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Case Report: Refractory variceal bleeding

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Thank you to Marika Rudler, Dominique Thabut, Adrian Gadano, and Jaime Bosch for the preparation of the presentation

Paris, January 14th 2019

Link of interest

Speaker/adviser: Abbvie, Gilead, MSD

A 54-year-old man with cirrhosis

Medical History:

- Ischemic cardiomyopathy

- Myocardial infection, coronary stenting (2015)
- No heart failure

- Obesity (BMI=39)
- Hypercholesterolemia
- Alcoholic cirrhosis

- Platelets=94000/mm3
- Child-Pugh B 9

- Endoscopy: Grade 2 EV

- Alcohol status: recent discontinuation

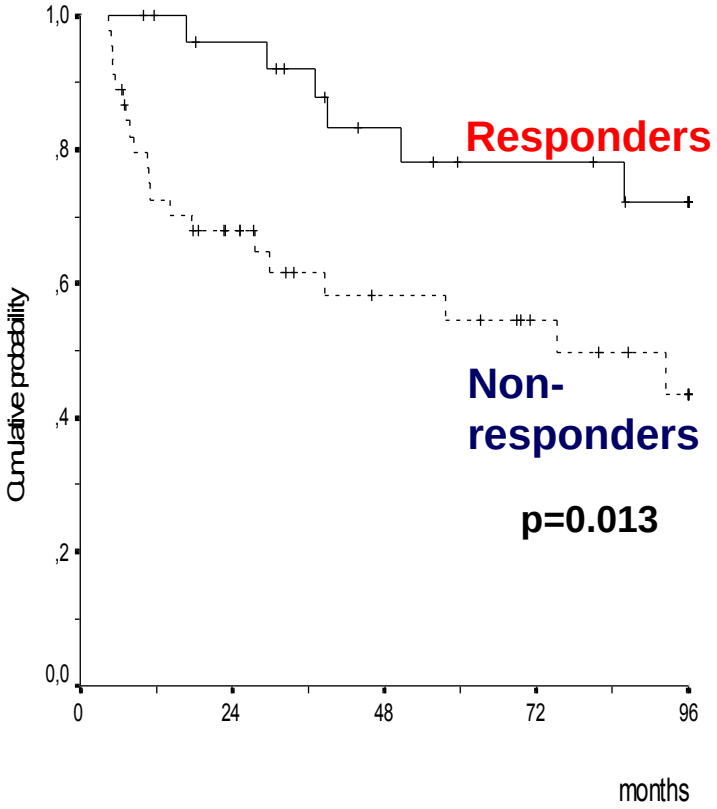
- Treatment: aspirin, atorvastatin

How do you manage portal hypertension?

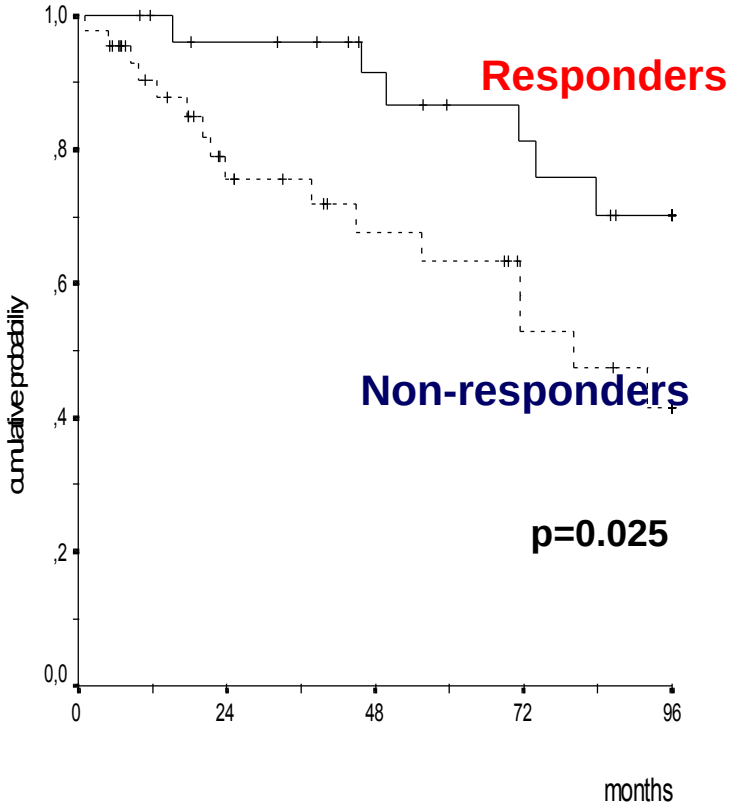
- Non selective beta blockers
- Band ligation
- Non selective beta blockers and Band ligation
- No treatment

HVPG responders to NSBB have less variceal rebleeding, a lower incidence of ascites, and better survival

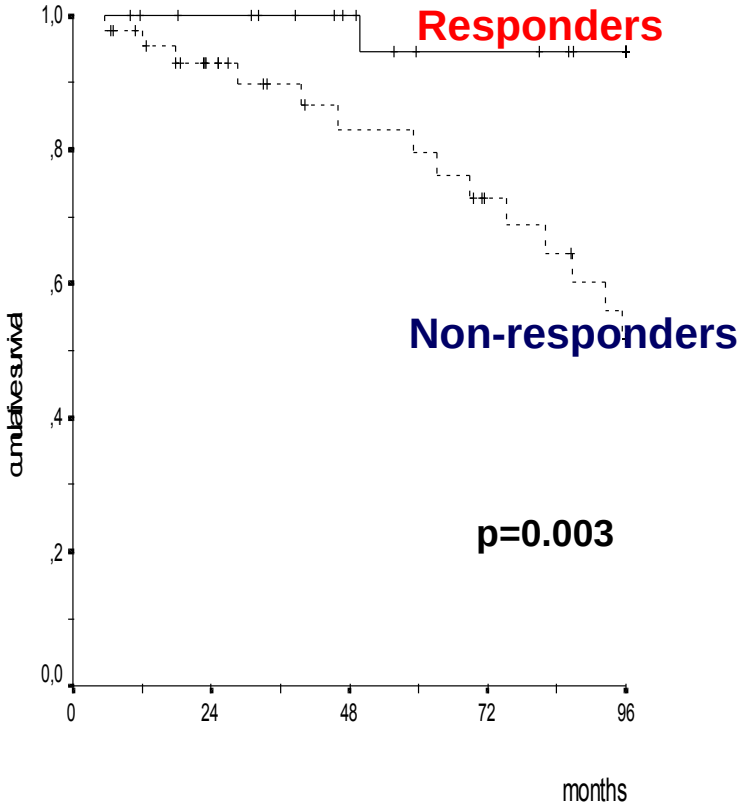
Variceal bleeding



Ascites

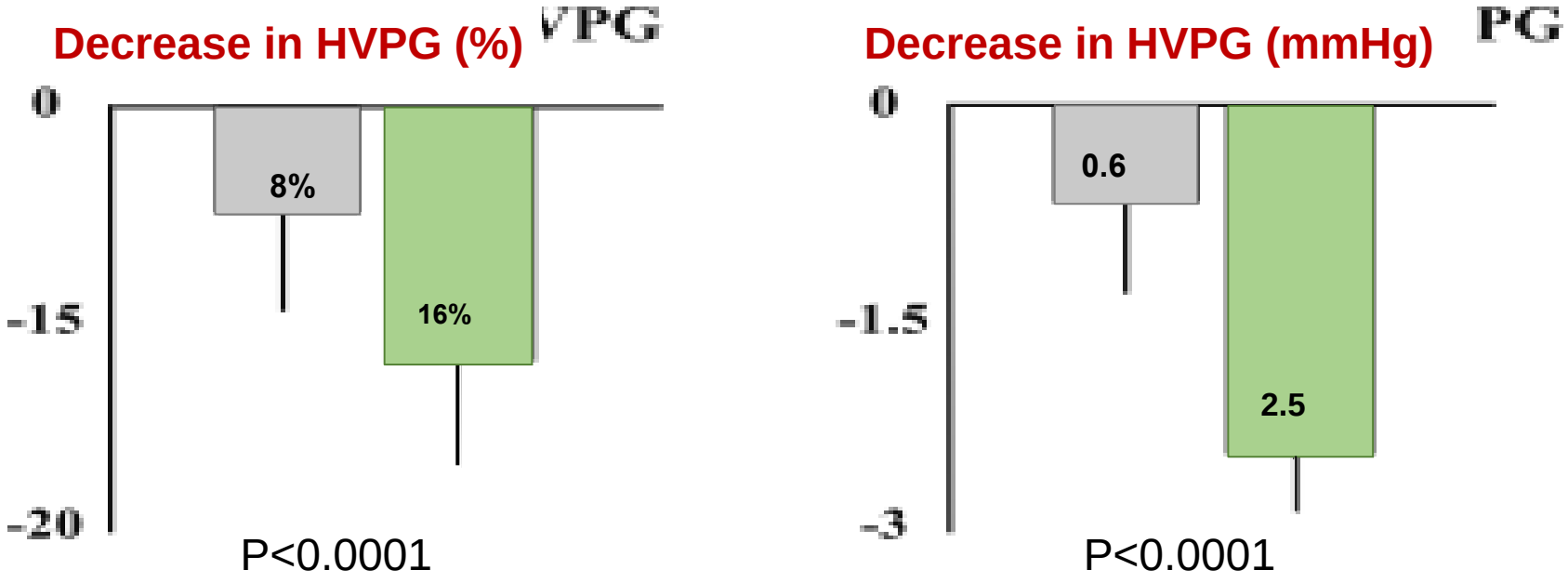


Survival



Abraldes….Bosch, Hepatology 2003

In compensated cirrhosis, response to Propranolol is almost negligible in patients without CSPH



Villanueva C…Bosch J, Hepatology 2015

Primary and Secondary Prophylaxis of Variceal Bleeding Current Guidelines

Prevention of First Variceal Bleeding

NSBB (non-selective beta-blocker)*

or

Endoscopic band ligation (**EBL**)

Prevention of Recurrent Variceal Bleeding

NSBB (non-selective beta-blocker)

plus

Endoscopic band ligation (**EBL**)

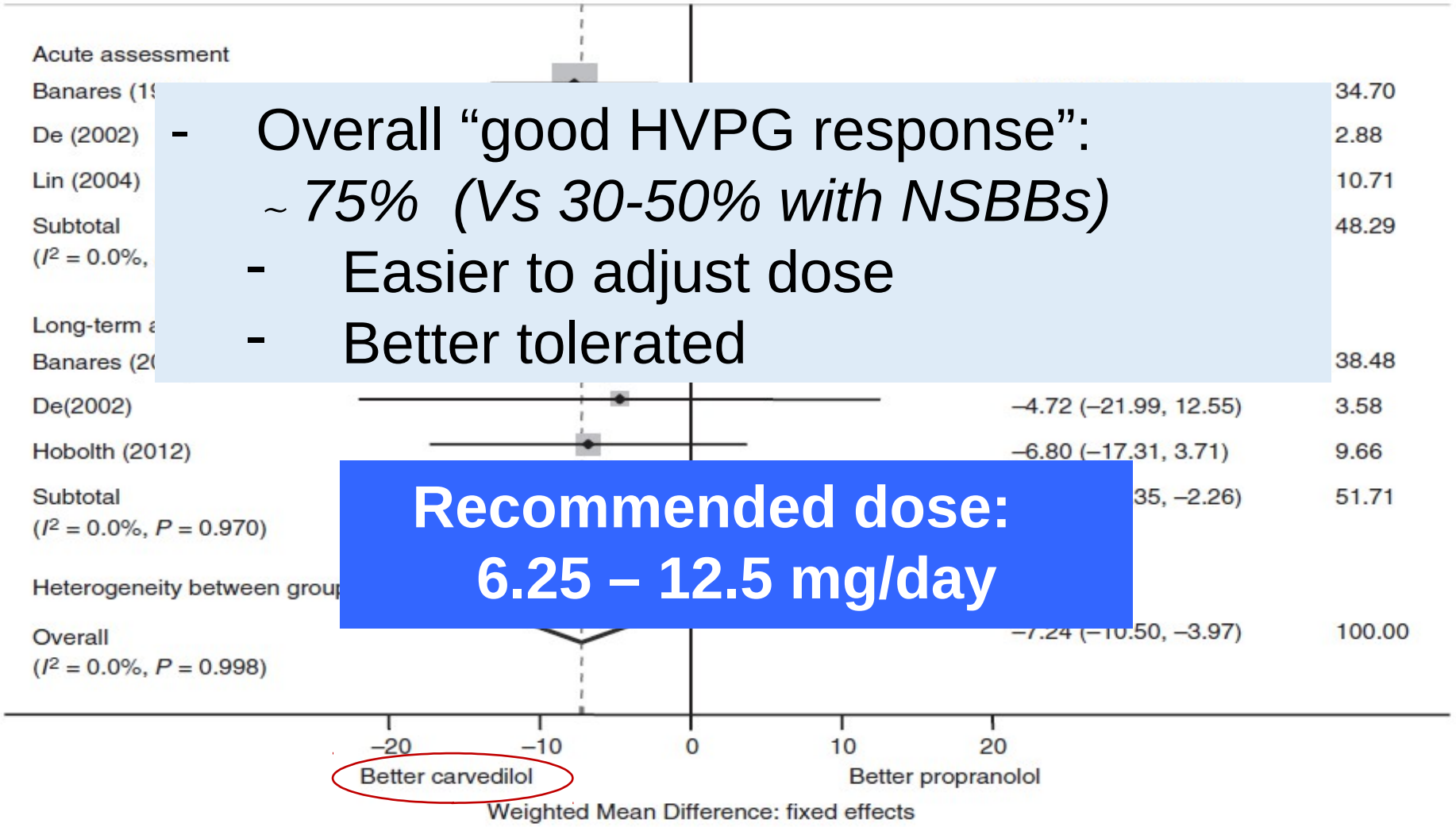
“There is no indication for treating patients without high-risk varices”
Negative timolol study (Grooszmann et al , NEJM 2005)

*Only recommended therapy for high-risk small varices

De Franchis et al Baveno VI, J Hepatol 2015

New!

Carvedilol, a NSBB with anti-α1 adrenergic activity has a greater effect decreasing HVPG



- Overall “good HVPG response”:
  - *~ 75% (Vs 30-50% with NSBBs)*
  - Easier to adjust dose
  - Better tolerated

Recommended dose: 6.25 – 12.5 mg/day

Sinagra et al, AP & T 2014

New!

New attempt at early therapy: The PREDESCI Study

PREventing the DEcompenSation of Cirrhosis with non-selective beta-blockers

- Cooperative, multicenter, placebo-controlled, randomized clinical trial
- Population studied: compensated cirrhotics with HVPG ≥ 10 mmHg (CSPH), **without varices requiring treatment** or previous decompensation (n=210)

Acute HVPG response to iv Propranolol*:

acute responders ➔ **Propranolol vs placebo**

non-responders ➔ **Carvedilol vs placebo**

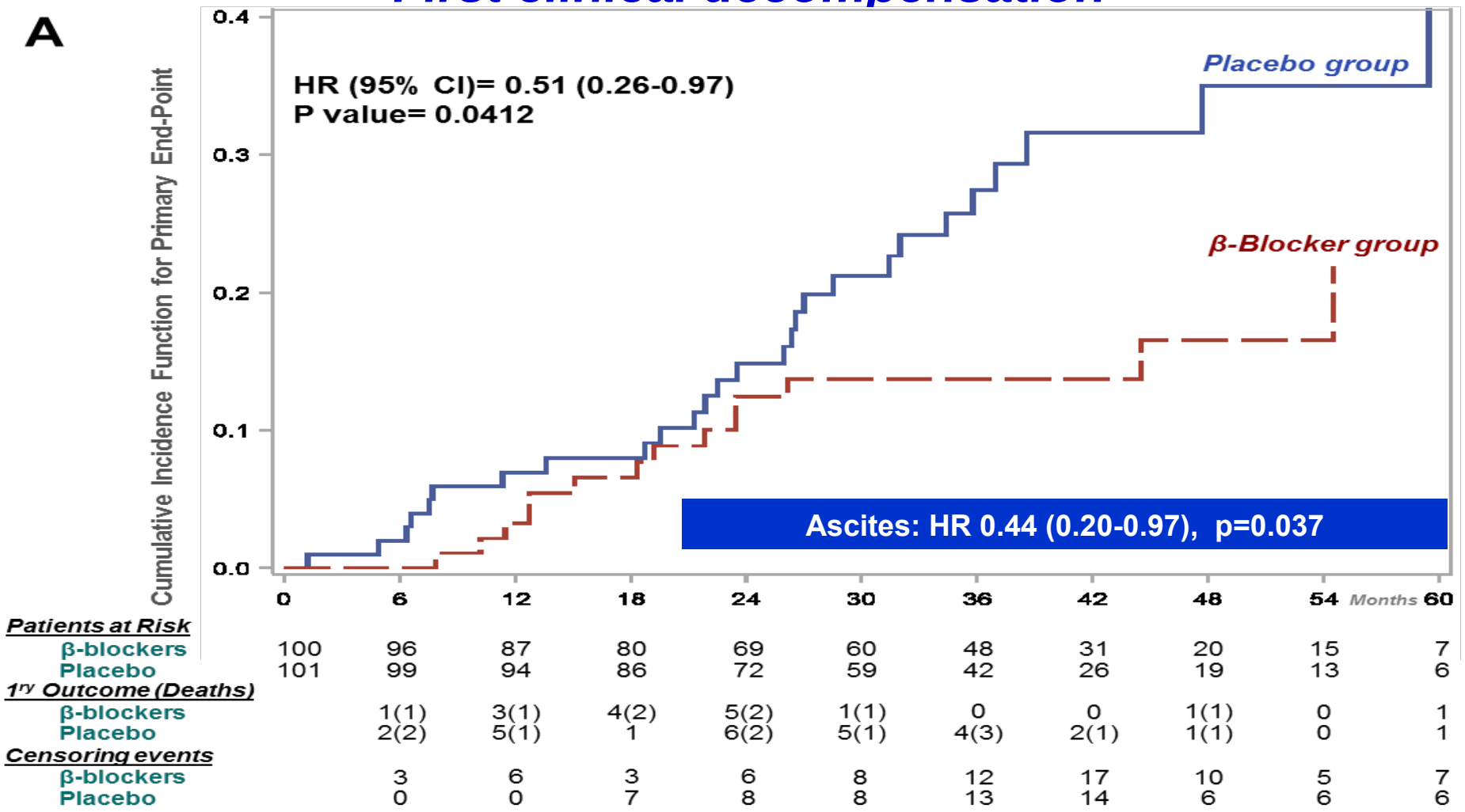
Patients developing varices requiring treatment received **EBL**

Villanueva C…Bosch J. Lancet (in press)

Propranolol/Carvedilol (according to HVPG response) prevents decompensation of cirrhosis: The **PREDESCI** Study

New!

First clinical decompensation

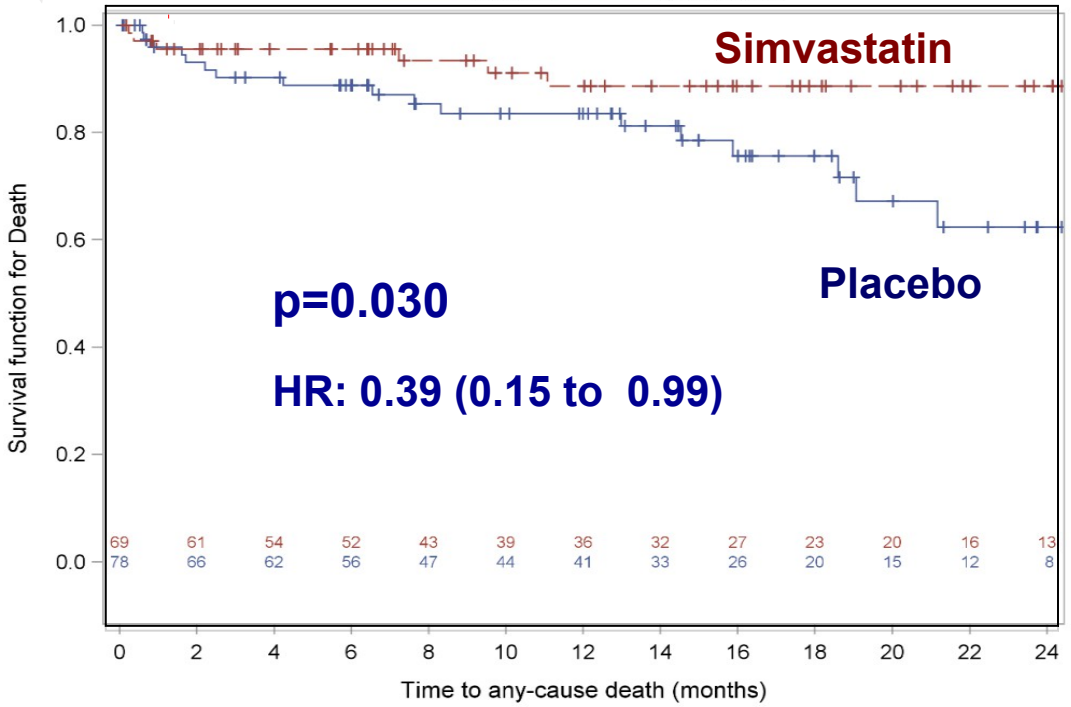


Villanueva C…Bosch J. Lancet (in press)

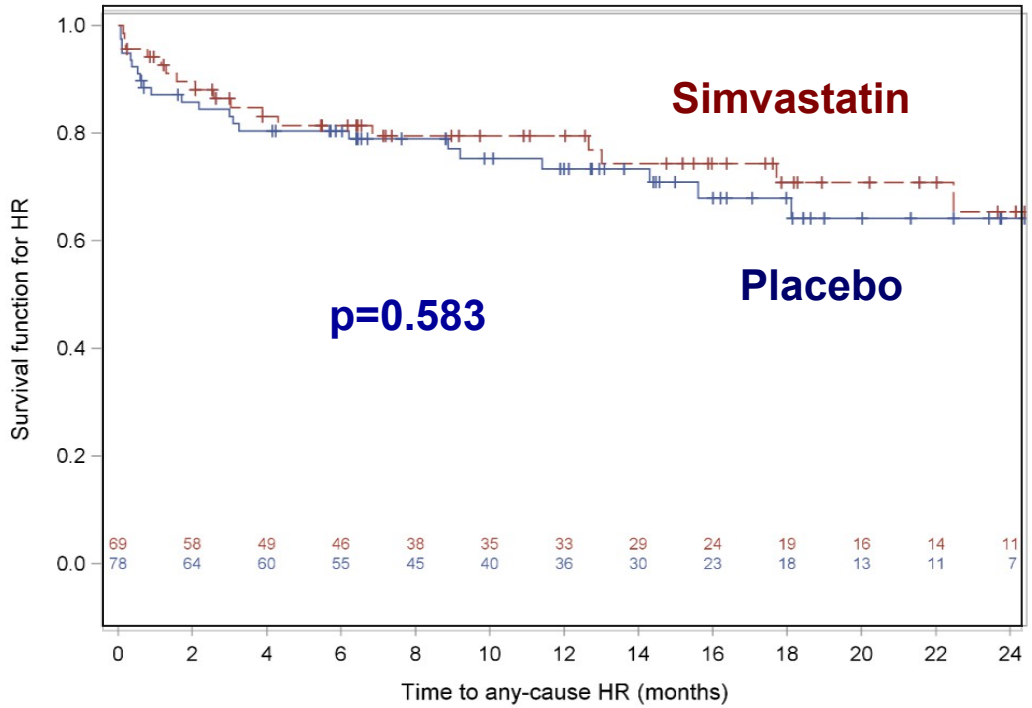
Simvastatin on top of standard of care (NSBB + EVL) improves prognosis after variceal bleeding **(BLEPS Study)**

New!

Death*



Rebleeding



* less deaths due to bleeding and infections

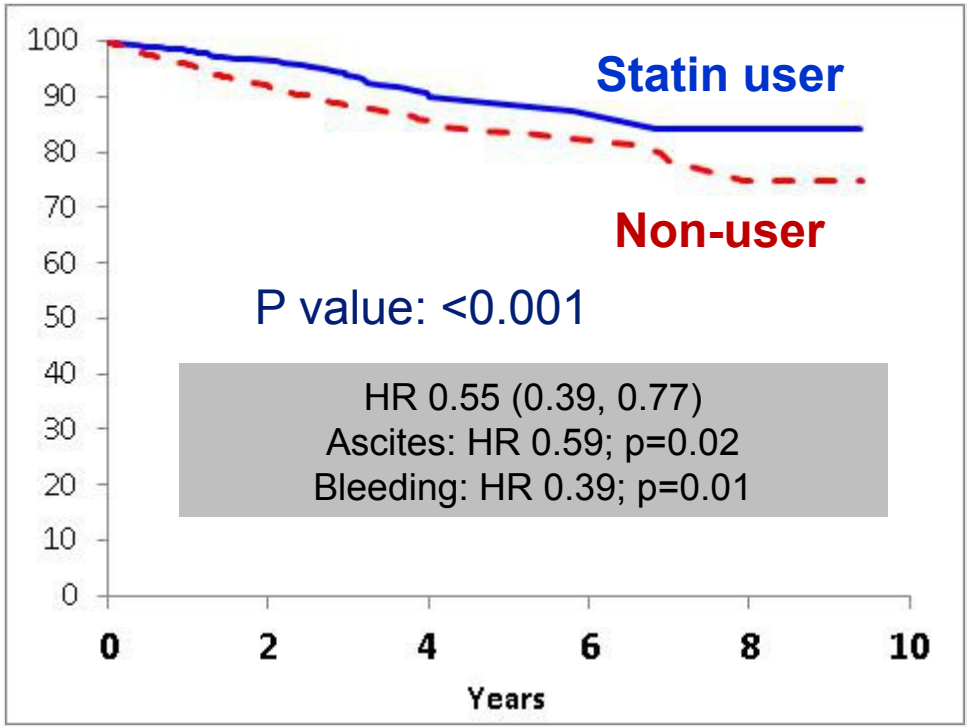
Abraldes, Villanueva,… Bosch. Gastroenterology 2016

Simvastatin prevents **ACLF** in cirrhotic rats (Tripathi et al, Gastroenterology 2018)
Simvastatin protects the liver from **LPS** induced injury (LaMura et al, Hepatology 2013)
Simvastation protects the cirrhotic liver during **acute bleeding** (Meireles et al, Shock 2016)

New!

Statins are associated with a decreased risk of decompensation and death in compensated HCV cirrhosis*

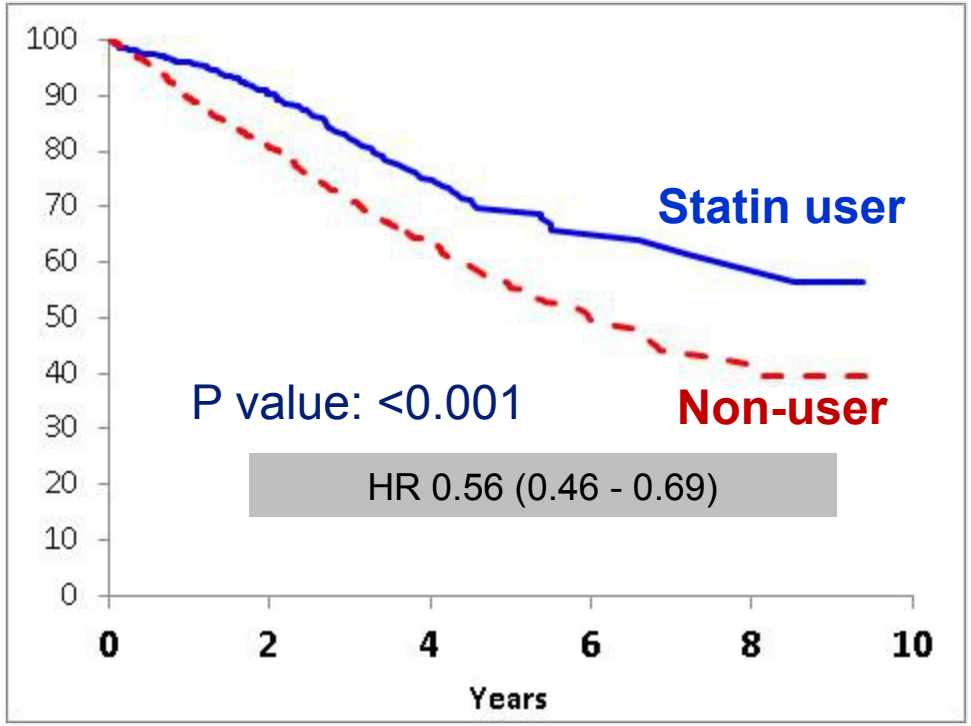
Decompensation



No. at risk

User	685	386	154	48	13
Nonuser	2062	924	333	92	22

Death



No. at risk

User	685	399	165	53	17
Nonuser	2062	991	370	107	27

*Propensity score matched study

Mohanty, et al. Gastroenterology 2016

A 56-year-old man presenting with hematemesis

Medical History:

- *Ischemic cardiomyopathy*

- Myocardial infection, coronary stenting (2015)

- No heart failure

- *Obesity (BMI=39)*
- *Hypercholesterolemia*
- Alcoholic cirrhosis diagnosed two years ago
- Propranolol (160 mg/day)
- No HCC

- Alcohol status: Active (relapse since 3 months) around 100g/day

- Treatment: propranolol, aspirin, atorvastatin

A 56-year-old man presenting with hematemesis

Medical report:

- Hematemesis
- No hepatic encephalopathy (WH), Glasgow score=1
- Blood pressure: 115/65 mmHg
- Heart rate: 76/min
- Ascites and jaundice
- Splenomegaly

Laboratory findings:

- Hb=7.5 g/dL
- Platelets=44000/mm3
- AST/ALT:75/44 IU/L; GGT=120 IU/L
- Bilirubin T/C=73/50 µmol/L
- PT=39%, INR=2.1
- Creatinine=100 µmol/L, natremia=120 mmol/L
- Albumin 25g/L

What is your initial management?

- Blood transfusion
- Non selective beta blockers
- Vasoactive drugs
- Antibiotic therapy with quinolones
- Lactulose to prevent HE

Initial management

- Initial resuscitation
- Blood transfusion (ischemic cardiopathy): 3 units
- Antibioprophylaxis: ceftriaxone IV
- Vasoactive treatment: somatostatin
- Proton pump inhibitors before endoscopy
- No prevention of hepatic encephalopathy
- Perfusion of erythromycin in the absence of contra indication
- Upper gastro-intestinal endoscopy

Specific treatment: Recommendations of Baveno VI

Lebrec, Eur J Hepatol Gastroenterol 2004

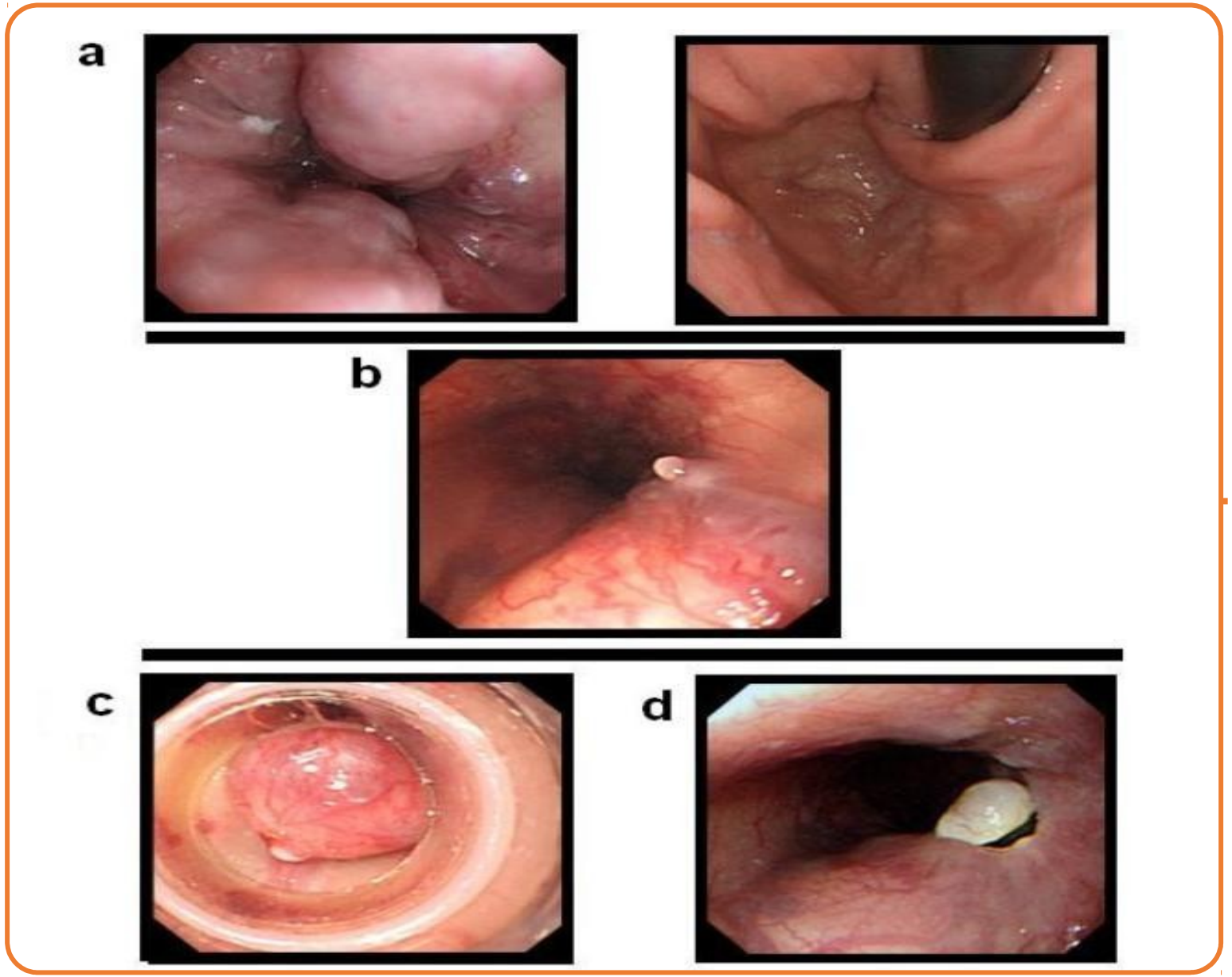
Garcia-Tsao, Hepatology 2007

De Franchis et al, J Hepatol 2015

Villanueva et al. NEJM 2013

Seo et al. Hepatology 2014

Upper endoscopy at admission



Evolution

- Suspected pneumonia (Day 3)

  Switch to piperacillin-tazobactam+ ciprofloxacin)

- Severe AH confirmed with transjugular liver biopsy

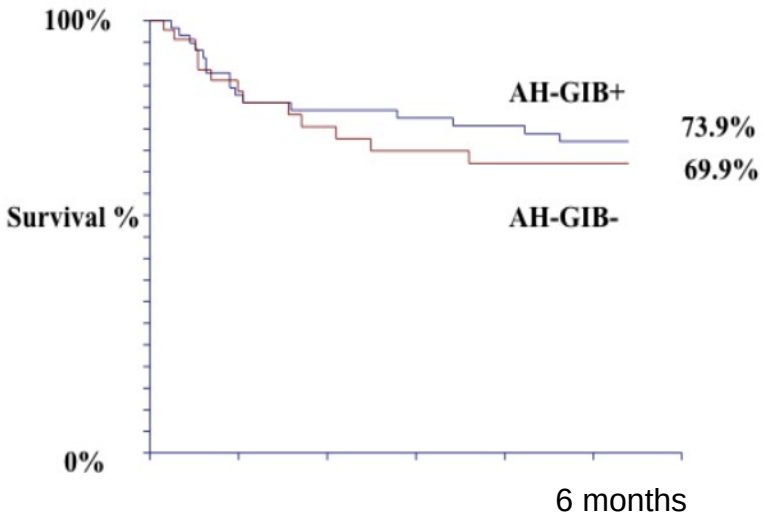
- HVPG=18mmHg

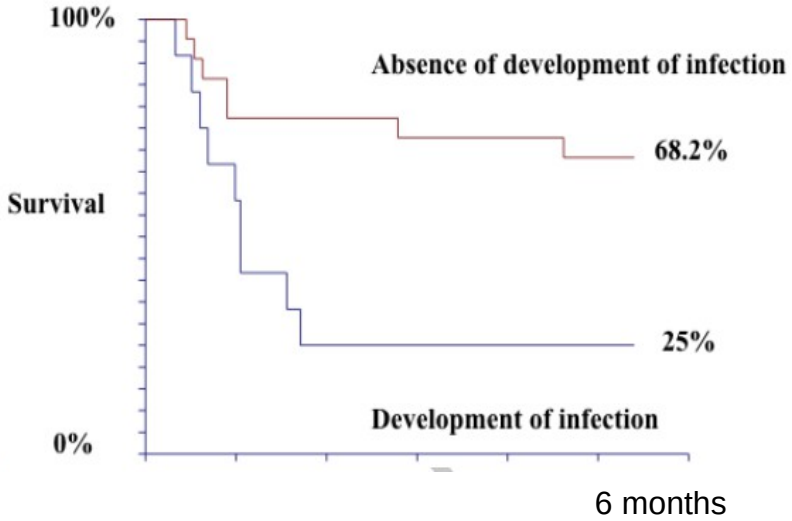
AH in the context of bleeding: what do you think?

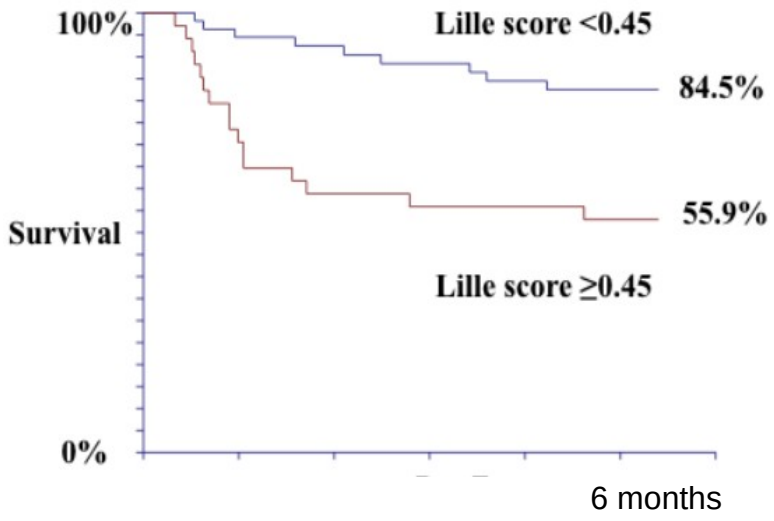
- It should not be treated because of high risk of infection
- The Lille model cannot be applied so there is not guidance for the treatment with corticoids
- Prognosis is poor in case of severe AH in the context of bleeding
- Antibiotic therapy is probably of interest in this context
- AH is rare in case of bleeding so no biopsy is needed

AH and bleeding: same history?

n=105







- *80% of patients GIB+ and DF>32 have histological signs of AH*
- AUC for the Lille model for predicting 6-month survival:
  similar for all patient (0.71±0.06) and AH-GIB+ patients (0.74±0.06)
- Less infection in GIB+ patients (24 vs 44%): due to systematic antibioprophylaxis?
- Encourage to perform the same diagnostic/therapeutic management

Rudler et al. J Hepatol 2014

Evolution

Hematemesis (day 2 after initiation of corticosteroids)

- Haemorrhagic shock (Hb=4.5 g/dL) requiring catecholamines
- Massive blood transfusion
- Alteration of consciousness
- Emergency orotracheal intubation
- Upper GI endoscopy: active bleeding from EV. EBL in emergency
- Uncontrolled bleeding

How do you manage?

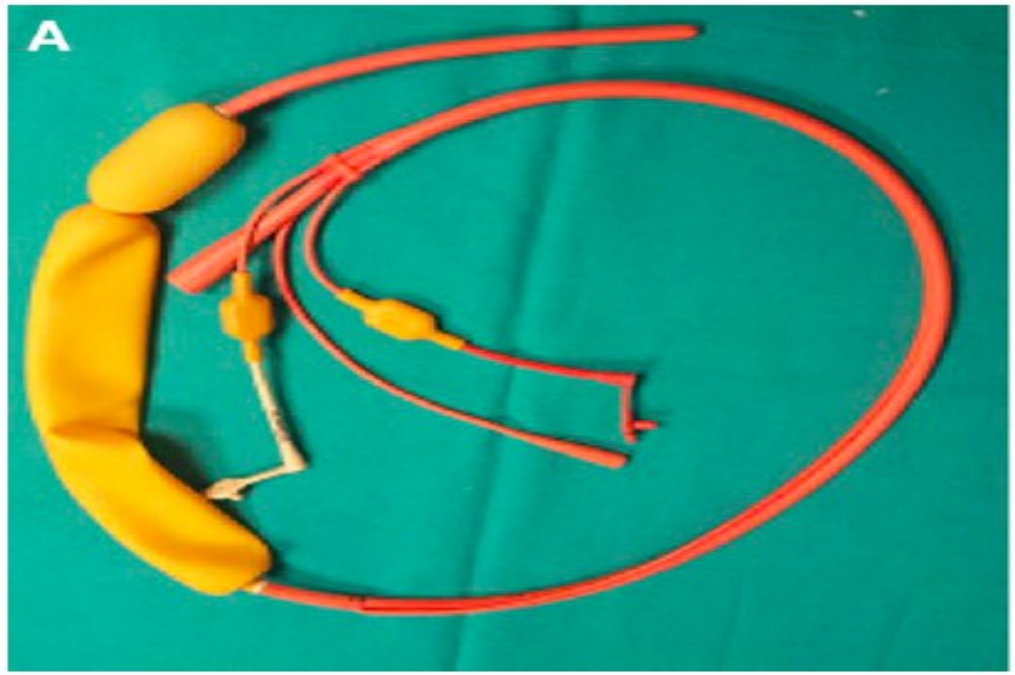
- Balloon tamponade
- Esophageal stents

Esophageal Balloon Tamponade Versus Esophageal Stent in Controlling Acute Refractory Variceal Bleeding: A Multicenter Randomized, Controlled Trial

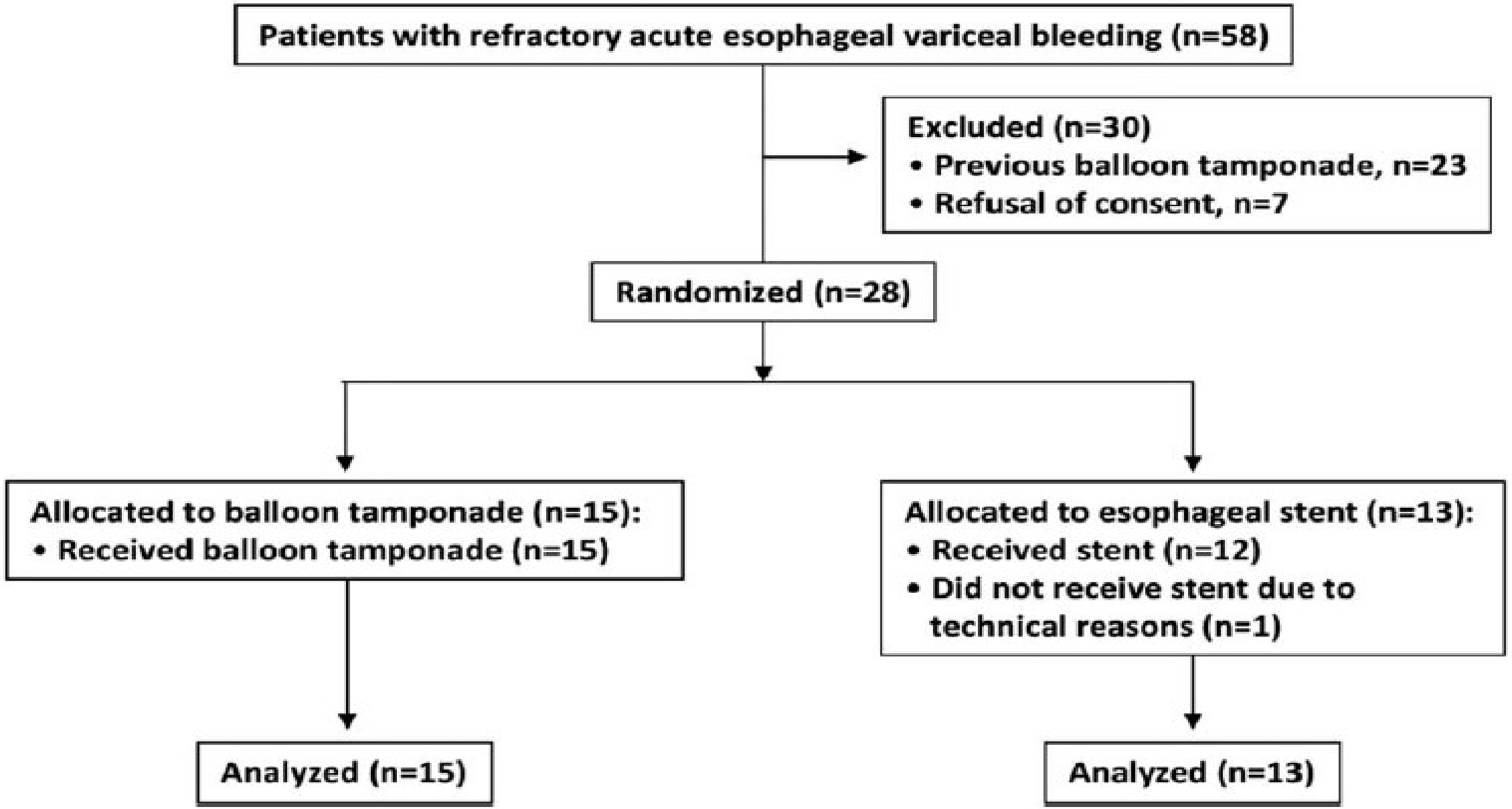
Àngels Escorsell,[1,2] Oana Pavel,[2,3] Andrés Cárdenas,[2,4] Rosa Morillas,[2,5] Elba Llop,[2,6] Càndid Villanueva,[2,3] Juan C. Garcia-Pagán,[1,2] and Jaime Bosch[1,2]; for the Variceal Bleeding Study Group

- **Primary endpoint**: composite
  Absence of rebleeding+ absence of SAE+Day15 survival

- **Secondary endpoints**
  - Rebleeding at day 15 and 42
  - Survival at day15 and 42



March 2009-January 2013



Escorsell A, et al. Hepatology 2016

Variable	Esophageal Stent (n = 13)	Balloon Tamponade (n = 15)	P Value
Inclusion criteria, n (%)			0.93
Failure of combined therapy	8 (62)	9 (60)	
Massive bleeding	5 (38)	6 (40)	
Interval admission-inclusion, days*	1.5 (0-7)	1 (0-25)	0.60
Absence of SAE, n (%)			
Survival at 15 days, n (%)	9 (69)	8 (47)	0.39
Absence of bleeding, 6 weeks, n (%)	7 (54)	7 (47)	0.25
Absence of device-related SAE, n (%)	12 (92)	9 (60)	0.049
Causes of death (15 days; n)			0.044
Hypovolemic shock	1	6†	
MOF after sepsis	3	1	
Survival at 6 weeks, n (%)	7 (54)	6 (40)	0.46
Use of additional resources (during the hospital stay), n (%)	4 (31)	11 (73)	0.059

Data suggest that esophageal stents are as effective as balloon tamponade and more safe in refractory variceal bleeding (3; C)

Escorsell A, et al. Hepatology 2016

How do you manage?

- Salvage TIPS

Salvage TIPS

Author	Patients	Child A/B/C	Control of bleeding	Lethality
Mc Cormick	20	1/7/12	100%	55%
Jalan	19	3/3/13	100%	42%
Sanyal	30	1/7/22	100%	40%
Chau	112	5/27/80	98%	37%
Gerbes	11	1/3/7	100%	27%
Banares	56	11/22/23	96%	28%
Azoulay	58	3/8/47	93%	30%
Bouzbib	106	6/32/68	80%	38% (d42)

RudlerM et al, Transplant Int 2014
Bouzbib, AFEF 2018

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Etiology of death

- **Liver failure**
- **Kidney failure**
- **Rebleeding**

RudlerM et al, Transplant Int 2014
Bouzbib, AFEF 2018

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Banares	[illegible]	[illegible]	[illegible]	[illegible]
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Mortality at 1 year without LT in C14-C15 = 100%

RudlerM et al, Transplant Int 2014
Bouzbib, AFEF 2018

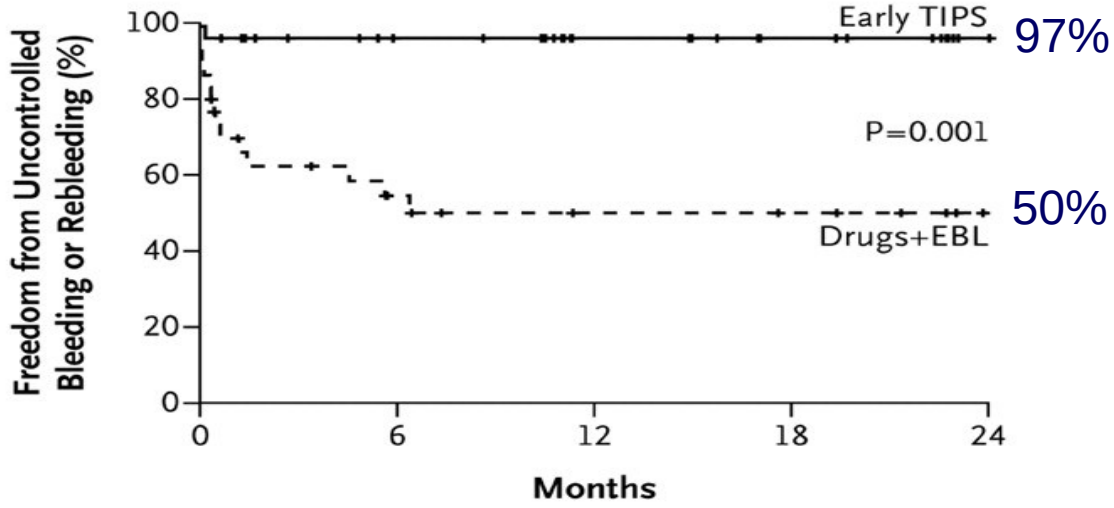
What could have been done to avoid this rebleeding episode?

- Early TIPS placement?
- How to select patients with a risk of rebleeding?

Clinical and biological criteria

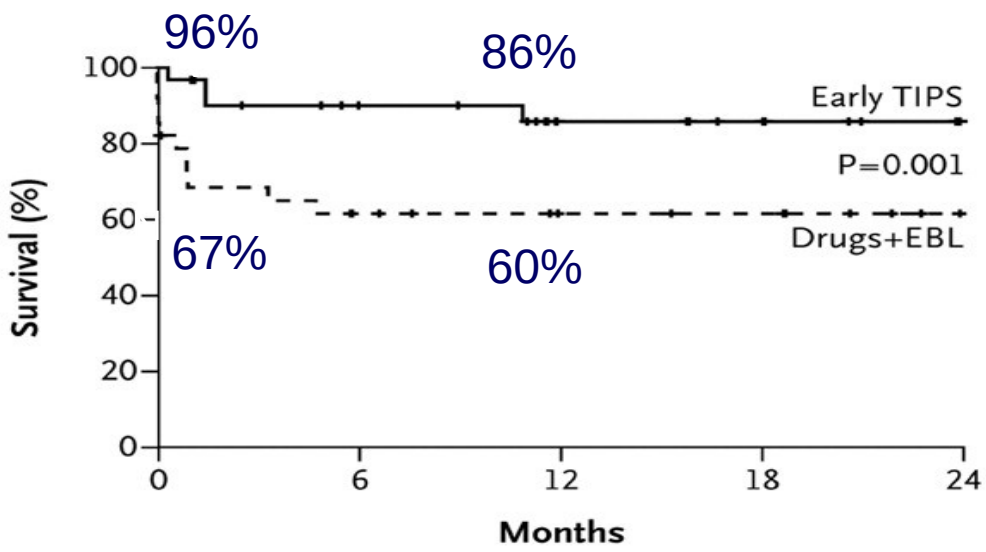
Child-Pugh B + active bleeding or Child-Pugh C ≤13 patients randomised
(no HCC, PVT..)

A



No. at Risk					
Early TIPS	32	24	15	11	5
Drugs+EBL	31	13	7	7	3

B

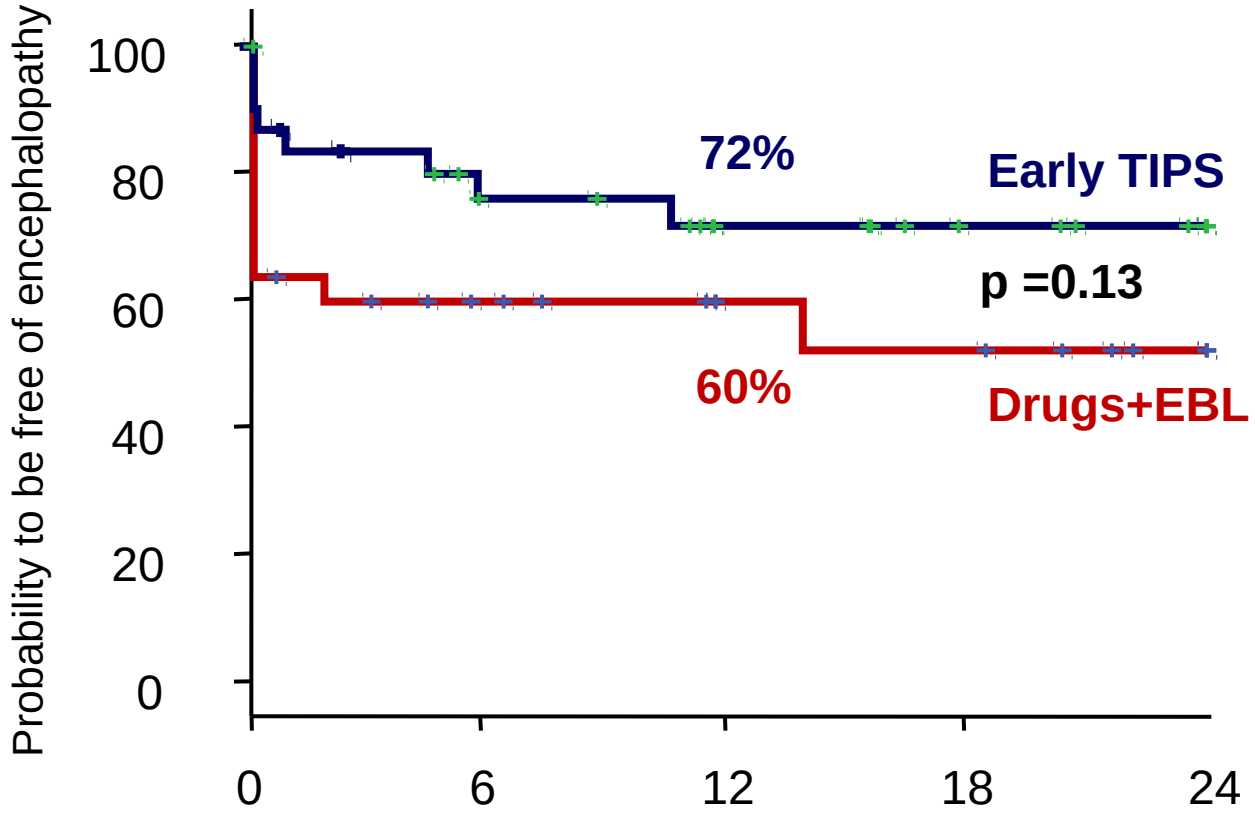


No. at Risk					
Early TIPS	32	24	17	12	7
Drugs+EBL	31	18	13	10	5

- Significant improvement of uncontrolled bleeding and rebleeding
- Improved short and long term survival in the Early TIPS group

Garcia-Pagan et al. NEJM 2010

More serious adverse events?



PTFE-TIPS	32	21	13	9	5
LVO + M	31	14	8	7	3

Development of hepatic encephalopathy or other serious events: no significant difference

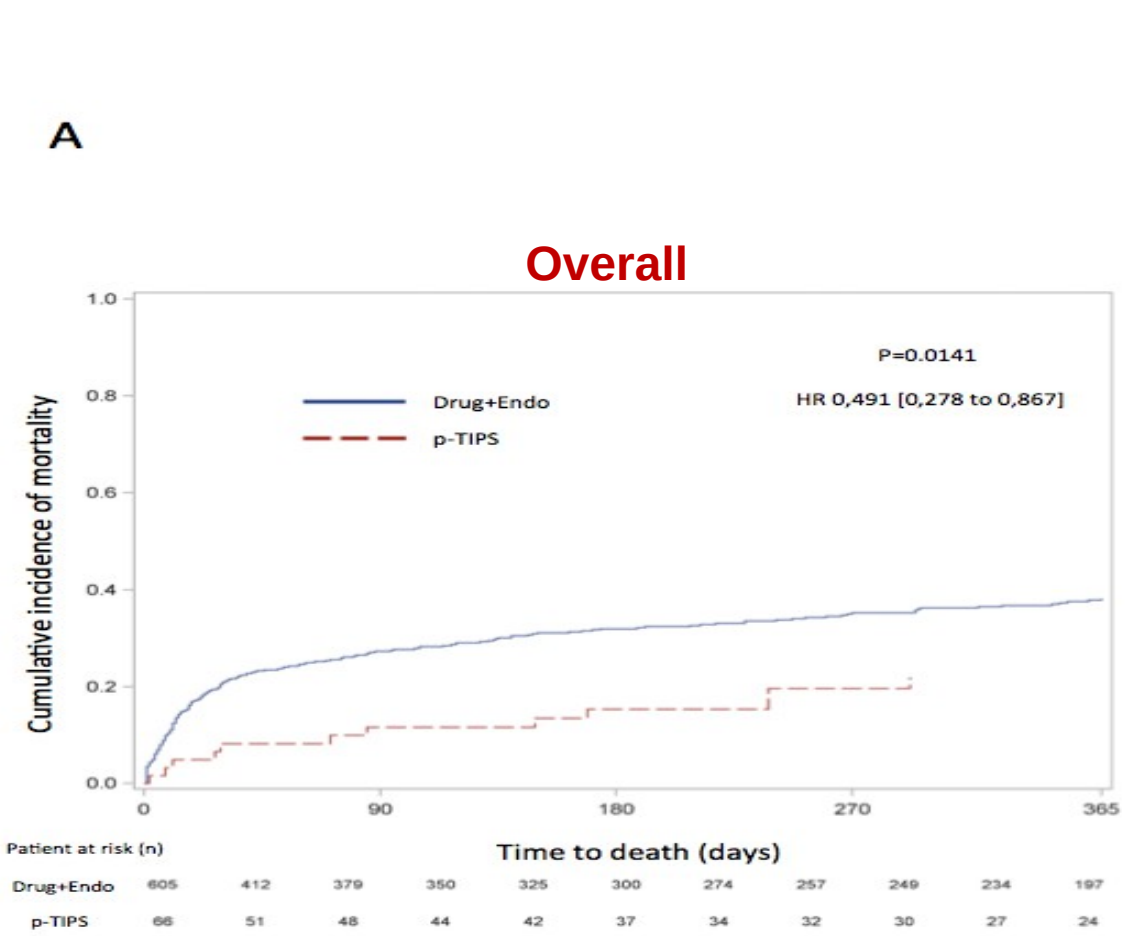
Garcia-Pagan et al. NEJM 2010

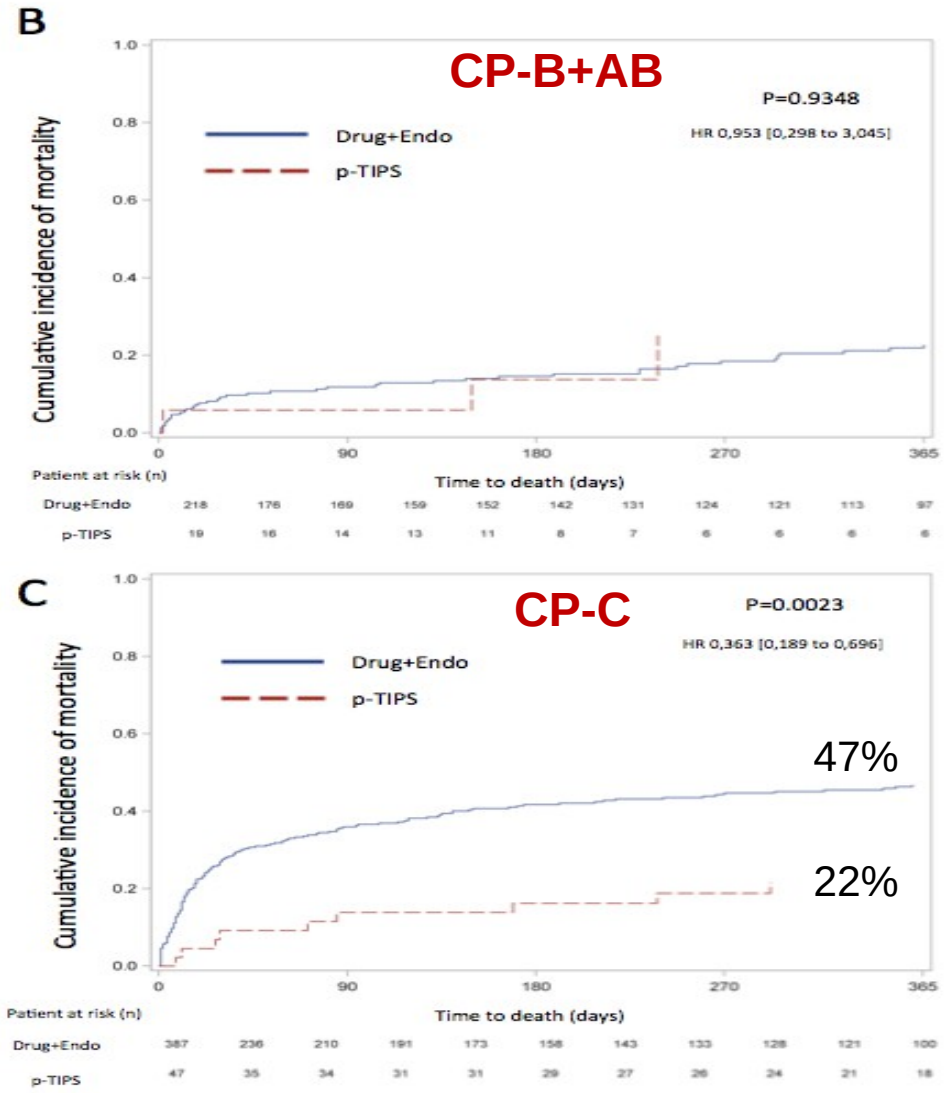
An early TIPS with PTFE-covered TIPS within 72 hours (ideally ≤ 24 hours) must be considered in patients bleeding from EV, GOV1 and GOV2 at high-risk of treatment failure (e.g. Child-Pugh class C <14 points or Child class B with active bleeding) after initial pharmacological and endoscopic therapy (1b;A). Criteria for high-risk patients should be refined

De Franchis, J Hepatol 2015

- Impact of early-TIPS on survival?
- Active bleeding in Child B patients: predictor?

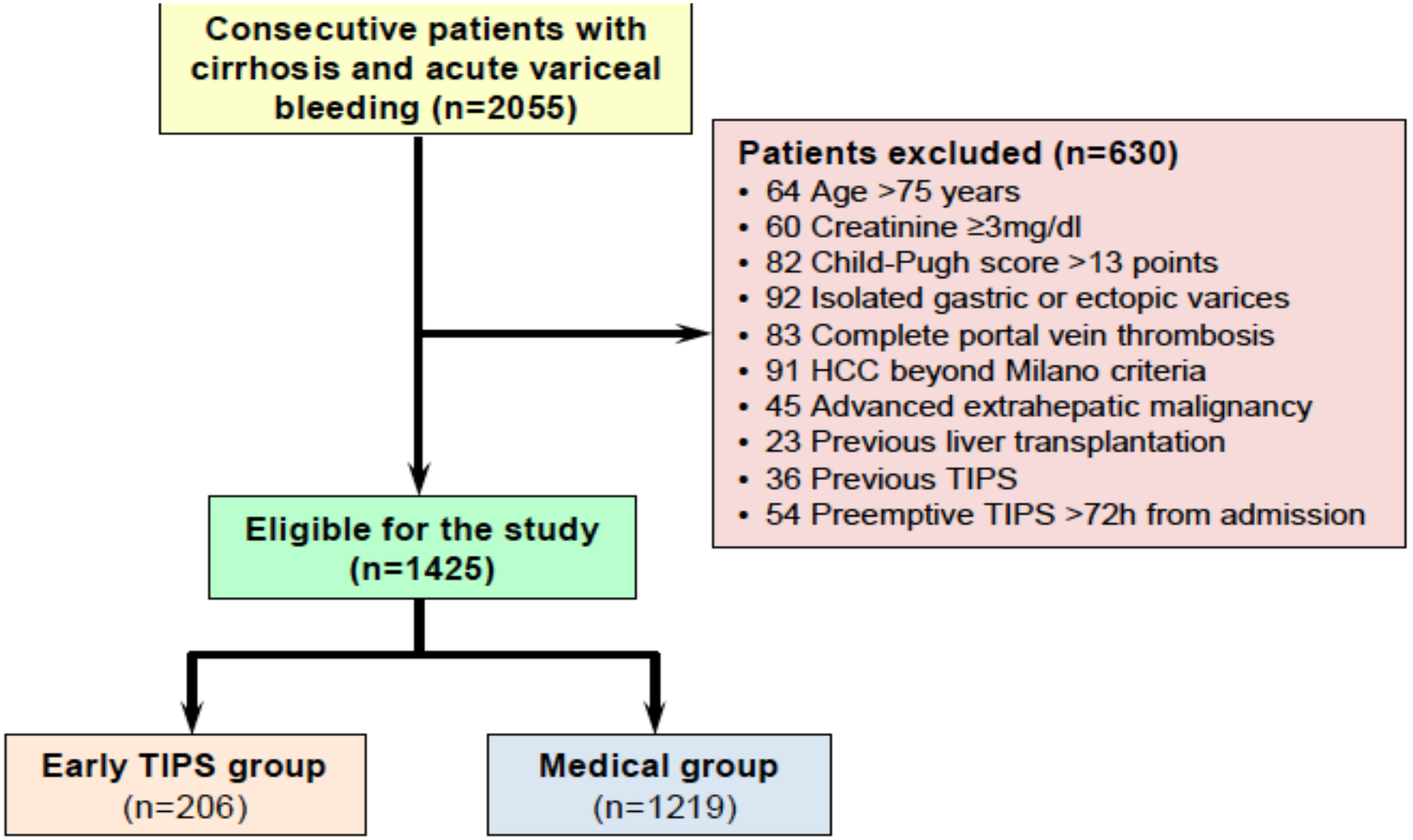
Preemptive - TIPS improves outcome in high - risk variceal bleeding: an Observational Study





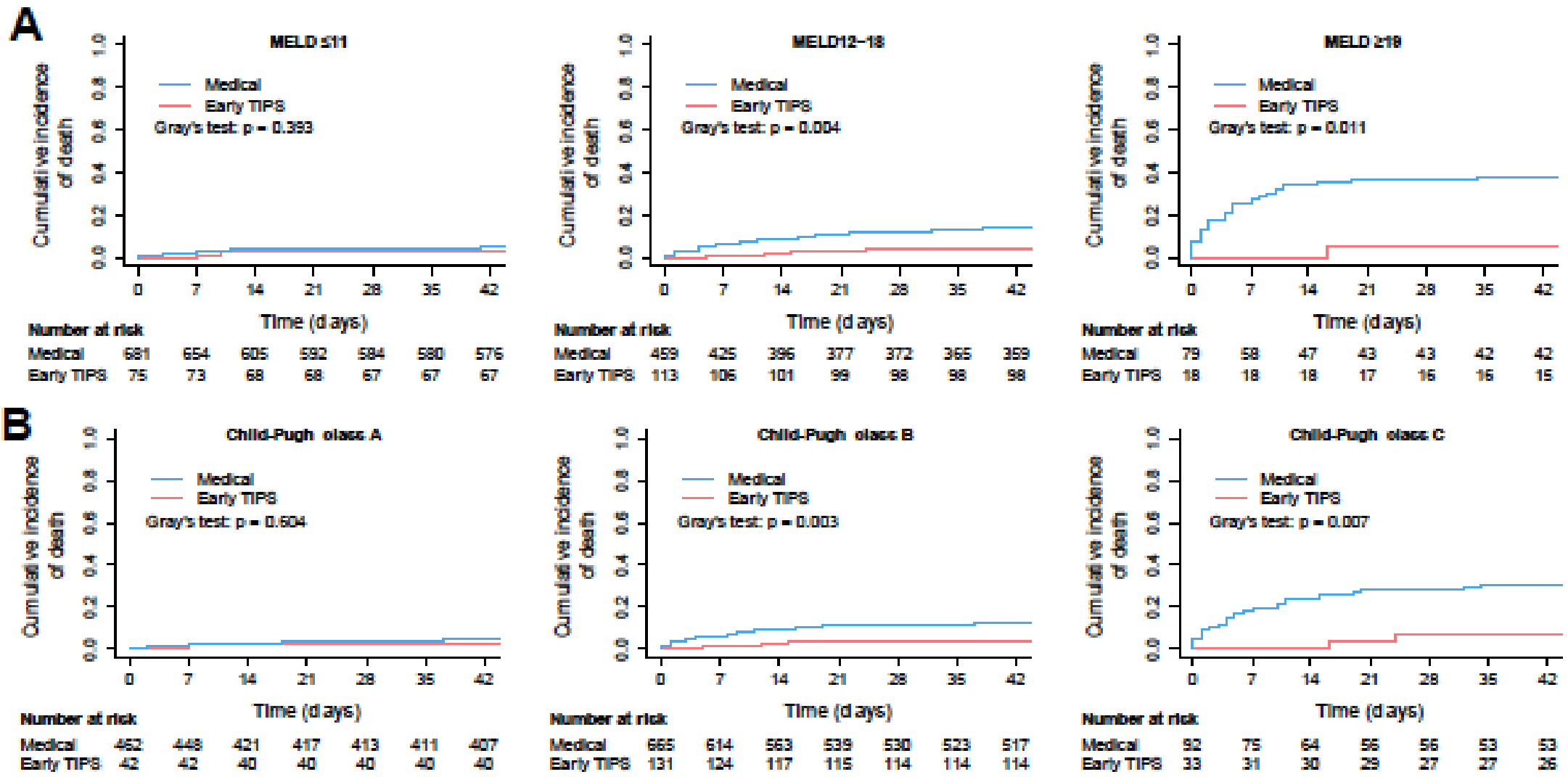
Hernandez-Gea V, et al. Hepatology 2019

Identifying optimal candidates for early TIPS among patients with cirrhosis and acute variceal bleeding: a multicentre observational study



Lv Y, et al. Gut 2018

Identifying optimal candidates for early TIPS among patients with cirrhosis and acute variceal bleeding: a multicentre observational study



Lv Y, et al. Gut 2018

In practice: CHOC French observatory (58 centres)

Academic centres	Study population	Non-academic centres
with PHT-related bleeding 600 cirrhotic patients	with PHT-related bleeding 964 cirrhotic patients	with PHT-related bleeding 364 cirrhotic patients
Child-Pugh C or B + active bleeding at endoscopy n = 301 (50%)	Child-Pugh C or B + active bleeding at endoscopy n = 460 (48%)	Child-Pugh C or B + active bleeding at endoscopy n = 159 (44%)
Patients eligible for early-TIPS n = 207 (69%)	Patients eligible for early-TIPS n = 326 (71%)	Patients eligible for early-TIPS n = 119 (75%)
Early-TIPS placement n = 19 (9%)	Early-TIPS placement n = 22 (7%)	Early-TIPS placement n = 3 (2.5%)

Thabut D, et al. J Hepatol 2017

Final outcome

- Not candidate for LT
- Death within 48 hours after TIPS insertion
- Multi-organ failure:
  - Persistent shock
  - Severe coagulopathy with diffuse mucosal bleeding
  - Acute kidney failure
  - Persistent coma in spite of discontinuation of drugs
  - Blood cultures positive with Pseudomonas *aeruginosa*

Take home messages

- Early TIPS must be discussed in high risk patients
- Esophageal stents are safer than balloon tamponade and should be available
- Salvage TIPS : high mortality in the most severe patients. Don’t forget liver transplant in good candidates!