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Procedimientos invasivos en el paciente con cirrosis y trastornos de la coagulación

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Outline

- Coagulopathy and cirrhosis
- Available tests used to predict bleeding
- Procedures and risk of bleeding
- Prophylatic measures

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

The Coagulopathy of Chronic Liver Disease

Armando Tripodi, Ph.D., and Pier Mannuccio Mannucci, M.D.

Change in paradigm

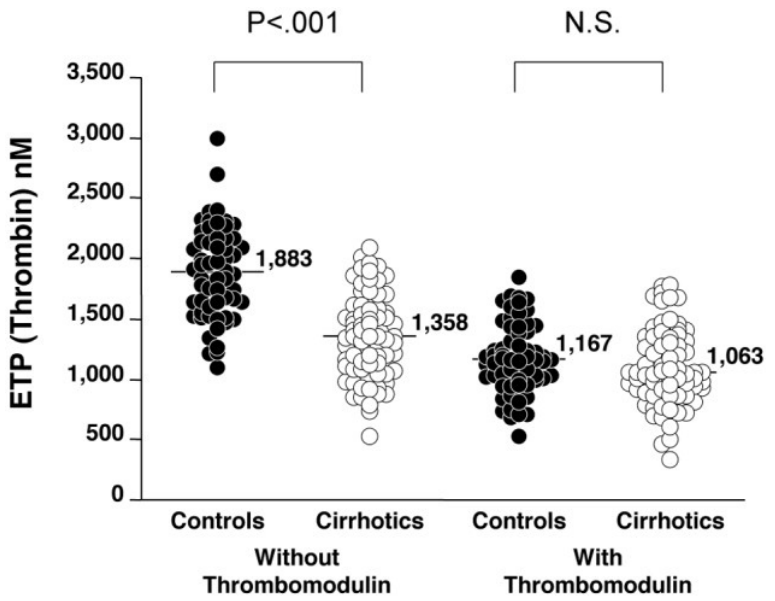
From cirrhosis being associated with a “coagulopathy” to cirrhosis being a prothrombotic disorder.

Re-balanced state

N Engl J Med. 2011 Jul 14;365(2):147-56

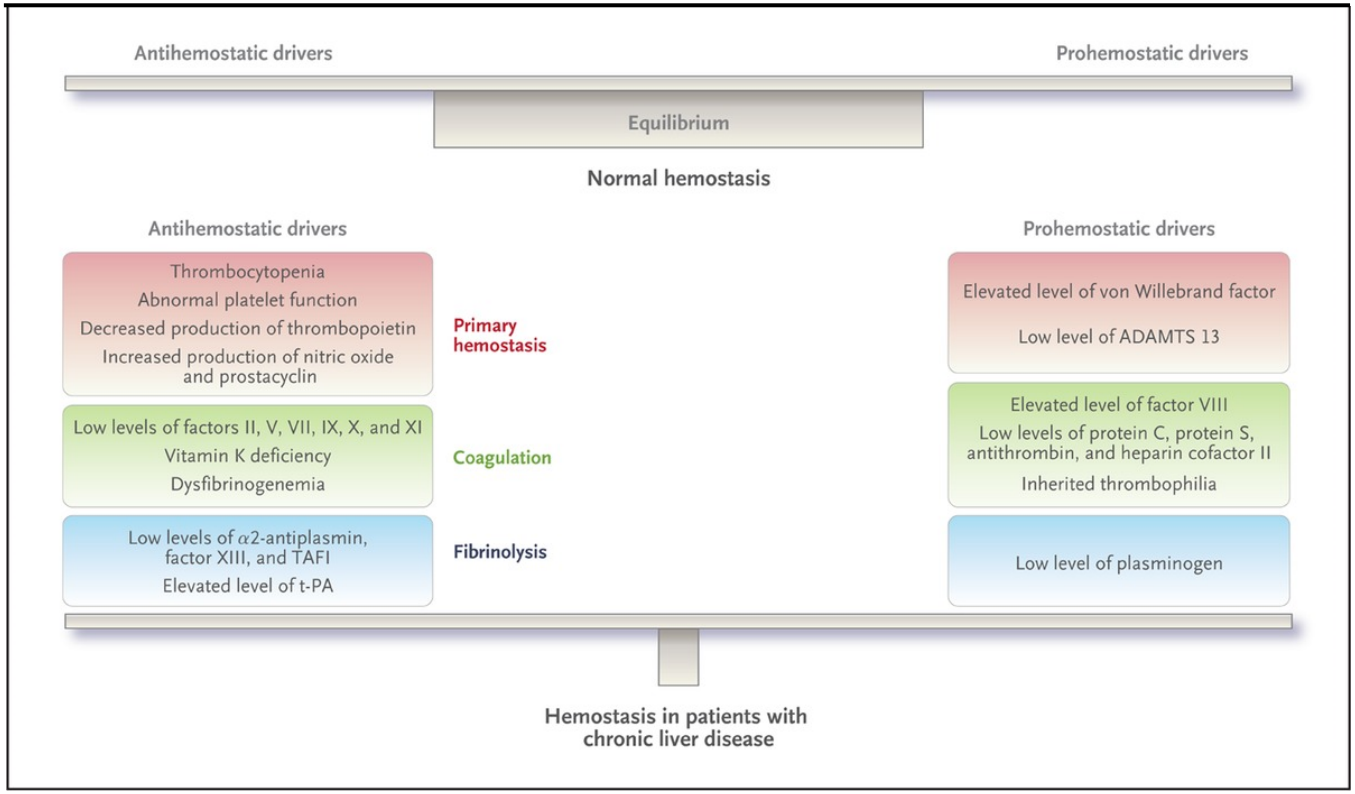
Thrombin and cirrhosis

- Plasma from patients with cirrhosis generates as much thrombin as plasma from controls.
- Thrombin generation in vivo and in vitro is down-regulated by thrombomodulin.
- Reagents that are used to measure the prothrombin time do not contain thrombomodulin
- Platelet count > 50,000 is needed to preserve thrombin generation



Tripodi, Hepatology, 2005

Features of Coagulation in Liver Disease Resulting in a "Rebalancing" of Hemostasis



N Engl J Med. 2011 Jul 14;365(2):147-56

CURRENT TESTS USED TO PREDICT BLEEDING

All have significant limitations & lack adequate prospective data as pre-procedure risk measures.

None account for variables such as volume status, infection, endothelial dysfunction, or renal function

N Engl J Med. 2011 Jul 14;365(2):147-56
O'Leary. Gastroenterology 2019

STANDARD COAGULATION TESTS

Table 1. Summary of Survey (n = 95)

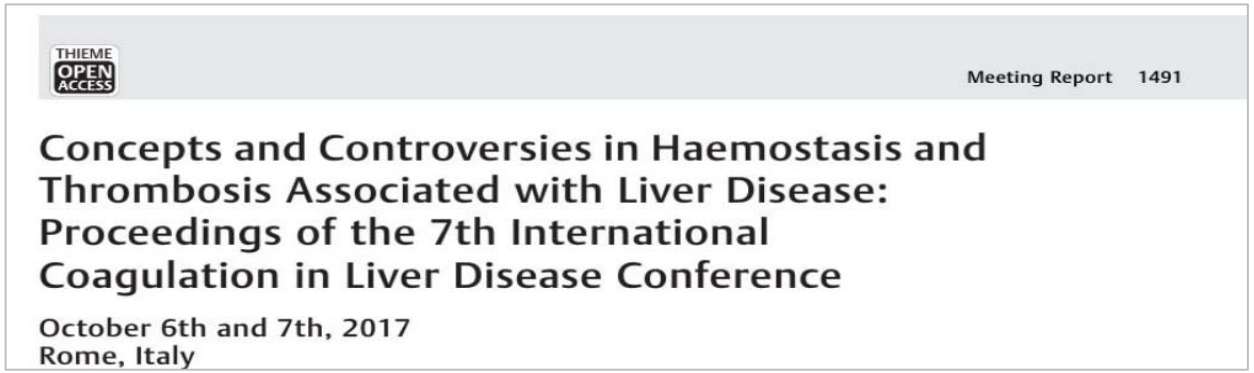
Respondents (%)	Primary role (%)	INR Predicts Postprocedure Bleeding	Threshold Platelets for Liver Biopsy	Threshold Platelets for ICP Monitor
GI-Hepatology (59)	Clinical MD (82)	Strongly agree (0)	<25,000 (4)	<25,000 (20)
Hematology (11)	Research (3)	Agree (21)	<30,000 (81)	<30,000 (46)
Blood Bank (14)	Non-MD HCP (13)	Don't know (8)	<50,000 (14)	<50,000 (34)
Surgery-Anesthesiology (10)	Pharmacology (5)	Disagree (58)	<100,000 (0)	<100,000 (0)
ICU (3)		Disagree strongly (13)		
Radiology (3)				

> 30000-/µl platelets

Caldwell, Hepatology 2006;44:1039-1046

Bleeding risk

PT/APTT	Designed for monitoring anticoagulation (warfarin) Does not help assess thrombin generation
Platelet count	Risk of spontaneous bleeding at very low levels (< 15,000). Risk of bleeding after procedures < 50,000 ?
Platelet function test*	Not widely done
Bleeding time	Does not predict the bleeding risk
Fibrinolysis*	Euglobulin lysis time not widely available
Global tests: **-Thrombin generation*** - **Viscoelastic tests:** **Thromboelastometry/graphy**	Great - clinical utility in cirrhosis is unexplored with current use confined mainly to research. Global viscoelastic tests (VETs) provide a more physiologic assessment of coagulation Thresholds have not been fully validated yet



1. INR and bleeding time do not measure bleeding risk in cirrhosis

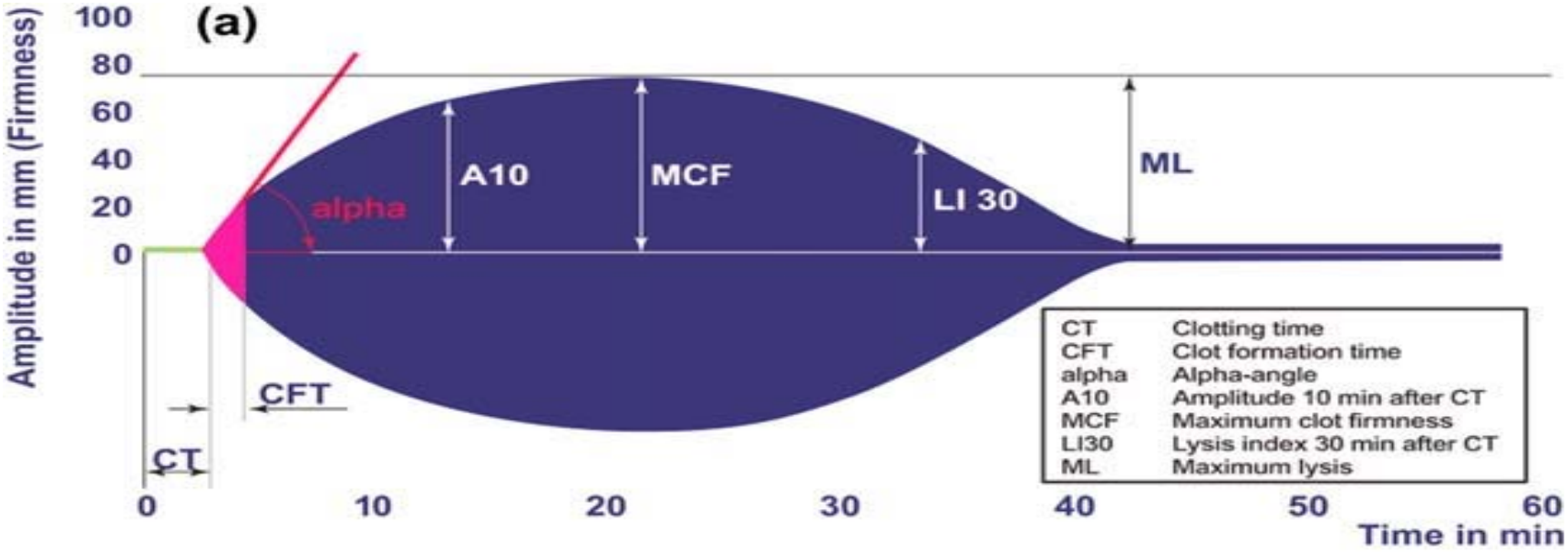
2. Platelet count values <50,000/μL may be associated with higher risk of bleeding

3. VETs are not standardized / do not appear to fully predict bleeding or thrombosis.

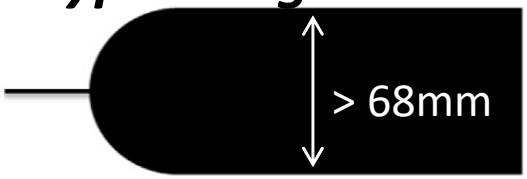
Intagliata et al Thromb Haemost 2018;118:1491

Thromboelastography/metry

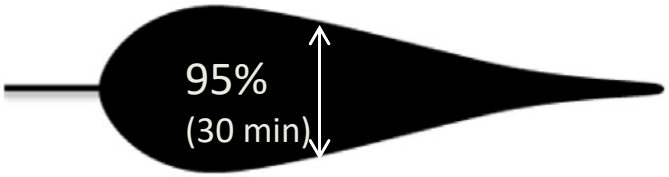
TEG and ROTEM : Point of care tests (bedside)
Measure the evolution of clot structural development and the ability of the clot to perform its basic role in promoting hemostasis.

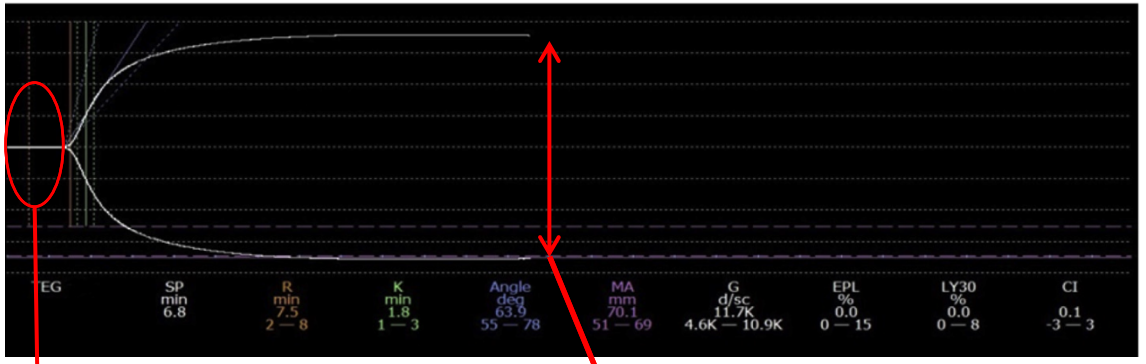


hypercoagulable



fibrinolisis





formation

Start

CT* problem with factors (plasma)

stability

Firmness

MCF* (fibrinogen / platelets)

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

-Invasive procedures (high and low risk)
- 60 patients , INR > 1.8 and/ or platelet count < $50x10^9$/L

TEG →
FFP if R time > 40 minutes
Platelets if MA was < 30 mm

	TEG Group ($n = 30$)	SOC Group ($n = 30$)	*P* Value
Overall blood products requirement (%)	5 (16.7)	30 (100)	<0.0001
Total amount of FFP infused, mL			
Low-risk procedure	4,000	11,050	0.002
High-risk procedure	0	6500	<0.0001
Total amount of PLTs pools infused, U			
Low-risk procedure	22	28	0.046
High-risk procedure	6	78	0.001
FFP only (%)	0	16 (53.3)	<0.0001
Procedure-related bleeding (%)	0	1 (3.3)	0.313

TEG did not predict risk for procedure-related bleeding
FFP does not correct INR or reduce bleeding events

De Pietri, Hepatology 2016;63:566-573

Guidelines	INR	Platelets (x 10 ^{9})	Fibrinogen (g/dL)
AASLD, 2009 *Liver biopsy*	There is no specific PT-INR and/or platelet count cutoff at or above which potentially adverse bleeding can be reliably predicted (Class I, Level C)		
AASLD, 2017 *PHT bleeding*	Correcting INR is not recommended	No recommendations can be given regarding platelet transfusion in patients with variceal bleeding	
AASLD, 2010 TIPS placement	INR > 5 contraindicate TIPS	< 20 contraindicate TIPS procedure	
AASLD, 2013 *Paracentesis*		ntesis should be	
AGA, 2019	by evidence.	or high-risk	For management of active bleeding or high-risk procedures, >1.2
BAVENO VI, 2015	Recomendations for management for coaguloptahy cannot be made based on current evidence		
Society of Interventional Radiology, 2019	Low risk: NA High risk: < 2.5	Low risk: > 20 High risk: > 30	Low risk: >1 High risk: > 1

Too many guidelines!
None are based on data.
Expert opinion

Procedures and the risk of bleeding

Post-procedural bleeding in cirrhotic patients, in relation to platelet counts and INR values.

Post-procedural bleeding in cirrhotic patients, in relation to platelet counts and INR values.

Procedures	Study references	Bleeding following the procedure	Low platelet count ($\leq 50–60 \times 10^9$)[a]	INR > 1.5 no
Paracentesis	[19,88–91]	0.3–3%	No	No
Thoracentesis	[92,93]	2%	Unknown	Unknown
Percutaneous liver biopsy	[13,94–97]	0.5%	Yes	Likely
Transjugular liver biopsy	[98–100]	<1%	Unknown	Unknown
Dentistry	[101,102]	2.9%	No	No
Endoscopic variceal ligation	[103,104]	3–7.3%	No	No
Endoscopic polypectomy	[105,106]	3–12.4%	No	No
Percutaneous ablation HCC	[107,110]	1%	Unknown	Unknown
OLT	[28,111–114]		No	No
Liver surgery	[115]	3.9–6.6%	No	No
Cholecystectomy	[116,117]	3.9–6.6%	No	No
Hernioplasty	[118,119]	2.3–10.8%	Unknown	Unknown

[a] Definition of the low threshold value varied among studies but is usually taken as $\leq 50 \times 10^9$.

Digestive and Liver Disease 48 (2016) 455–467

PROCEDURAL RISK

Low-Moderate (<3-5%)	**High (≥5%)**
Polypectomy < 1 cm	Mucosectomy /Polypectomy ≥1 cm
Central line placement	Therapeutic thoracentesis
Cardiac catheterization	Enteral or biliary dilatation
Hepatic catheterization	Lumbar puncture
Paracentesis	Biliary sphincterotomy
Transjugular liver biopsy	Radiofrequency of HCC
Dental extraction	Percutaneous liver biopsy
Enteral/biliary stenting	Percutaneous HCC therapy
Pacemaker/defibrilator	Transarterial HCC therapies
Esophageal band ligation	Percutaneous gastrostomy
Diagnostic thoracentesis	Percutaneous biopsy of extrahepatic organ
EUS- fine needle aspiration	All major surgery (cardiac, intra-abdominal, orthopedic)
Skin biopsy	TIPS
Other	Other

Modified from : Intagliata et al Thromb Haemost. 2018 Aug;118(8):1491-1506.

Received: 5 May 2020 | First decision: 3 June 2020 | Accepted: 17 August 2020
DOI: 10.1111/apt.16078

APT Alimentary Pharmacology & Therapeutics WILEY

Systematic review with meta-analysis: abnormalities in the international normalised ratio do not correlate with periprocedural bleeding events among patients with cirrhosis

- 29 studies were targeted for analysis, including 13, 276 patients with cirrhosis undergoing indicated procedures (endosocpy, paracentesis, dental extraction, renal biopsy, central line, etc)
- There was no significant association between periprocedural bleeding events and pre-procedural INR [pooled odds ratio 1.52; 95% CI 0.99, 2.33; *P = 0.06*
- INR fails to serve as a significant correlate for periprocedural bleeding events among patients with cirrhosis

Kovalic et al . Aliment Pharmacol Ther. 2020;52:1298–1310.

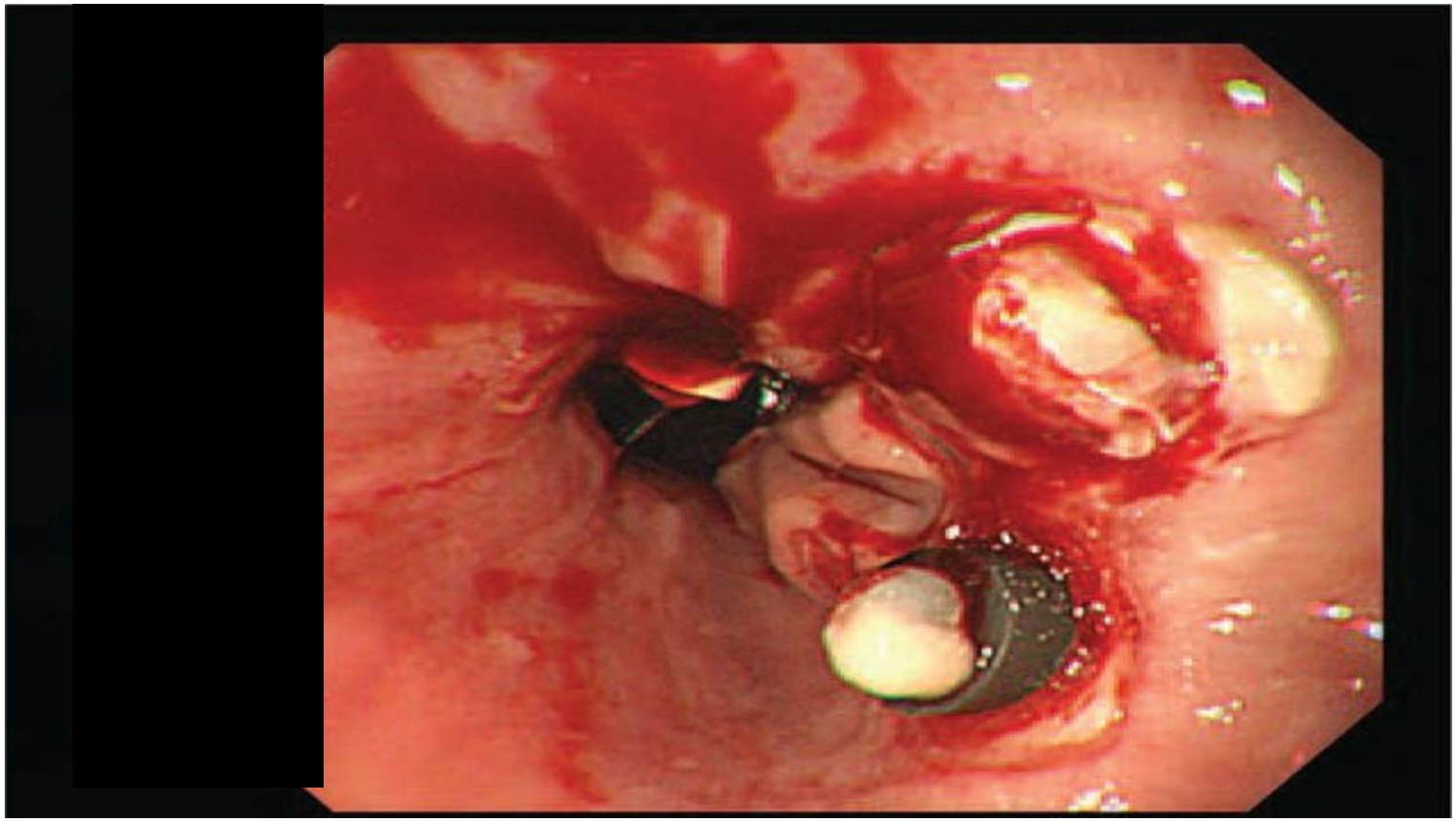
A Prospective Study of Conventional and Expanded Coagulation Indices in Predicting Ulcer Bleeding After Variceal Band Ligation

Table 2. Post-EVL Ulcer Bleeding According to Child–Pugh Status, Platelet Count, Levels of INR and APTT

Parameter	With post-EVL ulcer bleeding (n = 11)	Without post-EVL ulcer bleeding (n = 139)	*P* value
Child–Pugh class			.0174
A/B	5 (45%)	111 (80%)	
C	6 (55%)	28 (20%)	
Platelet count			1.000
$<50 \times 10^3$	1 (8%)	17 (12%)	
$\geq 50 \times 10^3$	10 (91%)	122 (88%)	
INR			
>1.5	3 (27%)	25 (18%)	.4310
≤1.5	8 (73%)	114 (82%)	
APTT			
≥1.2	4 (36%)	24 (17%)	.1248
<1.2	7 (64%)	115 (83%)	

Predictor of bleeding: Child C

Vieira da Rocha ,Clin Gastroenterol Hepatol 2009;7:988-93



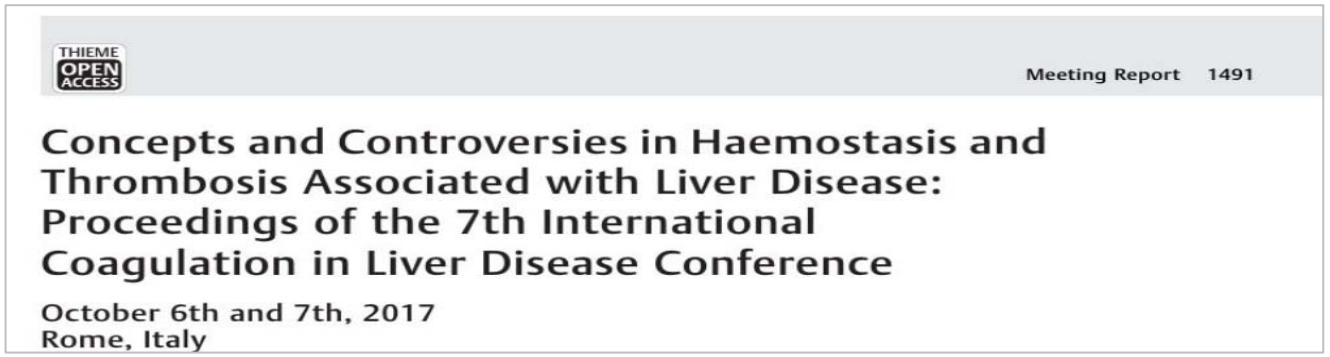
Post-EVL ulcer bleed and predictors

First author (year)	N with EVL	N with bleeding	Time from EVL (days)	Deaths	Clinical predictors of bleeding
Da Rocha (2009)	150	11 (7.4 %)	9.4	-	Child C
Vanbiervliet (2010)	605	21 (3.4%)	13.5	11/21 (52%)	APRI score Prothrombin index*
Xu (2011)	342	26 (7.6)	8.0	7/26 (27%)	Ascites**
Sinclair (2015)	347	21(2.8%)	.	5(28%)	Reflux MELD
Cho (2017)	430	33(7.7%)	8.5+/-5.1	9(28%)	MELD
Blasi /Cardenas (2020)	1472	33(2.2%)	10-14	3(11%)	MELD

**Child score on univariate but not entered in model*

*** endoscopic predictors were number of bands and extent of esophageal varices*

Prophylatic measures



1. Pre-procedure testing of fibrinogen and platelets is recommended for high-risk procedures and pre-procedure correction is recommended for high risk procedures.
2. Routine prophylaxis for low or moderate risk procedures is generally not recommended.
3. Platelet transfusion prior to high-risk procedures or with active bleeding has a rational in vitro basis but lacks high level supportive data. Thrombopoetin agonists may have a role in pre-planned procedural prophylaxis.

Intagliata et al .Thromb Haemost 2018;118:1491

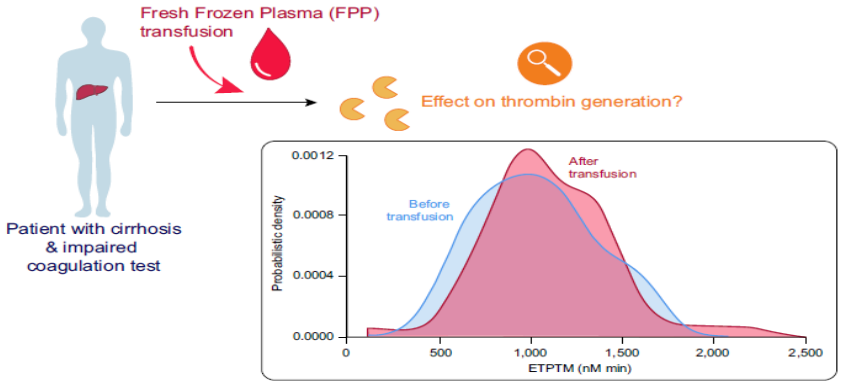
Plasma

- Fresh frozen plasma (FFP) to ‘correct’ a prolonged INR in cirrhosis does not increase thrombin production (factor II) and can exacerbate portal hypertension
- Fresh frozen plasma is not recommended to correct any coagulation factor deficiency

Hepatology 2014;60:1442
O’Leary Gastroenterology 2019

Fresh frozen plasma transfusion in patients with cirrhosis and coagulopathy: Effect on conventional coagulation tests and thrombomodulin-modified thrombin generation

- 53 pts - standard dose FFP to treat bleeding and/or before invasive procedures – if INR > 1.5
- Endpoint: mitigation of endogenous thrombin potential (ETP) with thrombomodulin after therapy
- FFP tx before procedures enhanced amount of thrombin by only 5.7%.
- Responses to FFP transfusion were similar in patients with compensated/decompensated cirrhosis, ACLF, infection or shock



> Enhanced thrombin generation & coagulation tests in a limited number of patients
> Slight decrease of thrombin generation in 34% of cases

Benefit of FFP transfusion in cirrhosis was too modest to justify its indiscriminate use

Rassi et al. Journal of Hepatology 2020 vol. 72 j 85–94

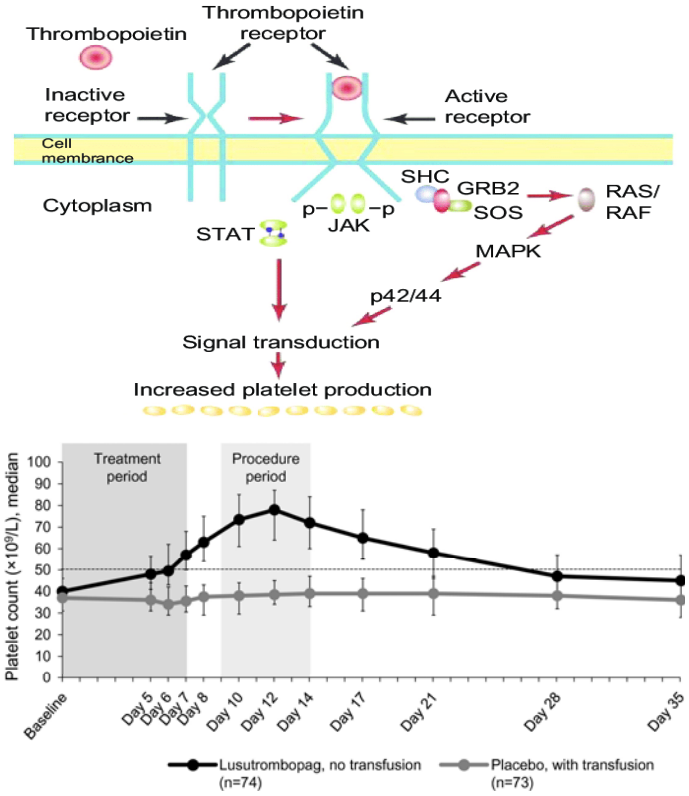
Platelets

- Should be > 50,000 with active bleeding
  - *no data from randomized studies*
- Prophylaxis used for < 50,000
  - *no data from randomized studies*
- Rise in platelets occurs within first hour and decreases over 72 hr.
- 1 pool of platelets can be expected to increase the platelet count by 5-10,000.
- Total volume infused is ~250-500 mL of platelet-rich plasma
- Risk of adverse reactions

O'Leary Gastroenterology 2019

TPO agonists

- Small molecule TPO-R agonists bind to the TPO receptors that activate the downstream signalling cascade to stimulate platelet production
- *Eltrombopag*
- *Avatrombopag*
- *Lusotrombopag*



Peck-Radosavljevic M. Hepatology. 2019 Oct;70(4):1336-1348
Terrault N.Gastroenterology. 2018 Sep;155(3):705-718.

PROCEDURAL RISK & TRANSFUSION

LOW RISK PROCEDURE

- INR – not relevant
- Fibrinogen ≤1
- Platelets ≤ 30.000

- TRANSFUSE
  - Fibrinogen 50mg/kg
  - Platelets or TPO agonist

HIGH RISK PROCEDURE

- INR – not relevant
- Fibrinogen < 1.2
- Platelets ≤ 50.000

- TRANSFUSE
  - Fibrinogen 50 mg /kg
  - Platelets or TPO agonist

Modified from : O'Leary Gastroenterology 2019

ACTIVE BLEEDING AND CIRRHOSIS

ALL PATIENTS

- INR – not relevant
- Fibrinogen ≤ 1.2
- Platelets ≤ 50.000

TRANSFUSE

Fibrinogen (50mg/kg)
Platelets (1 pool)

Modified from : O'Leary Gastroenterology 2019

CONCLUSION

1. There are no reliable tests that predict risk of bleeding
2. Viscoelastic tests may reduce the blood product transfusion, but do not predict bleeding and thresholds need to be validated
3. FFP can be deleterous (increased portal pressure)
4. Do not routinely correct thrombocytopenia and coagulopathy before low-risk procedures
5. Active bleeding or high-risk procedures: consider platelet and fibrinogen.
6. Thrombopoietin agonists are promising

Thank you

- Unidad de Hepatología
- Unidad de Hemodinámica Hepática
- Unidad de Cuidado Intensivo
- Unidad de Trasplante Hepático
- Unidad de Endoscopia Digestiva
- Dra A Blasi (Anestesia)
- Dr. JC Reverter (Hematologia)

A Randomized Control Trial of Thromboelastography-Guided Transfusion in Cirrhosis for High-Risk Invasive Liver-Related Procedures

58 patients with coagulopathy
invasive procedures: percutaneous liver biopsy (n=48), TIPS (n=2), TACE (n=2), percutaneous injection (n=2)

Parameter	TEG group ($n=29$)	SOC group ($n=29$)	P value
FFP or platelets infused, n (%)	8 (27.6%)	28 (96.6%)	<0.001
FFP transfused, n (%)	7 (24.1%)	8 (27.6%)	0.764
Platelets infused, n (%)	3 (10.3%)	22 (75.9%)	<0.001
FFP only, n (%)	6 (20.7%)	7 (24.1%)	0.753
Platelets only, n (%)	2 (6.9%)	21 (72.4%)	<0.001
FFP and platelets, n (%)	1 (3.4%)	1 (3.4%)	>0.999
Procedure-related bleeding complications	0	0	

All values are presented as n (%)

TEG thromboelastography, *SOC* standard of care, *FFP* fresh frozen plasma

TEG did not predict risk for procedure-related bleeding

Vuyyuru et al .Dig Dis Sci. 2019 Nov 13. doi: 10.1007/s10620-019-05939-2.

Conclusions

✓Consensus guidelines to monitor coagulation and guiding transfusion are an unmet need in this population.

✓A platelet count target > 30-50,000 is still advised

✓No clear reccomendations in regards to INR

✓There is no clear role for FFP administration

✓Viscoelastic tests seems to reduce the blood products transfusion, but suitable thresholds need to be validated.

✓Platelet stimulators may be useful in patients with cirrhosis undergoing invasive procedures

Low platelets & Eltrombopag

Thrombopoietin agonist ▲**platelets**

-Invasive procedures:

N= 288: Placebo vs ETPG 15 days prior

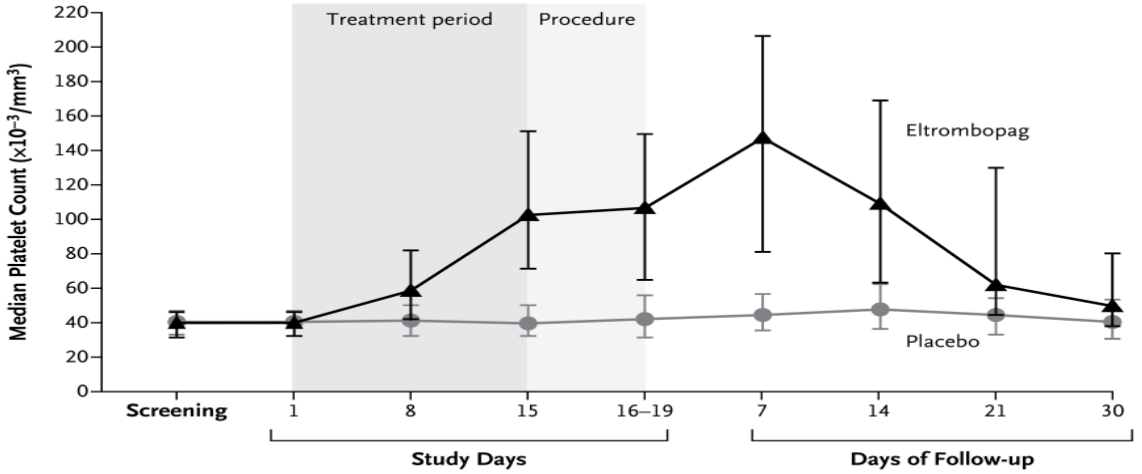
Endpoint: plts pre-procedure

72% (PCB) vs 19% (ETPG)

PVT & other thrombosis:

7 ETPG (4%) - Plaq > 200x10^9/L

2 PCB (1%)

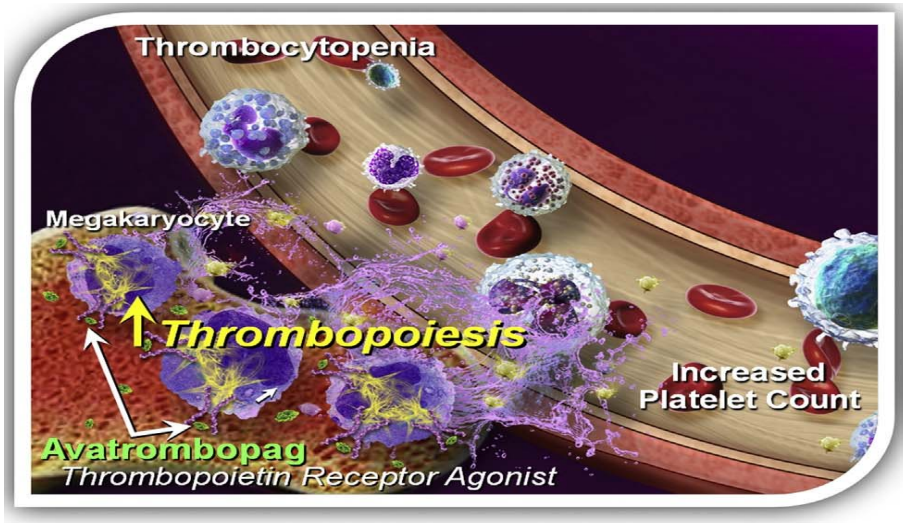


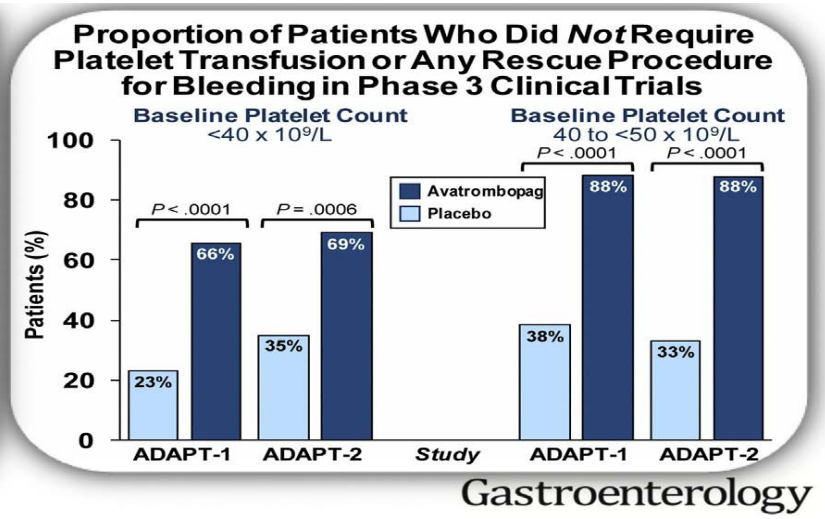
No. with Available Data									
Placebo	147	145	139	132	50	128	116	120	125
Eltrombopag	144	141	134	131	49	125	125	117	127

Afdhal et al, *NEJM* 14

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] and Tarek Hassanein[8]

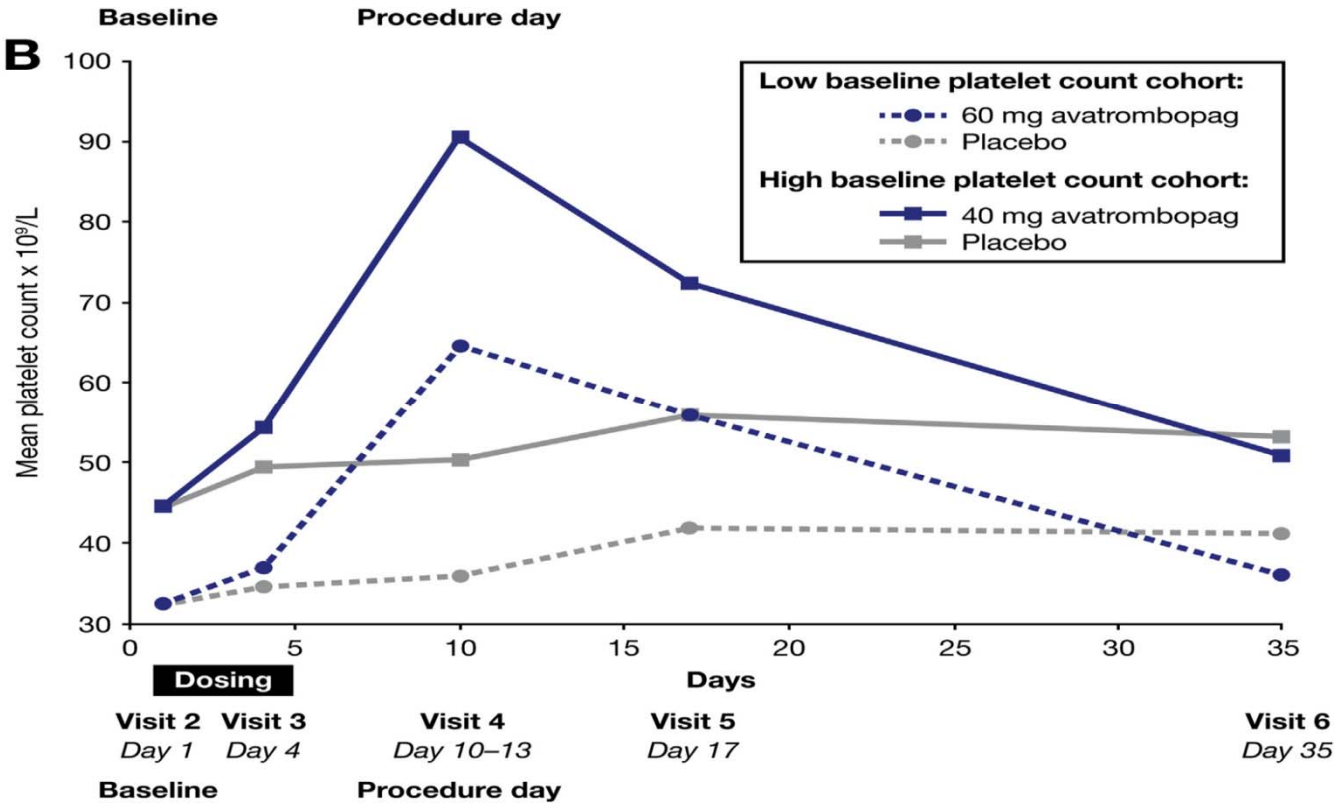




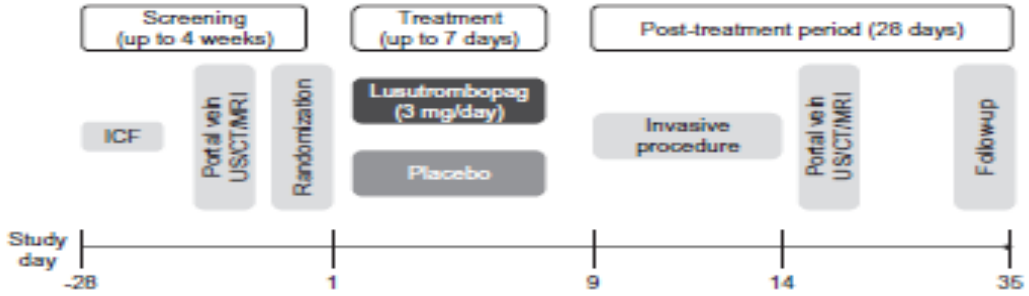
Gastroenterology

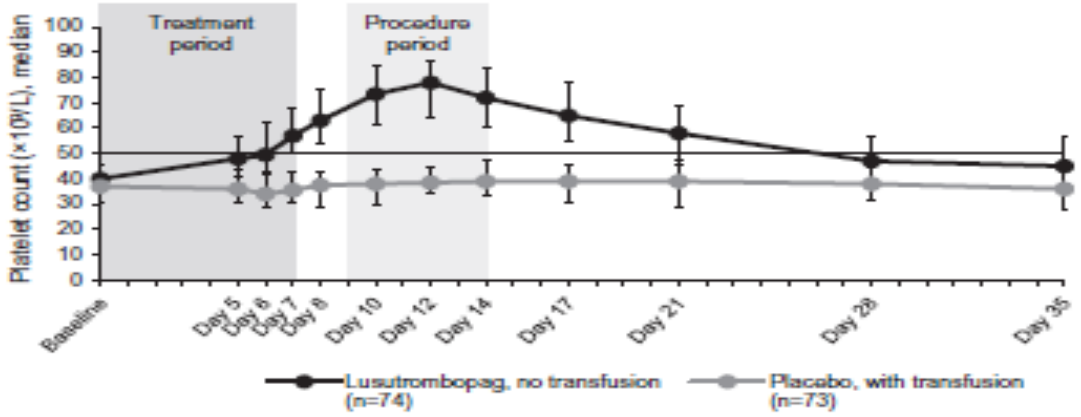
Gastroenterology 2018

Low platelets & Avatrombopag



Lusutrombopag for the Treatment of Thrombocytopenia in Patients With Chronic Liver Disease Undergoing Invasive Procedures (L-PLUS 2)





Future studies

- Studies that compare the current prophylactic coagulation correction approach with an approach consisting of not administering prophylactic transfusion are needed in order to reduce unnecessary transfusions, morbidity, and costs.

Muchas gracias

- Unidad de Hemodinámica Hepática
- Unidad de Cuidado Intensivo – Instituto de Enfermedades Digestivas
- Unidad de Hepatología
- Unidad de Trasplante Hepático
- Unidad de Endoscopia Digestiva

THE LACK OF BENEFIT OF PROPHYLACTIC TRANSFUSIONS IN PATIENTS WITH CIRRHOSIS AND ESOPHAGEAL VARICES UNDERGOING ENDOSCOPIC VARICEAL LIGATION

- 467 patients underwent 1174 EBL procedures
- The prophylactic transfusion protocol was followed in 15% and 21% of patients that met criteria for an elevated INR and/or low platelets respectively.
- FFP and/or platelets were administered in only 26 patients (5.6%)
- Bleeding was due to post-EBL ulcer in 11 patients (2.8%) and due to varices in 2.

Blasi A. J Hepatol 2019; 70, S1: SAT-023

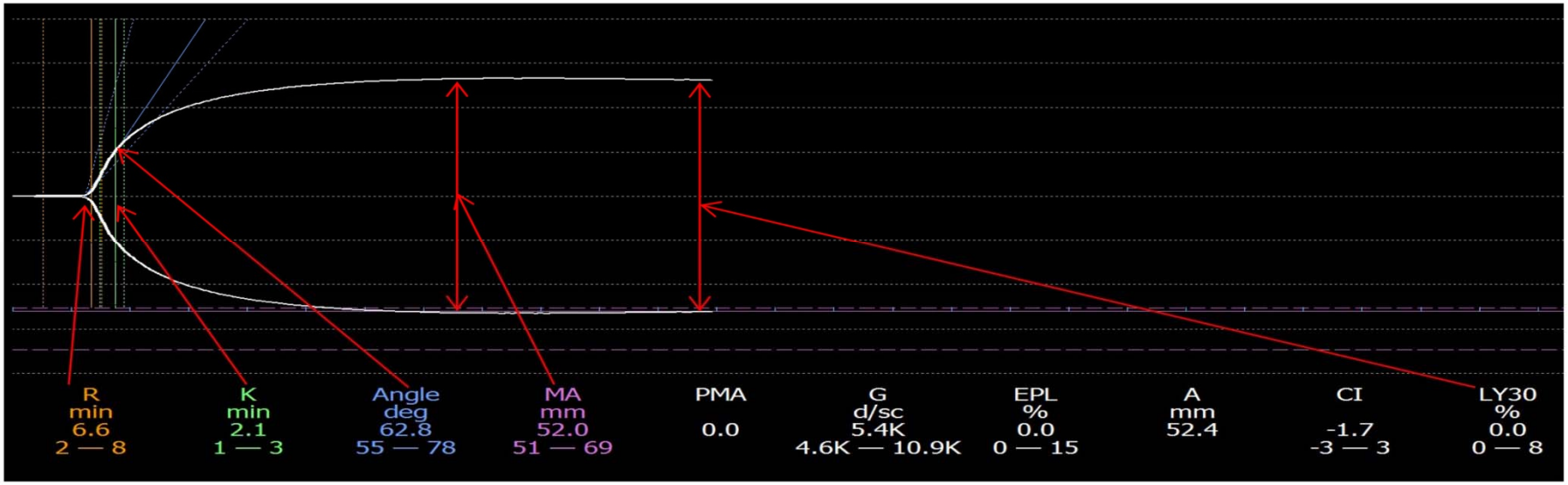
	post-EVL bleeding yes	post-EVL bleeding no	
Number (%)	13(2.8)	453(97)	
Age (years)	63(47-69)	60(51-69)	0.91
Sex (m/f)	10/4	322/131	1.00
Child (num)	7(6-9)	6(6-8)	0.22
Child group (A,B,C,%)	36/57/7	62/31/7	0.11
MELD	13(11-15)	11(8-13)	0.02
Etiology: Virus, OH, others (%)	36/29/36	40/27/33	0.93
Prophylaxis 1 / prophylaxis 2 [a] (n,%)	3/11(21/79)	232/221(51/59)	0.03*
Ratio prothrombin time	1.3(1.3-1.4)	1.3(1.2-1.4)	0.09
Platelet count (x 10^9)	79(58-124)	91(58-122)	0.72
APTT (seconds)	31(29-38)	31(28-34)	0.30
Fibrinogen (g/L)	2 (1.4-3.2)*	2.7(2-3.6)*	0.10
Num banding (first/ repeated)	4/10	150/303	0.40
Prophylactically transfusion (yes,%)			
FFP	1 (7)	12(2.6)	0.33
Platelets	1 (7)	15(3.3)	0.39

Data expressed as median (25-75%) . *n=9, **n=111, * late bleeding

				Bleeding Complications n(%)		*p*
	n		n	Yes (11)	No (297)	
Ratio PT>1.5	82	FFP transfusion	13(15)	**1**(9%)	11(3.7%)	0.14
		no FFP transfusion	70(85)	0	70(24%)	
Platelet <50x10^9/L	72	platelet transfusion	16(21)	0	15(5%)	1
		no platelet transfusion	57(79)	**2**(18%)	55(19%)	

In those that bled, 3 met criteria for transfusion; 1 received FFP and 2 with low platelets did not receive transfusion; the remaining 10 patients did not meet criteria for transfusion.

Blasi A. J Hepatol 2019; 70, S1: SAT-023



R time: latency from the time the blood is placed in the reaction vessel until initial clot formation- factor deficiency- > plasma

Alpha angle; kinetics of fibrin cross-linking or speed of clot strengthening

MA is a direct function of the properties of fibrin and platelet bonding- platelets

LY30: Measure of rate of clot breakdown 30 minutes after MA

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Position Paper

Hemostatic balance in patients with liver cirrhosis: Report of a consensus conference

Under the auspices of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI)

- *In patients with cirrhosis, procedure-related bleeding is uncommon, and standard coagulation tests are not good predictors of post-procedure bleeding. Although formal trials are lacking, thrombocytopenia (i.e., platelet count <50–60 × 10^9/L) may be predictive of bleeding.*

- *Current evidence does not support the use of PT values as predictors of bleeding or to monitor the effectiveness of hemostasis-modifying therapy in patients with cirrhosis*

Digestive and Liver Disease 48 (2016) 455–467

Features of Coagulation in Liver Disease Resulting in a "Rebalancing" of Hemostasis

Hemostasis Stage	Hemostatic Forces Favoring Thrombosis	Hemostatic Forces Favoring Bleeding
Primary hemostasis: platelet interaction with vessel walls	• Low levels of ADAMTS 13 • Increased levels of von Willebrand factor	• Thrombocytopenia
Secondary hemostasis: fibrin clot formation	• Elevated levels of factor VIII • Decreased levels of proteins C and S, antithrombin, and heparin cofactor II	• Low levels of factors II, V, VII, IX, X, and XI • Low levels of fibrinogen • Vitamin K deficiency (malabsorption in cholestatic disorders)
Fibrinolysis	• Low plasminogen levels	• Low levels of factor XIII and thrombin-activated fibrinolysis inhibitor • Elevated levels of tissue plasminogen activator

Olson, Clin Liv Dis (Hoboken) 2019

Introduction

- Patients with advanced liver disease can have abnormal:
  - prothrombin time / INR and platelet count
- They provoke “fear” of risk of bleeding during or after procedures without a basis in evidence to justify such fear.
- This leads to requests from procedural-based specialists for “correction” of coagulation test abnormalities.