

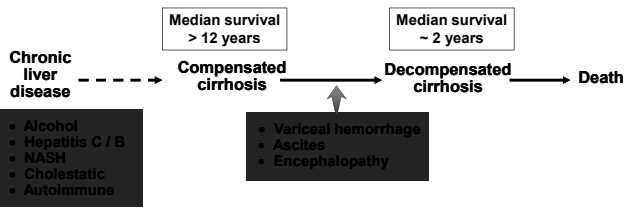
Management of Varices

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Yale University

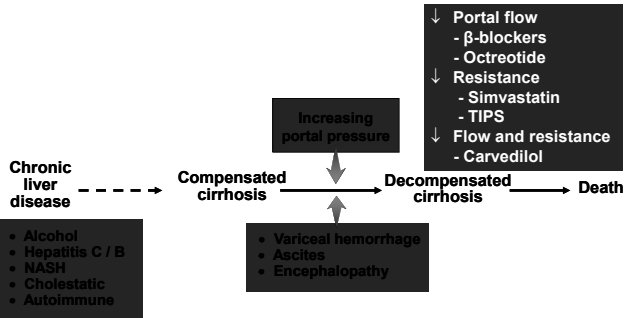
Chief, Digestive Diseases Section
VA-CT Healthcare System

Siemens has provided me with ARFI software (no funds). I will be discussing unlabeled/unapproved use of propranolol, nadolol and carvedilol.

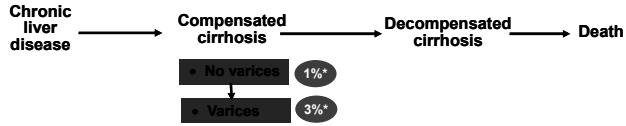
Natural History of Chronic Liver Disease



Natural History of Chronic Liver Disease



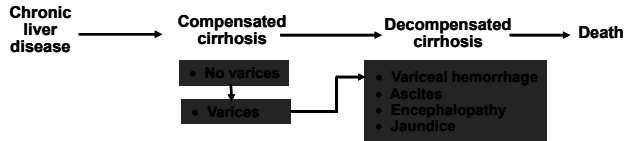
In compensated cirrhosis two subpopulations can be identified based on the presence or absence of varices



D'Amico, Garcia-Tsao, Pagliaro. *J Hepatol* 2006;44:217-231.

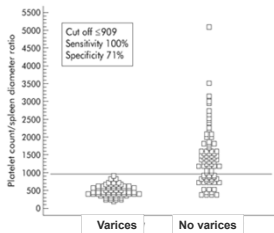
* 1-year mortality

Variceal hemorrhage can be prevented but this requires screening for the presence / size of varices



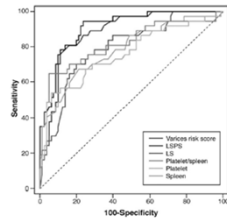
Non-endoscopic methods to screen for varices

Platelet/spleen ratio = platelet count (mm³) / spleen diameter (mm)
 >909 rules out varices



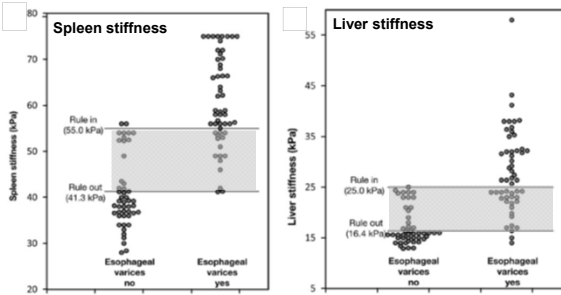
Giannini et al. *Gut* 2003.

Adding liver stiffness to platelet count and spleen diameter discriminated better than platelet/spleen ratio



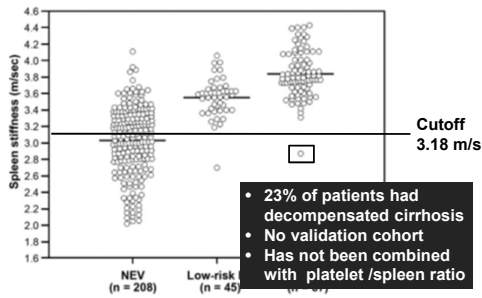
Berzigotti et al. *Gastroenterology* 2013.
 Kim et al. *Am J Gastroenterol* 2010.

Spleen stiffness* discriminates better than liver stiffness* in the diagnosis of varices



Colecchia et al. *Gastroenterology* 2012;143:646-54. * by transient elastography

Spleen stiffness measurements (by ARFI) were useful to rule out the presence of varices

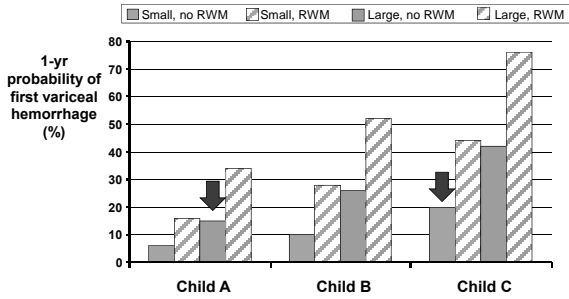


Takuma et al. *Gastroenterology* 2013;144:92-101.

Non-endoscopic methods to diagnose or exclude varices

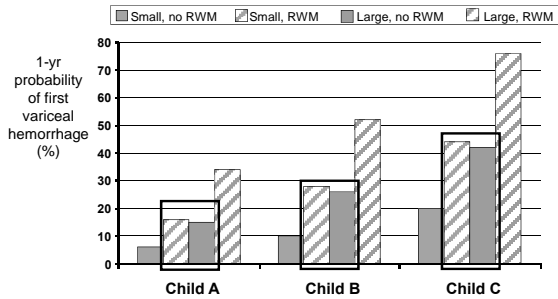
- Several methods alone or in combination look promising
 - Spleen stiffness
 - Platelet count/spleen diameter
 - Liver stiffness
- Their main utility is in identifying patients who are unlikely to have varices
- Endoscopy is still gold standard

Risk of first variceal hemorrhage is determined by size of varices, Child class and presence of red wale marks (RWM) on varices



NIEC. N Engl J Med 1988; 319:983

Risk of first variceal hemorrhage is determined by size of varices, Child class and presence of red wale marks (RWM) on varices



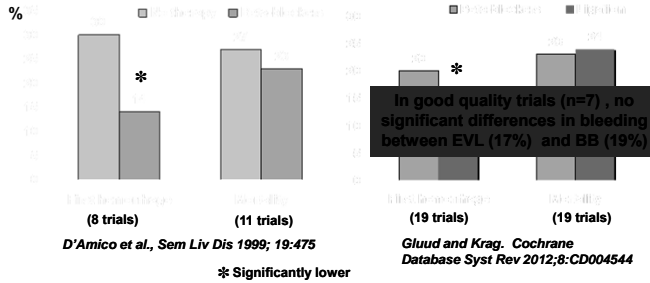
NIEC. N Engl J Med 1988; 319:983

AASLD and Baveno recommendations for small varices that have not bled

- **High risk (Child C or presence of red wale marks on varices):**
Should be treated with NSBB to prevent first variceal hemorrhage
- **Low risk:**
May be treated with NSBB although their long term benefit remains to be established

Garcia-Tsao et al. Hepatology 2007, Am J Gastroenterol 2007; de Franchis. J Hepatol 2010

Two treatments reduce the risk of first variceal hemorrhage in pts with medium/large varices:

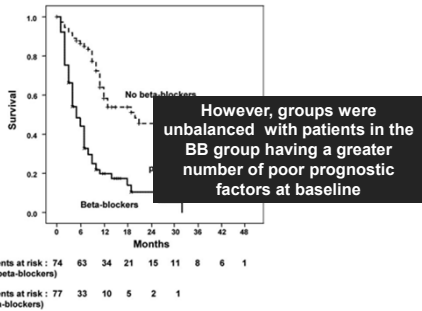


Baveno V recommendations for pts with medium / large varices that have not bled

- **Either NSBB or endoscopic band ligation is recommended in primary prophylaxis**
- **The choice of treatment should be based on local resources and expertise, patient preference and characteristics, side effects, and contra-indications**

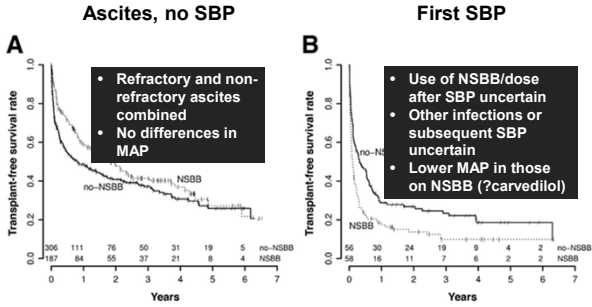
deFranchis. J Hepatol. 2010 Oct;53(4):762-8

Patients with refractory ascites on NSBB may have a poorer survival than those not on NSBB



Serste et al. Hepatology 2010;52:1017

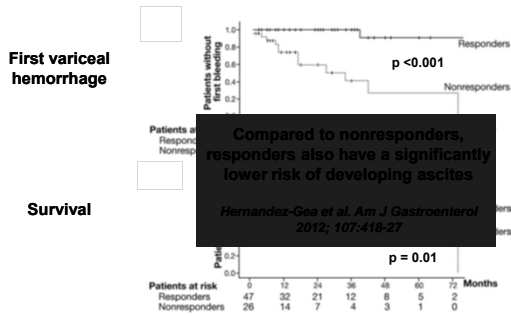
Patients who develop SBP on NSBB may have a poorer survival than those not on NSBB*



Mandorfer et al. *Gastroenterology* 2014;146:1680

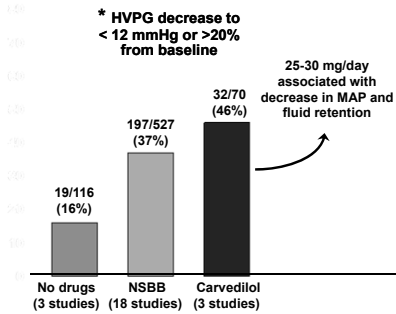
*Retrospective, non-consecutive, non-inception cohort study

In patients with large varices that have not bled, a decrease in HVPG >10% improves outcomes



Villanueva et al. *Gastroenterology* 2009;137:119-128

Carvedilol has a higher rate of hemodynamic responders* compared to other NSBB



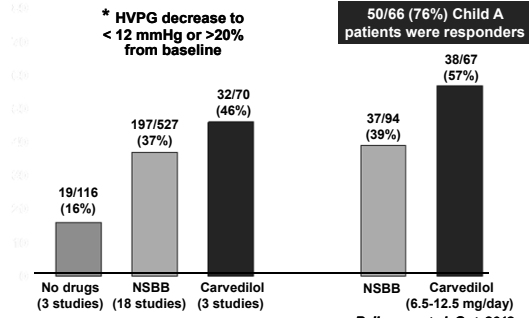
Miñano and Garcia-Tsao, *Gastro Clin N Am* 2010;39:681

Carvedilol (non-selective, vasodilating β -blocker) was more effective than EVL in preventing first variceal hemorrhage

	EVL	Carvedilol*	p
n	75	77	p
Median follow-up (mos)	25.5	26.2	ns
First variceal hemorrhage	23%	10%	0.04
Overall mortality	37%	35%	ns
Bleeding-related mortality	2%	3%	ns
Treatment discontinuation due to intolerance	12%	16%	ns

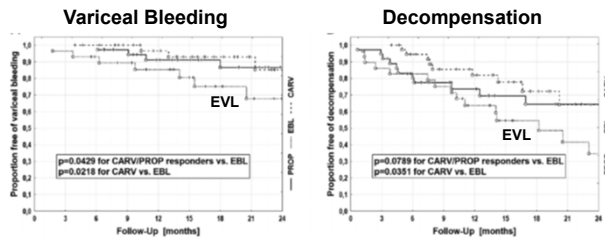
Tripathi et al. Hepatology 2009;50(3):825-33 *12.5 mg/day

Carvedilol has a higher rate of hemodynamic responders* compared to other NSBB



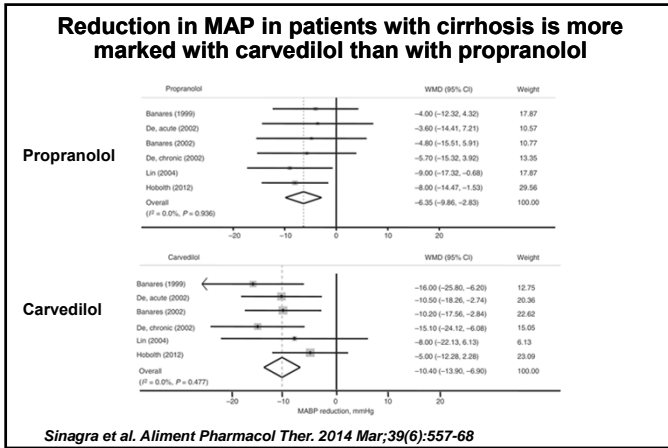
Miñano and Garcia-Tsao, Gastro Clin N Am 2010;39:681

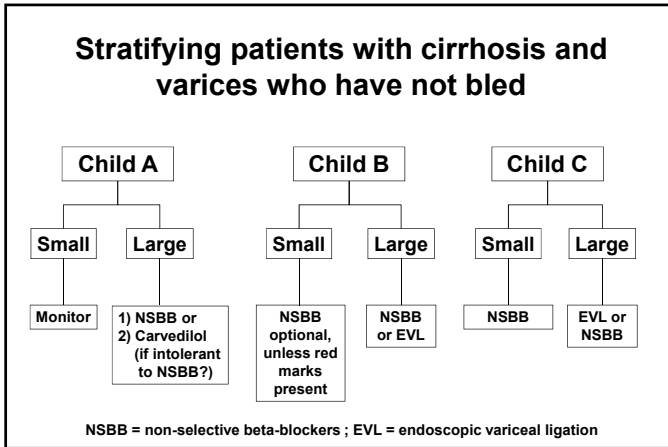
Propranolol and carvedilol hemodynamic responders* have a lower probability of variceal bleeding and decompensation than EVL

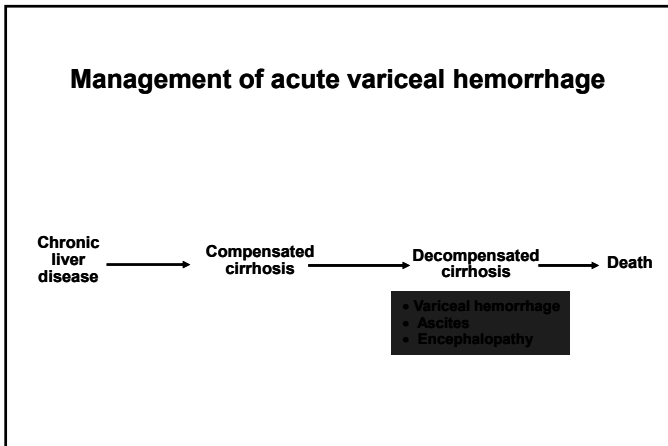


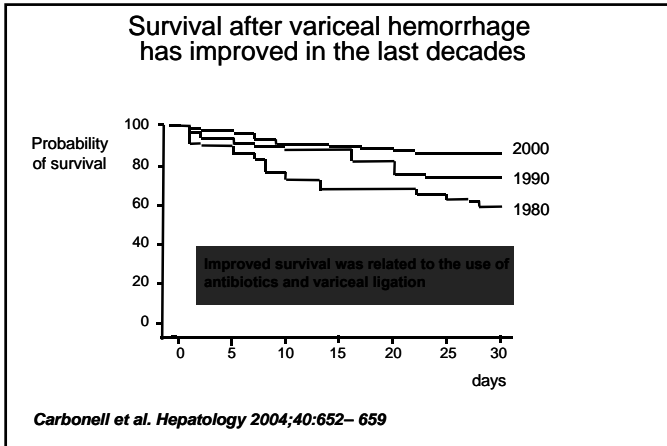
Reiberger et al. Gut 2012 [Epub ahead of print]

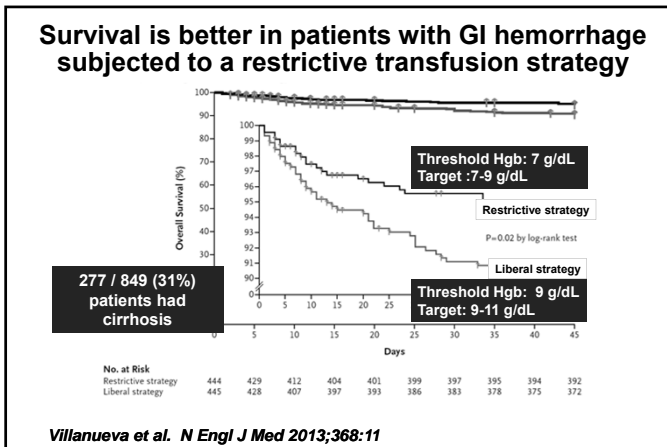
* HVPG decrease to < 12 mmHg or >20% from baseline

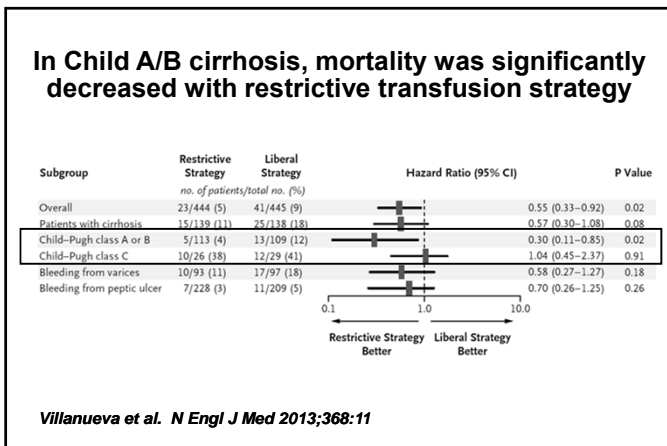












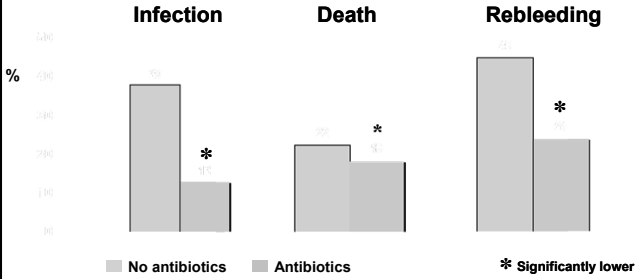
In Child A/B cirrhosis, rebleeding was significantly decreased with restrictive transfusion strategy

Further bleeding — no. of patients/total no. (%)	Restrictive strategy	Liberal strategy		
Overall	45/444 (10)	71/445 (16)	0.62 (0.43-0.91)	0.01
Patients with cirrhosis	16/139 (12)	31/138 (22)	0.49 (0.27-0.90)	0.02
Child-Pugh class A or B	12/113 (11)	23/109 (21)	0.53 (0.27-0.94)	0.04
Child-Pugh class C	4/26 (15)	8/29 (28)	0.58 (0.15-1.95)	0.33
Bleeding from esophageal varices	10/93 (11)	21/97 (22)	0.50 (0.23-0.99)	0.05
Rescue therapies				
Balloon tamponade	3/139 (2)	11/138 (8)		0.03
TIPS	6/139 (4)	15/138 (11)		0.04

- HVPG increased with liberal transfusion strategy (n=77)
- HVPG did not change with restrictive transfusion strategy (n=74)

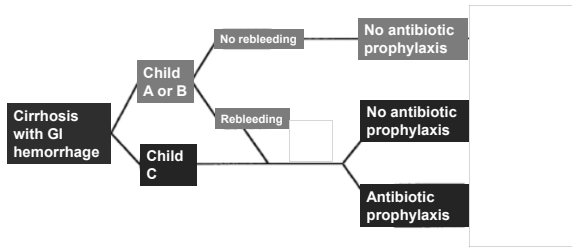
Villanueva et al. N Engl J Med 2013;368:11

Prophylactic Antibiotics Improve Outcomes in Cirrhotic Patients with GI Hemorrhage



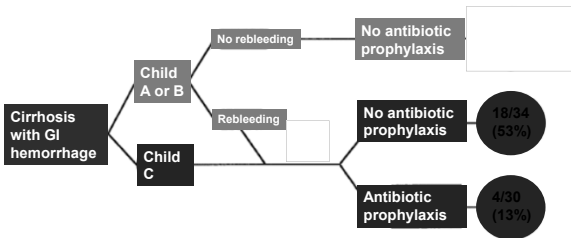
Chavez-Tapia et al. Cochrane 2010 . CD002907; Soares-Weiser et al. Cochrane 2002 CD002907

Do we need to stratify patients with cirrhosis and GI hemorrhage for antibiotic prophylaxis?



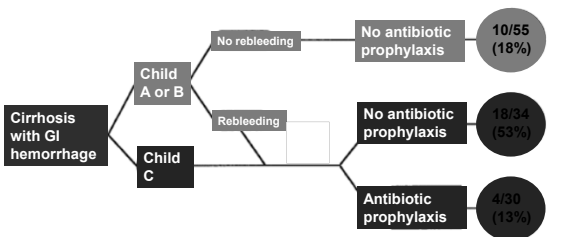
Pauwels et al. Hepatology 1996;24:802-806

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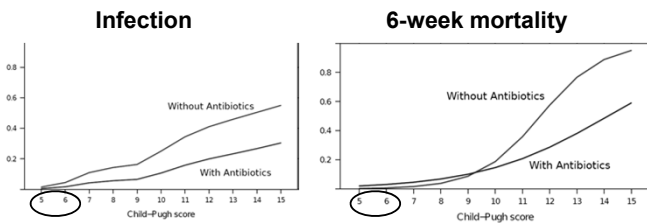
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Do we need to stratify patients with cirrhosis and GI hemorrhage for antibiotic prophylaxis?



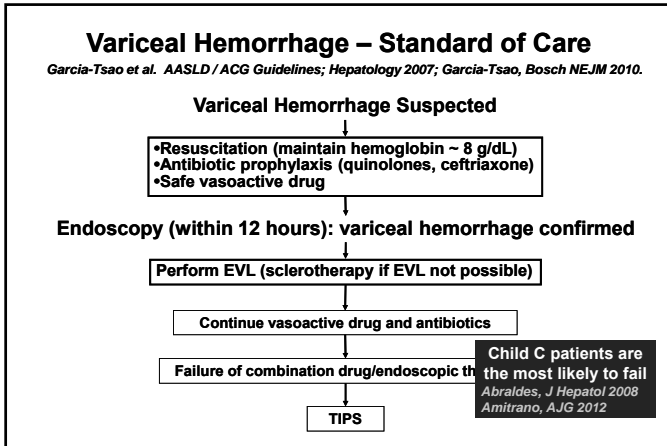
Pauwels et al. Hepatology 1996;24:802-806

Child A patients with acute variceal hemorrhage have a low risk of infection and death



Tandon et al. AASLD 2013 #1627. Submitted

Retrospective database (1996-2009); 252 patients who had not received antibiotic prophylaxis

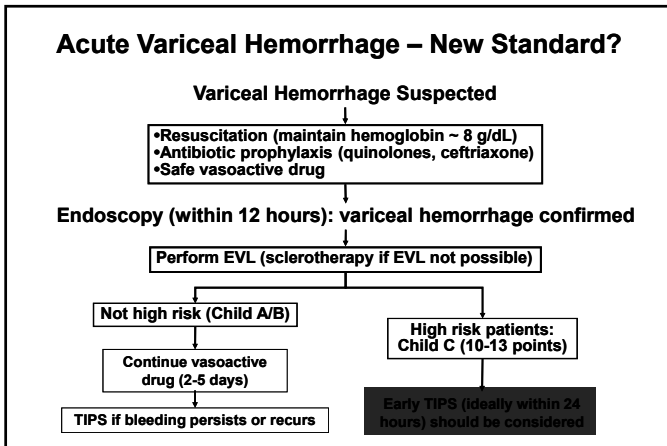


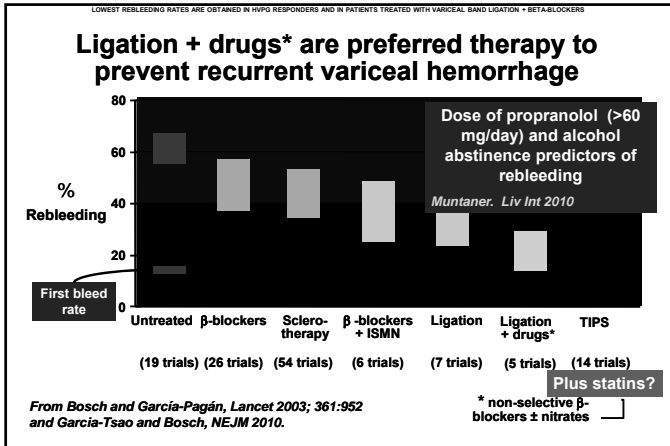
Multicenter RCT of early TIPS in high-risk patients with variceal hemorrhage

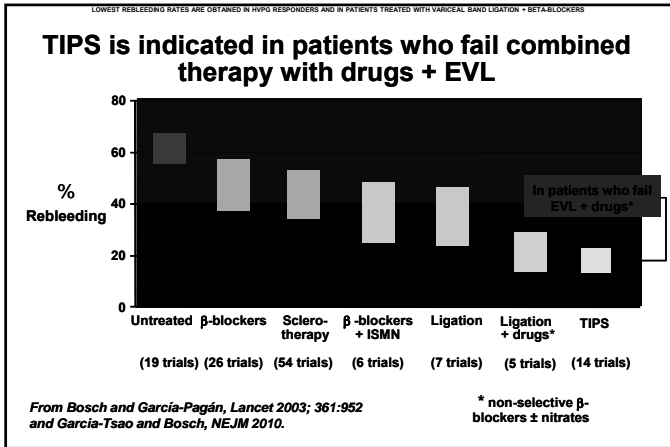
- 63 patients: Child C (10-13 points) or Child B with active bleeding (on vasoactive drugs) 18% of admissions with VH
- TIPS within 72 hours of admission vs. standard therapy
- Median follow-up 16 months

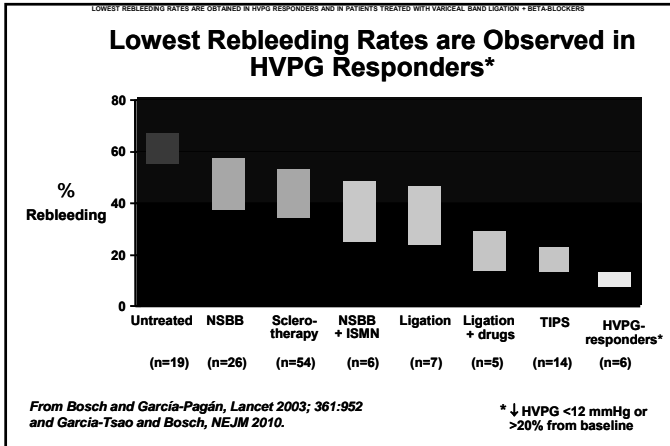
Endpoint	TIPS (n=32)	Std (n=31)
Failure to control bleed	1 (3%)*	14 (45%)
- Early rebleed (<6 wks)	1	4
- Early rebleed (<6 wks)	0	7
- Late rebleed (6 wk-1 yr)	0	3
Death	4 (12%)*	12 (39%)
Encephalopathy	8 (25%)	12 (39%)

García-Pagán et al. N Engl J Med 2010; 24:2370-9.

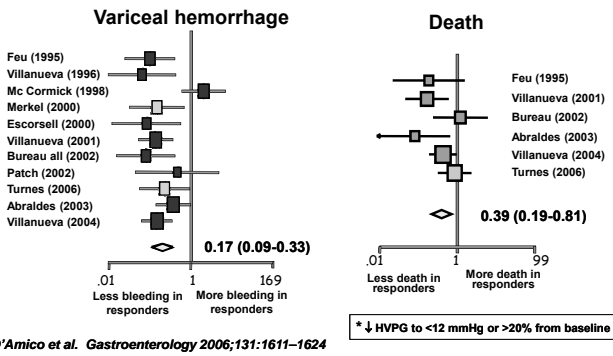






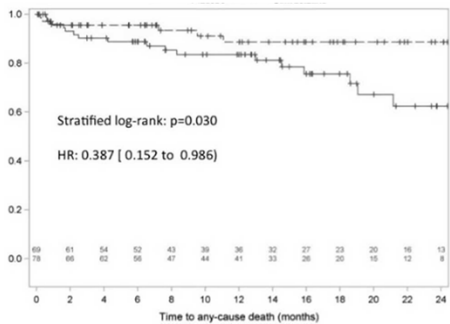


Bleeding and death are significantly lower in HVPG responders*

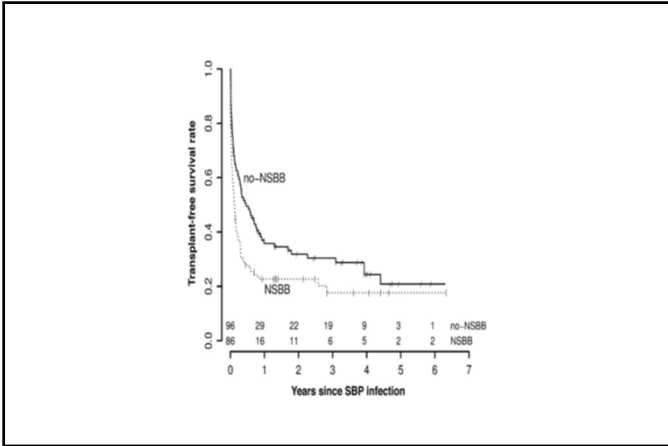


Future

- **Refine stratification strategies**
 - New “recalibrated” MELD? (<11, low risk; >19 high risk)
 - *Reverter et al. Gastro 2014.*
- **Investigate non-invasive indicators of hemodynamic response**
- **Develop therapies or combination of therapies that will increase the proportion of “responders”**



Abralde et al. EASL 2013.



Child A patients with acute variceal hemorrhage have a low risk of infection

- Retrospective database (1996-2009)
- Selected 252 patients with cirrhosis who had not received antibiotic prophylaxis
- 51 (20%) developed infection
 - Child A: 5%; Child B: 16%; Child C: 34%
- Child A patients had a 6-week mortality rate of only 2% (one died of HCC)

Tandon et al. AASLD 2013 #1627
