
INAUGURAL
LIVER
CONNECT
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Chronic Liver Disease Foundation

INAUGURAL LIVER CONNECT

Thrombocytopenia in CLD

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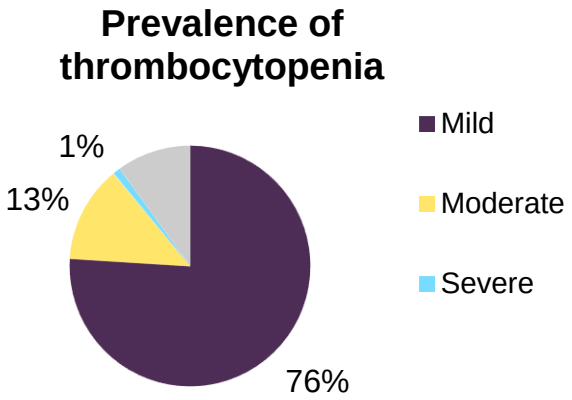
Epidemiology

- Thrombocytopenia is the most common hematological abnormality in patients with ESLD

Definition	Platelet count
Thrombocytopenia	<150,000/μL
Mild	100−150,000/μL
Moderate	50−100,000/μL
Severe	<50,000/μL



Afdhal NH. *J Hepatol.* 2008.

Pathophysiology

- Thrombocytopenia in CLD: multifactorial

Splenic sequestration

↓ production of thrombopoietin

Bone marrow suppression

Platelet destruction

Mitchell O. *Hepat Med.* 2016; Miller JB. *Gastroenterology & Hepatology.* 2017.

Risk of Bleeding With Procedures

Liver biopsy

AASLD 2009 guideline: platelets <56-60,000/mm3

HALT-C study of maintenance peginterferon-α in HCV

2740 liver biopsies

16 bleeding events

Hemoperitoneum (8)

Subcapsular hematoma (4)

Hemobilia (3)

Hemothorax (1)

Platelet count ($x10^3/mm^3$)	Total	Bleeding complication	
		No.	%
> 150	1331	3	0.2
101-150	738	5	0.7
61-100	509	3	0.6
≤ 60	76	4	5.3
Total	2654	15	0.6

Rockey DC. *Hepatology.* 2009; Seeff LB. *Clin Gastroenterol Hepatol.* 2010.

Risk of Bleeding With Invasive Procedures

Patients: 121 consecutive patients undergoing liver transplant evaluation

Thrombocytopenia definitions

Moderate: <150,000/µL

Severe: <75,000/µL.

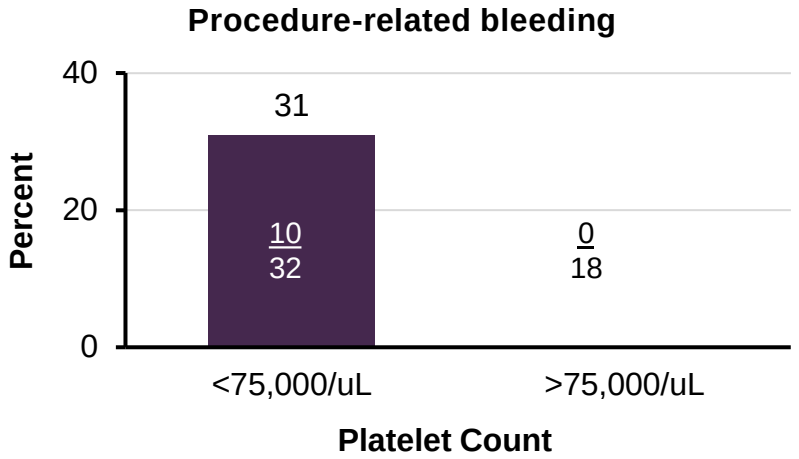
Results

Thrombocytopenia present in 102/121 (84.3%)

Invasive procedures in 50

32 with severe thrombocytopenia

18 with moderate thrombocytopenia



Procedures with bleeding complication: polypectomy (2), dental extraction (4), transcatheterarterial chemoembolization (1), radiofrequency thermal ablation (1), gastric biopsies (1), large volume paracentesis (1)

Giannini EG. *Clin Gastroenterol Hepatol.* 2010.

Risk of Bleeding With Procedures

Approach to reducing the bleeding risk with procedures in patients with chronic liver disease and thrombocytopenia

Gastroenterology 2019;157:34–43

AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

AGA Clinical Practice Update: Coagulation in Cirrhosis

Jacqueline G. O'Leary,[1] Charles S. Greenberg,[2] Heather M. Patton,[3] and Stephen H. Caldwell[4]

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O'Leary JG. *Gastroenterology.* 2019.

Bleeding Risk Varies By Type of Procedure

Lower risk procedures	Intermediate risk procedures	Higher risk procedures
Endoscopy Diagnostic EGD or colonoscopy Variceal ligation Uncomplicated polypectomy	Endoscopy PEG Cystgastrostomy Biliary sphincterotomy	Endoscopy Complicated polypectomy EMR or ESD NOTES
Paracentesis	Percutaneous or transjugular liver biopsy	All major surgery (cardiac, abdominal, orthopedic)
Thoracentesis	Percutaneous biopsy of extrahepatic organ	Brain or spinal surgery
Dental extraction	Transjugular intrahepatic portosystemic shunt	Intracranial pressure catheter insertion
Cardiac catheterization	Transarterial or percutaneous HCC therapies	
Central line placement	Lumbar puncture	

Intagliata NM. *Thrombosis and Hemostasis.* 2018.

Assessment Prior to Procedure

AGA Best Practice Advice 1:
Global tests of clot formation, such as rotational thromboelastometry, thromboelastography, sonorheometry, and thrombin generation, may eventually have a role in the evaluation of clotting in patients with cirrhosis, but currently lack validated target levels.

O'Leary JG. *Gastroenterology.* 2019.

Low Risk Procedures

AGA Best Practice Advice 2:
In general, clinicians should not routinely correct thrombocytopenia and coagulopathy before low-risk therapeutic paracentesis, thoracentesis, and routine upper endoscopy for variceal ligation in patients with hepatic synthetic dysfunction–induced coagulation abnormalities.

Caveat: clinician judgment required

O'Leary JG. *Gastroenterology.* 2019.

Platelet Transfusions

Additional limitations include:

Short duration of efficacy

No globally accepted guidelines regarding the platelet dosing or platelet count goals for invasive procedures

Transfusion Thresholds

AGA Best Practice Advice 4:
Transfusion thresholds for management of active bleeding or high-risk procedures to optimize clot formation in advanced liver disease

- Hematocrit ≥ 25%
- Platelet count > 50,000
- Fibrinogen > 120 mg/dL

O'Leary JG. *Gastroenterology.* 2019.

Use of Thrombopoietin Agonists

AGA Best Practice Advice 5:
Thrombopoietin agonists are a good alternative to platelet transfusion, but require time (about 10 days) to elevate platelet levels

O'Leary JG. *Gastroenterology.* 2019.

Desmopressin if Renal Failure?

AGA Best Practice Advice 9:
Desmopressin releases von Willebrand factor as its primary hemostatic mechanism. As this factor is usually elevated in cirrhosis, the agent lacks a sound evidence-based foundation, but may be useful in patients with concomitant renal failure.

"Desmopressin enhances platelet function in uremia but lacks a physiologic basis in patients with isolated liver disease."

Desmopressin dosing
- 0.3 mg/kg IV or subcu
- 3 mg/kg intranasally
- Effect within 1 hour, lasts for 6–8 hours

O'Leary JG. *Gastroenterology.* 2019.

AGA Clinical Practice Update: Coagulation Correction in Patients With Cirrhosis

Key Interventions in Procedural Bleeding Risk Mitigation, Thrombotic Complications in Cirrhosis, and Active Bleeding
Platelets ≥ 50,000 by infusion or with TPO agonist if elective
Fibrinogen ≥ 120 mg/dL
Control infection
Optimize renal function
Hematocrit of > 25% suggested

O'Leary JG. *Gastroenterology.* 2019.

Procedures in Patients With Hypersplenism

Splenectomy:

- **Increases platelet count, with persistent effect, even after antiviral therapy; however, invasive procedure with high risk factors**

Partial splenic artery embolization

- **Decreased post-procedure bleeding rate and lower morbidity rate**
- **Associated complications include pneumonia, peritonitis, splenic abscess, portal vein thrombosis**
- Administer vaccine for pneumococcal, H. Influenzae and meningococcal before splenic embolization or surgery

TPO Agonists

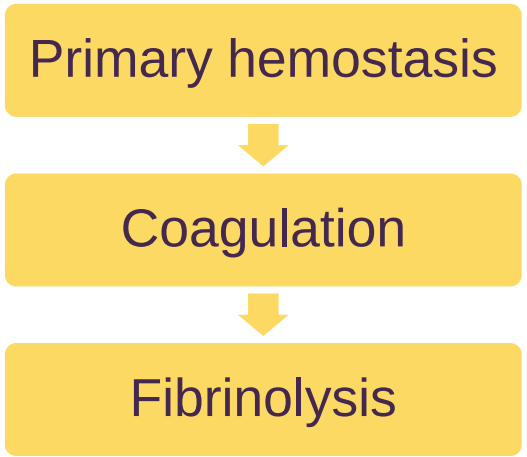
Agent	Route	FDA approval	FDA indication
Romiplostin	Subcu	2008	ITP
Eltrombopag	P.O.	2008	ITP, aplastic anemia Thrombocytopenia to allow HCV therapy
Avatrombopag	P.O.	2018	Thrombocytopenia in CLD before procedure ITP 2019
Lusutrombopag	P.O.	2018	Thrombocytopenia in CLD before procedure

Nplate FDA package insert; Promacta FDA package insert; Doptelet FDA package insert; Mulpleta FDA package insert.

Aren't Patients With Liver Disease Auto-Anticoagulated?

No
Incorrect assumption due to thrombocytopenia

Phases of coagulation



All phases abnormal

- ↑ vWF
- ↓ coagulation factors
- ↓ fibrinogen
- ↓ protein C

Northup PG. *Clin Gastroenterol Hepatol* 2013; Kalambokis GN. *J Hepatol* 2016.

Avatrombopag

TPO agonist, oral

Indication: “treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure”

Dosing:

Begin 10-13 days prior to scheduled procedure

Procedure should occur within 5-8 days of last dose

ITP 2019

Recommended dose and duration		
Platelet count ($x10^9$/L)	**Once daily dose**	**Duration**
< 40	60 mg	5 days
40 – 50	40 mg	5 days

Doptelet FDA package insert.

Avatrombopag

ADAPT-1 and ADAPT-2

Multicenter, global, randomized, double-blind, placebo-controlled, phase 3 studies

Patients:

Adults with CLD, MELD < 24

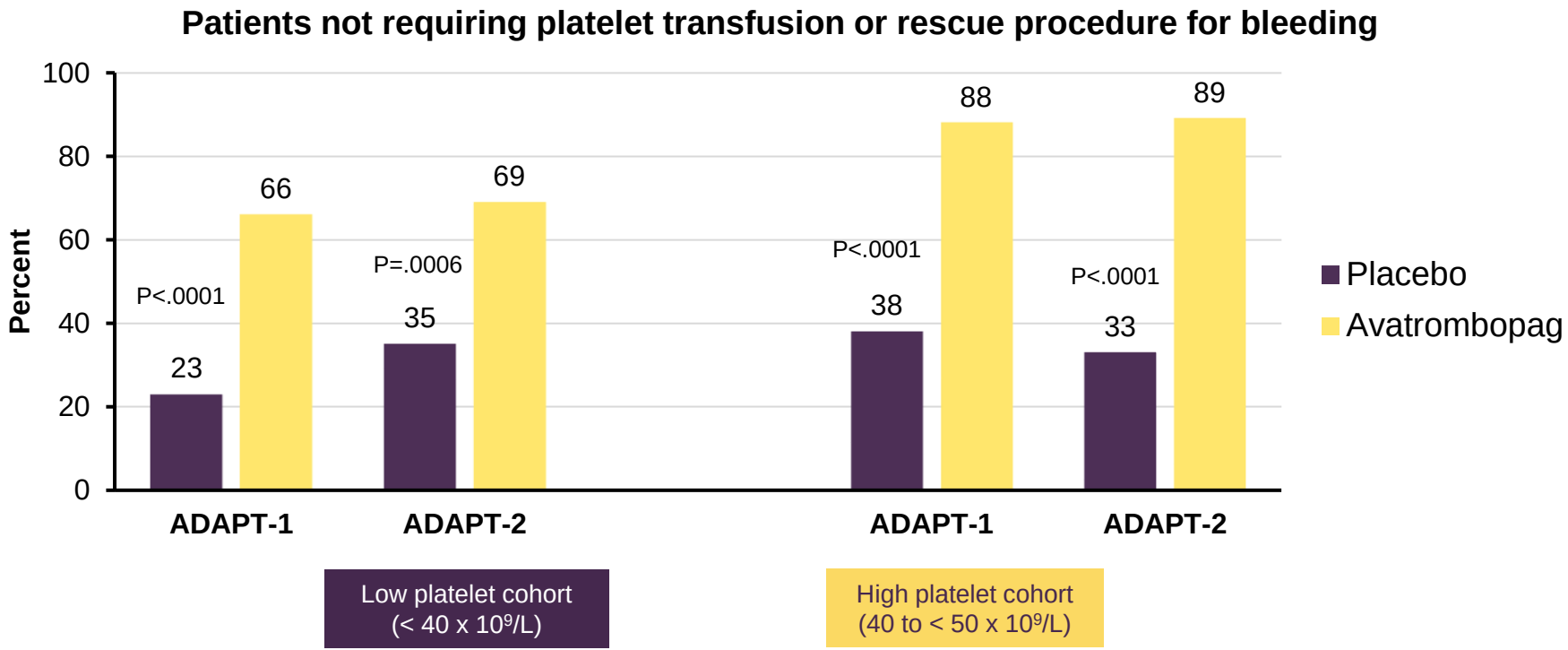
Platelet count < 50 x 10^9/L

Planned procedure with risk of bleeding and need for platelet transfusion

Primary endpoint: proportion of patients who did not require a platelet transfusion or rescue procedure after randomization and up to 7 days after a scheduled procedure

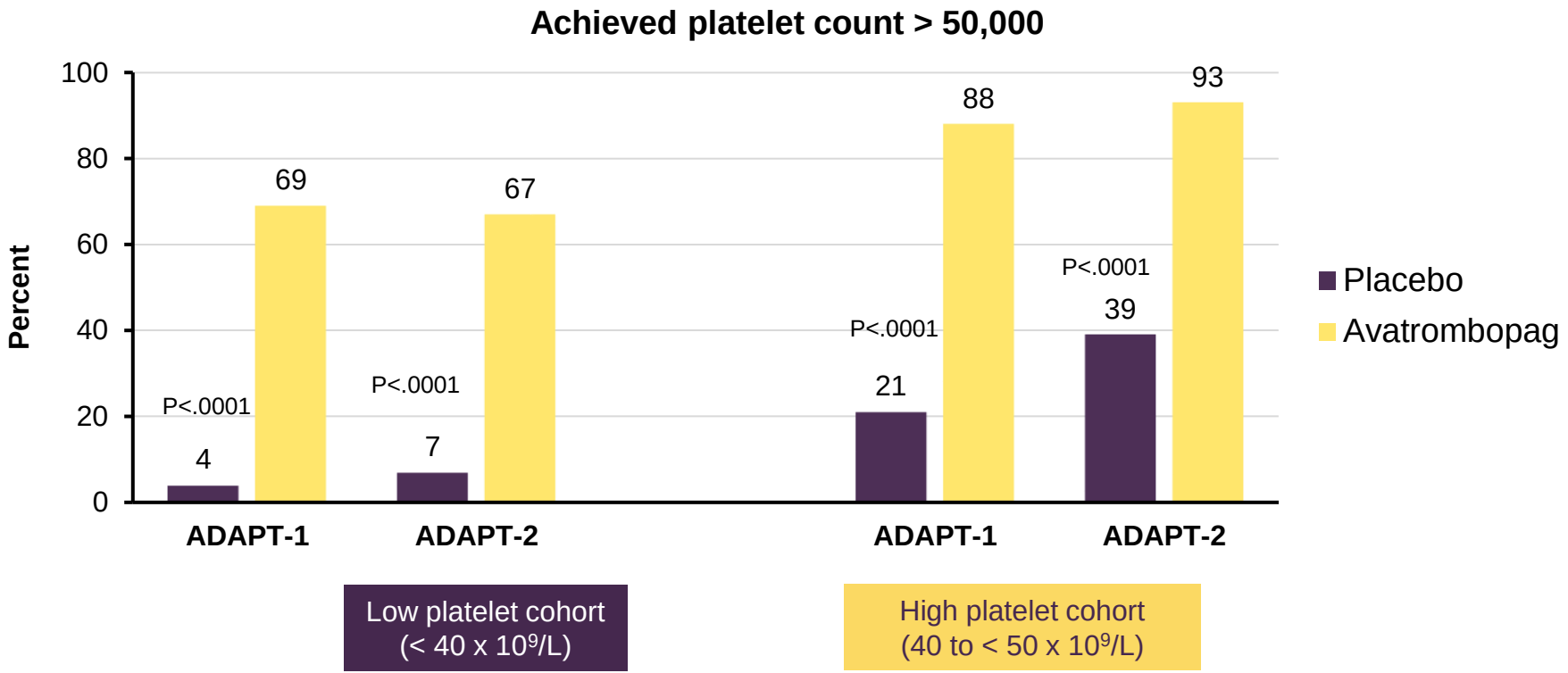
Terrault NA. *Gastroenterology.* 2018.

Avatrombopag



Terrault NA. *Gastroenterology.* 2018.

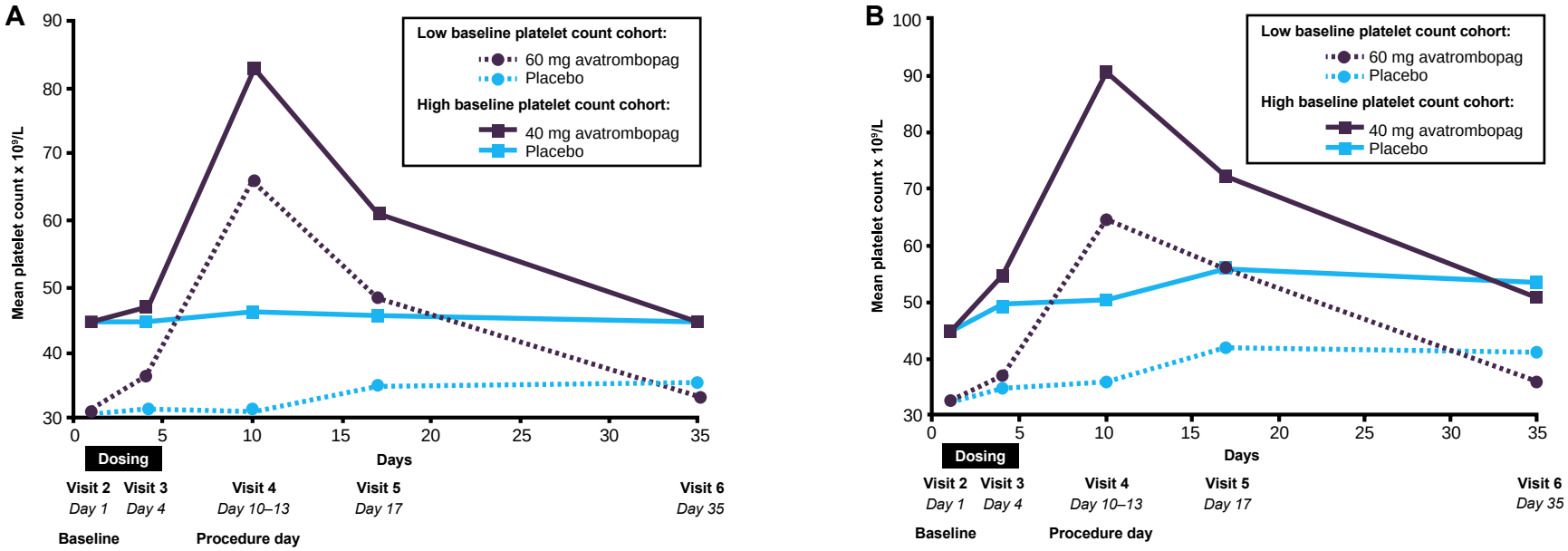
Avatrombopag



Terrault NA. *Gastroenterology.* 2018.

Avatrombopag

Mean platelet count by treatment group and visit day



Terrault NA. *Gastroenterology.* 2018.

Avatrombopag

Treatment emergent adverse events

Thromboembolic events

ADAPT-1

- No thromboembolic TEAE's
- One non-TEAE
  - Portal vein thrombosis at day 36
    - Assessed as not related

ADAPT-2

- 1 partial portal vein thrombosis
  - Avatrombopag 40 mg
  - Day 18 (13 days after last dose)
  - Platelet count 45,000 to peak 77,000 and down to 61,000 on day pf procedure (EGD)
- Placebo group
  - 1 acute MI
  - 1 pulmonary embolus

Terrault NA. *Gastroenterology.* 2018.

Lusutrombopag

TPO agonist, oral

Indication: “treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure”

Dose: 3 mg orally once daily with or without food for 7 days

Dosing schedule:

Begin 8-14 days prior to scheduled procedure

Procedure should occur 2-8 days after last dose

Monitoring: obtain platelet count

Prior to initiation

Not > 2 days before the procedure

Mulpleta FDA package insert.

Lusutrombopag

L-PLUS 1

Multicenter, randomized, double-blind, parallel-group, phase 3 study in Japan

Patients: CLD and platelet counts < 50,000/mL) undergoing invasive procedures

Intervention: Lusutrombopag (3 mg) daily or placebo for up to 7 days

Primary efficacy endpoint: proportion of patients not requiring platelet transfusion before the invasive procedure

L-PLUS 2

Multicenter, global, randomized, double-blind, parallel-group, phase 3 study

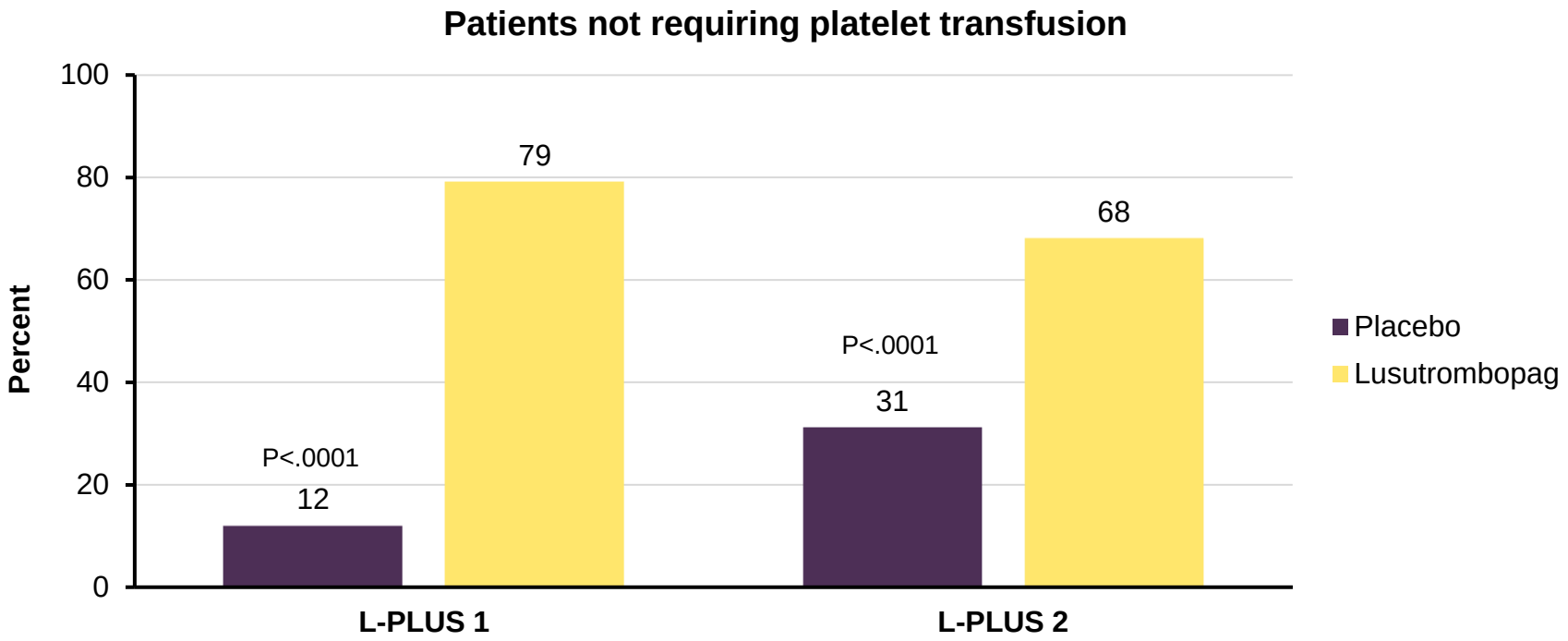
Patients: CLD and platelet counts < 50,000/mL) undergoing invasive procedures

Intervention: Lusutrombopag (3 mg) daily or placebo ≤ 7 days.

Primary efficacy endpoint: avoidance of preprocedure platelet transfusion and avoidance of rescue therapy for bleeding

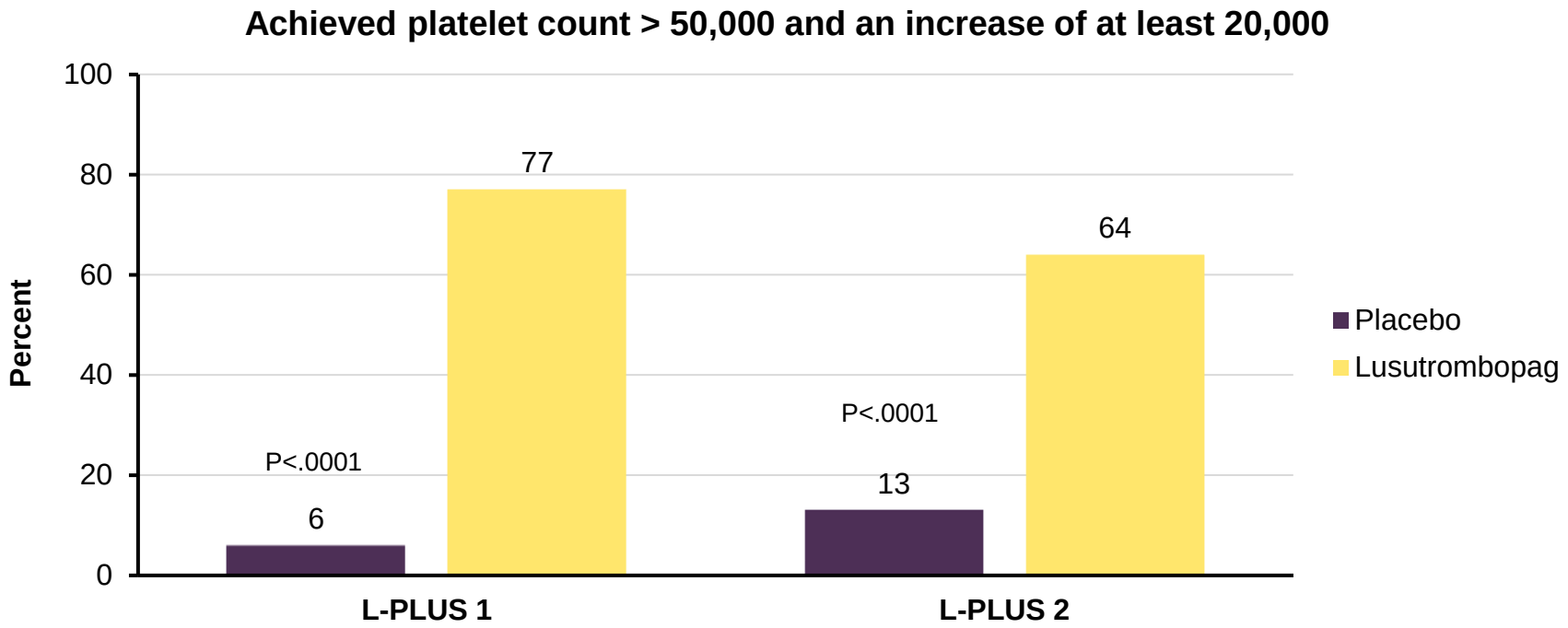
Hidaka H. *Clin Gastroenterol Hepatol.* 2019; Peck-Radosavljevic M. *Hepatology.* 2019.

Lusutrombopag



Hidaka H. *Clin Gastroenterol Hepatol.* 2019; Peck-Radosavljevic M. *Hepatology.* 2019.

Lusutrombopag

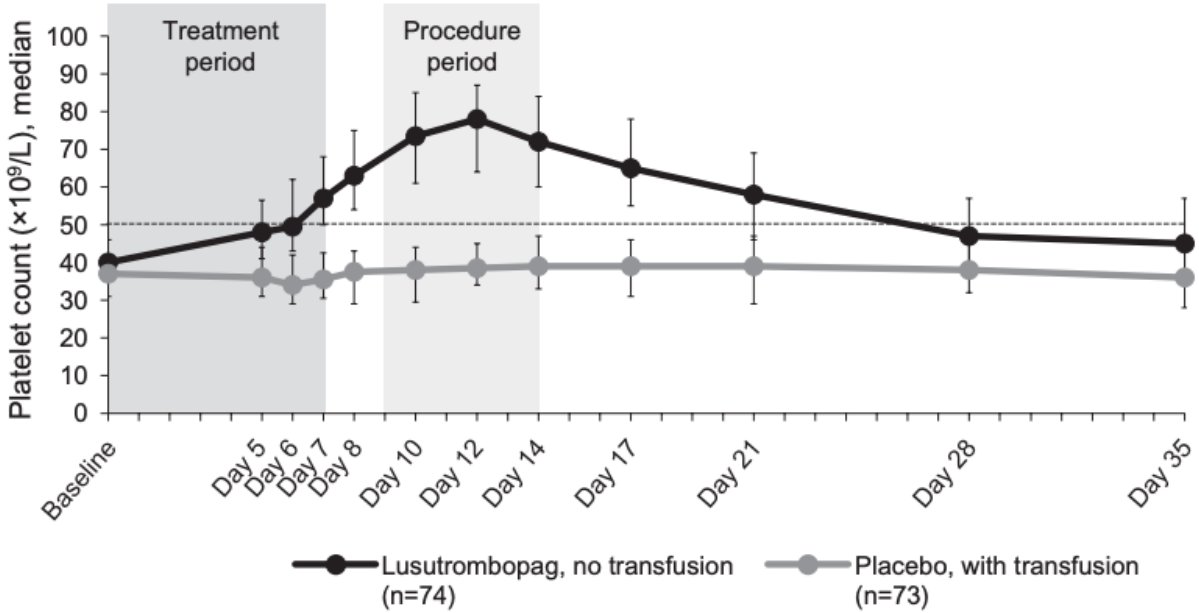


Hidaka H. *Clin Gastroenterol Hepatol.* 2019; Peck-Radosavljevic M. *Hepatology.* 2019.

Lusutrombopag

L-PLUS 2

Mean platelet count by day



Peck-Radosavljevic M. *Hepatology.* 2019.

Lusutrombopag

Treatment emergent adverse events

Thromboembolic events

L-PLUS 1

- 2 thrombotic events
- 1 Lusutrombopag
  - PVT day 14 after surgery
  - Max platelet count 79,000/μL
- 1 placebo
  - Superior mesenteric thrombosis study day 20
  - Max platelet count 60,000/μL

L-PLUS 2

Protocol included imaging before randomization and after study

- 4 thrombotic events
  - 2 with Lusutrombopag
  - 2 placebo

Hidaka H. *Clin Gastroenterol Hepatol.* 2019; Peck-Radosavljevic M. *Hepatology* 2019.

Summary

- Patients with chronic liver disease and thrombocytopenia have risk of bleeding complications with invasive procedures
- Risk varies according to procedure and severity of liver disease
- Supplement of fresh frozen plasma is not routinely recommended
- Thrombopoietin agonists provide an alternative to manage thrombocytopenia with elective procedures
- Clinician judgment crucial in the management of complex patients with chronic liver disease