# Telfer B. Reynolds Lecture: Coagulation Disorders in Liver Disease

*Southern California Society of Gastroenterology*
*Post-AASLD Program 2018*

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# Conflict of Interests

Consultant or speaker fees within last year:  None

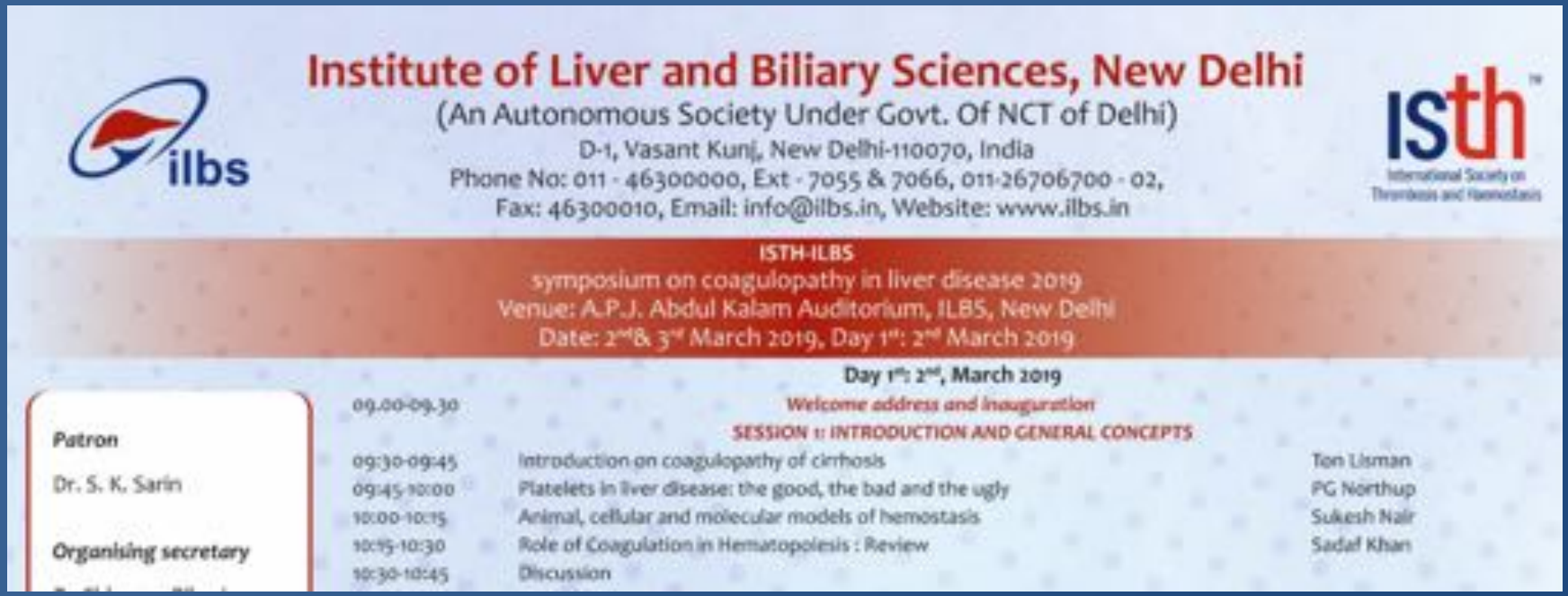
Off label discussions: None

I certify that there is no conflict of interest with any financial organization regarding the material discussed in this presentation.

# Overview

- Physiology of rebalanced coagulation in cirrhosis
- Blood products commonly used in cirrhosis
- Non-operative procedural coagulation management
- Portal vein thrombosis and anticoagulation

# Institute of Liver and Biliary Sciences, New Delhi, Symposium on Coagulopathy in Liver Disease 2019



## Institute of Liver and Biliary Sciences, New Delhi

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**ISTH-ILBS**

symposium on coagulopathy in liver disease 2019

Venue: A.P.J. Abdul Kalam Auditorium, ILBS, New Delhi

Date: 2nd & 3rd March 2019, Day 1st: 2nd March 2019

**Patron**

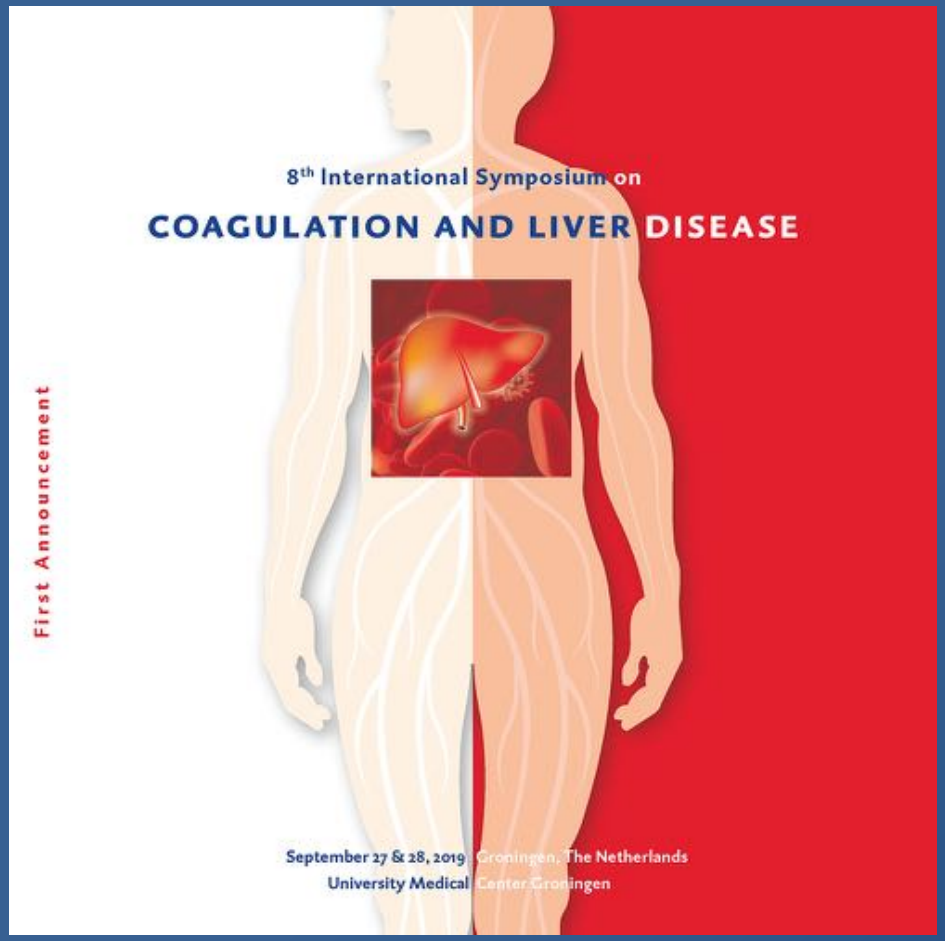
Dr. S. K. Sarin

**Organising secretary**

**Day 1st: 2nd, March 2019**

| | | |
|---|---|---|
| 09.00-09.30 | *Welcome address and inauguration* | |
| | **SESSION I: INTRODUCTION AND GENERAL CONCEPTS** | |
| 09:30-09:45 | Introduction on coagulopathy of cirrhosis | Ton Lisman |
| 09:45-10:00 | Platelets in liver disease: the good, the bad and the ugly | PG Northup |
| 10:00-10:15 | Animal, cellular and molecular models of hemostasis | Sukesh Nair |
| 10:15-10:30 | Role of Coagulation in Hematopoiesis : Review | Sadaf Khan |
| 10:30-10:45 | Discussion | |

# 8th International Symposium on Coagulation and Liver Disease 2019





www.coagulationinliverdisease.org

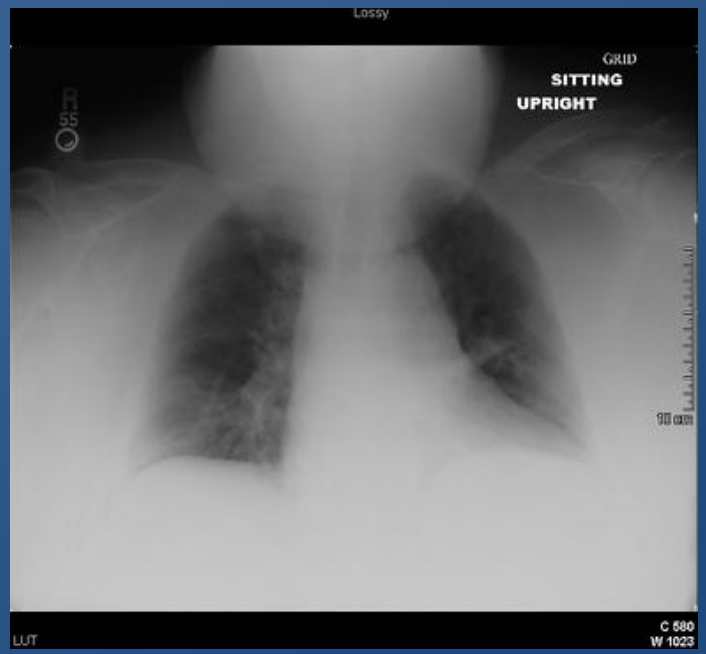
# The Blind Men and the Elephant

…One's subjective experience is inherently limited by its failure to account for other truths or a totality of truth…

# Case Presentation

- 52 yo male hospitalized with cirrhosis
- Type 1 hepatorenal syndrome
- INR 3.1, PLT 22
- Needed HD catheter

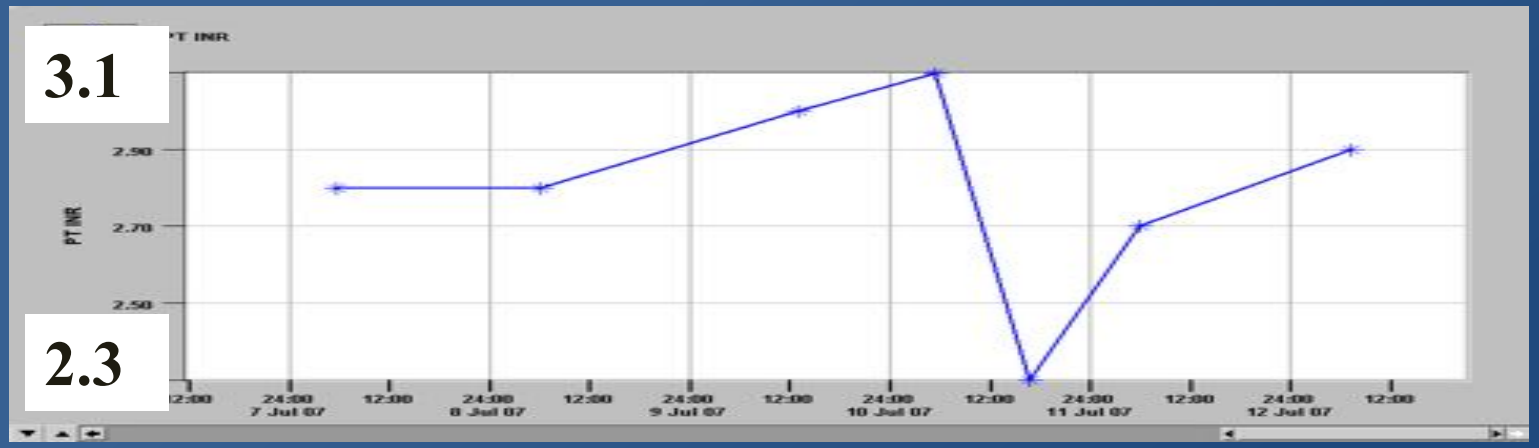
- Transfused prior to procedure:
  - 6 Units FFP
  - 4 units of PLTs



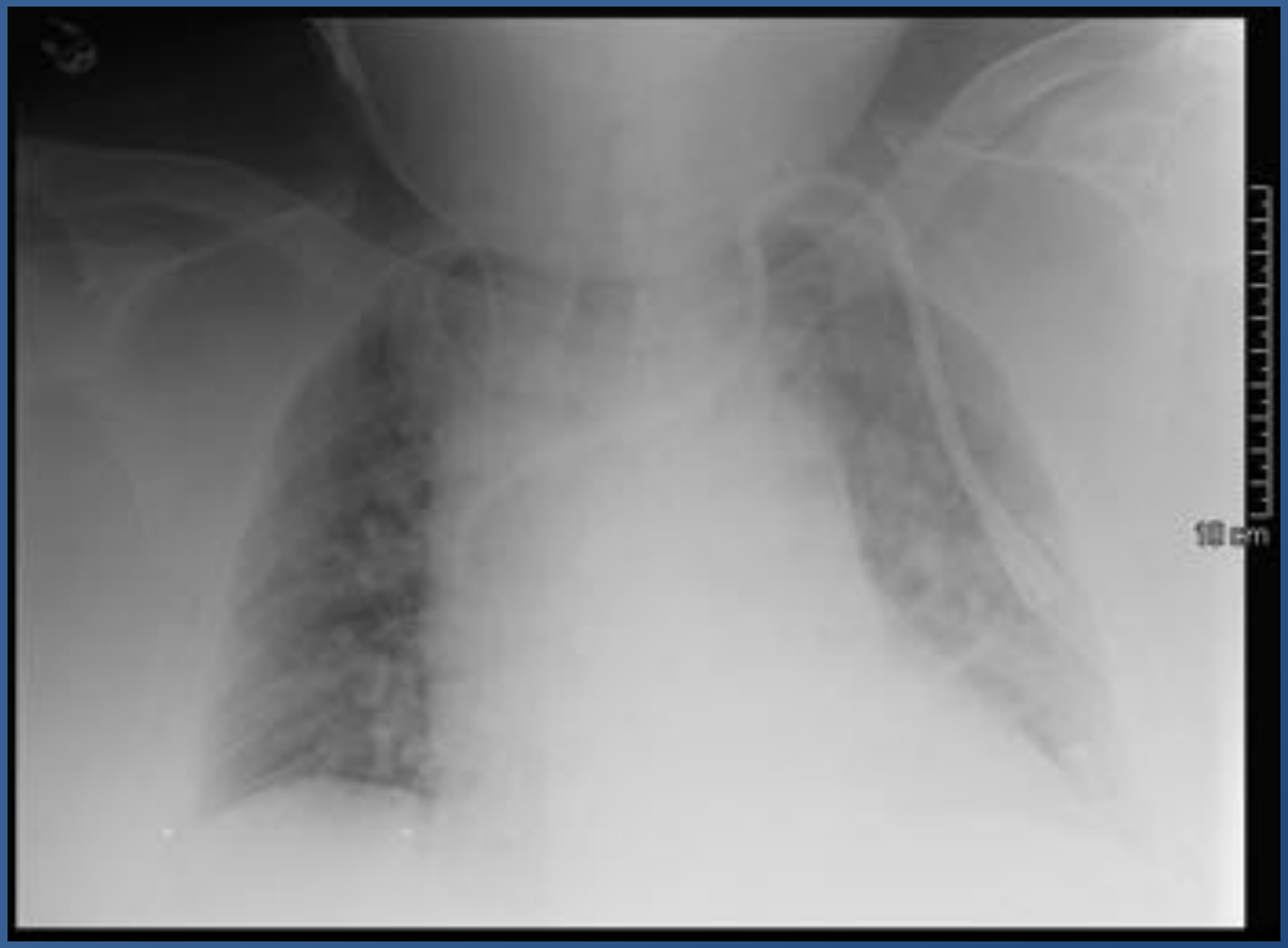
# Case Presentation: Labs

**PLT**


**INR**

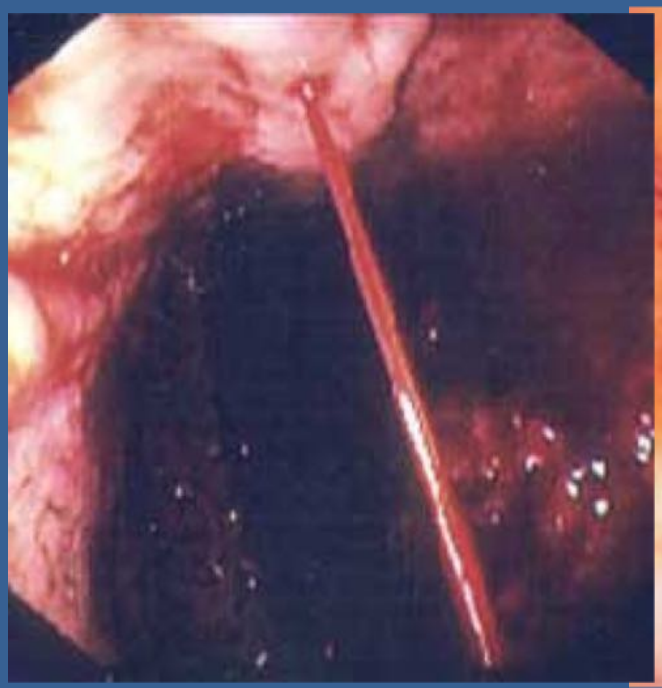


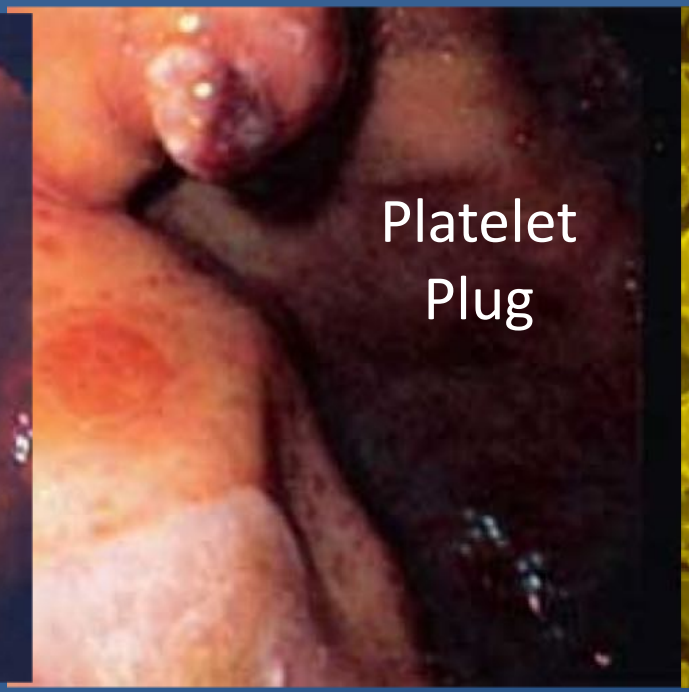
# Coagulation and Anticoagulation in Liver Disease

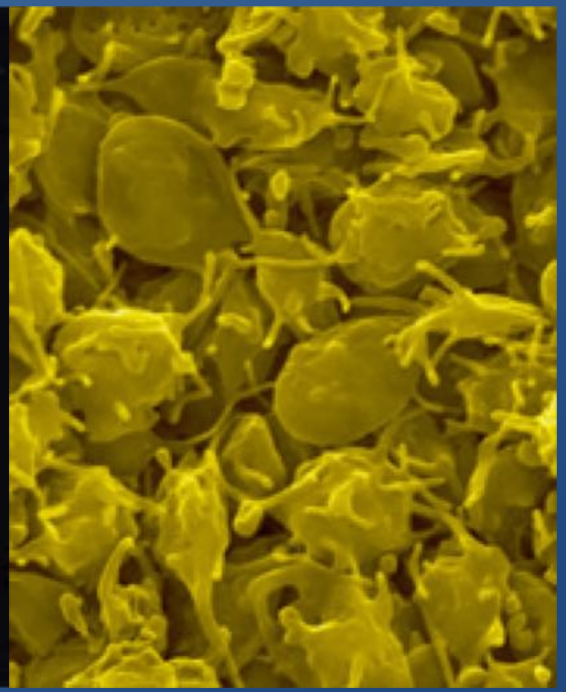


# The “Coagulopathy” of Liver Disease

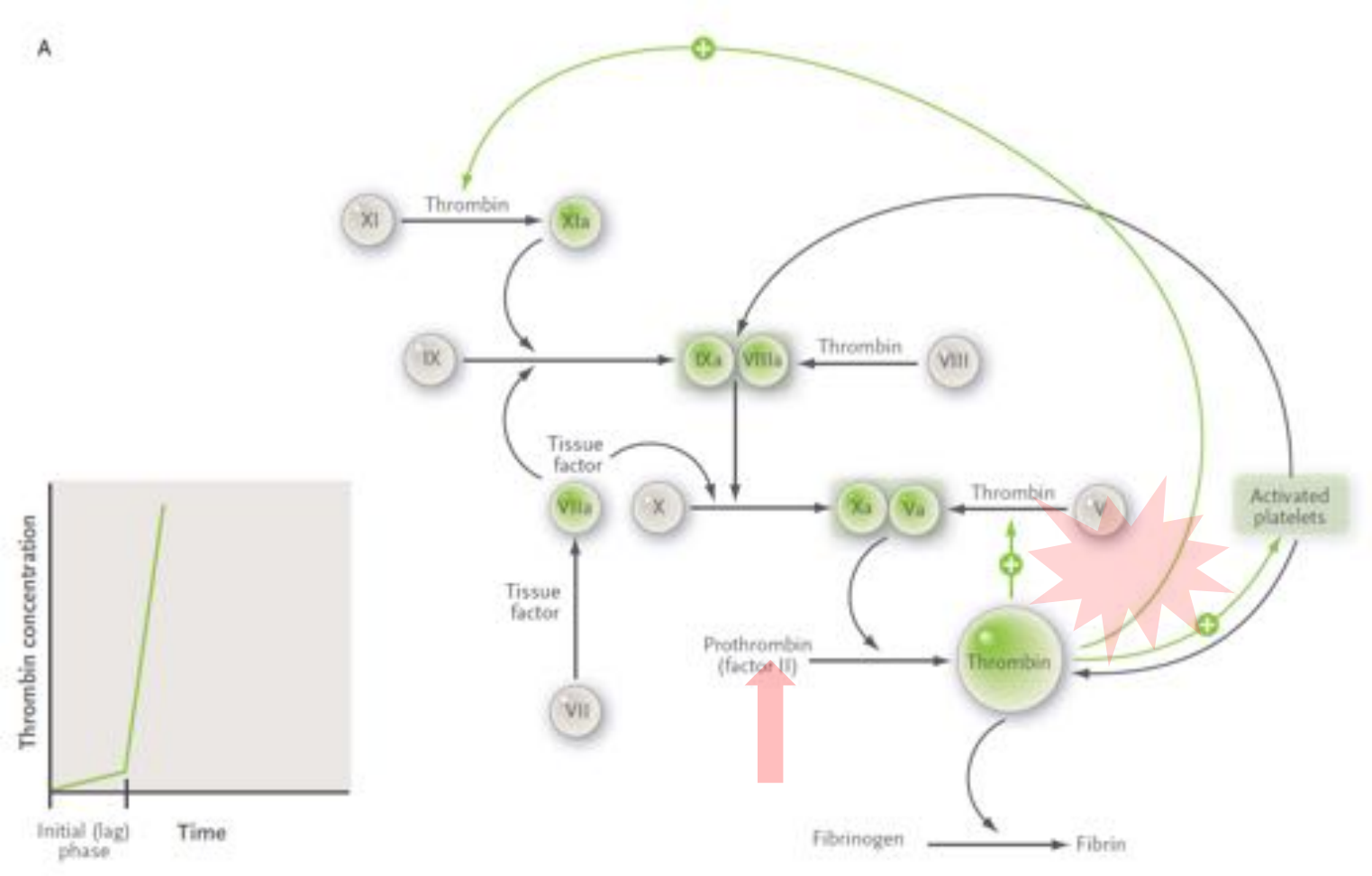
# Step 1 - Primary Hemostasis





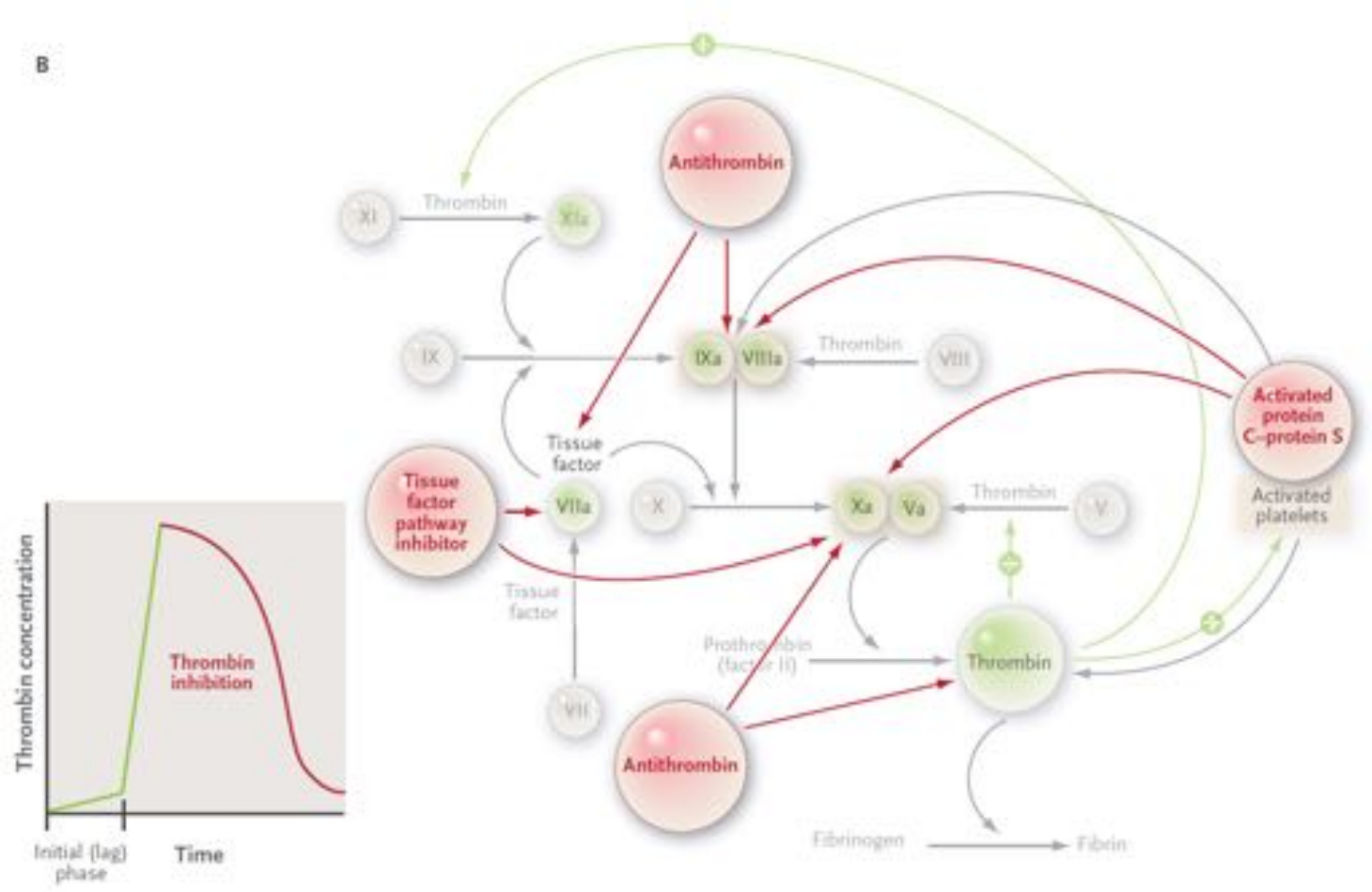



# Step 2 - Coagulation



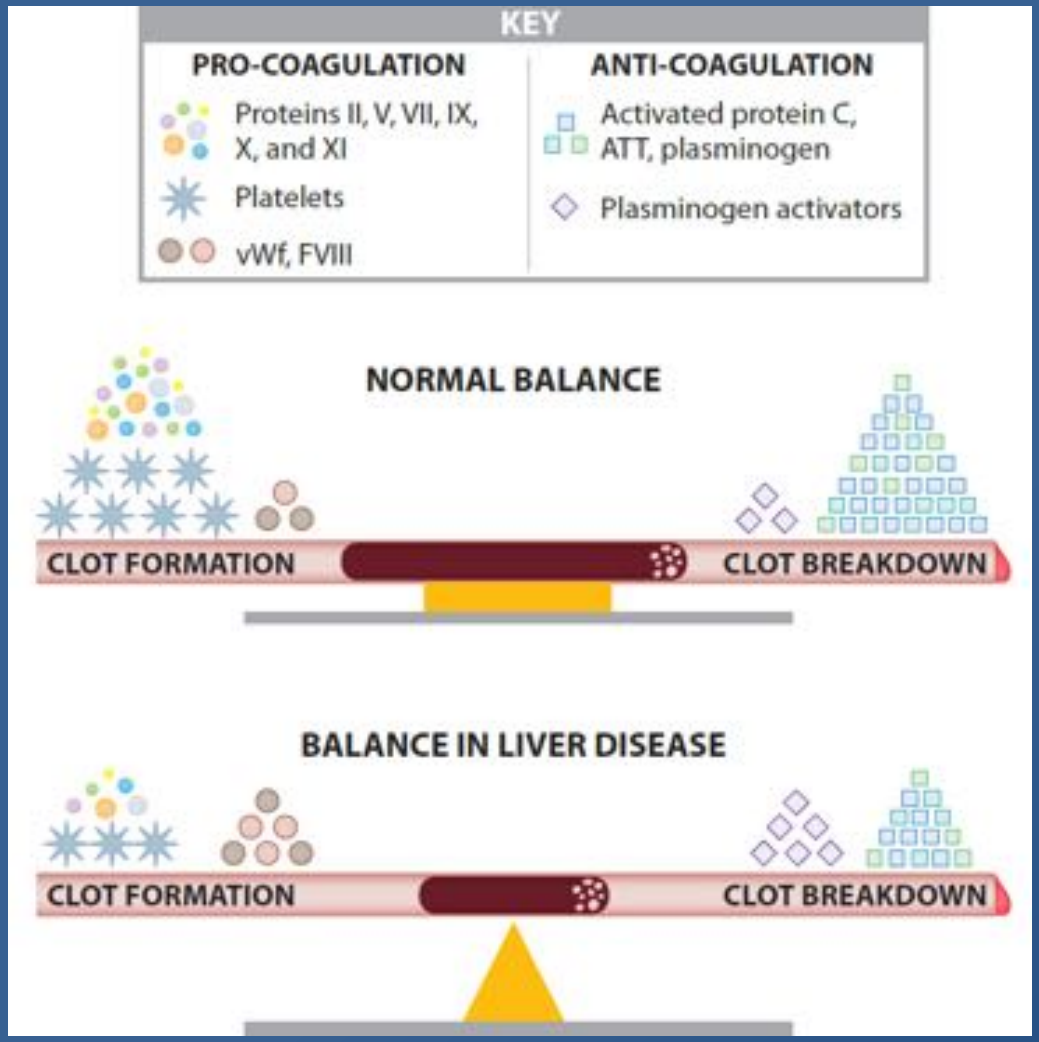

Tripodi, Mannuccio, NEJM, July 14, 2011, 147-156.
Monroe DM, Hoffman M, Clinics in Liver Disease, Feb 2009;13:1-9.

# Step 3 - Fibrinolysis




Tripodi, Mannuccio, NEJM, July 14, 2011, 147-156.

# The “Rebalanced” State

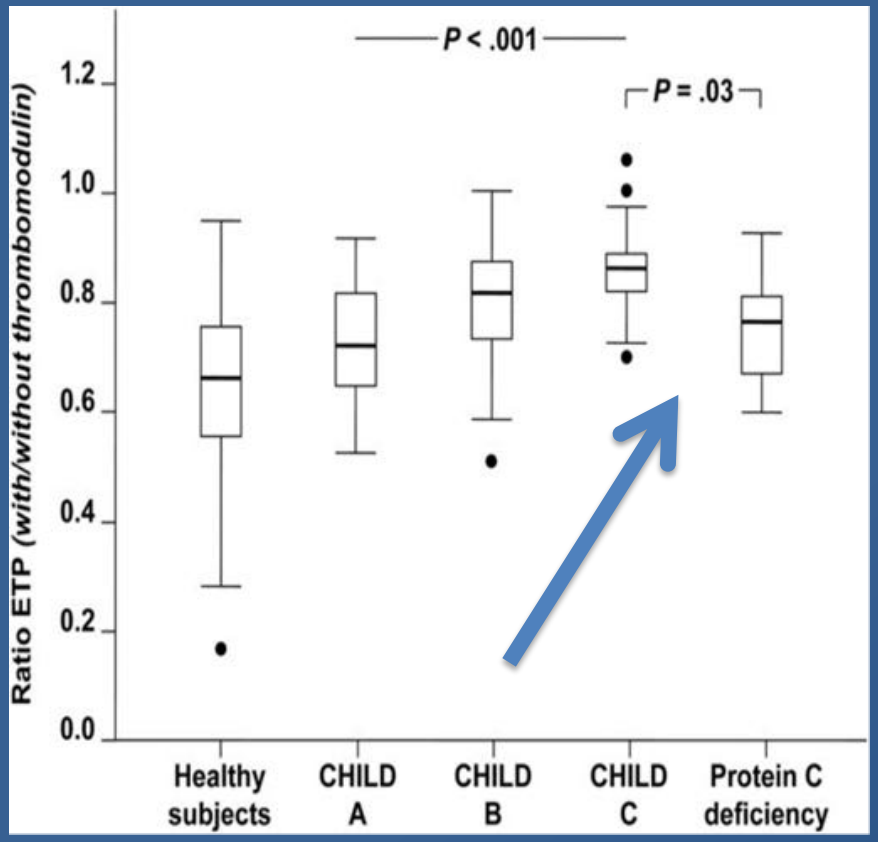



- Decrease in synthesis of procoagulants
- Increase in persistence of anticoagulants
- Decrease in platelets
- Increase in platelet adhesion molecules

A Rebalanced State

Northup P., Intagliata N., Shah N. (2015) Coagulation Disorders in Patients with Cirrhosis. In: Keaveny A., Cárdenas A. (eds) *Complications of Cirrhosis*. Springer, Cham.

# Some cirrhosis patients are prothrombotic



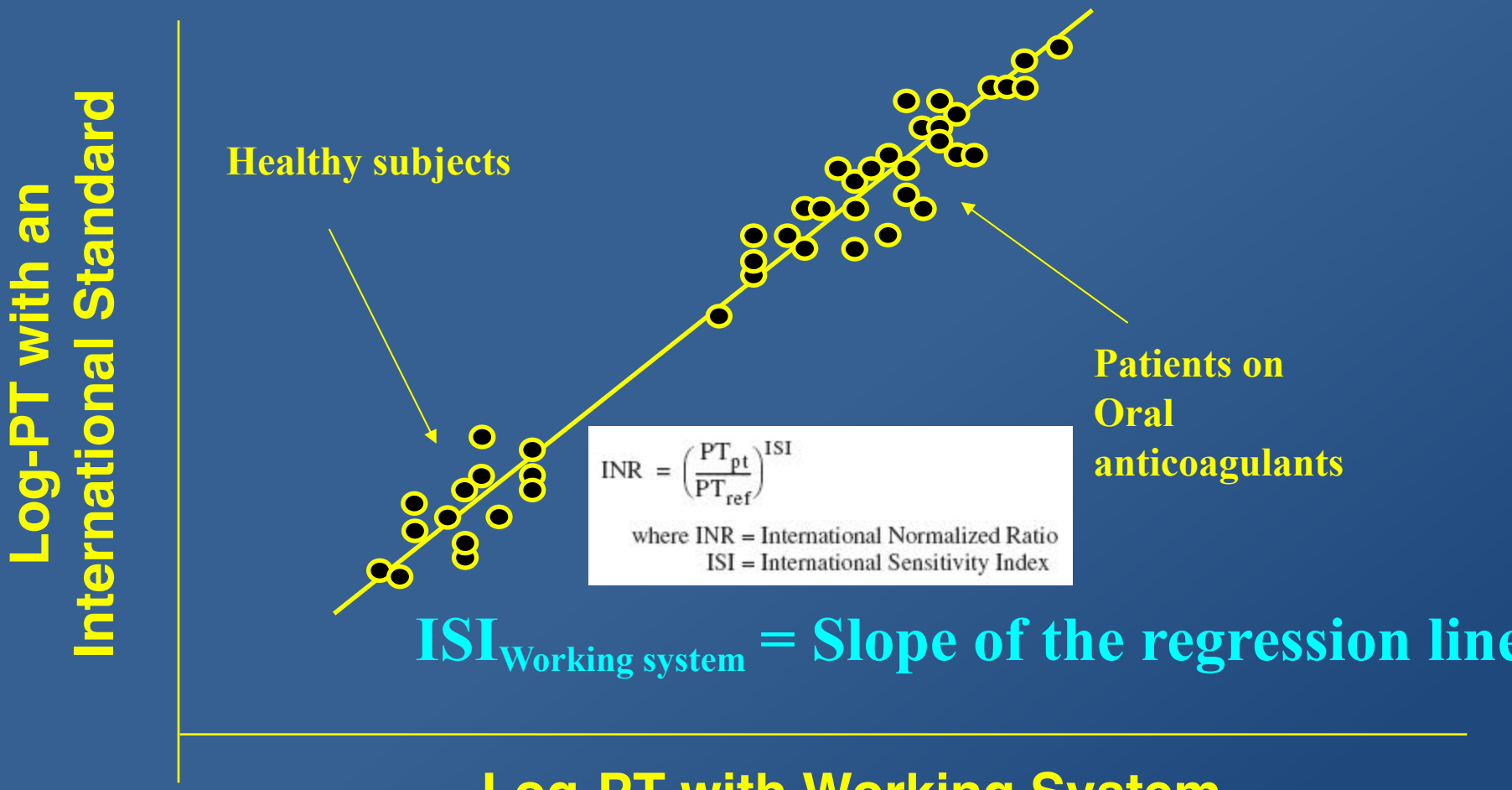

Some cirrhosis patients have protein C activity levels similar to those with congenital protein C deficiency.

Protein C deficiency = thrombosis

Tripodi, et al., *Gastroenterology* 2009. 137(6): 2105-11

# How Do We Measure the Ability to Clot or Disposition to Bleed: The INR?
# (No)

# Derivation of the INR



# The INR is bad at assessing bleeding risk in liver disease

There are now more than 30 studies affirming the lack of utility of INR in accurately predicting procedural bleeding in liver disease patients in a very broad array of procedures

- Percutaneous liver biopsy Gilmore *Gut* 1995
- Laparoscopic liver biopsy Ewe *Dig Dis Sci* 1981, Denzer *Am J Gastro* 2003
- Transjugular liver biopsy Segal *Transfusion* 2005, Bruzzi *Abdom Imaging* 2002
- Therapeutic paracentesis Grabau *Hepatology* 2004
- Colonoscopy with polypectomy Jeon *Surg Endosc* 2012
- Percutaneous endoscopic gastrostomy Baltz *Gastrointest Endosc* 2010
- Dental extractions Stanca *J Oral Maxillofacial Surg* 2010
- Bronchoscopy Segal *Transfusion* 2005
- Transjugular and percutaneous renal biopsy Segal *Transfusion* 2005
- Central venous catheter placement Segal *Transfusion* 2005
- Arteriography Segal *Transfusion* 2005
- Coronary artery catheterization Townsend *Am J Cardiol* 2012

# Prophylactic Transfusion

## Usefulness of International Normalized Ratio to Predict Bleeding Complications in Patients With End-Stage Liver Disease Who Undergo Cardiac Catheterization

Jacob C. Townsend, MD[a,*], Richard Heard, MD[b], Eric R. Powers, MD[a], and Adrian Reuben, MBBS[c]

Patients with end-stage liver disease frequently require invasive cardiac procedures in preparation for liver transplantation. Because of the impaired hepatic function, these patients often have a prolonged prothrombin time and elevated international normalized ratio (INR). To determine whether an abnormal prothrombin time/INR is predictive of

**"…Of the 157 patients who underwent isolated RHC, 11 received FFP before the procedure. The mean INR in these patients was 2.4 (range 1.9 to 3.3). Despite transfusion of 2 U of FFP, only 1 patient had their INR decrease to 1.9."**

**"…No major vascular complications or procedure-related bleeding events were identified in any patient."**

**Am J Cardiol 2012;110: 1062–1065**

# “Fix” the INR

But the patient already has massive ascites and you want 6 units of FFP?

I don’t care about that. You’ll have to fix the INR before I’ll do the paracentesis.

Hepatology

Radiology

# Common coagulation products

FFP: Typically prepared form a single unit of blood and contains all of the coagulation proteins with degradation of factor levels through storage and thawing processes (~40%). Typical INR = 1.3

Cryoprecipitate: A byproduct from thawing FFP. Contains concentrated factor VIII, fibrinogen, XIII, vWF, and others

# How much FFP is needed?

One unit of FFP is about equal to 200 ml of volume

**Predicted Fresh Frozen Plasma Transfusion Volume, Dose, and Expected Factor Increment for Various Target INR Values**

| | Target INR | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1.3 | | | 1.5 | | | 1.7 | | | 3.0 | | |
| Initial INR | Volume (L) | Dose (mL/kg) | Factor (%) | Volume (L) | Dose (mL/kg) | Factor (%) | Volume (L) | Dose (mL/kg) | Factor (%) | Volume (L) | Dose (mL/kg) | Factor (%) |
| 6.0 | 4.5 | 64 | 45 | 3.5 | 50 | 35 | 2.5 | 36 | 25 | 1.5 | 21 | 15 |
| 5.0 | 4.3 | 61 | 43 | 3.0 | 43 | 30 | 2.3 | 32 | 23 | 1.0 | 14 | 10 |
| 4.0 | 4.0 | 57 | 40 | 2.5 | 36 | 25 | 2.0 | 29 | 20 | 0.5 | 7 | 5 |
| 3.0 | 3.5 | 50 | 35 | 2.0 | 29 | 20 | 1.5 | 21 | 15 | — | — | — |
| 2.0 | 2.5 | 36 | 25 | 1.5 | 21 | 15 | 0.5 | 7 | 5 | — | — | — |

Holland *Am J Clin Pathol* 2006

# Fibrinogen, Platelets, and Bleeding

HEPATOLOGY

AASLD

HEPATOLOGY, VOL. 64, NO. 2, 2016

## Coagulation Parameters and Major Bleeding in Critically Ill Patients With Cirrhosis

Andreas Drolz,[1,2] Thomas Horvatits,[1,2] Kevin Roedl,[1,2] Karoline Rutter,[1,2] Katharina Staufer,[3] Nikolaus Kneidinger,[4] Ulrike Holzinger,[1] Christian Zauner,[1] Peter Schellongowski,[5] Gottfried Heinz,[6] Thomas Perkmann,[7] Stefan Kluge,[2] Michael Trauner,[1] and Valentin Fuhrmann[1,2]

# Fibrinogen, Platelets, and Bleeding

Fibrinogen levels (<100 mg/dL) and platelet counts (<100k) were specific but not sensitive measures of predicting bleeding in ICU patients with cirrhosis.

TABLE 4. Prediction of Major Bleeding in ICU Patients With Cirrhosis

| Parameter | Number of patients (%) | NNB | Sensitivity | Specificity | Accuracy | PPV | NPV | LRP | LRN | DOR | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fibrinogen | | | | | | | | | | | |
| <200 mg/dL | 99 (47%) | 3.5 | 80% | 60% | 63% | 28% | 94% | 1.98 | 0.34 | 5.82 | <0.001 |
| <150 mg/dL | 64 (30%) | 3.2 | 57% | 75% | 72% | 31% | 90% | 2.29 | 0.57 | 4.02 | <0.001 |
| <100 mg/dL | 34 (16%) | 3.1 | 31% | 87% | 78% | 32% | 86% | 2.4 | 0.79 | 3.04 | <0.01 |
| <70 mg/dL | 24 (11%) | 2.4 | 29% | 92% | 82% | 42% | 87% | 3.59 | 0.78 | 4.60 | <0.001 |
| <60 mg/dL | 14 (7%) | 1.6 | 26% | 97% | 85% | 64% | 87% | 9.05 | 0.76 | 11.91 | <0.001 |
| Platelet count | | | | | | | | | | | |
| <80 ($10^9$/L) | 102 (48%) | 4.3 | 69% | 56% | 58% | 24% | 90% | 1.55 | 0.56 | 2.77 | <0.01 |
| <70 ($10^9$/L) | 80 (38%) | 3.8 | 60% | 66% | 65% | 26% | 89% | 1.79 | 0.6 | 2.98 | <0.01 |
| <50 ($10^9$/L) | 46 (22%) | 3.1 | 43% | 82% | 76% | 33% | 88% | 2.43 | 0.69 | 3.52 | <0.001 |
| <30 ($10^9$/L) | 16 (8%) | 2 | 23% | 95% | 83% | 50% | 86% | 5 | 0.81 | 6.17 | <0.001 |
| aPTT (seconds) | | | | | | | | | | | |
| >50 | 94 (45%) | 4.1 | 66% | 59% | 60% | 24% | 90% | 1.62 | 0.58 | 2.79 | <0.01 |
| >70 | 36 (17%) | 2.6 | 40% | 87% | 79% | 39% | 88% | 3.18 | 0.69 | 4.61 | <0.001 |
| >100 | 16 (8%) | 2 | 23% | 95% | 83% | 50% | 86% | 5 | 0.81 | 6.17 | <0.001 |

Drolz, et al. Hepatology 2016; 64: 556-68

# Thrombopoietin Receptor Agonists

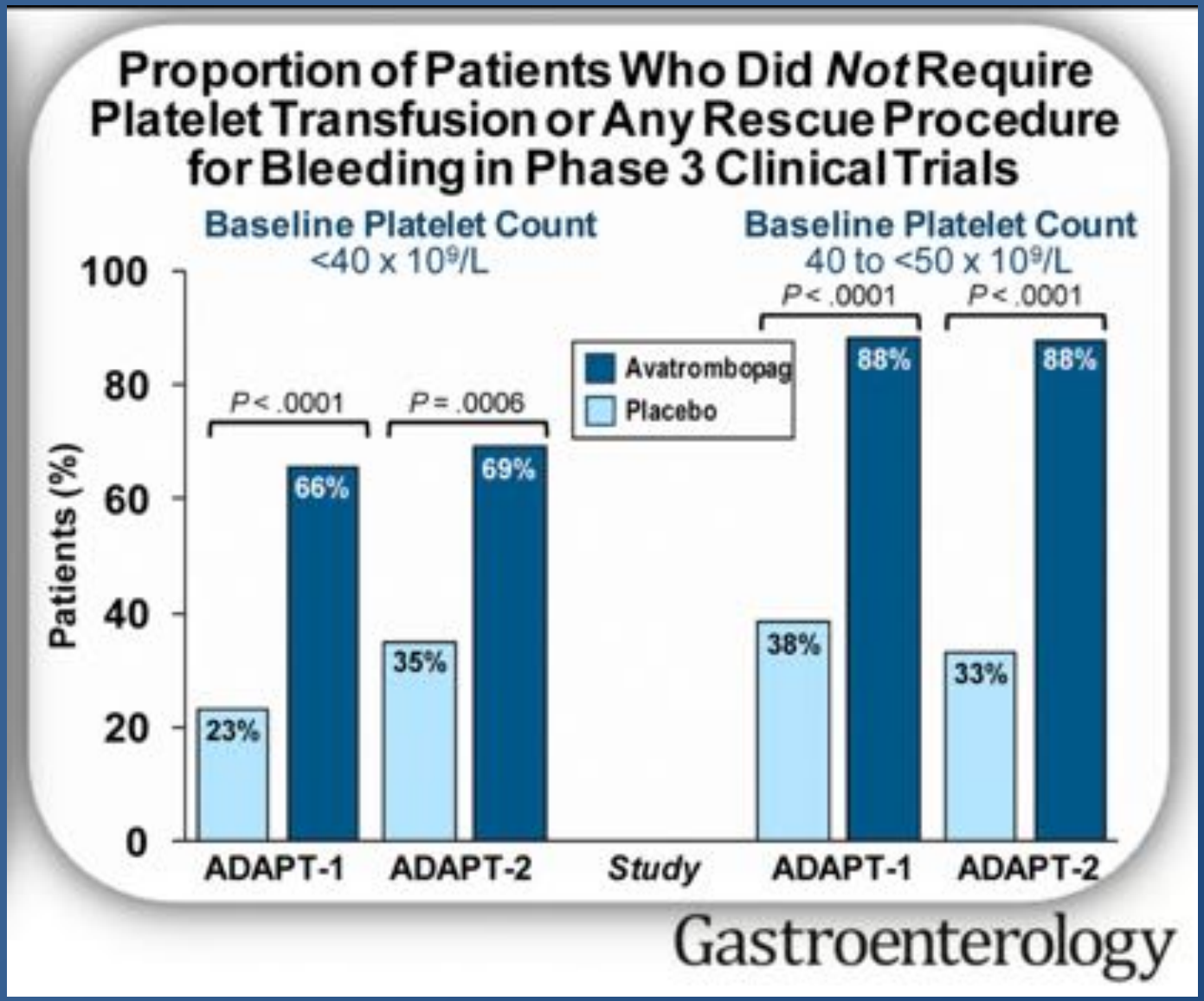
Gastroenterology
Volume 155, Issue 3, September 2018, Pages 705-718

Original Research
Full Report: Clinical—Liver

## Avatrombopag Before Procedures Reduces Need for Platelet Transfusion in Patients With Chronic Liver Disease and Thrombocytopenia

Norah Terrault [1], Yi-Cheng Chen [2], Namiki Izumi [3], Zeid Kayali [4], Paul Mitrut [5], Won Young Tak [6], Lee F. Allen [7], Tarek Hassanein [8]

# Thrombopoietin Receptor Agonists



# Thrombopoietin Receptor Agonists

- “Overall across the 2 studies, the incidence of bleeding events (World Health Organization Grade ≥ 2) was comparable between the avatrombopag and placebo treatment groups in both the low and high baseline platelet count cohorts (3.8% vs 3.3% and 2.6% vs 4.6%, respectively)”

- Two PVT’s in the studies, both in the AVA group, p=NS.

Terrault, et al. *Gastroenterology* 2018; 155: 705-718

# Procedural Bleeding Risk: How Common is it?

# The SHIP Trial

## SHIP Trial (Study of Hemostasis and Invasive Procedures)

INR 1.3 -1.9

Randomize

No Rx

FFP
10mL/kg

**Primary outcome: Bleeding**
**Ultrasound with > 1 mL/kg bleed**
**Drop in Hgb > 1.6 g/dL**
**Need for transfusion**

**Hypothesis based on a non-inferiority trial.**

**Sample size: n = ~ 1300**

ClinicalTrials.gov Identifier: NCT00233246

Stopped prematurely due to inadequate enrollment

# Paracentesis: Safety

1,100 therapeutic paracenteses on 628
513 procedures were in patients with cirrhosis
No ultrasound localization
Mean duration of procedure 97 +/- 24 minutes
Mean volume removed 8.7 L (max 31 L!)

| Prothrombin Time (INR) | Number of Patients |
|---|---|
| ≤1.4 | 277 |
| 1.5–2.0 | 531 |
| 2.1–2.5 | 208 |
| ≥2.5 | 84 |
| Platelet count ($\times 10^3/\mu L$) | Number of Patients |
| ≥60 | 210 |
| 50–59 | 292 |
| 40–49 | 361 |
| 30–39 | 188 |
| 20–29 | 48 |
| ≤20 | 1 |

Grabau, C.M., S.F. Crago, L.K. Hoff, J.A. Simon, C.A. Melton, B.J. Ott, and P.S. Kamath, Performance standards for therapeutic abdominal paracentesis. *Hepatology, 2004. 40(2): p. 484-8.*

# Paracentesis: Safety

- No procedural complications requiring hospitalization
- 3 episodes of postural hypotension responsive to albumin and observation
- 1 episode of “bloody tap”-discharged
- 4 episodes of fluid leakage for >48h
- No significant bleeding in any patient

# Society Recommendations

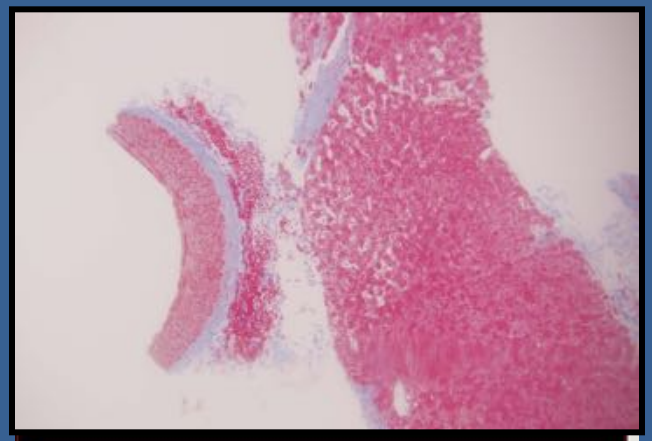
The practice guidelines from the American Association for the Study of Liver Diseases, which have been recently updated:

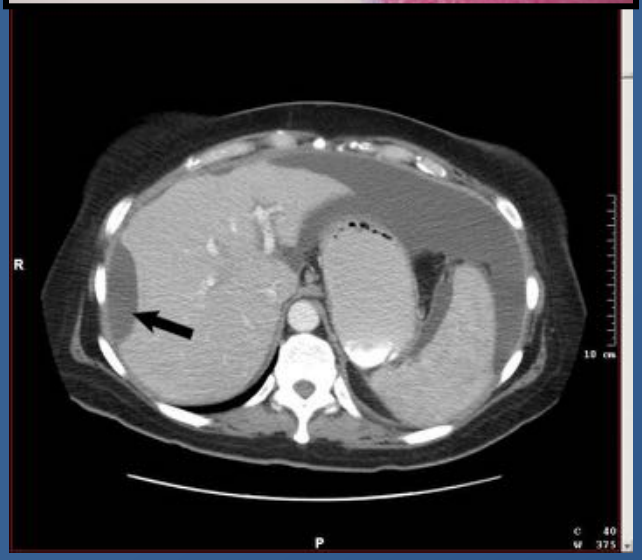
"RECOMMENDATION 2

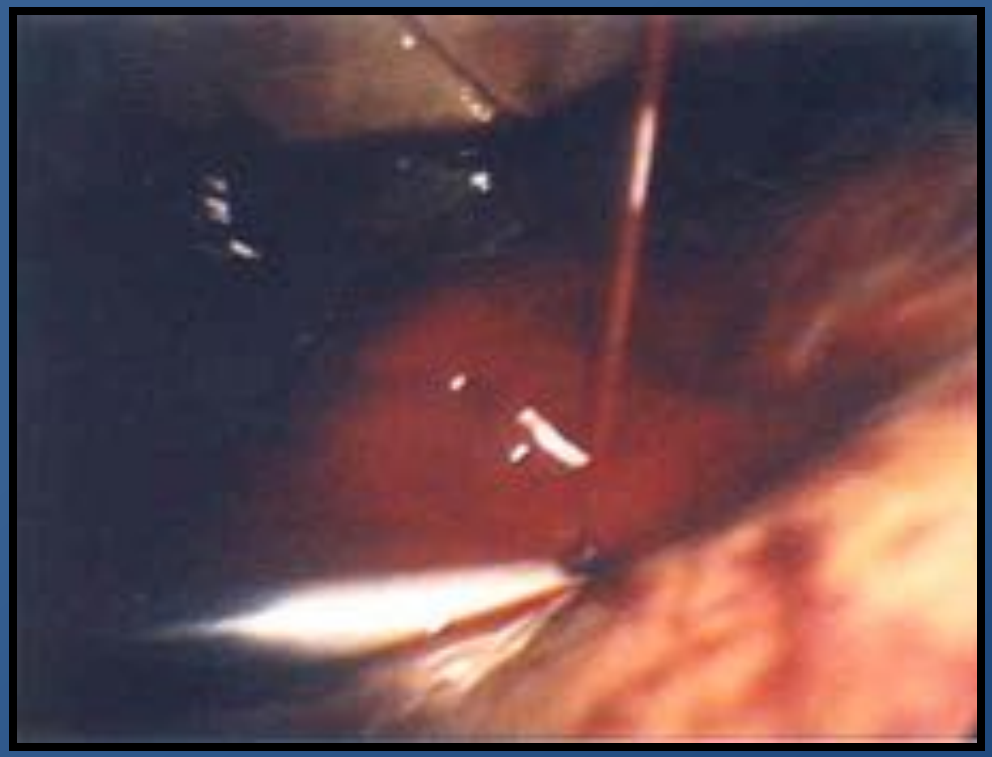
Since bleeding is sufficiently uncommon, the routine prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended. (Class III, Level C)"

Runyon *Hepatology* 2013, page 4

# Liver Biopsy Complications





# Liver Biopsy: Safety

**Table 3.** Description of Complications Recorded as an SAE Among 2740 Liver Biopsies Performed

| Description | SAEs, n | Percentages/ liver biopsy | Percentages/ SAEs |
|---|---|---|---|
| Bleeding[a] | 16 | 0.58 | 55.2 |
| Severe pain | 7 | 0.26 | 24.1 |
| Punctured gall bladder | 2 | 0.07 | 6.9 |
| Marked hypotension | 1 | 0.04 | 3.4 |
| Pneumothorax | 1 | 0.07 | 3.4 |
| Syncope | 1 | 0.07 | 3.4 |
| Dehydration | 1 | 0.07 | 3.4 |
| Total | 29 | 1.06 | 100.0 |

[a]Hemoperitoneum, 8 cases; subcapsular hematoma, 4 cases; hemobilia, 3 cases, hemothorax, 1 case.

**Table 6.** Liver Biopsy Bleeding Complication Relative to Platelet Count Cut-Off Values

| Platelet count | Total | Bleeding complication | |
|---|---|---|---|
| | | No. | % |
| >150,000/mm$^3$ | 1331 | 3 | 0.2 |
| 101,000–150,000/mm$^3$ | 738 | 5 | 0.7 |
| 61,000–100,000/mm$^3$ | 509 | 3 | 0.6 |
| ≤60,000/mm$^3$ | 76 | 4[a] | 5.3 |
| Total | 2654 | 15[b] | 0.6 |

There were 15 bleeding complications in 2,654 cirrhosis biopsies, 4 occurred in patients with PLT < 60 k/mcL. 8 occurred in those with PLT > 100 k/mcL.

Seeff, L.B., G.T. Everson, T.R. Morgan, T.M. Curto, W.M. Lee, M.G. Ghany, M.L. Shiffman, R.J. Fontana, A.M. Di Bisceglie, H.L. Bonkovsky, and J.L. Dienstag, *Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol, 2010. 8(10): p. 877-83.*

# Endoscopy Safety

ORIGINAL ARTICLE: Clinical Endoscopy

## Safety of endoscopic interventions in patients with thrombocytopenia

Somashekar G. Krishna, MD, MPH,[1,3] Bhavana B. Rao, MD,[1] Selvi Thirumurthi, MD,[1] Jeffrey H. Lee, MD, MPH,[1] Srinivas Ramireddy, MD,[1] Michele Guindani, PhD,[2] William A. Ross, MD, MBA[1]

Houston, Texas; Columbus, Ohio, USA

**Background:** The risk of endoscopic interventions in thrombocytopenia has received little attention in the medical literature.

**Objective:** The aim of this study was to assess the safety of endoscopic interventions including evaluation of GI bleeding (GIB) in patients with thrombocytopenia.

**Design and Setting:** Retrospective study, tertiary oncology center.

*Gastrointestinal Endoscopy* Sept 2014; 80 (3): 425-434

# Endoscopy Safety

| **617 Endoscopic Procedures<br>351 Upper, 266 Lower (90 Colonoscopies)** | **Odds ratio** | **95% CI** |
|---|---|---|
| Age | 1.02 | 1.00-1.04 |
| Platelet count before endoscopy, × $10^3/\mu L$ | 0.98 | 0.96-1.01 |
| Aggregate PRBC transfusion 3 days before endoscopy | 1.32 | 1.16-1.49 |
| Aggregate platelet units 3 days before endoscopy | 1.02 | 0.98-1.05 |
| Aggregate FFP transfusion 3 days before endoscopy | 0.95 | 0.81-1.10 |

"Endoscopy and routine interventions can be safely performed in patients with thrombocytopenia (Common Terminology Criteria for Adverse Events grade ≤3). The risk of interventional bleeding is minimally increased but is typically minor and easily controlled…"

Krishna, et al, *Gastrointestinal Endoscopy* Sept 2014; 80 (3): 425-434

# Colonoscopy: Safety

Retrospective study of 30 patients with “early liver cirrhosis” (Child A or B)

- 66 polyps removed
- 2 sites (3%) showed “mild oozing” controlled with clips
- No other bleeding or complications
- Oozing polyps were bigger than others: 22.5 mm vs. 7.22 mm
- Platelet counts, INR, and Child-Pugh scores did not significantly differ between groups

Jeon JW, et al., *Surg Endosc* 2012; 26(11): 3258-63.

Choosing Wisely®

An initiative of the ABIM Foundation

American Association for the Study of Liver Diseases

AASLD

# Five Things Physicians and Patients Should Question

## 1 Don't perform surveillance esophagogastroduodenoscopy (EGD) in patients with compensated cirrhosis and small varices without red signs treated with non-selective beta blockers for preventing a first variceal bleed.

In patients with cirrhosis and small varices that have not bled and have no criteria for increased risk of bleeding (Child A, no red signs on varices), beta blockers can be used. In patients with cirrhosis and medium or large varices that have not bled and are not at the highest risk of bleeding (Child A and no red signs), beta blockers are preferred, adjusted to the maximal tolerated dose. In both scenarios, follow-up EGD is not necessary.

## 2 Don't continue treatment for hepatic encephalopathy indefinitely after an initial episode with an identifiable precipitant.

In circumstances where the precipitating factors are identified and well-controlled (e.g., recurrent infections, variceal bleeding) or liver function or nutritional status improved, prophylactic therapy may be discontinued.

## 3 Don't repeat hepatitis C viral load testing outside of antiviral therapy.

Highly-sensitive quantitative assays of hepatitis C RNA are appropriate at diagnosis and as part of antiviral therapy. Otherwise, the results of virologic testing do not change clinical management or outcomes.

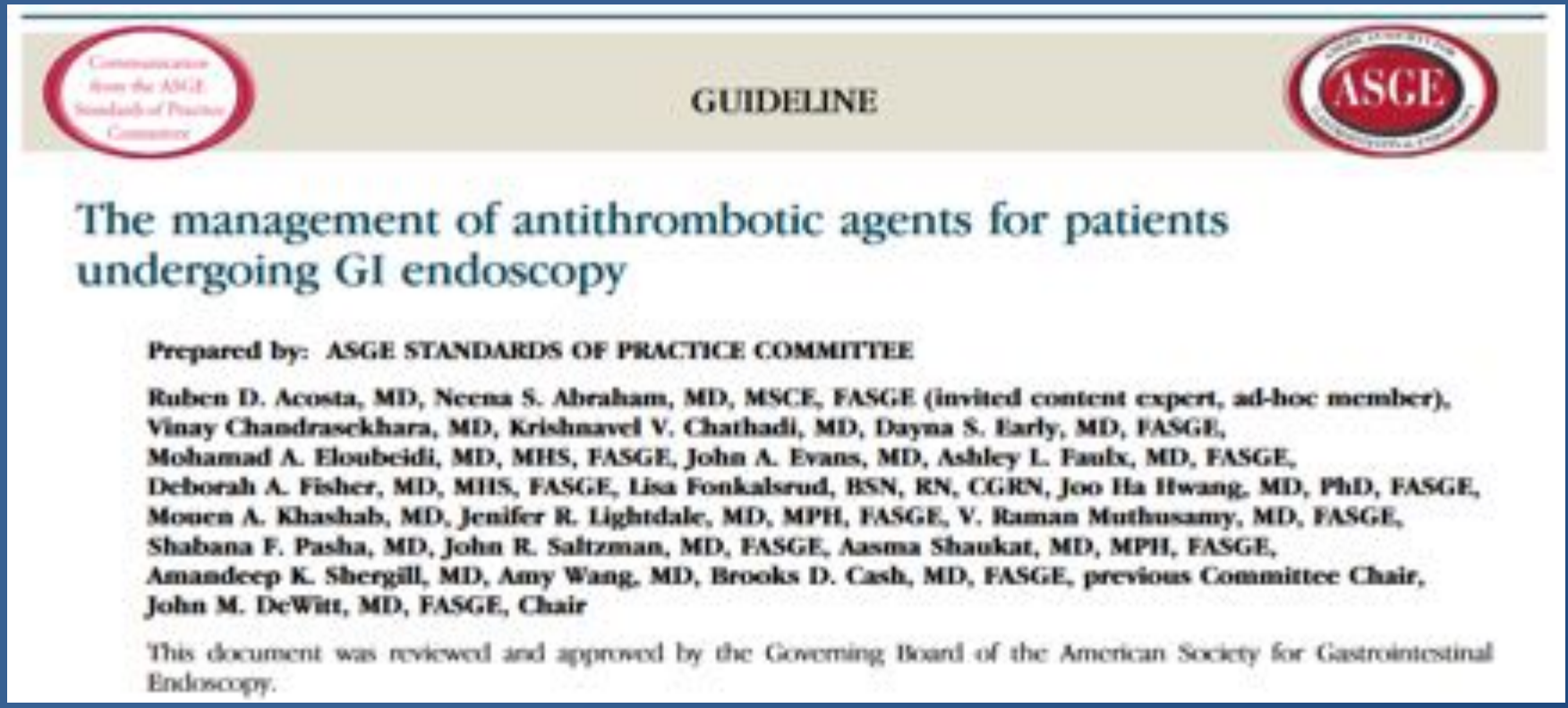
## 4 Don't perform computed tomography or magnetic resonance imaging routinely to monitor benign focal lesions in the liver unless there is a major change in clinical findings or symptoms.

Patients with benign focal liver lesions (other than hepatocellular adenoma) who don't have underlying liver disease and have demonstrated clinical and radiologic stability do not need repeated imaging.

## 5 Don't routinely transfuse fresh frozen plasma and platelets prior to abdominal paracentesis or endoscopic variceal band ligation.

Routine tests of coagulation do not reflect bleeding risk in patients with cirrhosis and bleeding complications of these procedures are rare.

# ASGE Recommendation



GUIDELINE

## The management of antithrombotic agents for patients undergoing GI endoscopy

**Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE**

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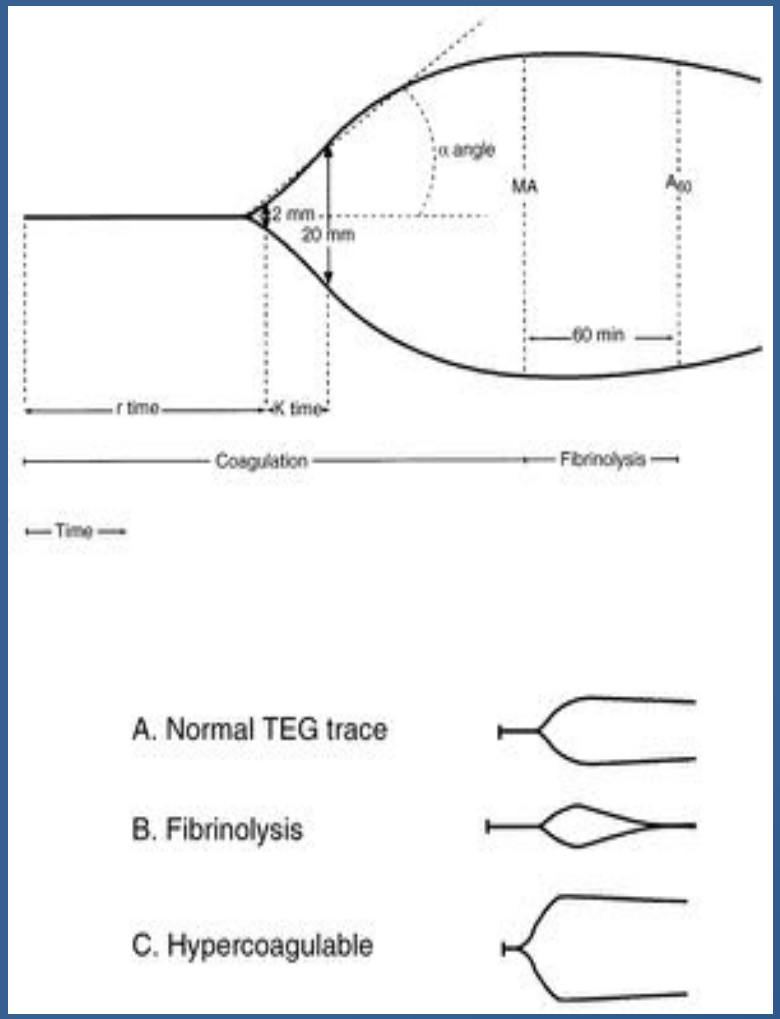
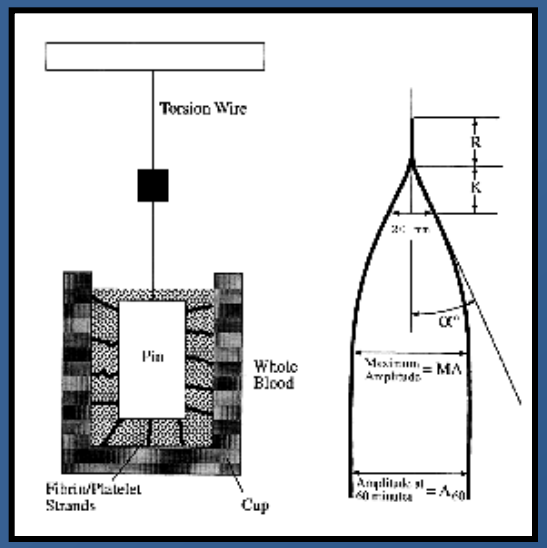
This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

# What Should We Check to Assess Bleeding Risk?

# Thromboelastography (TEG)

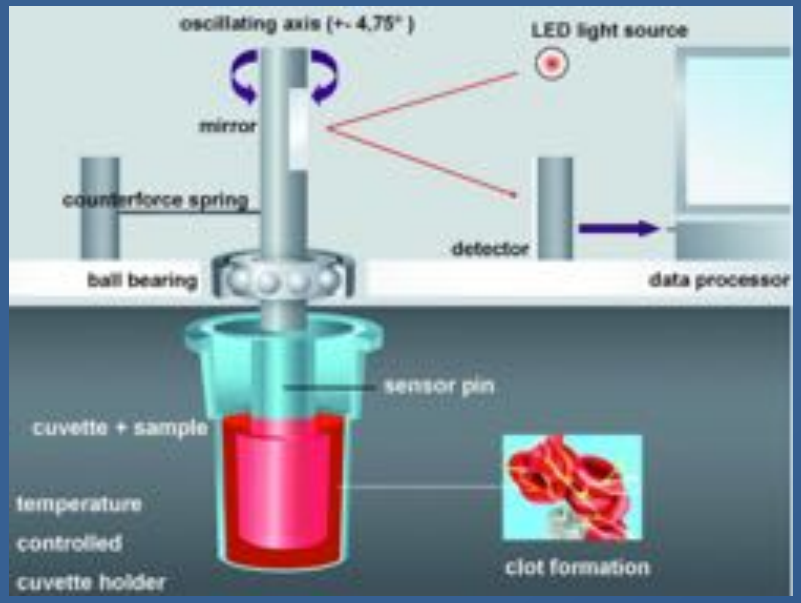


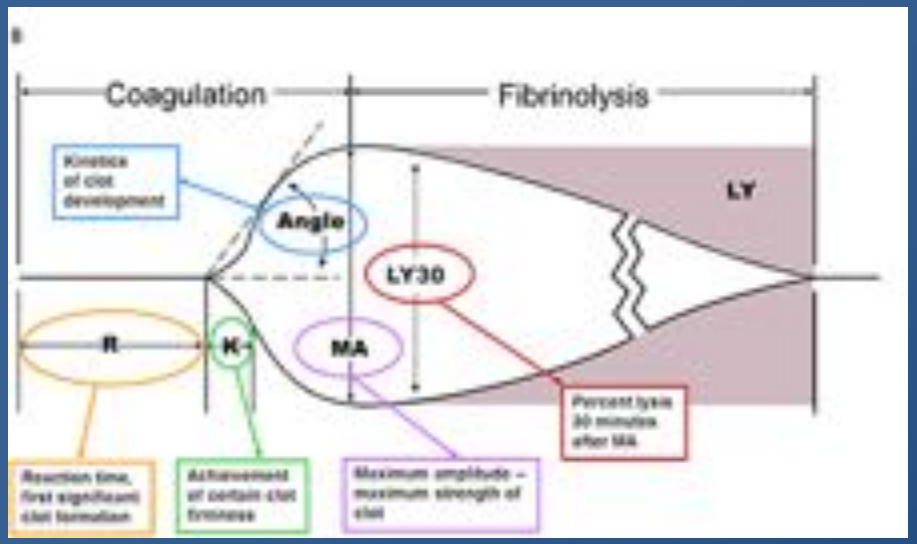



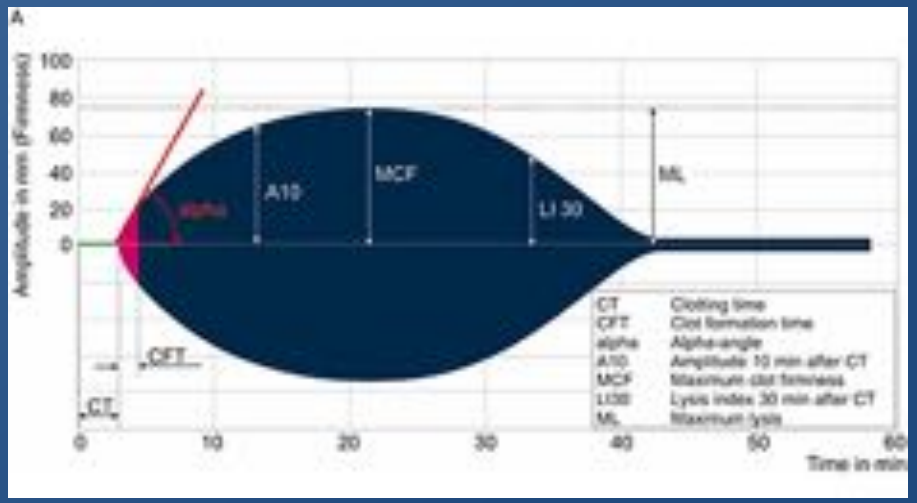

- Whole blood test
- Rotation - shear not natural
- Not very practical
- Somewhat subjective

Davis JPE, et al, Ann Hepatol 2018 Mar; 17(2): 205-13

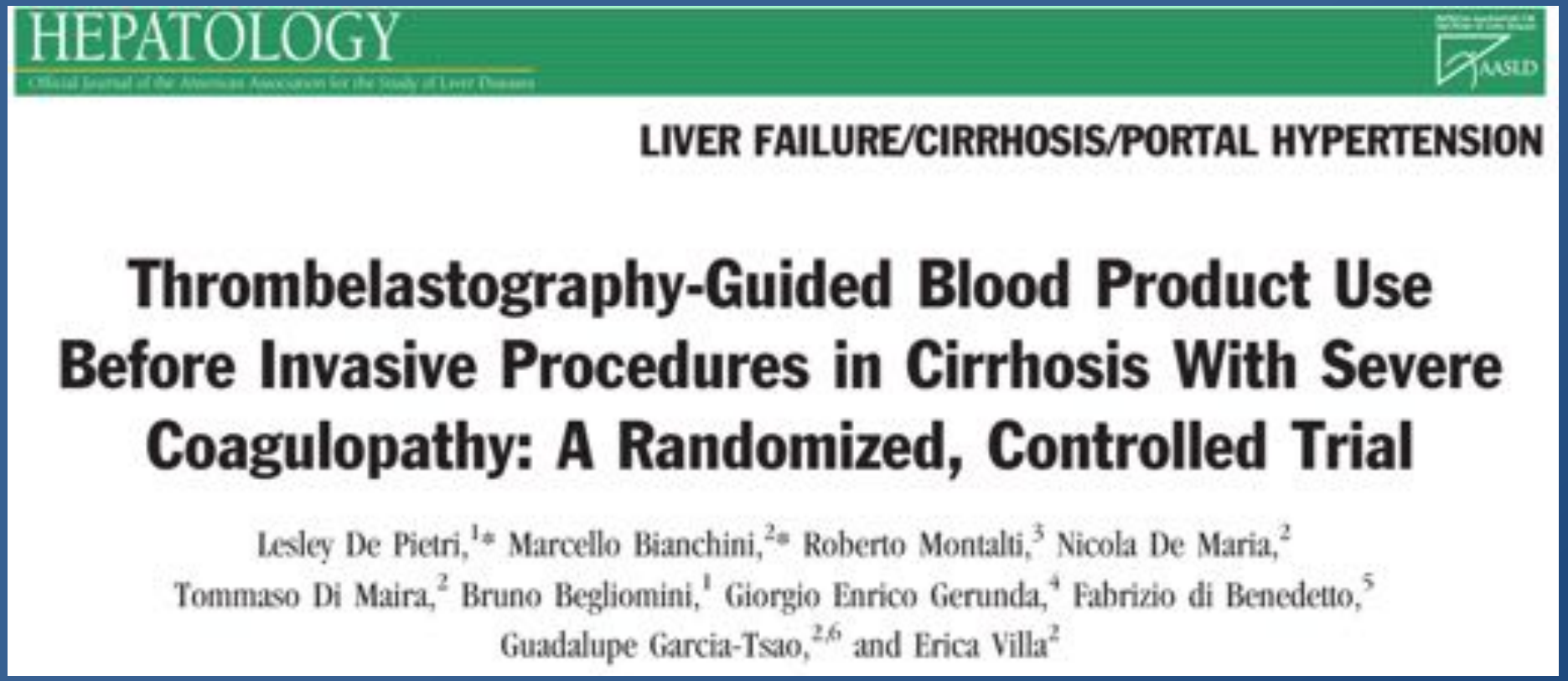
# Rotational Thromboelastometry (ROTEM)



# TEG and Blood Products



HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

LIVER FAILURE/CIRRHOSIS/PORTAL HYPERTENSION

## Thrombelastography-Guided Blood Product Use Before Invasive Procedures in Cirrhosis With Severe Coagulopathy: A Randomized, Controlled Trial

Lesley De Pietri,[1*] Marcello Bianchini,[2*] Roberto Montalti,[3] Nicola De Maria,[2] Tommaso Di Maira,[2] Bruno Begliomini,[1] Giorgio Enrico Gerunda,[4] Fabrizio di Benedetto,[5] Guadalupe Garcia-Tsao,[2,6] and Erica Villa[2]

*Hepatology* 2016; 63(2): 566-73

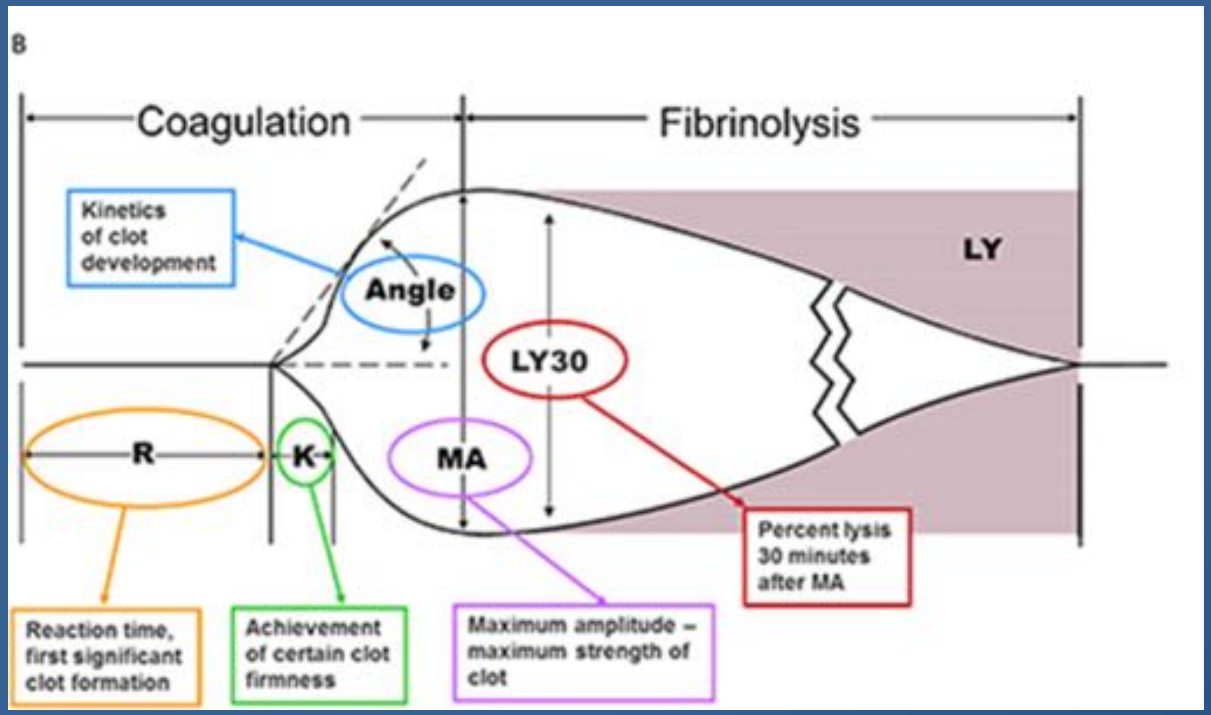
# TEG and Blood Products

**Table 2. Distribution of the Procedure Performed in the TEG and SOC groups, Divided in Procedures at Low or High Risk of Bleeding[19-26]**

| | TEG Groupn (%) | SOC Groupn (%) | *P* Value |
|---|---|---|---|
| Low risk of bleeding | | | |
| Paracentesis | 12 (40) | 7 (23.3) | 0.165 |
| Thoracentesis | 0 | 5 (16.7) | 0.052 |
| Central vein cannulation | 1 (3.3) | 2 (6.7) | >0.999 |
| TIPSS | 0 | 1 (3.3) | 0.313 |
| High risk of bleeding | | | |
| Endoscopic variceal banding | 6 (20) | 4 (13.3) | 0.730 |
| Hepatic resection | 3 (10) | 2 (6.7) | >0.999 |
| Other abdominal surgery | 2 (6.7) | 2 (6.7) | >0.999 |
| Radiofrequency ablation | 2 (6.7) | 1 (3.3) | >0.999 |
| Endoscopic polipectomy | 3 (10) | 0 | 0.119 |
| Percutaneous liver biopsy | 0 | 3 (10) | 0.237 |
| Biopsy of other sites | 0 | 1 (3.3) | 0.313 |
| Drainage other sites | 0 | 1 (3.3) | 0.313 |
| ERCP with sphincterotomy | 0 | 1 (3.3) | 0.313 |
| Thoracotomy | 1 (3.3) | 0 | 0.313 |

De Pietri, et al, *Hepatology* 2016; 63(2): 566-73

# TEG and Blood Products




- R > 40 seconds = FFP transfusion
- MA < 30 = PLT transfusion

De Pietri, et al, *Hepatology* 2016; 63(2): 566-73

# TEG and Blood Products

**Table 4. Postprocedure Assessment and Complications**

| | TEG Group (n = 30) | Control Group (n = 30) | *P* Value |
|---|---|---|---|
| Postprocedure Hb, g/dL | 10.7 ± 1.8 | 9.9 ± 1.2 | 0.043 |
| % difference from baseline mean Hb | −0.9 | −3.8 | |
| Postprocedure INR | 1.9 ± 0.64 | 1.75 ± 0.41 | 0.225 |
| % difference from baseline mean INR | +1.6 | −12.9 | |
| Postprocedure PLTs count ($10^9$/L) | 55.2 ± 27.5 | 58.3 ± 31.3 | 0.692 |
| % difference from baseline mean PLTs count | −2.3 | −4.8 | |
| Transfusion-related side effects (%) | 0 | 1 (3.3) | 0.313 |
| Procedure-related bleeding (%) | 0 | 1 (3.3) | 0.313 |
| RBC transfusion (%) | 4 (13.3) | 4 (13.3) | 0.718 |

De Pietri, et al, *Hepatology* 2016; 63(2): 566-73

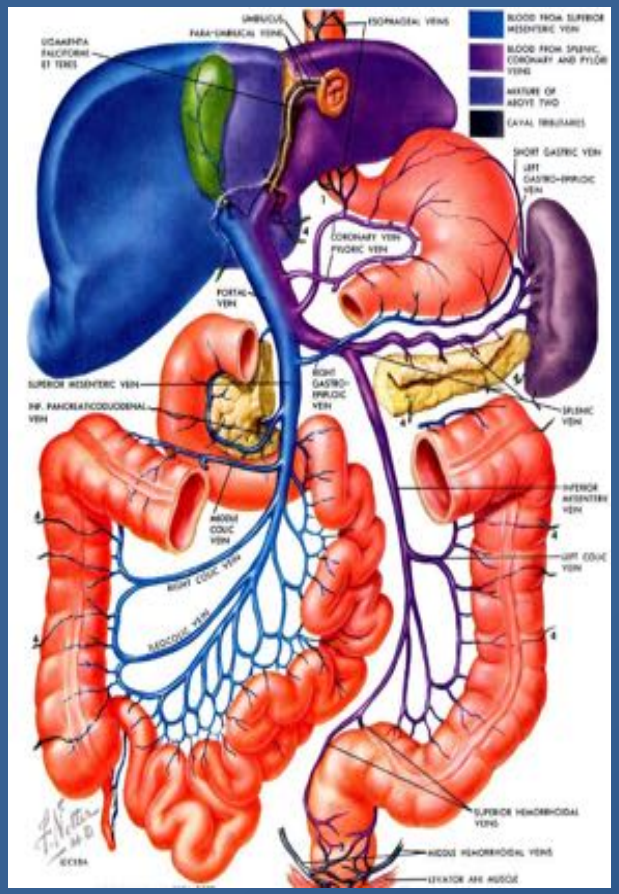
# How to estimate bleeding risk?

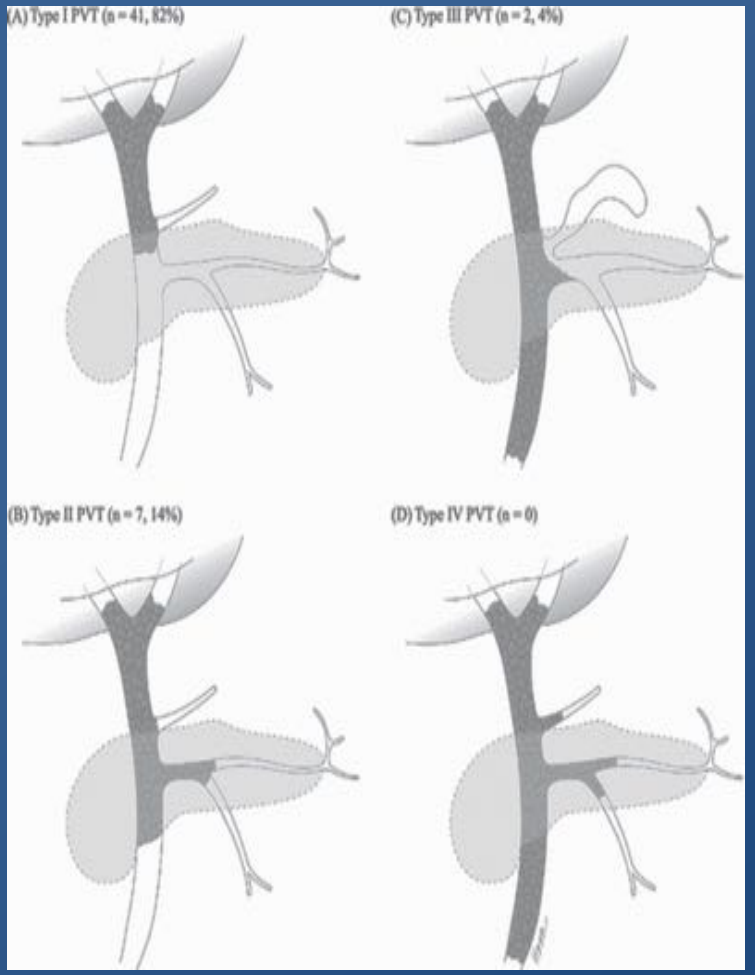
| Low risk procedure | High risk procedure |
|---|---|
| Assess bleeding history, explore more in depth if bleeding history is severe | Address comorbidities especially infection and renal failure if possible |
| No specific laboratory parameter checks recommended | Check fibrinogen level, platelet count, consider TEG/ROTEM, hepatology/hematology consultation |
| | Fibrinogen > 100-150 mg/dL with cyroprecipitate if needed by TEG/ROTEM |
| | PLT > 50,000 /mcL with platelet transfusion or thrombopoietin receptor agonist if needed by TEG/ROTEM |

Northup PG, Friedman LS, Kamath PS. AGA Clinical Practice Update: Surgical Risk Assessment and Perioperative Management in Cirrhosis. *Clin Gastroenterol Hepatol* 2018 [In Press]

# Portal Vein Thrombosis

# Classification of portal vein thrombosis



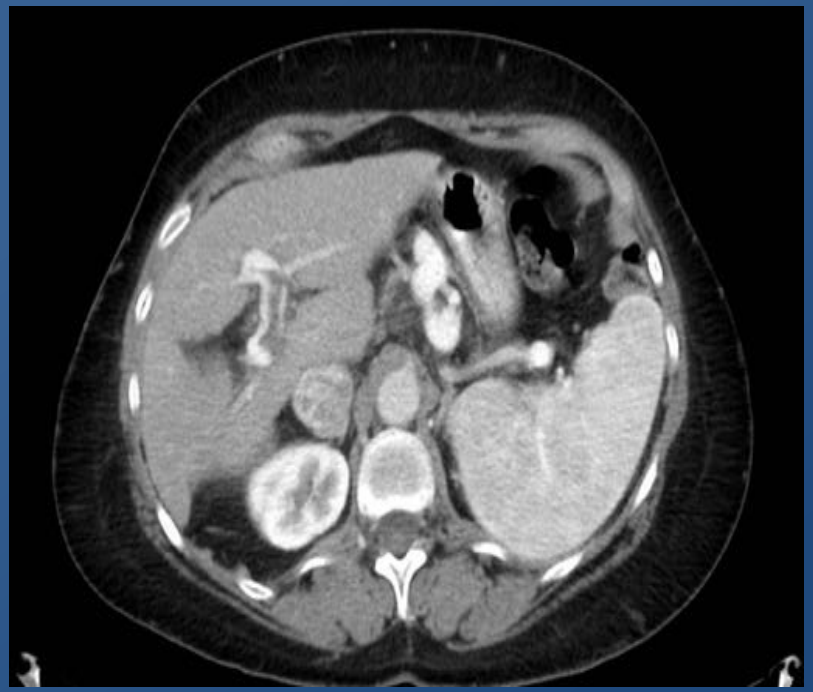



Kim, et al, *Clin Transplant* 2011:25: 111-18

# Incidence and diagnosis of PVT in cirrhosis

Incidence

- 1,243 patient screening cohort (ultrasound)
- 5-year cumulative incidence was 10.7%
- Many were partial and regression or resolution was common (~70%)

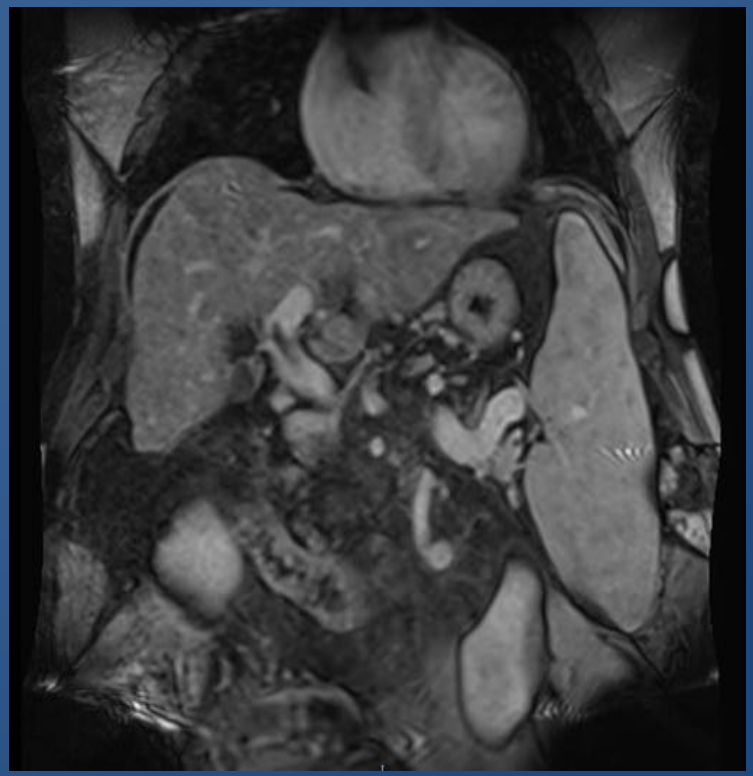


Nery et al., *Hepatology* 2015; 61: 660-667

# Presentation of subacute PVT in cirrhosis

Frequently marked by acute worsening of portal HTN

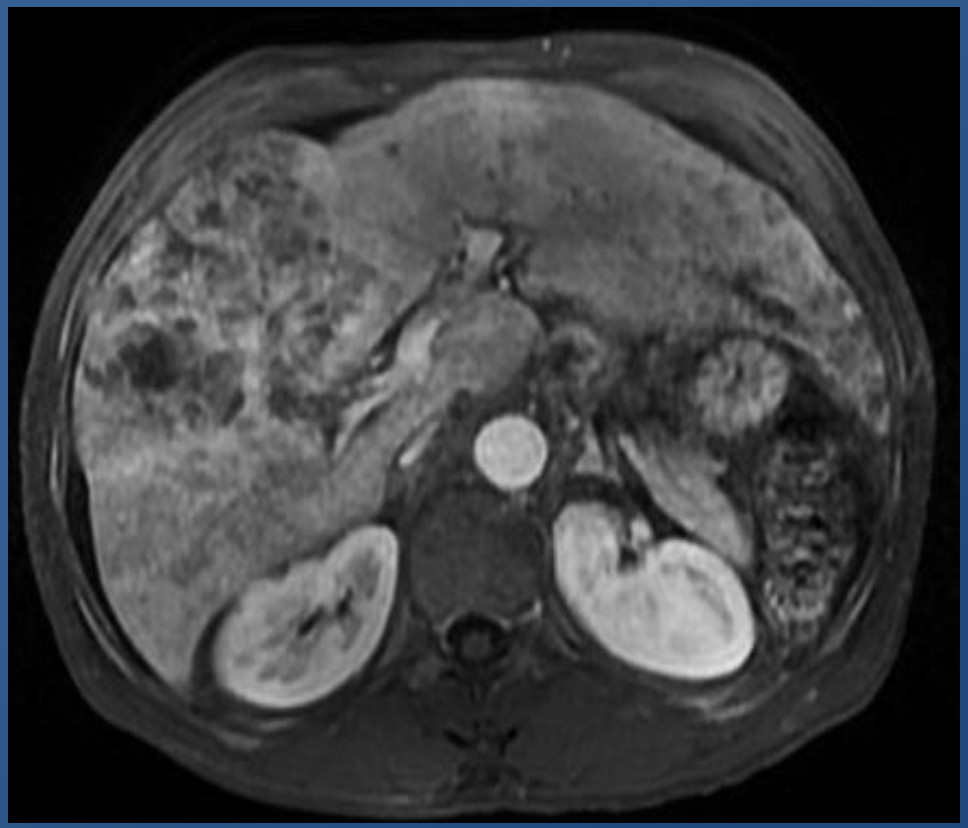
- 62% asymptomatic (26/42)
- 38% symptomatic:
  - 24% portal hypertensive bleeding
  - 14% worsening of ascites



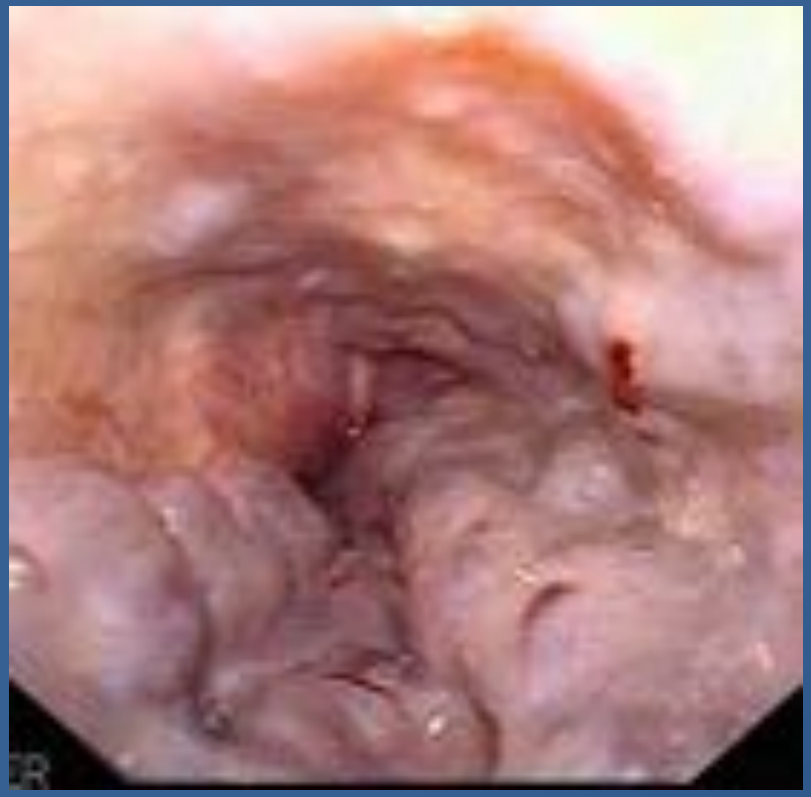
**Maruyama, et al. *AJG* 2013;108:568-574**

# Beware of hepatocellular carcinoma

- HCC spreads by macrovascular involvement
- Typically into the PV
- Enhancing thrombus will not improve with anticoagulation



# Once PVT is diagnosed…



- Perform serial EVBL until no appreciable varices are seen (q 2 weeks)
- NSBB are controversial but indicated
- No need for hospital admission if asymptomatic from PVT

# How to Treat: Anticoagulation, Low Molecular Weight Heparins

| Author | n | Bleeding Complications |
|---|---|---|
| Cui (2015) | 65 | 23.5% (1.5 mg/kg daily enoxaparin)<br>6.4% (1.0 mg/kg BID) |
| Senzolo (2012) | 35 | 8.6% |
| Amitrano (2010) | 28 | 7.1% |
| Francoz (2005) | 19 | 5.2% |

Once varices are controlled, overall bleeding rates appear similar or modestly higher than non-cirrhosis patients. Severe bleeding is rare.

Adapted from Intagliata, et al, *Clinical Liver Disease*; 28 June 2016

# How to Treat: Meta-analysis

| | Complete Recanalization of PVT | | Progression of PVT | | Variceal Bleeding | |
|---|---|---|---|---|---|---|
| | Pooled OR | P | Pooled OR | P | Pooled OR | P |
| **LMWH (vs untreated)** | 8.386 | .011 | 0.062 | <.001 | 0.103 | .041 |
| **Warfarin (vs untreated)** | 2.232 | .226 | 0.338 | .004 | 0.713 | .499 |
| **Warfarin (vs LMWH)** | 0.266 | .147 | 5.446 | .004 | 6.925 | .0924 |

Adapted from Loffredo *Gastroenterology* 2017; 153: 480–7

# Direct-acting oral anticoagulants (DOAC)

| Agent | Dosing | Liver Disease | Renal Disease Dose Adjustment | Reversal Agent |
|---|---|---|---|---|
| Apixaban (Eliquis) | Twice daily | Child A&B | Yes | Andexanet alfa |
| Betrixaban (Bevyxxa) | Once daily | Not Recommended | Yes | None specifically approved |
| Dabigatran (Pradaxa) | Twice daily | Child A&B | Yes | Idarucizumab |
| Edoxaban (Savaysa) | Once daily | Child A only | Yes | None specifically approved |
| Rivaroxaban (Xarelto) | Once daily | Child A only | Yes, contraindicated with CrCl<30 | Andexanet alfa |

# DOACs in cirrhosis patients

39 patients with cirrhosis, 20 on DOAC and 19 on traditional anticoagulation (not all for PVT)

| | Any | Major | Moderate | Mild |
|---|---|---|---|---|
| Traditional group (LMWH and/or warfarin) | 3/19 (16 %) | *Fatal*<br>ICH (1)<br>*Non-fatal*<br>Retroperitoneal (1) | GI bleed (1) | – |
| DOAC group (factor Xa inhibitors) | 4/20 (20 %) | *Non-fatal*<br>ICH (1) | GI bleed (1) | Vaginal bleeding (1)<br>GI bleed (1) |

Major bleeding rates are similar between traditional agents and the DOACs in cirrhosis patients.

Intagliata, et al., *Dig Dis Sci* 2016; 61: 1721-27

# Results of Anticoagulation for PVT

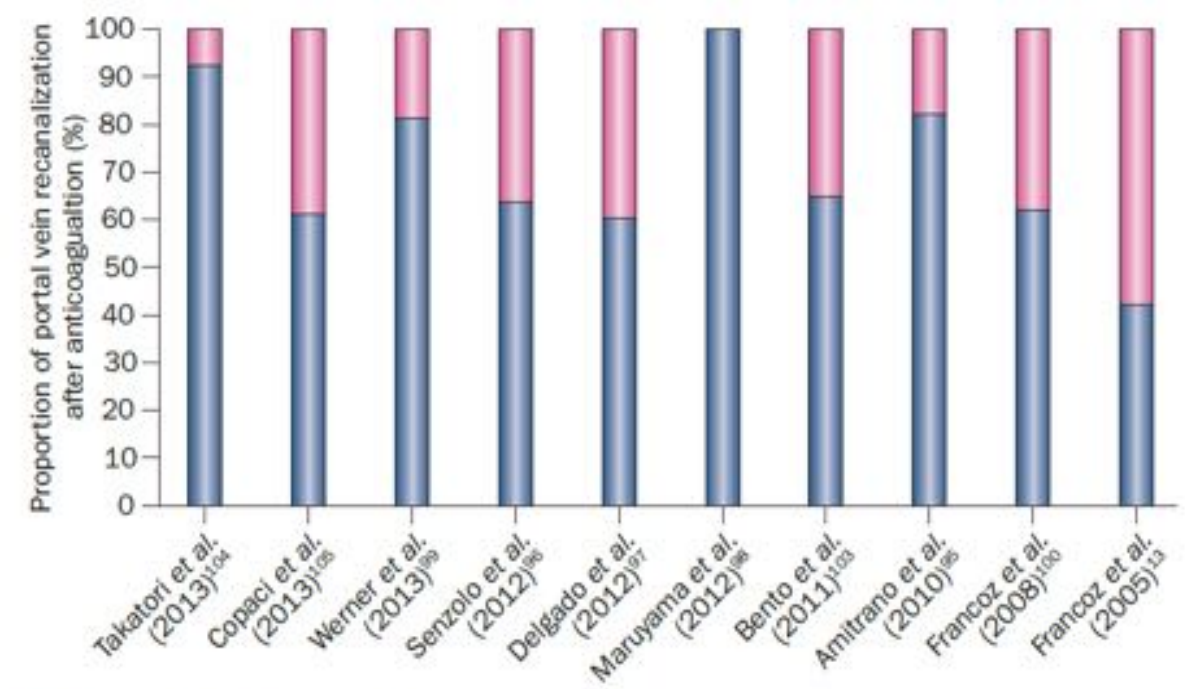



**Figure 2** | Outcome of anticoagulation for the treatment of portal vein thrombosis in patients with cirrhosis.

Qi, et al., *Nat Rev, Gastroenterol and Hep* 2014; 11:435-46

# Summary

- Hemostasis in cirrhosis is not reflected well by INR and other traditional measures of coagulation
- INR should not be used to gauge bleeding risk prior to procedures in cirrhosis patients
- Viscoelastic whole blood assays may be helpful in gauging bleeding risk in cirrhosis patients
- Portal vein thrombosis is a significant risk factor for poor outcome in liver transplantation and may have pathophysiologic effects on the progression of liver disease
- Therapeutic anticoagulation can be safely managed in cirrhosis patients

# Thank you