

Acute variceal bleeding – How can we improve outcomes?

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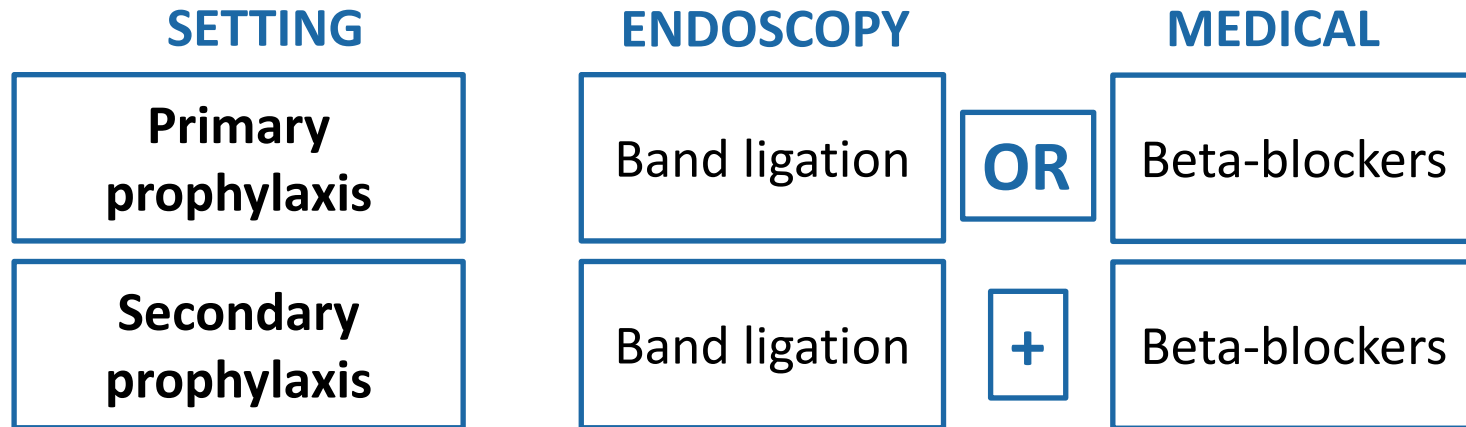
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Financial Interest Disclosure

(over the past 24 months)

Commercial Interest	Relationship
Gilead Sciences	Speaker fees
Mallinckrodt Pharma.	Investigator

Current status



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SETTING	ENDOSCOPY		MEDICAL
Primary prophylaxis	Band ligation	OR	Beta-blockers
Secondary prophylaxis	Band ligation	+	Beta-blockers
Acute variceal bleeding	Within 12 hours	+	Octreotide Antibiotics

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Secondary prophylaxis	Band ligation	+	Beta-blockers
Acute variceal bleeding	Within 12 hours	+	Octreotide Antibiotics
Gastric varices	Cyanoacrylate injection	+	Octreotide Antibiotics

Outline

- Esophageal varices: before and during the endoscopy
- Esophageal varices: after the endoscopy
- Esophageal varices: after discharge
- Gastric varices

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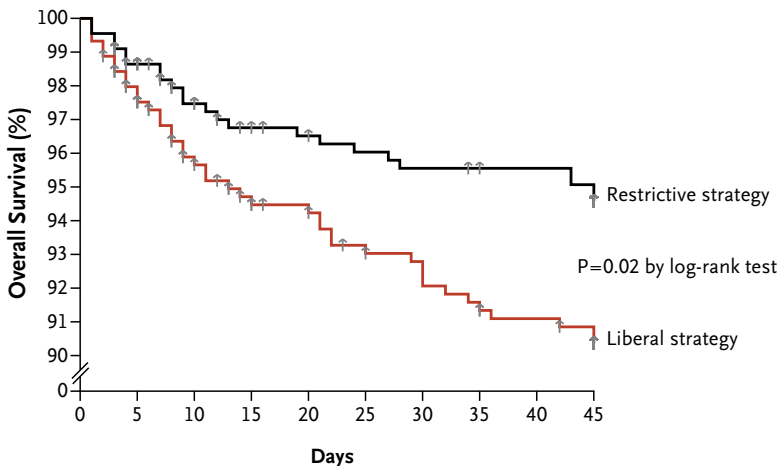
Patient stratification

- Identification of patients at risk of rebleeding and death

Criteria	6-week mortality
MELD \geq 19 vs < 19	46 vs 8%
Child C and creatinine > 88 μ M (ChildC-C1)	52 vs 10%
Child C vs Child B	36 vs 12%
Child B with active bleeding/ChildC vs others	28 vs 7%
Child B with active bleeding vs no active bleeding	12 vs 12%
Hepatic venous pressure gradient \geq 20 vs < 20 mmHg	64 vs 20% at 1 y

Transfusion strategy in variceal bleeding

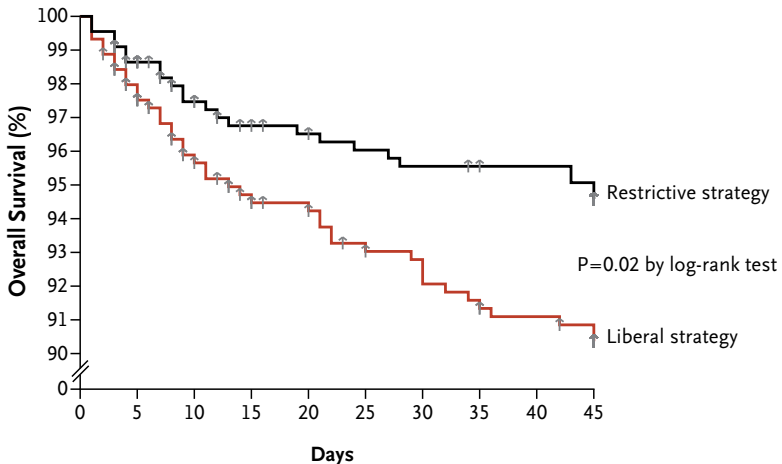
- RCT comparing restrictive (target hemoglobin > 70g/L vs liberal > 90 g/L) transfusion strategies



	n	6 week mortality HR	P value
All patients	889	0.55 (0.33-0.92)	0.02
Cirrhotics	277	0.57 (0.30-1.08)	0.08
Child A-B	222	0.30 (0.11-0.85)	0.02
Child C	55	1.04 (0.45-2.37)	0.91
Variceal bleeding	190	0.58 (0.27-1.07)	0.26

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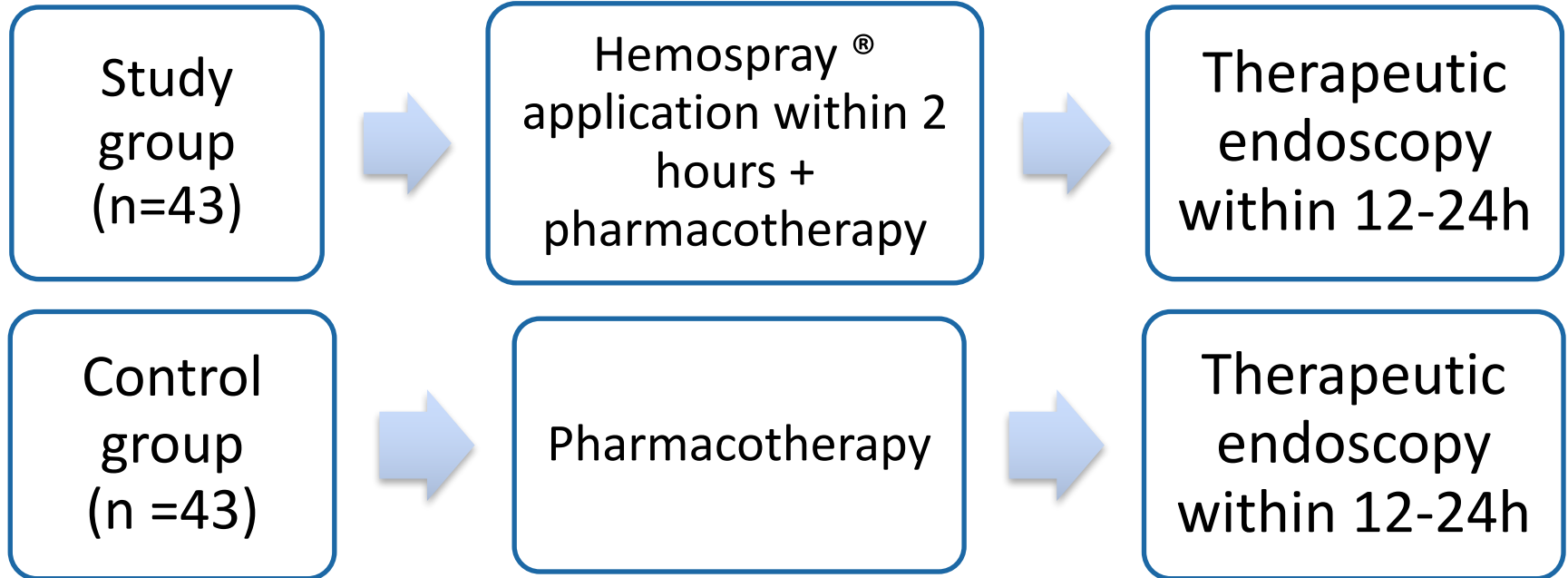
Avoid volume overexpansion that will increase variceal pressure

Choice of vasoactive agent

- Octreotide is the standard treatment in North America
- Terlipressin not approved by Health Canada or FDA
- Promising results in HRS1 from the CONFIRM trial
- Historical studies demonstrated survival benefit with terlipressin in AVB
- Large RCT comparing terlipressin, somatostatin and octreotide

	Terlipressin (n = 261)	Octreotide (n = 260)	p
Active bleeding at endoscopy	43.7%	43.5%	NS
Rebleeding at day 5	3.4%	3.4%	NS
Mortality	8.0%	8.9%	NS

Hemostatic powder in acute variceal bleeding?



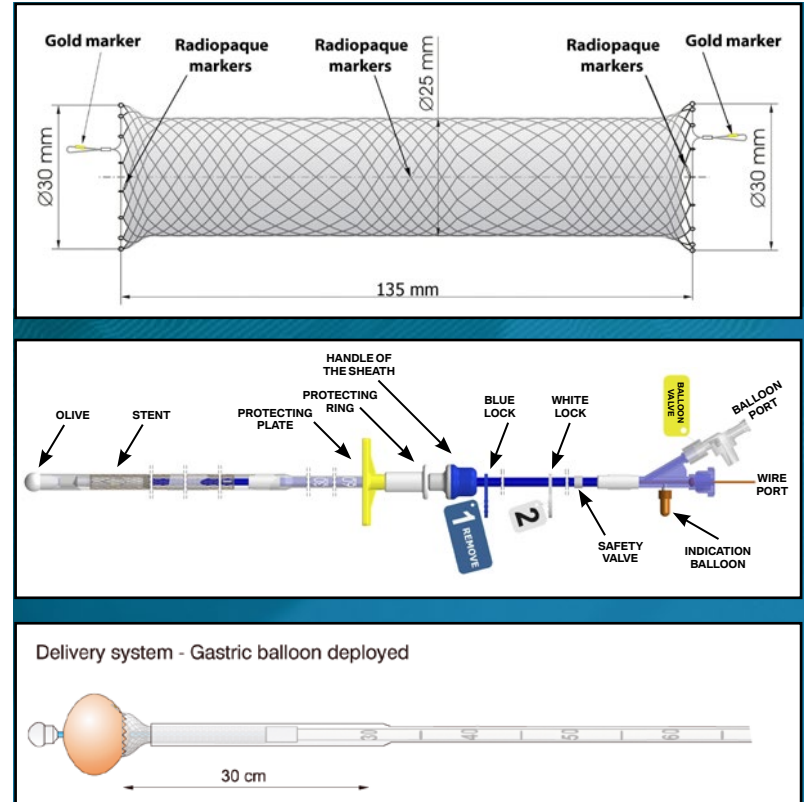
- Good results in short term endoscopic hemostasis
- Decrease in 6-week mortality (7% vs 30%, $p=0.006$)

Hemostatic powder in acute variceal bleeding?

- Interesting option if:
 - Endoscopist unqualified for treatment (esophageal or gastric varices)
 - Massive bleeding
- Highlights importance of early endoscopic treatment

Use of esophageal stents for refractory bleeding

- Alternative to balloon tamponade
- 13.5 cm X 3.0 cm stent
- Solely for esophageal varices
- Should be left in place for ≤ 7 days



Use of esophageal stents for refractory bleeding

	Esophageal stent (n=13)	Balloon tamponade (n=15)	P-value
MELD	16.5	17	NS
Adverse events	6	14	0.024
Absence of bleeding at day 15	85%	47%	0.037
Survival at day 15	69%	47%	NS
Survival at 6 weeks	54%	40%	NS

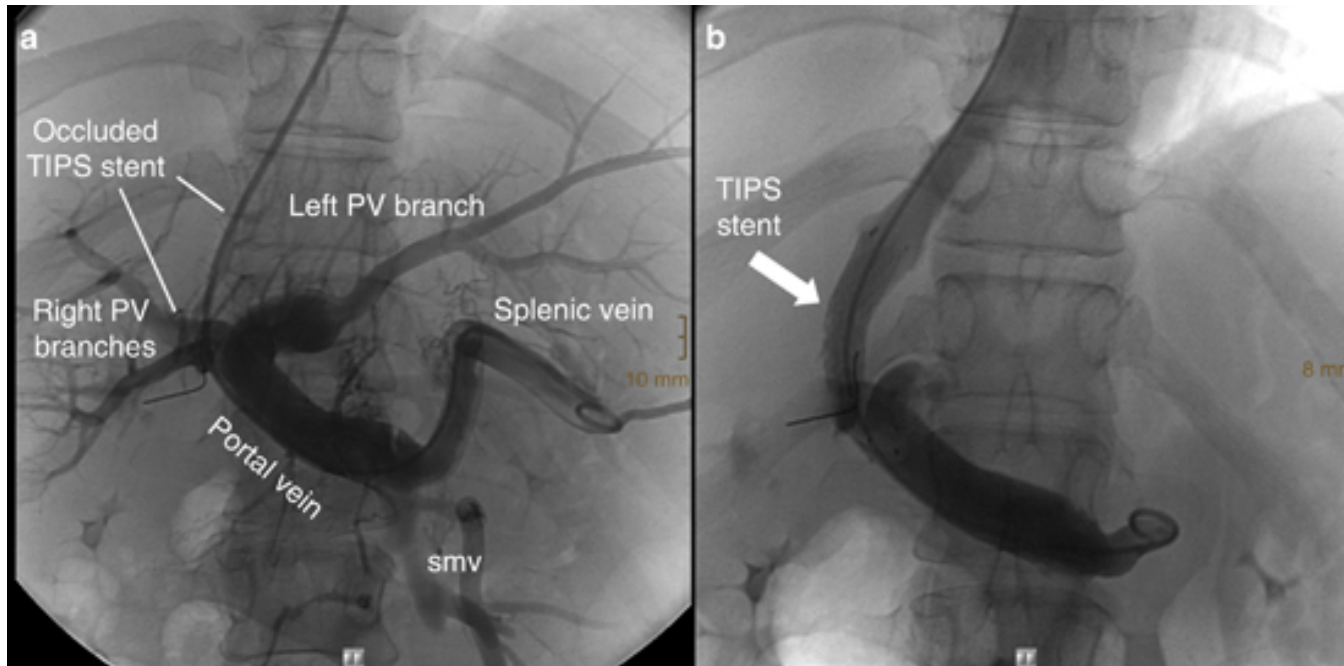
Use of esophageal stents for refractory bleeding

- Published results
 - Hemostatic success: 79-96%
 - Rebleeding rate: 18-29%
 - 30-day survival: 64-68%
 - High rates of stent migration
- Hemostatic and survival benefit in acute-on-chronic liver failure (ACLF) patients

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- Esophageal varices: before and during the endoscopy
- **Esophageal varices: after the endoscopy**
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- Gastric varices

TIPS



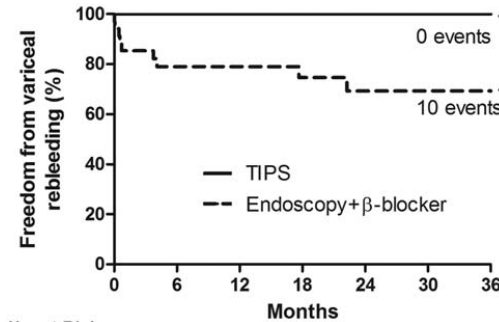
Objective : porto-systemic gradient ≤ 10 mmHg

Common indications for TIPS in AVB

- Bleeding not controlled by endoscopic therapy
- Early rebleeding

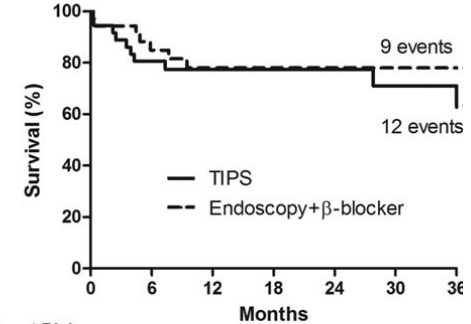
TIPS in unselected patients

- Randomization after initial stabilization and endoscopy for gastric or esophageal variceal bleeding
- All comers with cirrhosis, CPT \leq 13, no advanced HCC, no MOF
- 37 TIPS vs 35 endoscopic treatment + β -blockers



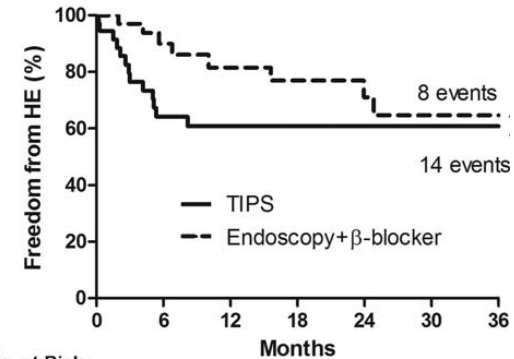
No. at Risk	
TIPS	37
Endoscopy	35

28	24	23	15	10	6	6
22	18	17	10	6	3	



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TIPS	37
Endoscopy	35

28	24	23	15	10	6
26	21	21	14	9	6

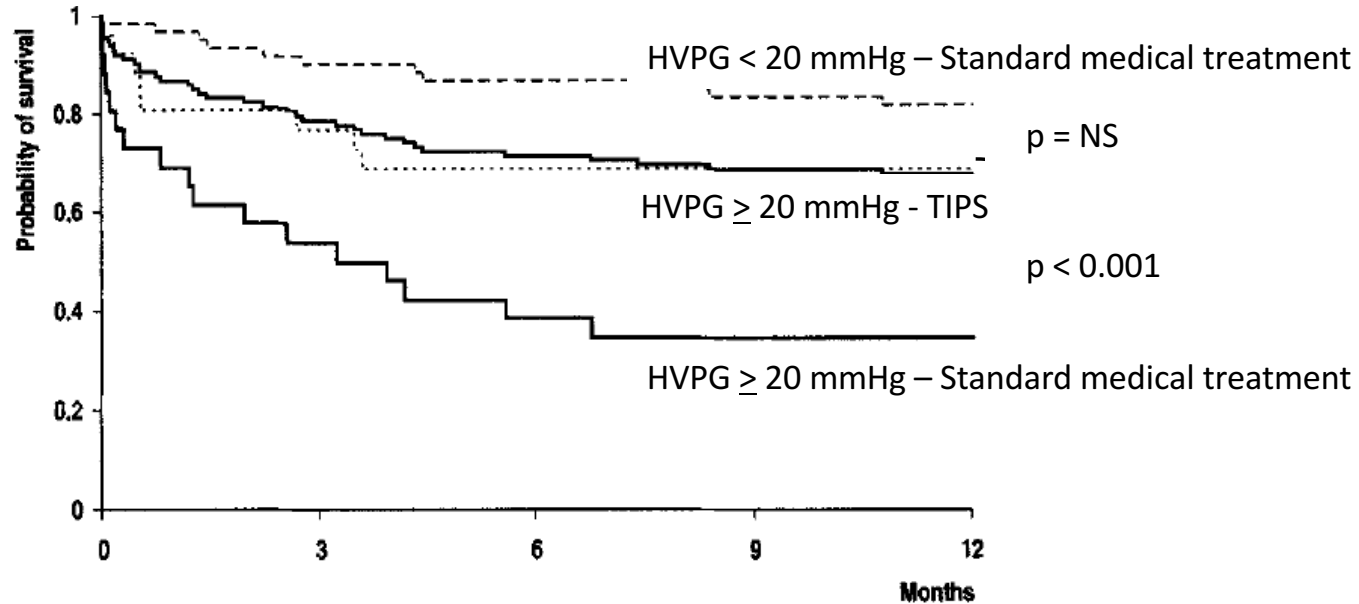


No. at Risk	
TIPS	37
Endoscopy	35

21	18	17	11	9	5
23	18	17	12	7	4

TIPS based on HVPG

- Consecutive patients with AVB treated by sclerotherapy
- HVPG measurement within 24h
- TIPS vs SMT in those > 20 mmHg

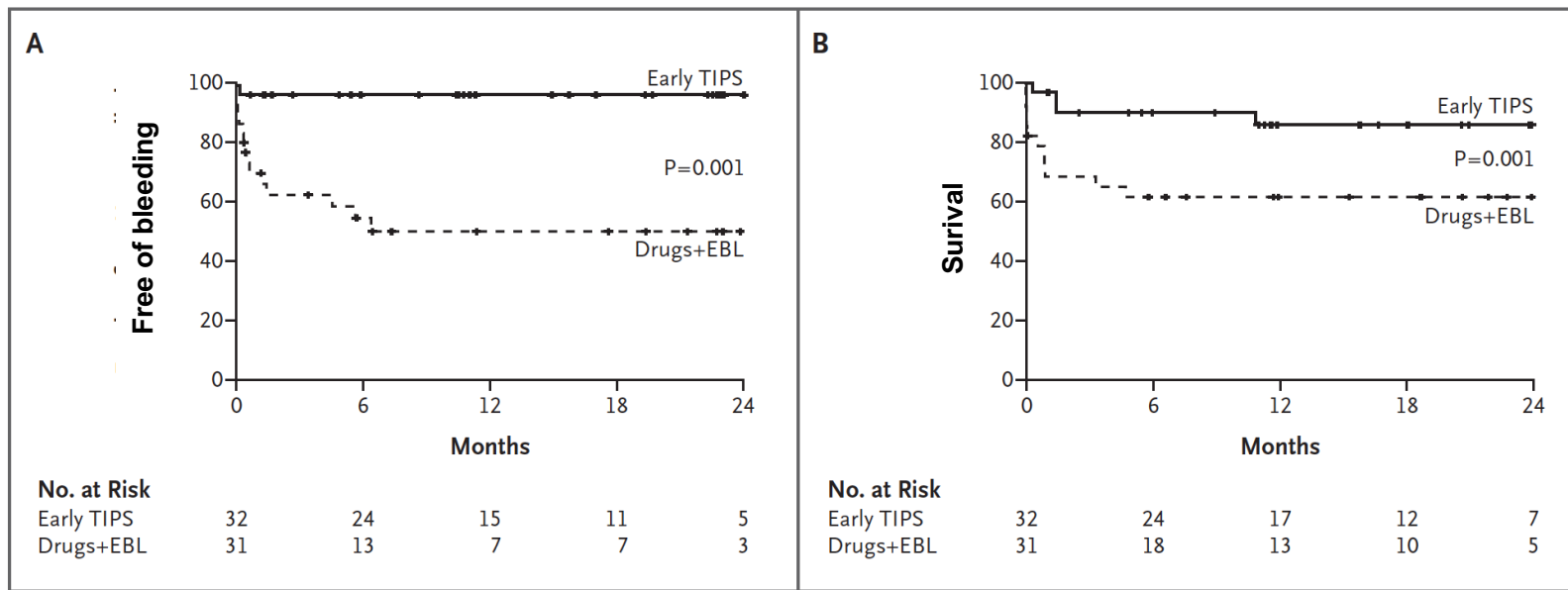


Clear survival benefit when selecting patients with high HVPG

Early TIPS for acute variceal bleeding

- Inclusion criteria
 - Esophageal variceal bleeding
 - Child C (10-13)
 - Child B (7-9) with active bleeding
- Exclusion criteria
 - CHC beyond Milan criteria
 - Complete portal vein thrombosis
 - Creatinine > 266 μ M
 - Heart failure

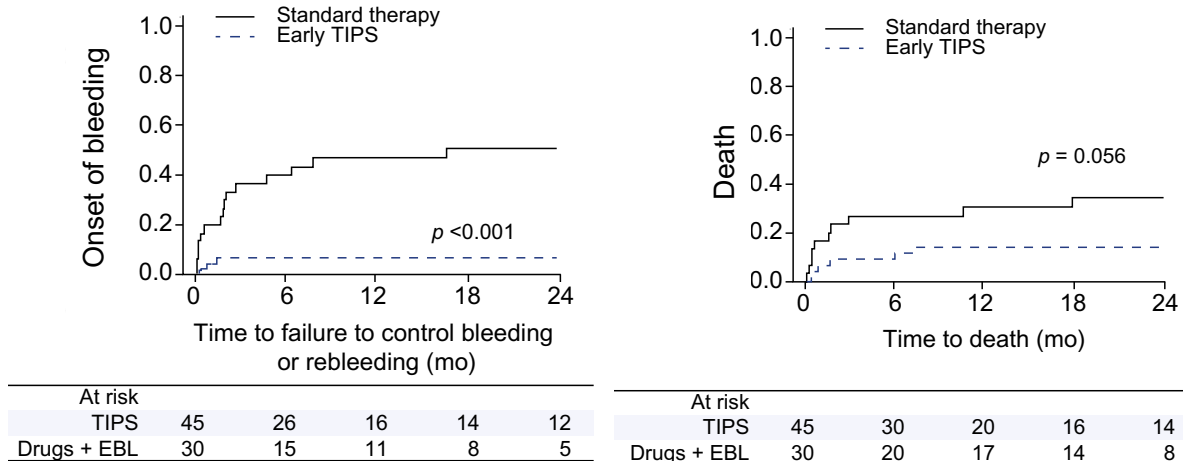
Early TIPS for acute variceal bleeding



No difference in the rates of hepatic encephalopathy

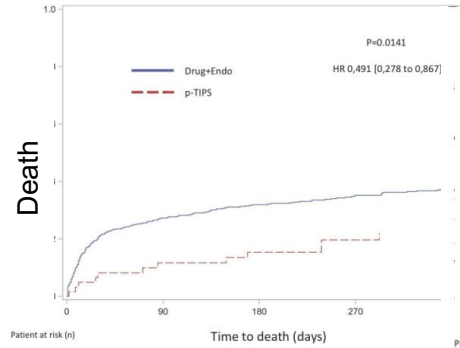
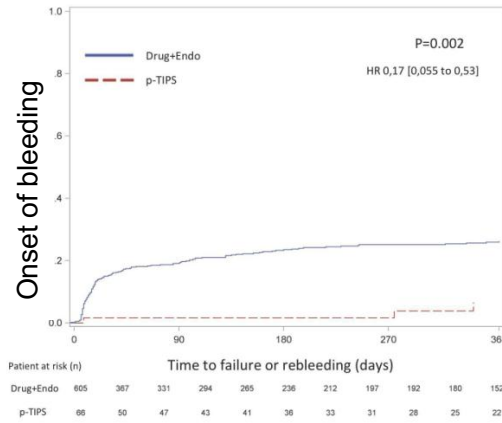
Early TIPS: validation studies

- Observational study

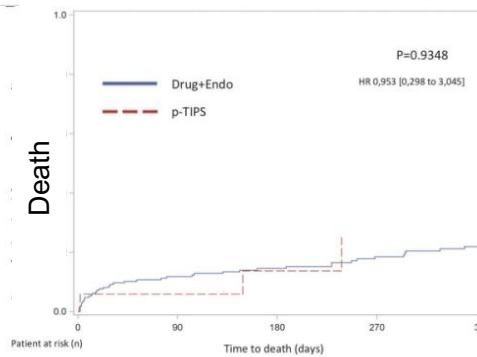


Results from RCT reproduced

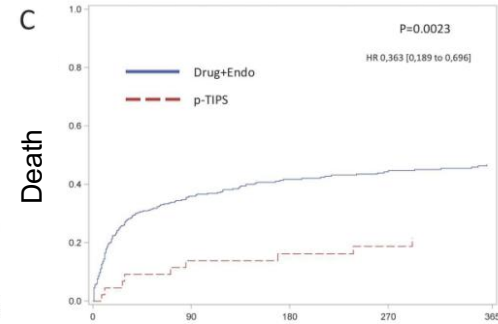
Early TIPS: validation studies



Overall



Child B + active
bleeding



Child C

Early TIPS

- 132 patients with Child B or C cirrhosis and AVB randomized after initial endoscopic therapy
- 86 early TIPS vs 46 standard medical treatment
- Mostly young patients with HBV cirrhosis and Child-Pugh B

	TIPS	SMT	p
Free from rebleeding at 1y	89%	66%	0.001
6-week survival	99%	82%	0.02
1-year survival	86%	73%	0.046
Hepatic encephalopathy	35%	36%	NS
Serious adverse events	12%	24%	NS

Early TIPS: the real life

- 964 patients with portal hypertension-related bleeding
- 326/931 eligible for early TIPS
 - 57 (18%) underwent TIPS
 - 22 (7%) underwent an early TIPS
 - No trend in mortality benefit
- Reasons for not performing early TIPS
 - No local availability
 - Lack of belief in beneficial effect

Early TIPS: bottom line

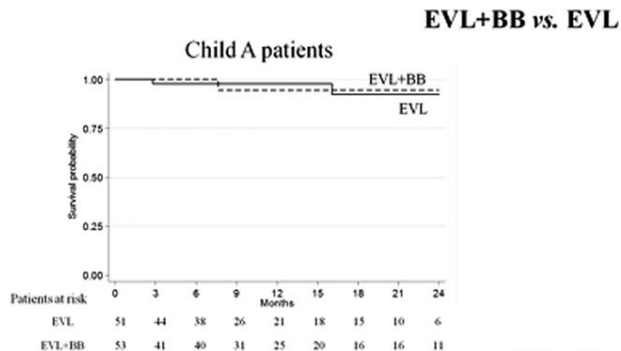
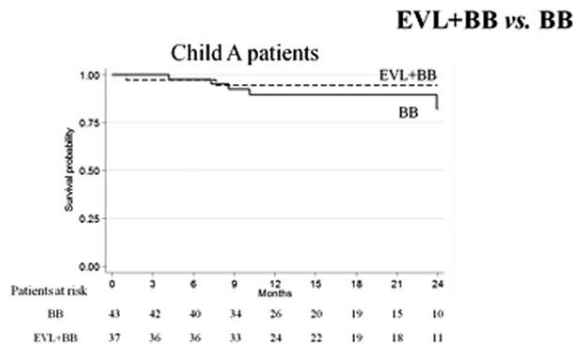
- Mortality benefit demonstrated in two RCT
- Active bleeding criteria put into question
- Availability is an issue
- Are results from European and Asian populations valid in North America?
- RCT underway with results expected soon
 - Scotland (NCT02377141) Child ≥ 8
- Decision on a case-by-case approach for now

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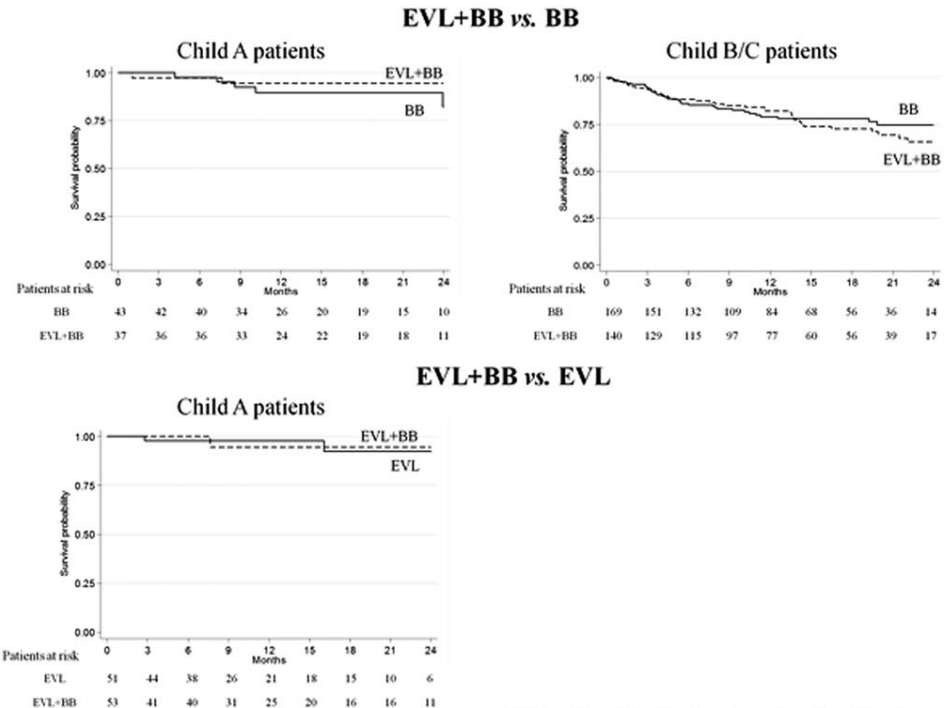
Importance of beta-blockers in Child B/C patients

- Benefit of combination therapy (BB+EVL) only proven for reducing rebleeding rate
- Meta-analysis using individual patient data (n = 815)



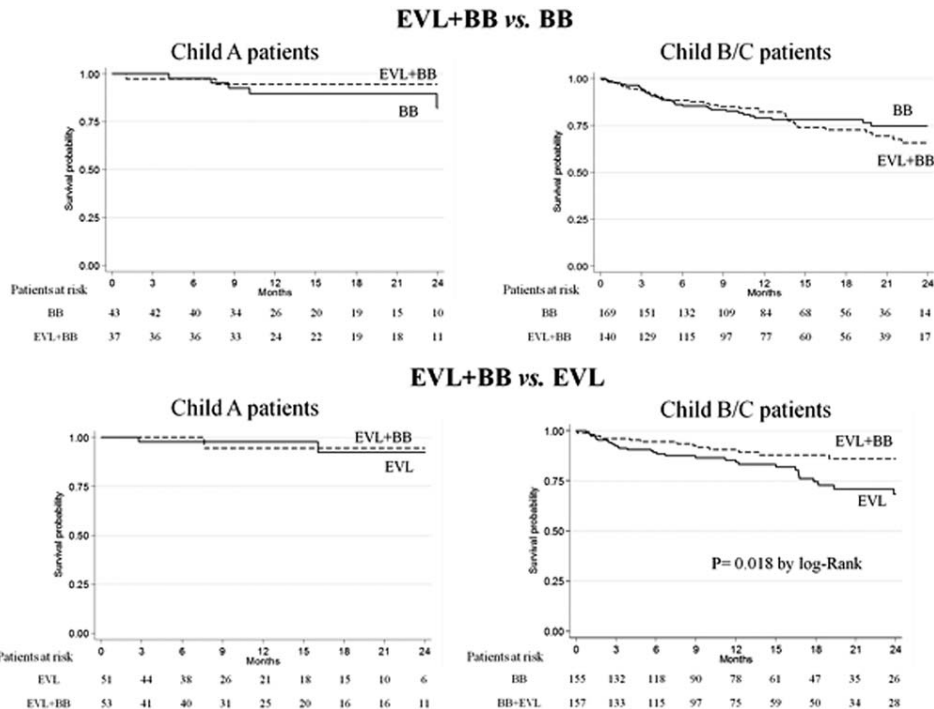
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Beta-blockers in advanced cirrhosis: is there still a controversy?

Studies showing benefit	Leithead 2015	Waitlisted	↓ Mortality
	Mookerjee 2016	ACLF	↓ Mortality
	Aday 2016	Ascites	↓ Mortality
	Bang 2016	Ascites	↓ Mortality (dose < 160 mg/d)
	Sinha 2017	Ascites	↓ Mortality (carvedilol)
	Onali 2017	Ascites	↓ Mortality
Neutral studies	Galbois 2011	Sepsis in ICU	Mortality
	Robins 2014	Ascites	Survival
	Mandorfer 2014	Ascites/SBP	↓ Mortal. if ascite/ ↑ Mortal. After SBP
	Kimer 2015	Refractory ascites	Mortality
	Bossen 2016	Ascites	Mortality
	Njei 2016	Ascites	↑ Mortality w/ carvedilol
	Kim 2017	Waitlisted	↓Mortal. w/o ascites/↑Mortal. if ascites
	Bhutta 2017	Ascites, hospit.	Mortality
Studies showing increased risk	Sersté 2010	Refractory ascites	↑ Mortality
	Sersté 2011	Refractory ascites	↑ Post paracentesis circulatory dysfunction
	Sersté 2015	Alcoholic hepatitis	↑ AKI
	Kalambokis 2016	At risk varices	↑ Mortality/AKI if Child C

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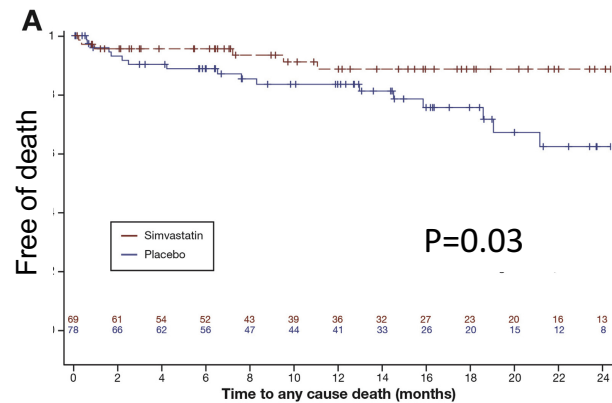
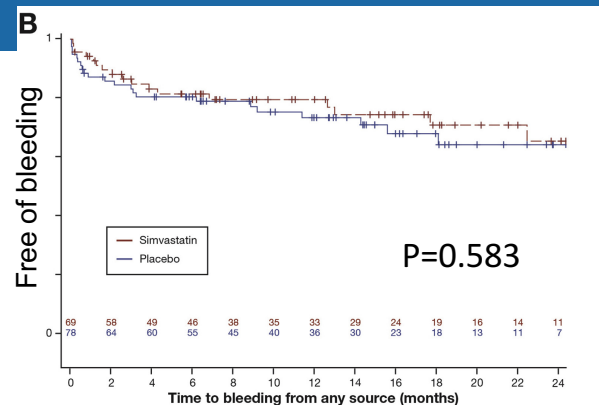
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Consider discontinuation if :

- Systolic BP < 90 mmHg
- Acute kidney injury
- Hyponatremia (< 130)
- ? SBP

Statins as secondary prevention

- Simvastatin lowers HVPG
- Decreased risk of death or decompensation in cohorts of patients with viral cirrhosis
- RCT of simvastatin vs placebo as secondary prophylaxis over SMT
- RCTs underway
 - LIVERHOPE (NCT03150459)
 - SACRED (NCT03654053)
 - STATLiver (NCT04072601)

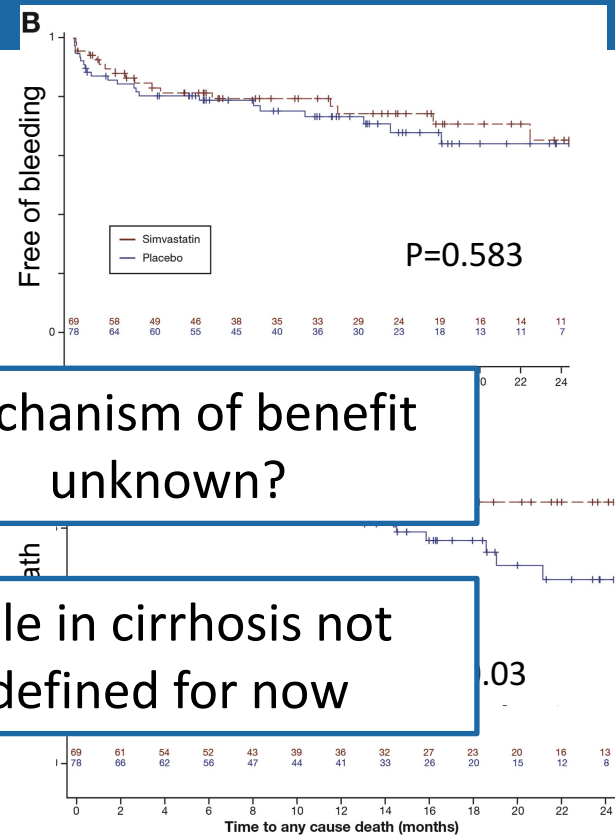


Abraldes, Villanueva *Gastroenterology* 2016

Abraldes *Gastroenterology* 2009, Chang *Hepatology* 2017, Mohanty *Gastroenterology* 2016

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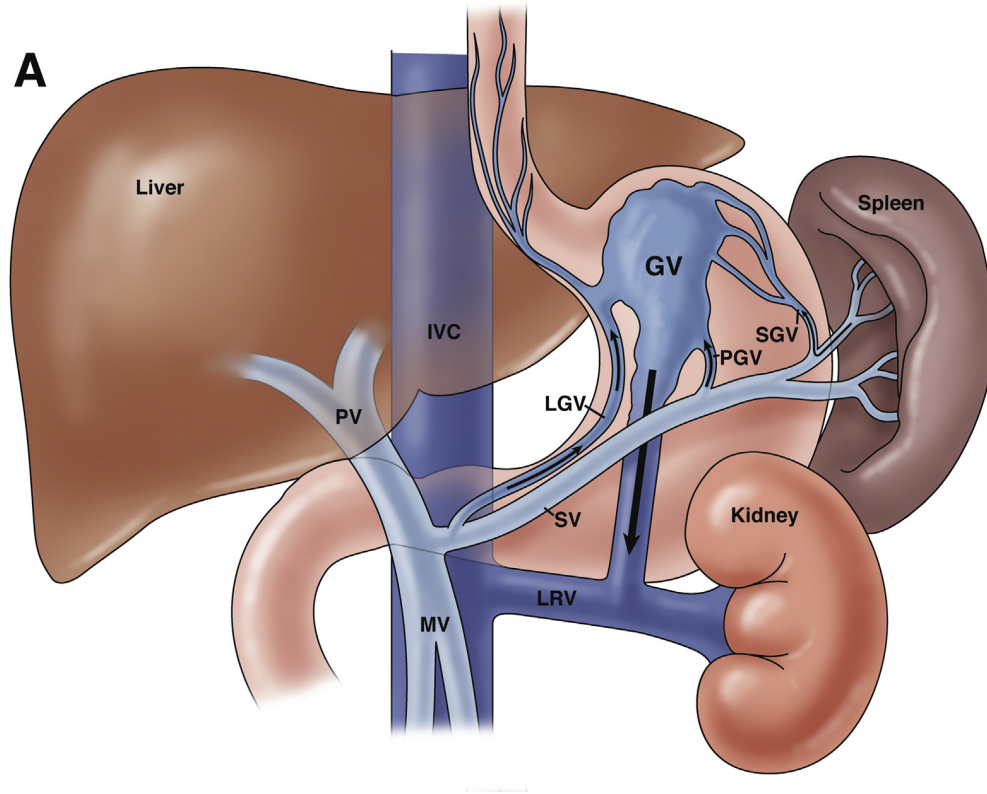
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Gastric variceal bleeding

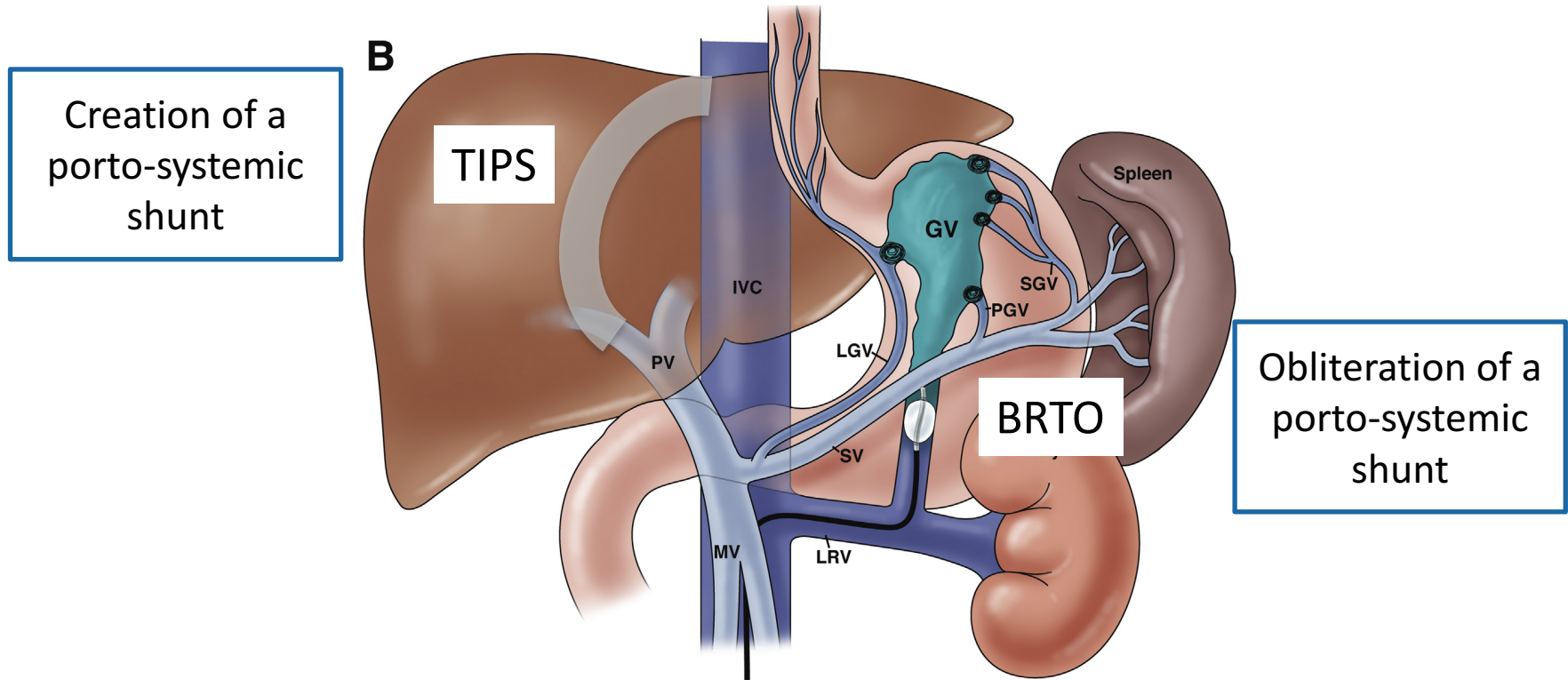
- Lower endoscopic hemostatic success
- Higher rates of treatment complications
- Higher mortality

- Endoscopic variceal obliteration

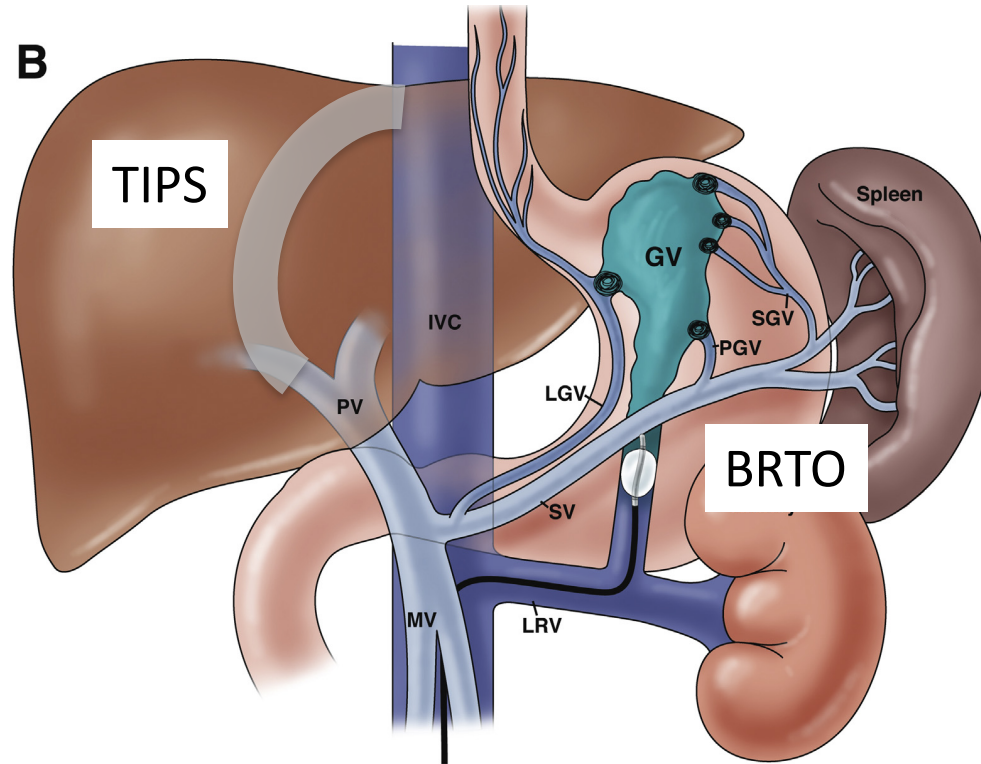
Anatomy of gastric varices



Endovascular treatment options



Endovascular treatment options



Endovascular treatment options

	TIPS	BRTO
Portal pressure	↓	↑
Hepatic encephalopathy	↑	↓
Ascites	↓	↑
Effect on esophageal varices	↓	↑ (?)

TIPS, BRTO or both?

- No prospective comparative study
- Hemostatic success > 90% with both
- Lower rate of ascites with combined technique
- Lower rebleeding rate with combined embolization
- Embolization usually performed based on post-TIPS portography

	BRTO (n = 462) vs TIPS (n = 219)
Technical success	p = NS
Hemostasis	p = NS
Complications	p = NS
Rebleeding	Favors BRTO
Encephalopathy	Favors BRTO
1-year survival	Favors BRTO

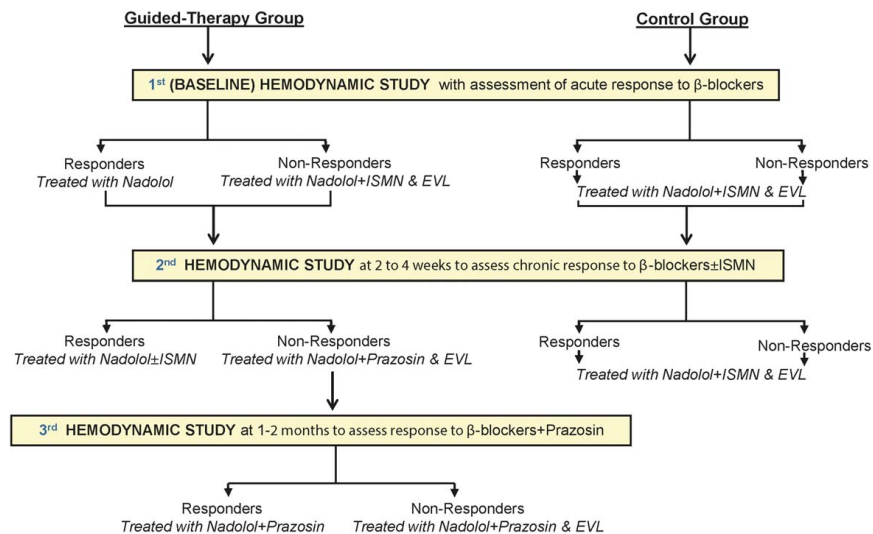
TIPS, BRTO or both?

- Factors to take into consideration
 - Presence of ascites
 - Presence of encephalopathy
 - Individual vascular anatomy
 - Contra-indications to TIPS
 - Local experience

Conclusions

- New options for initial hemostasis
- TIPS: to be considered in patients at high risk, once they are adequately identified
- Importance of beta-blockers in secondary prophylaxis
- Precise role of statins to be defined
- Gastric varices: discuss with your interventional radiologists

HVPG-guided pharmacologic treatment



	HR in study group	P-value
Rebleeding	0.53 [0.29-0.98]	0.04
Decompensation	0.68 [0.46-0.99]	0.05
Mortality	0.59 [0.35-0.99]	0.04

TIPS: Systematic early revision?

- General anesthesia may underestimate the real pressure gradient

	Immediate	Early (1-14d)	P-value
Final pressure gradient (mmHg)	8.5±3.5	10±3.5	0.01

- Fewer complications if gradient < 12 mmHg on follow-up (HR 0.11 [0.04-0.27], p < 0.001)
- Consider in those with final PPG 10-12 mmHg or those with massive bleeding?