliferative disease.
 - In 5%-10% of patients with PVT, JAK2 was undetectable whereas bone marrow biopsy provided evidence for a myeloproliferative disorder.

Acute Portal Vein Thrombosis

- Sudden onset abdominal or lumbar pain
- When extensive thrombosis involves distal mesenteric veins, intestinal ischemia and infarction can occur, leading to severe pain and bloody diarrhea.
- The presence of ascites, thinning of the intestinal wall, or the development of multiorgan failure indicate that intestinal infarction is likely and surgical exploration should be considered

Treatment of Acute PVT

- Anticoagulation therapy for at least 3 months
- Long- term anticoagulation in patients with permanent risk factors
- Optimal duration of anticoagulation has not been determined. Complete recanalization can be delayed until the sixth month of anticoagulation.
- Initiate heparin or LMWH in order to achieve rapid anticoagulation → oral anticoagulation when patient's condition has stabilized and no invasive procedures are planned.
- In the absence of contraindications, also consider long term anticoagulation for patients with acute PVT and thrombus extension distal into the mesenteric veins

Budd Chiari Syndrome

- term “Budd-Chiari” coined in late 1800s after George Budd, who described three cases of hepatic vein thrombosis in 1845 and Hans Chiari, Austrian pathologist, who reported the first pathologic description of “obliterating endophlebitis of the hepatic veins” in 1899
- any pathophysiologic process that results in hepatic venous outflow tract obstruction independent of the level (hepatic veins, IVC) or mechanism of obstruction
 - Cardiac disorders (constrictive pericarditis, chronic R sided heart failure) and sinusoidal obstruction syndrome/veno-occlusive disease typically excluded
 - Primary – due to primary venous disease (thrombosis, phlebitis)
 - Secondary – compression or invasion by external lesion
- Obstruction of hepatic venous outflow → increased hepatic sinusoidal pressure → decrease portal venous perfusion of the liver → ischemic damage and centrilobular necrosis
 - Chronically can lead to centrilobular fibrosis, nodular regenerative hyperplasia and cirrhosis



Table 6. Indications for Permanent Anticoagulation Therapy for Noncirrhotic Portal Vein Thrombosis and for Primary Budd-Chiari Syndrome

Primary Budd-Chiari syndrome	All patients <i>Recommendation Class I – Level C</i>
Portal vein thrombosis acute or chronic, no cirrhosis	Permanent, non correctable prothrombotic disorder <i>or</i> Superior mesenteric vein currently or previously involved <i>when</i> Primary or secondary prophylaxis for gastrointestinal bleeding has been instituted <i>Recommendations Class IIa – Level C</i>

Conclusions

- Coagulation in chronic liver disease is a complex, “balanced” process
- More information is needed about use of clotting tests in cirrhosis
- Risk of thrombosis may be present even in setting of apparent mild, moderate or severe coagulopathy
- Recognize superimposed conditions: sepsis, uremia, hyperfibrinolysis
- Start the use of TEG at your institution to help decrease factor use
- Don't treat the INR: treat the patient

Thank you to:

- Todd Stravitz, Carrie Frenette, Patrick Kamath and Yuko Kono for use of their slides