Esophageal Variceal Bleed and Gastric Variceal Bleed

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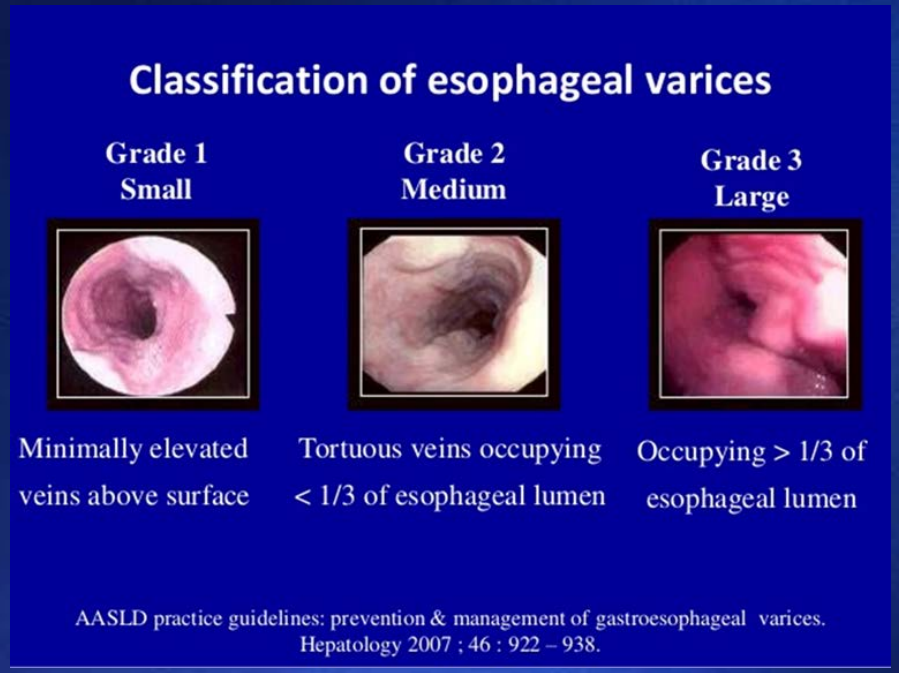
VARICEAL HEMORRHAGE

- Gastro-esophageal varices = 50% cirrhotics
  - Child A = 40%
  - Child C = 85%
- Varices form at rate of 5-15%/year; in 30% (25-40%) they will bleed at some time; mean bleed 2.9 units.
- Bleeding only if Portal Pressure >12mm Hg;
  - "clinically significant portal HTN" is >/= 10 mm Hg
- Risk of bleeding:
  - a) small varices </= 5 mm (F1) < 10% /y
  - b) medium/large (F2/F3) = 30% /year
- Mortality from variceal bleed = 15-30% (mean 20%)/ episode
- If untreated, 70% will die within a year.

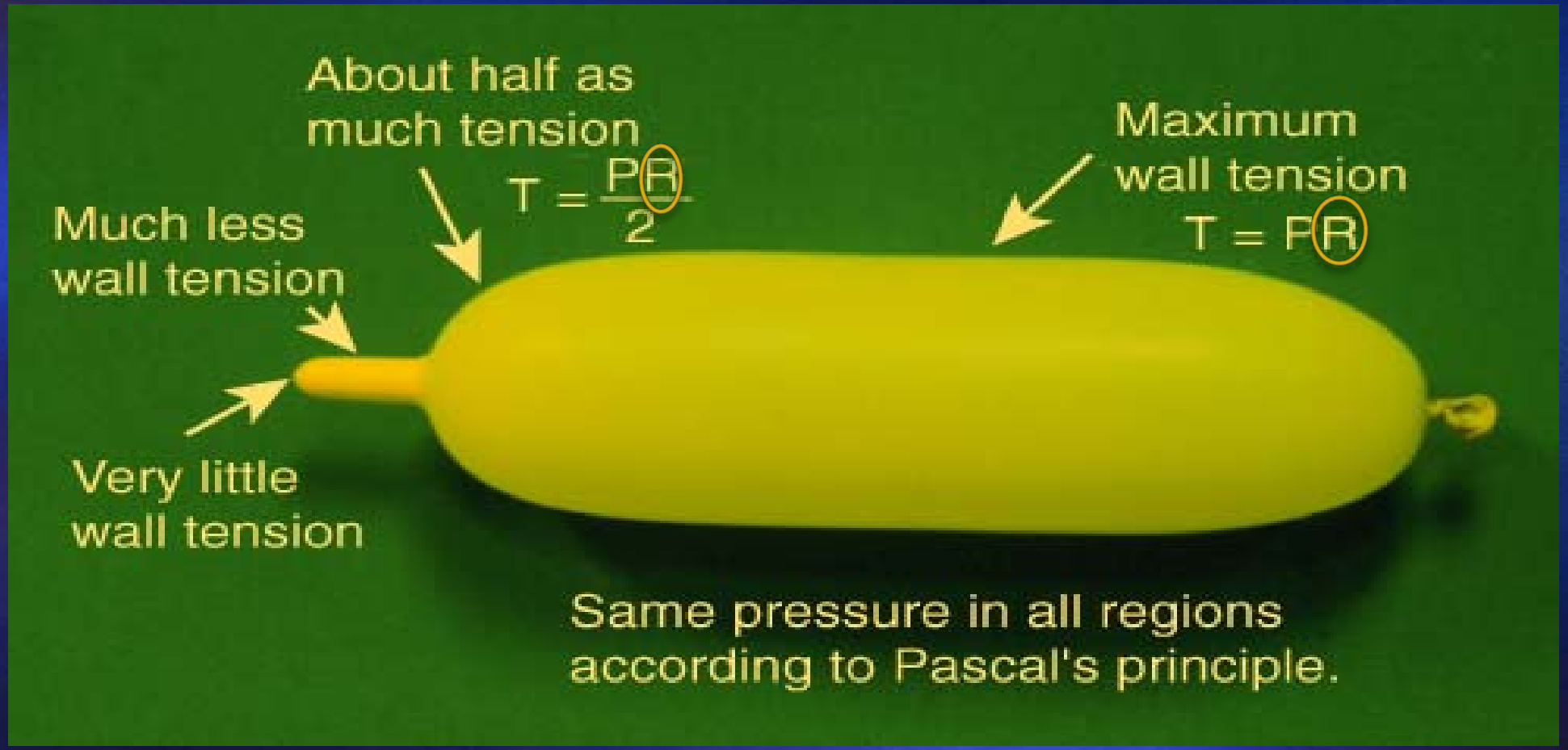
Morphologic Classification of Esophageal Varices

- Grade F0: no EV detected;
- Grade F1: small (</= 5 mm) straight EV;
- Grade F2: slightly enlarged (6 mm or more) tortuous EV occupying less than one-third of the esophageal lumen; and
- Grade F3: large coil-shaped EV that occupied more than one-third of the esophageal lumen



Determinants of Variceal Bleeding

Laplace's Law



Primary Prophylaxis

One-year Risk of Bleeding (%) of Esophageal Varices

Red wale markings and Child-Pugh Score

de Franchis R et al. N Engl J Med 1988;319:983

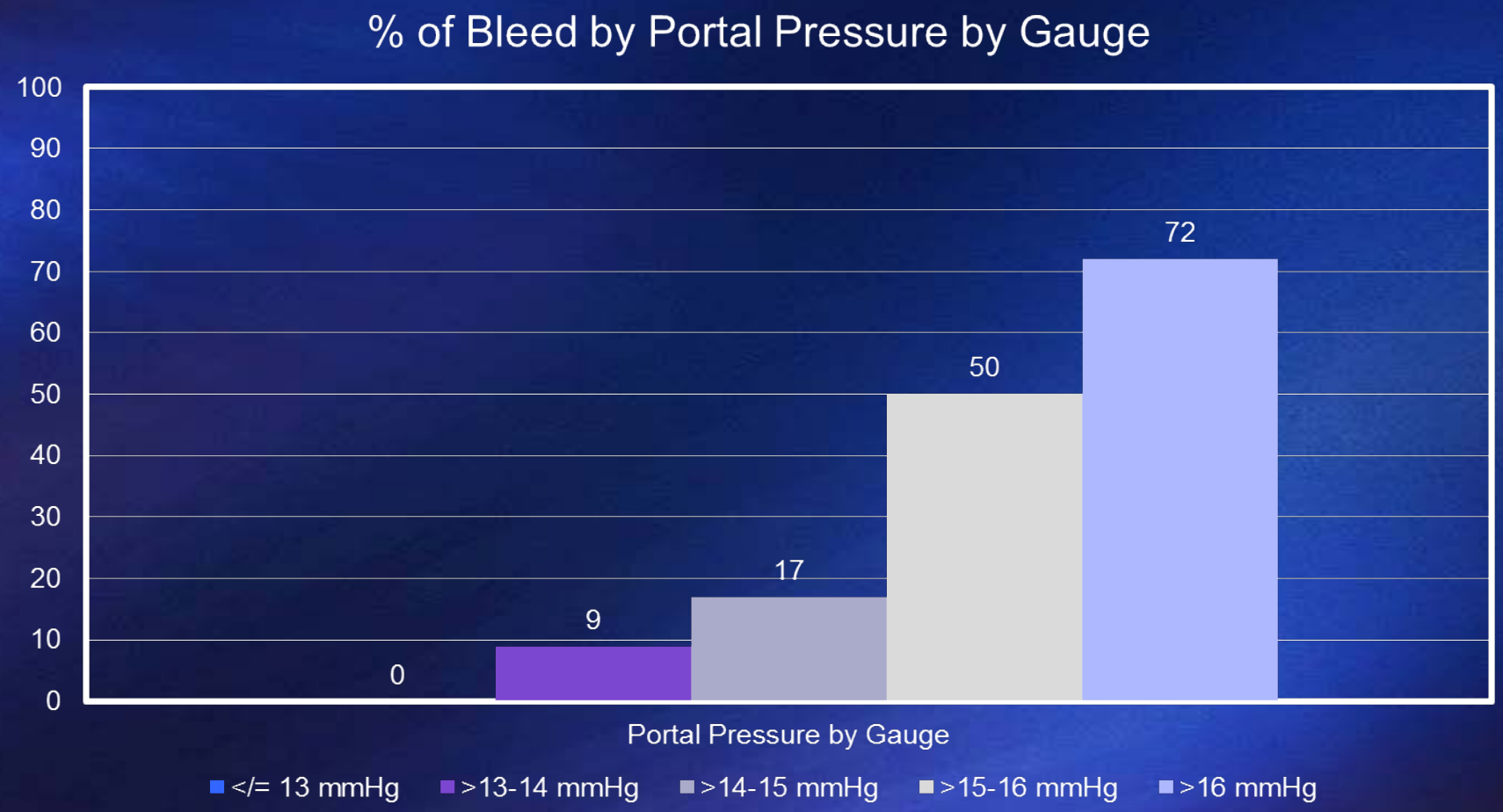
Red Markins	Child-Pugh A			Child-Pugh B			Child-Pugh C		
	F1	F2	F3	F1	F2	F3	F1	F2	F3
-	6	**10**	**15**	**10**	**16**	**26**	**20**	**30**	**42**
+	**8**	**12**	**19**	**15**	**23**	**33**	**28**	**38**	**54**
++	**12**	**16**	**24**	**20**	**30**	**42**	**36**	**48**	**64**
+++	**16**	**23**	**34**	**28**	**40**	**52**	**44**	**60**	**76**

The Risk of Bleeding from Esophageal Varices Increases with their Diameter, Child-Pugh Stage, and the Severity or "Red Markins"

Number in BOLD = beta-blocker; Number in Red = beta-blocker or banding

Incidence of Variceal Bleeding According to Variceal Pressure (by gauge)

Nevens F et al. Hepatology 1998; 27:15



Indications for Primary Prophylaxis of Esophageal Variceal Hemorrhage (VH)

- Annual rate of first hemorrhage: 12%
- **Medium or Large Varices (>/= F2; 6 mm or more):** Either traditional NSBBs (propranolol, nadolol), carvedilol, or EVL is recommended. Weight loss in obese patients.
- **Small Varices with high-risk:** high-risk defined as in CTP-C or with red wale marks; NSBB or carvedilol is the recommended therapy (EVL difficult). Weight loss in obese patients.
- **Choice and Follow-up:**
  - Choice of treatment should be based on patient preference and characteristics.
  - Patients on NSBBs or carvedilol for primary prophylaxis do not require monitoring with serial EGD. In EVL follow with EGD q 6-months.
- **Not Recommended:**
  - Combination therapy NSBB plus EVL.
  - TIPS placement is not recommended in the prevention of first VH.

Beta-Blockers as Primary Prophylaxis

- **Effect of Beta-Blockers**
  - Decreases 1st bleed rate (12% vs 23% with placebo) and death rate from bleeding;
    - gives trend to improved survival.
  - NNT to prevent one bleed = 11
  - Reduces progression from small to large varices.
    - Titrate to resting pulse of 55-60 bpm in each clinic visit, or
    - Titrate to HVPG < 12 mmHg or 20% drop (>/= 10% drop with IV propranolol)
  - Caution in refractory ascites and low MAP < 84 mmHg; Also in SBP?

Beta-Blockers as Primary Prophylaxis

- **Effect of Beta-Blockers**
- Carvedilol is non-selective beta-blocker with mild anti-alpha-1 effect hence also decreases hepatic vascular resistance.
  - More potent than propranolol but also drops MAP more.
  - More effective than EVL in preventing first bleed.
  - Not recommended for Secondary prophylaxis.
  - Dose: * Child A: 12.5 mg BID; * Child B or C: 6.25 BID

Management of Patients With Moderate/Large Varices That Have Not Bled

Therapy	Recommended Dose	Therapy Goals	Maintenance/Follow-up
Propranolol	•20-40 mg orally *twice* a day •Adjust every 2-3 days until treatment goal is achieved •Maximal daily dose: • 320 mg/day in patients without ascites • 160 mg/day in patients with ascites	•Resting heart rate of 55-60 beats per minute •Systolic blood pressure should not decrease <90 mm Hg	•At every outpatient visit make sure that heart rate is on target •Continue indefinitely •No need for follow-up EGD
Nadolol	•20-40 mg orally *once* a day •Adjust every 2-3 days until treatment goal is achieved •Maximal daily dose: • 160 mg/day in patients without ascites • 80 mg/day in patients with ascites	•Resting heart rate of 55-60 beats per minute •Systolic blood pressure should not decrease <90 mm Hg	•At every outpatient visit make sure that heart rate is on target •Continue indefinitely •No need for follow-up EGD
Carvedilol	•Start with 6.25 mg *once* a day •After 3 days increase to 6.25 mg twice-daily •Maximal dose: 12.5 mg/day (except in patients with persistent arterial hypertension) **•Not recommended in Secondary prophylaxis.**	•Systolic arterial blood pressure should not decrease <90 mm Hg	•Continue indefinitely •No need for follow-up EGD
EVL	•Every 2-8 weeks until the eradication of varices	•Variceal eradication (no further ligation possible)	•First EGD performed 3-6 months after eradication and every 6-12 months thereafter

Primary Prophylaxis for Esophageal Variceal Hemorrhage
Controversial & Not-Indicated Therapies

- **CONTROVERSIAL**
  - Addition of Nitrates to beta-blocker:
    - NNT 10 to prevent one additional hemorrhage over Beta Blocker.
    - No clear survival benefit but had a trend (Merkel C et al. Lancet 1996;348:1677).
  - Simvastatin (Zocor): increase hepatic nitric oxide; decrease HVPG by up to 8% (Abraldes JG et al. Gastroenterol 2009;136:1651)
    - A recent multicenter, placebo-controlled RCT showed that addition of simvastatin did not reduce rebleeding (compared to placebo), but had a significant improvement in survival, related to a decrease in deaths from bleeding or infections. There was a higher-than-expected incidence of rhabdomyolysis, limited to patients with severe liver dysfunction (Abraldes JG et al. *Gastroenterology 2016;150:1160-1170)*.
    - 20 mg/day x 2 weeks, then 40 mg/day
- **NOT INDICATED:**
  - Variceal Sclerotherapy: not effective
  - Surgical Shunt: higher mortality and PSE.
  - TIPS: Lack of Evidence.
  - Cyanoacrylate injection in gastric varices: effective but high complication risk (Mishra SR et al. J Hepatol 2011;54:1161)

Algorithm for Primary Prophylaxis (Baveno VI)

(de Franchis R.; J Hepatology 2015;DOI:http://dx.doi.org/10.1016/j.jhep.2015.05.022)

FINDING	RESPONSE
Diagnosis of Cirrhosis	EGD to R/O Varices
No Varices	-Compensated cirrhosis + no active injury: re-scope in 3 years -Compensated cirrhosis + active injury: re-scope in 2 years -Decompensated cirrhosis: re-scope in 1 year
F1 without red wale and Child-Pugh A	-Compensated cirrhosis + no active injury: re-scope in 2 years -Compensated cirrhosis + active injury: re-scope in 1 year -Decompensated cirrhosis: re-scope in 1 year
F1 **and** Red wale or Child-Pugh B or C	-Beta Blocker
F2 without Red wale and Child-Pugh A	-Beta Blocker
F2 **and** Red wale or Child-Pugh B or C	-Beta Blocker, or -EVL
F3	-Beta Blocker, or -EVL

No Need for EGD if liver stiffness < 20 kPa and platelet count > 150,000
(Baveno VI: Repeat both tests yearly)

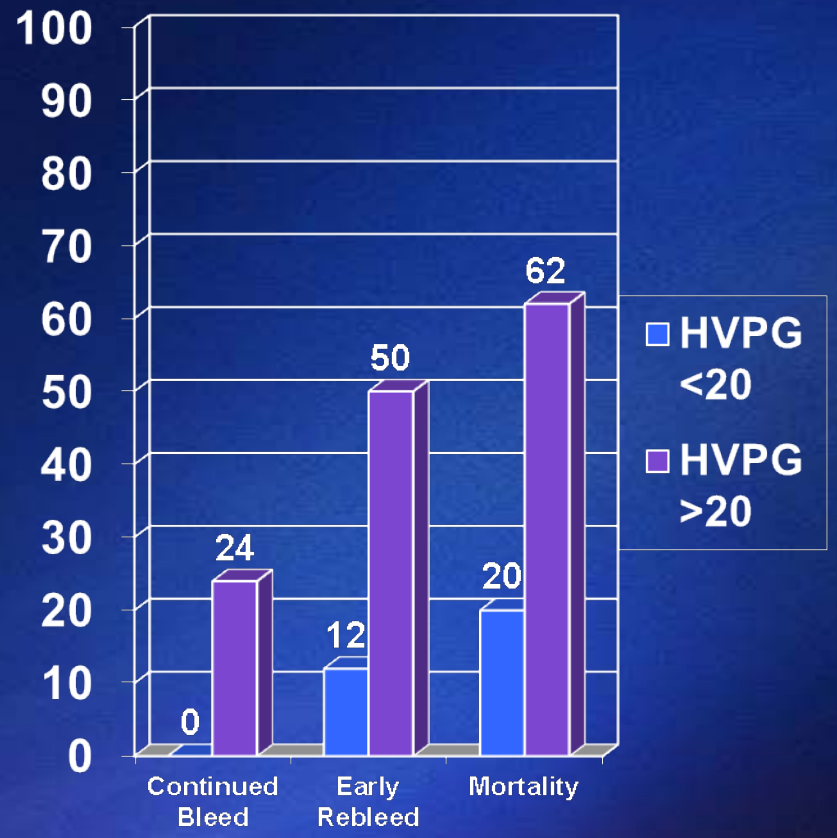
Acute Esophageal Variceal Hemorrhage

Natural History of Esophageal Variceal Hemorrhage

- **Spontaneous hemostasis**: 50%
  - Therapeutic failure: continuous bleeding or re-bleed within the initial 120 h (5 days), with:
    - hematemesis > 100 mL > 2 hours after treatment (EVL or drug), hypovolemic shock, or Hb drop >/= 3 gm in 24 h period
  - Early re-bleed: after day 5 but within 6 weeks
  - Late re-bleed: after 6 weeks
- **Rebleeding risk**: 30% in 1st 6 weeks; 70% at 1 year.
  - A) Maximum: first 48 hours,
  - B) High: within 3-4 initial days (> 50%),
  - C) Medium: 10 days to 6 weeks,
  - D) Average: after initial 6 weeks (risk identical to that who has never bleed).
- **In-hospital mortality**: 40 % (due to continuous bleed, rebleed, advanced disease, infection, HRS)
- **Mortality after 2 week survival**: 52 % at 1 year

Risk Factors
Failure to Control Acute Hemorrhage

- Spurting varix
- Child-Pugh C
- Portal vein thrombosis
- Infection
- HVPG > 20 mm Hg (present in 80% of CTP-C)



Gastroenterology 1999;117(3):626-31

Risk Factors

Rebleeding in < 6 weeks

- Age > 60
- Ascites
- Infection
- Renal Failure
- Severe Initial Bleed (Hb < 8 g/dL)
- HVPG > 20 mm Hg (present in 80% of CTP-C)
- Active bleeding at Endoscopy
- Red-color signs
- Platelet plug on varix
- Thrombocytopenia
- Hepatic Encephalopathy
- Alcoholic cirrhosis
- Bleeding from gastric varix
- Over transfusion to Hb >/= 9; (Hct goal 24%)

Risk Factors

Rebleeding in > 6 weeks

- Severity of Liver Failure
- Ascites
- Hepatoma
- Red-color signs
- Active Alcohol abuse

Treatment of Esophageal Variceal Bleed

- Antibiotic Prophylaxis
- Intravenous Terlipressin, Octreotide or Somatostatine
- Urgent Endoscopic Variceal Ligation (within 12 hours).
- Restrictive Blood Transfusion
- Selective use of Early TIPS
- Evaluate for Portal Vein Thrombosis and HCC.
- Correcting the INR with FFP or factor VIIa is not recommended.
  - The INR is not a reliable indicator of coagulation status in cirrhosis.
- No recommendations can be given regarding platelet transfusion in patients with VH.

Risk of Infection

Cirrhotic with Gastrointestinal Hemorrhage

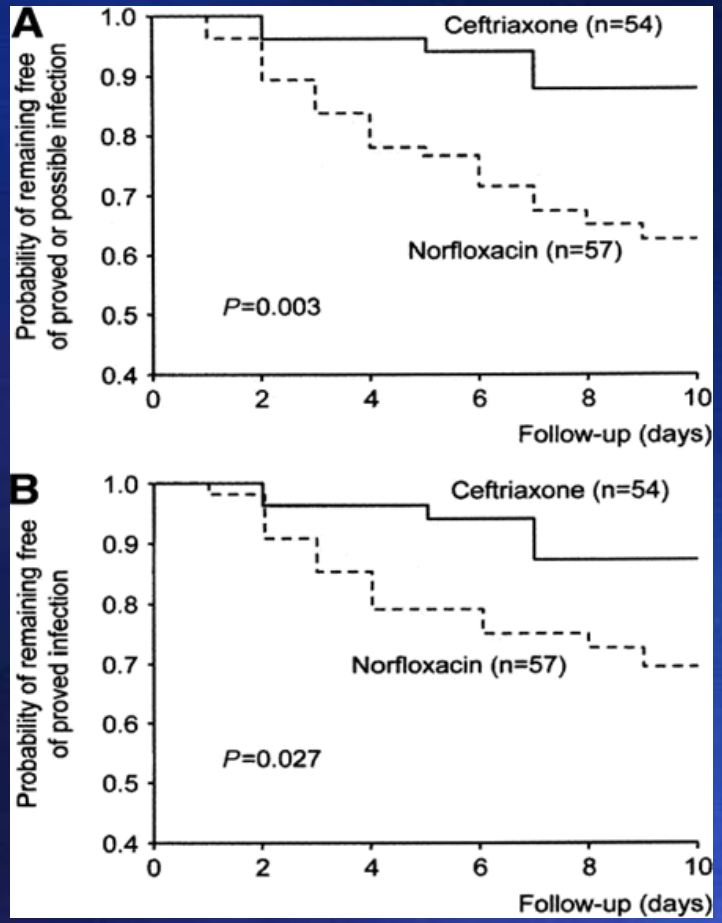
- **Risk of Infection: 60%**
- **Acquisition time**:
  - A) 1/3 before or at time of admission,
  - B) 2/3 after hospital admission.
- **Types of Infection**:
  - UTI (20-25%), - SBP (15-20%),
  - Respiratory (8%), - Bacteremia (8%).
- **In Child-Pugh A the risk of infection is very low (5%) and mortality is low:** consider no antibiotics to decrease antibiotic-resistant infections (Tandon P et al. AASLD 2013) (Pauwels A et al. Hepatology 1996;24:802-806)

Effect of Antibiotics
Cirrhotic with Gastrointestinal Hemorrhage

- **Prophylactic antibiotics vs Placebo** (several meta-analysis; Soares-Weiser K et al. Scan J Gastroenterol 2003;38:193 and Chavez-Tapia NC et al. Aliment Pharmacol Ther 2011;34:509-5018):
  - Decreases mortality by 21% **(RR 0.79)**,
  - Reduces infection risk by 65% **(RR 0.35)**
  - Reduces mortality from infection by 57% **(RR 0.43)**
  - Decrease re-bleeding rate by 47% **(RR 0.53)**
  - Decreases Transfusion needs **(2.7 vs 0.7 units)**
- **Regimens**: 7 to 10 days of
  - A) Ofloxacin 200 mg BID,
  - B) Norfloxacin 400 mg BID,
  - C) Ciprofloxacin 500 mg BID
  - **D) Ceftriaxone 1 g/d** (preferred in malnutrition, encephalopathy, ascites, jaundice or high quinolone-resistance prevalence) (de Franchis R. J Hepatol 2010;53:762-768)

Ceftriaxone 1 g/d x 7 d is superior to Norfloxacin 400 BID x 7d in preventing infections in cirrhosis with GI bleed

Fernandez J; Gastroenterology 2006;131:1049–1056



Free of Possible or Proved Infection

Free of Proved Infection

In cirrhosis with GI bleed, Ceftriaxone:

- decreases hospital infections & SBP,
- has no effect in hospital mortality.

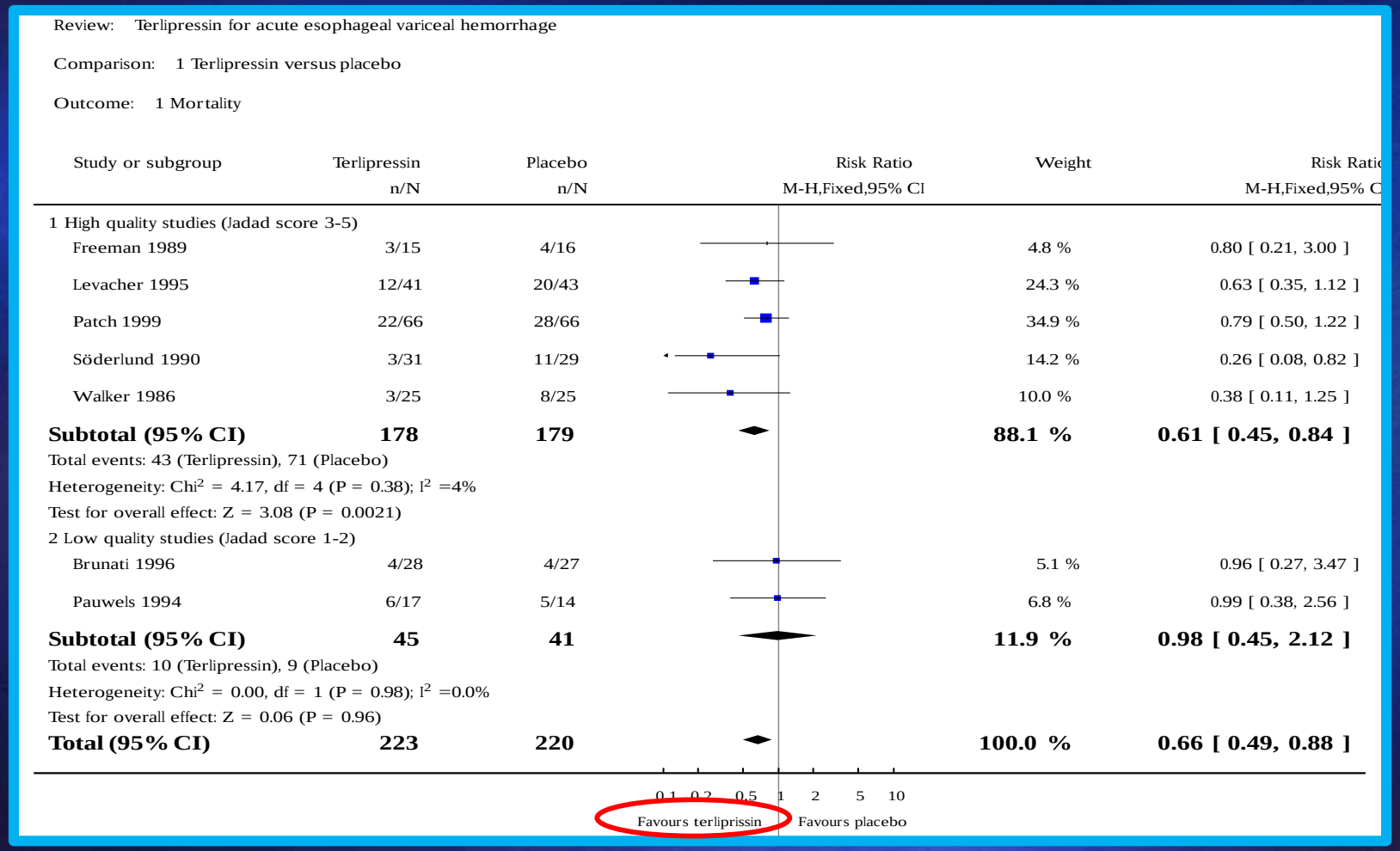
Terlipressin in Variceal Bleeding

- Dose: 2 mg IV q 4 hours; decrease to 1 mg q 4 hours after bleeding has bleed is controlled.
- Duration: 5 days
- Decreases all cause mortality (RR 0.66) (Cochrane Database Syst Rev 2003; CD002147)
- Bleeding control equal to Octreotide or Somatostatin
- Has sustained hemodynamic effect decreasing portal pressure and blood flow (Somatostatin and Octreotide have transitory hemodynamic effect).
- Risk of Hyponatremia: monitor closely.
- When combined with EVL, re-bleeding and mortality was similar to Somatostatin or Octreotide combined with EVL (Seo YS et al. Hepatology 2014;60:954-963)

Terlipressin vs Placebo

Acute Esophageal Variceal Hemorrhage Mortality

Ioannou G et al. Cochrane Database Syst Rev 2003 (CD002147)



Octreotide or Somatostatin in Variceal Hemorrhage

- *Octreotide Dose: 50 mcg bolus followed by 50 mcg/h infusion x 5 days.*
- *Somatostatin dose: 250 mcg bolus + 250 mcg/h infusion x 5 days*
- *In combination with endoscopic therapy decrease re-bleeding rate and major complications.*
- *Octreotide and Somatostatin have no survival benefit (vs placebo).*
- *When endoscopic hemostasis is not available, IV Octreotide or Somatostatin is:*
  - *safer and more effective than vasopressin,*
  - *Less effective than terlipressin, and*
  - *as effective as endoscopic therapy*

Vasoactive Agents Used in the Management of Acute Variceal Hemorrhage

Drug	Recommended Dose	Duration
Octreotide (SMT analogue)	Initial IV bolus of 50 micrograms (can be repeated in first hour if ongoing bleeding) Continuous IV infusion of 50 µg/hr	2-5 days
Vasopressin	Continuous IV infusion: 0.2-0.4 U/min; can be increased to 0.8 U/min It should always be accompanied by IV nitroglycerin at a starting dose of 40 µg/min, which can be increased to a maximum of 400 µg/min, adjusted to maintain a systolic blood pressure 90 mm Hg.	24 hours
SMT	Initial IV bolus 250 µg (can be repeated in the first hour if ongoing bleeding) Continuous IV infusion of 250-500 µg/h	2-5 days
Terlipressin (VP analogue)	Initial 48 hours: 2 mg IV every 4 hours until control of bleeding Maintenance: 1 mg IV every 4 hours to prevent rebleeding	2-5 days

Endoscopic Band Variceal Ligation (EVL)

Uses

- Primary prevention
- Treatment of acute hemorrhage
- Eradication after Index Bleed

Give 250 mg of IV Erythromycin 30-120 minutes before EGD

Banding (EVL) vs. Sclerotherapy (ES) in Acute Variceal Bleed

- **Hemostasis**: 86%-90% with both.
- **Complications**: **2% in banding vs. sclerotherapy 22%**
- **Effectiveness**:
  (***Relative Risk***: Banding vs. Sclerotherapy)
  - **A) Re-Bleed: 0.52,**
  - **B) Mortality from bleeding: 0.49,**
  - **C) Total Mortality: 0.67**
- **<u>Conclusion</u>: Banding is the endoscopic therapy of choice for esophageal varices.**

Meta-Analysis of EVL vs ES

Laine L et al. Ann Intern Med 1995;123:280-287

Esophageal varix Re-Bleed
EVL vs Endoscopic Sclerotherapy

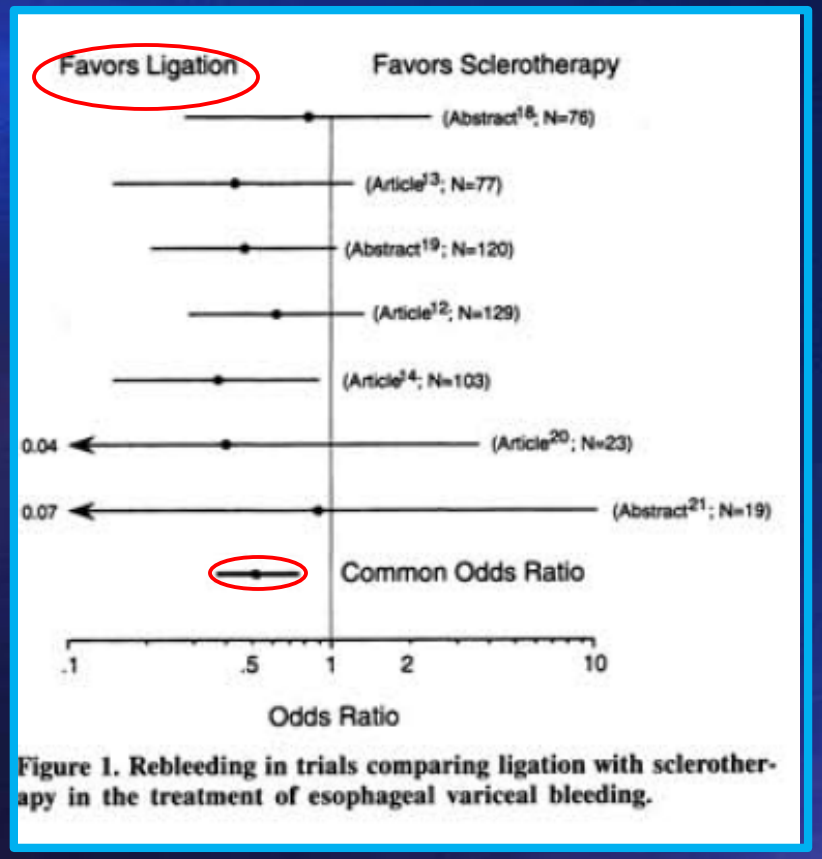


Figure 1. Rebleeding in trials comparing ligation with sclerotherapy in the treatment of esophageal variceal bleeding.

Mortality
EVL vs Endoscopic Sclerotherapy

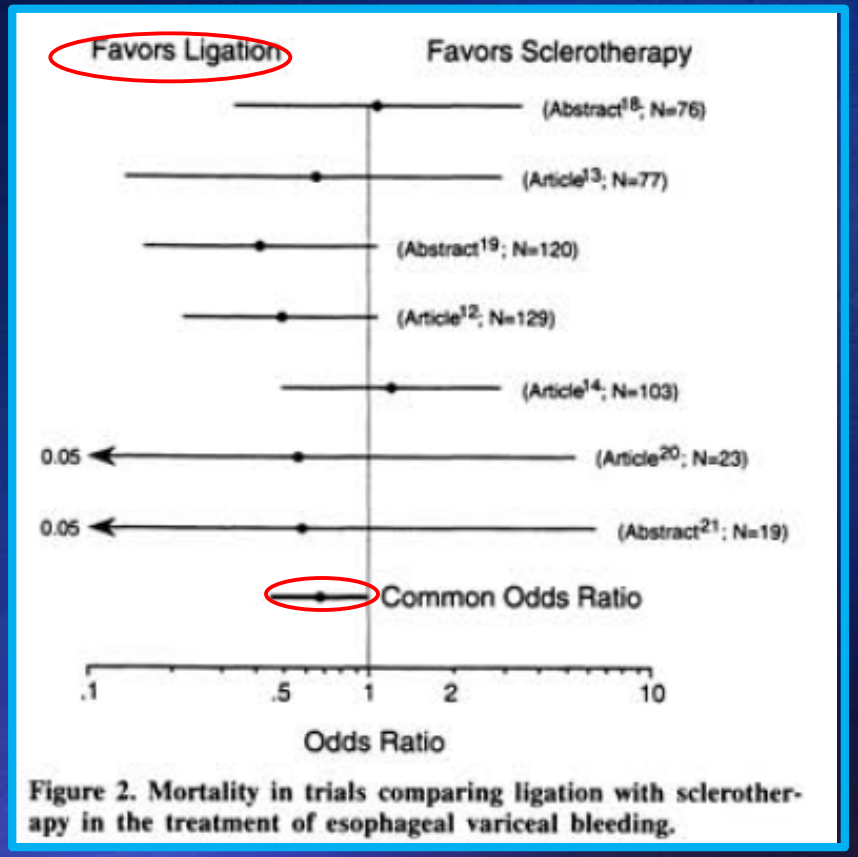
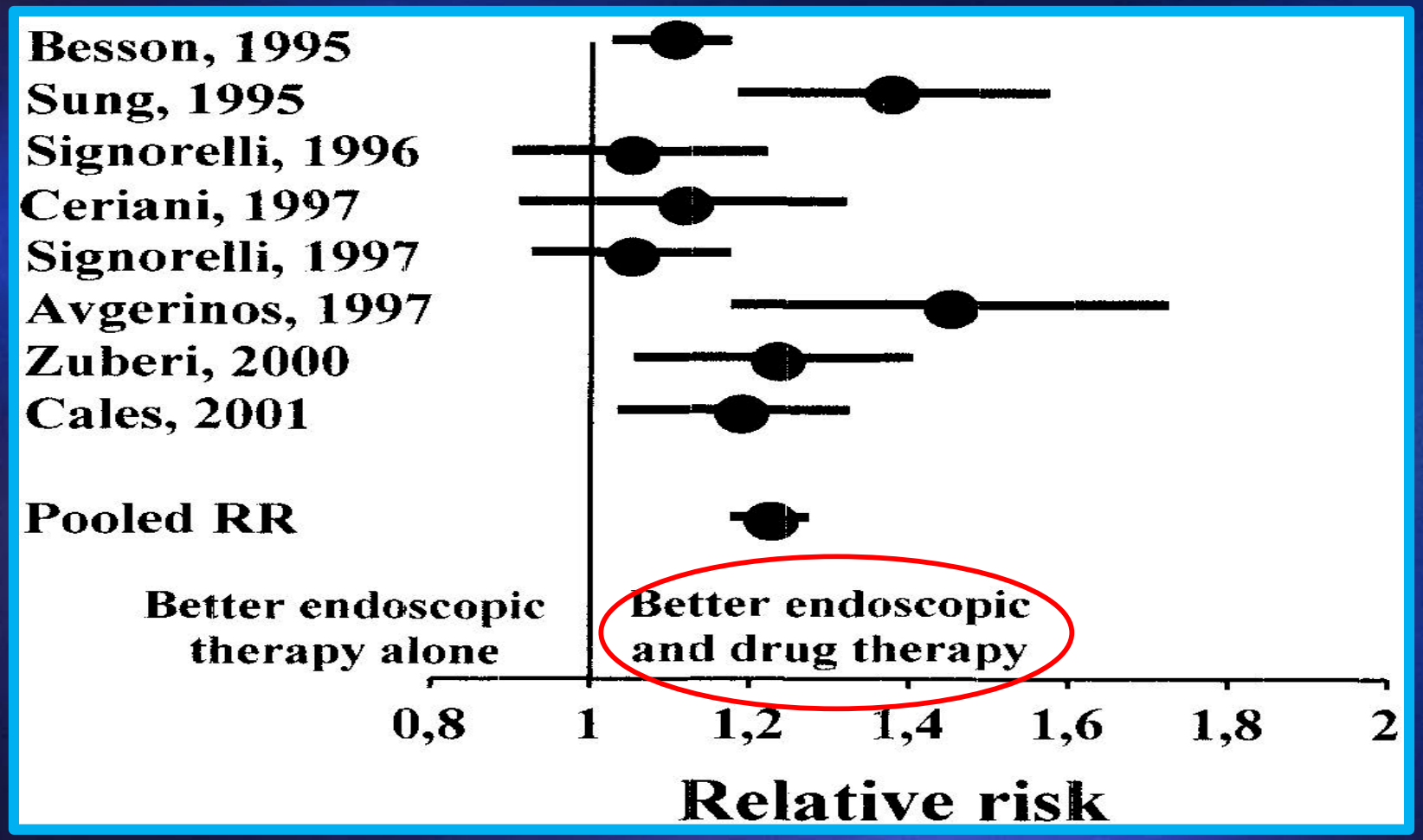


Figure 2. Mortality in trials comparing ligation with sclerotherapy in the treatment of esophageal variceal bleeding.

Endoscopy vs Endoscopy + Octreotide/Somatostatin

5-days Hemostasis in Acute Esophageal Variceal Hemorrhage

Banares R et al. **HEPATOLOGY 2002;35:609-615**



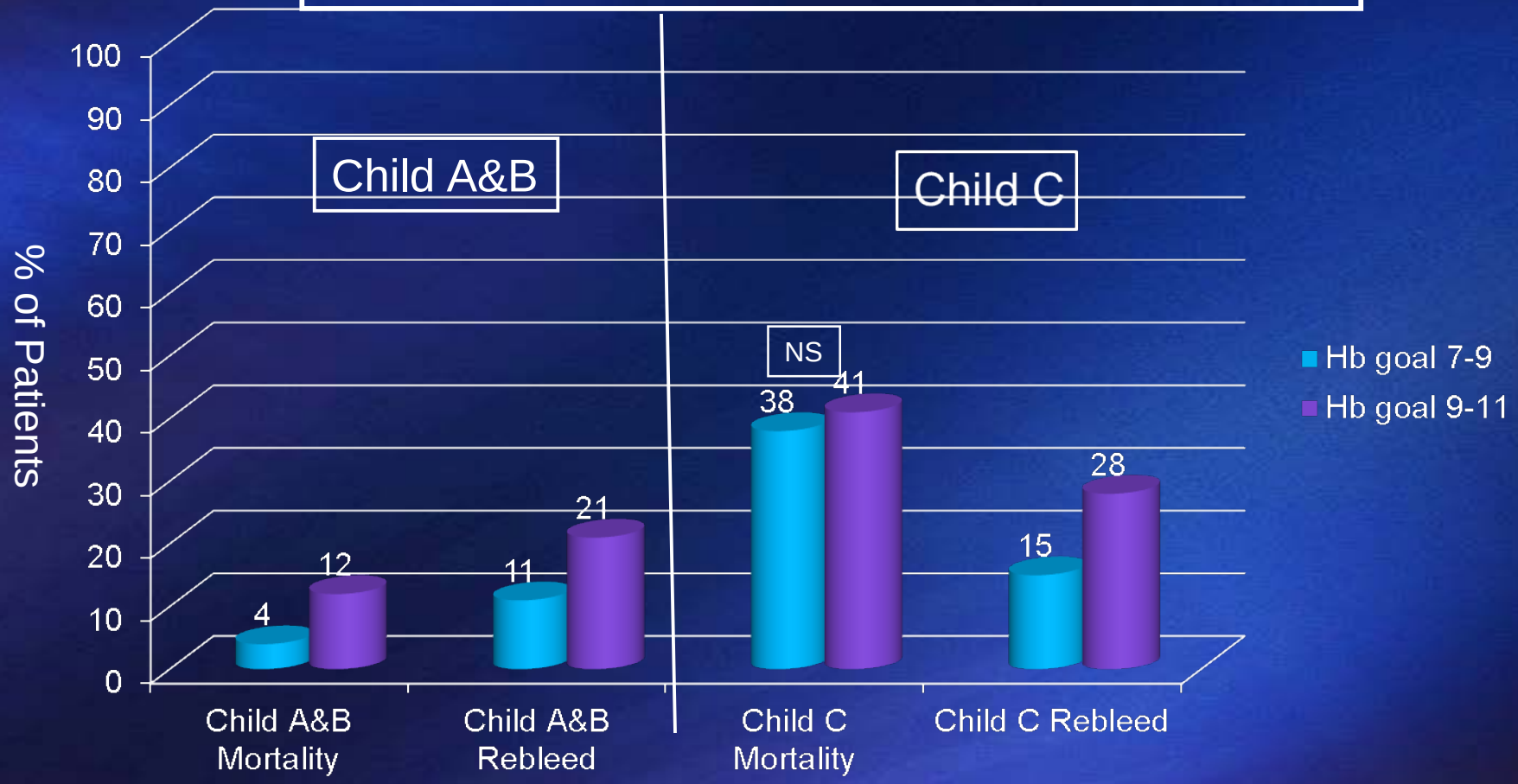
DECREASES RE-BLEEDING RATE
NO EFFECT ON SURVIVAL

Acute GI Bleed in Cirrhosis

Restrictive vs Liberal Transfusion in GI Bleed

Villanueva C; N Engl J Med 2013; 368:11-21

Excluded: exsanguinating bleed, Acute coronary syndrome, TIA, Stroke and symptomatic peripheral vascular disease



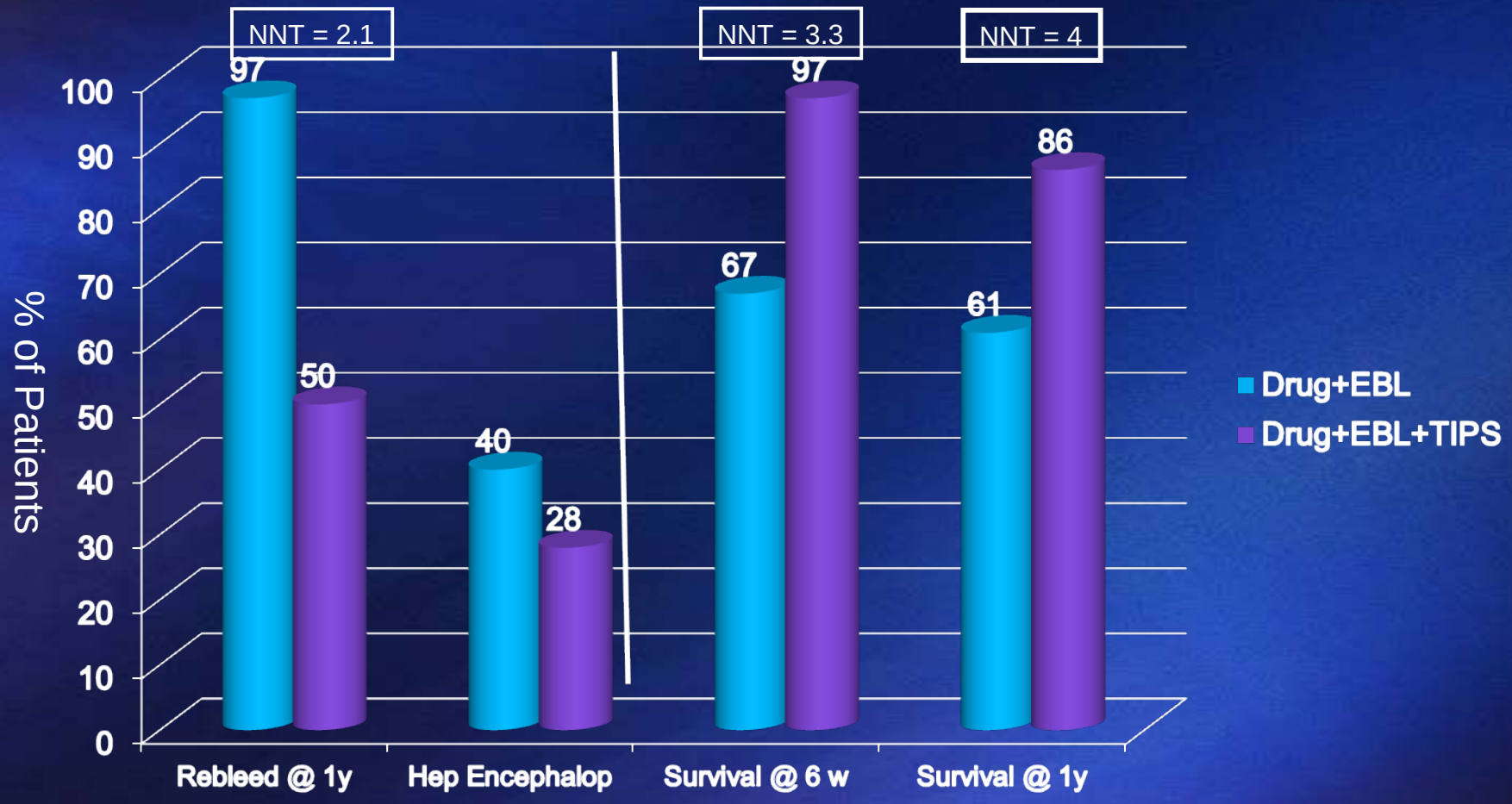
Restrictive transfusion (Hb goal 7-8) decreases re-bleeding rate in all patients and decreases mortality in Child-Pugh A and B patients

Acute GI Bleed in Cirrhosis

Variceal Bleed: Actively bleeding Child B, or any Child C (10-13)

Garcia-Pagan JC; N Engl J Med 2010; 362:2370-2379

Early TIPS with PTFE stent in



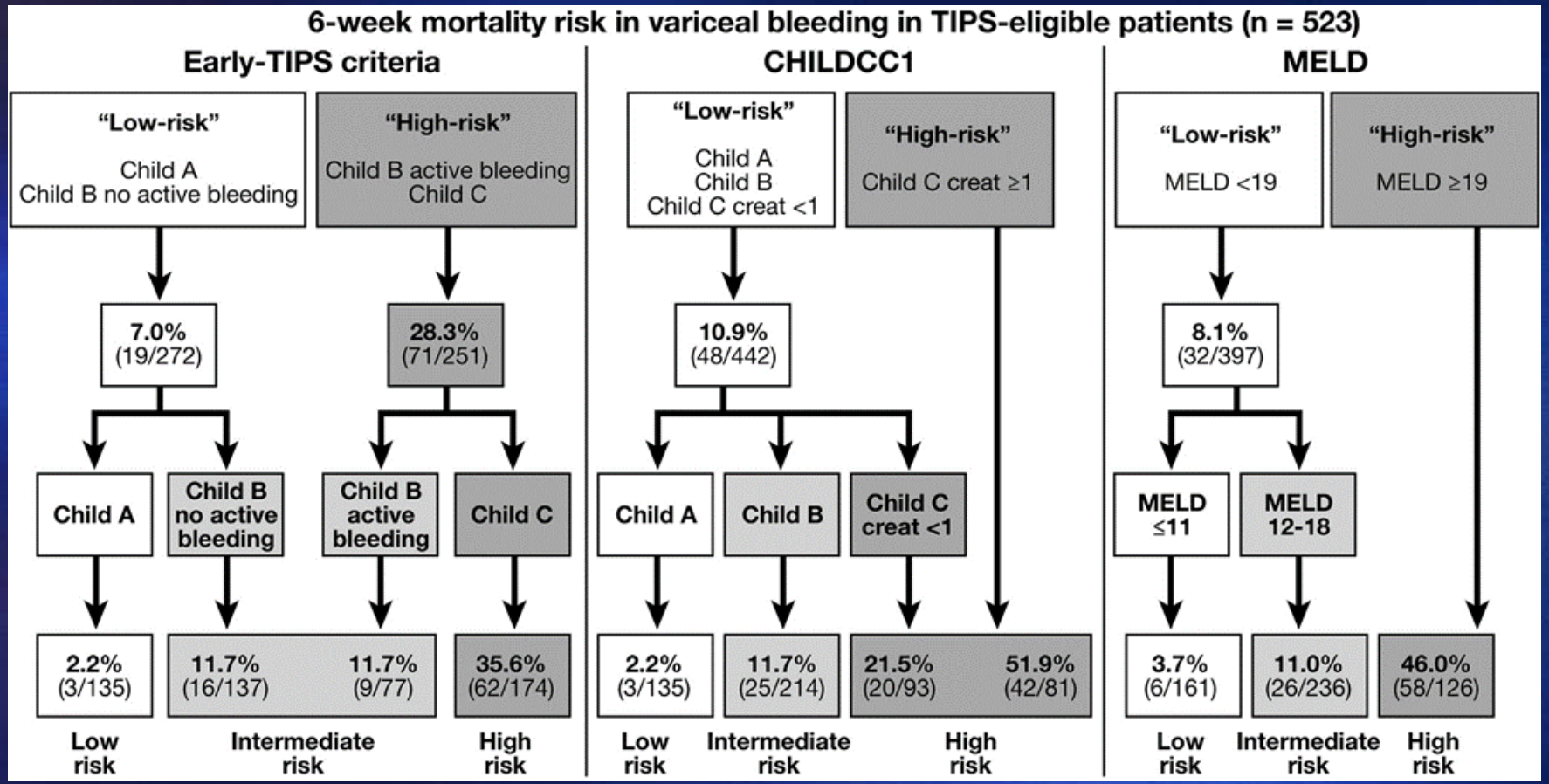
Conclusion: TIPS with PTFE covered stent is superior to EBL+BB in the treatment of first esophageal variceal bleed in:

Child B actively bleeding at time of EGD, and in

Child C with score 10-13.

Mortality (6-weeks) in Acute Variceal Bleeding without Early TIPS

Clinical Gastroenterology and Hepatology 2018;16:132–139



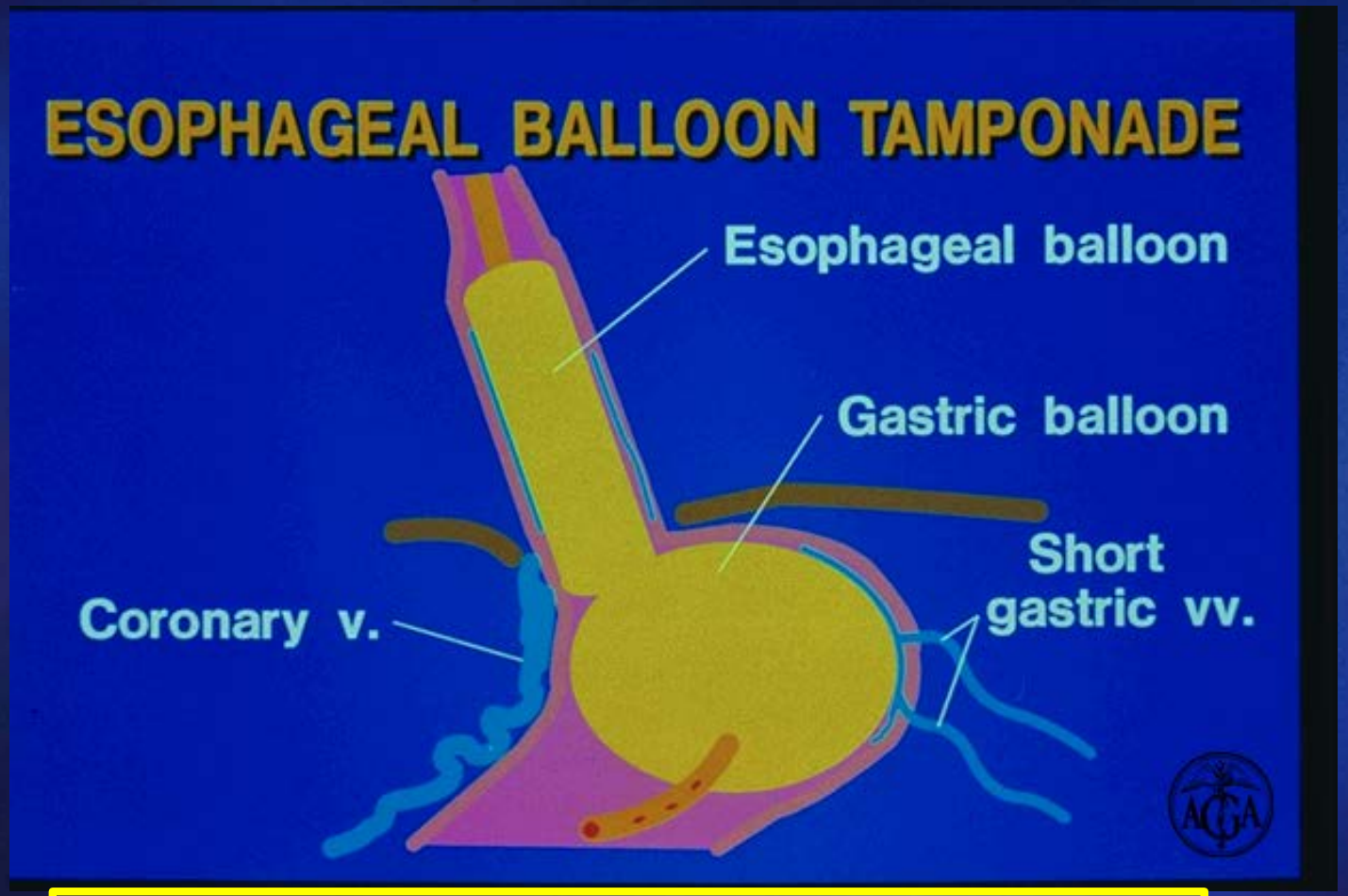
Eligible criteria for early TIPS included the following: age younger than 75 years, creatinine level less than 3 mg/dL, Child-Pugh score lower than 14, hepatocellular carcinoma within Milano criteria or Barcelona Clínic Liver Cancer staging system stages C or D, and no portal thrombosis.

6-week mortality with early TIPS is 3%;

Child-Pugh B with or without active bleeding at Endoscopy and MELD >/= 12, Child-Pugh C up to 13 points with or without bleeding at Endoscopy (6% and 19% 1-y mortality with early-TIPS, respectively), and patients with MELD 12-18 benefit from early-TIPS

Acute Variceal Bleeding

Direct Pressure Technique – Minnesota Tube

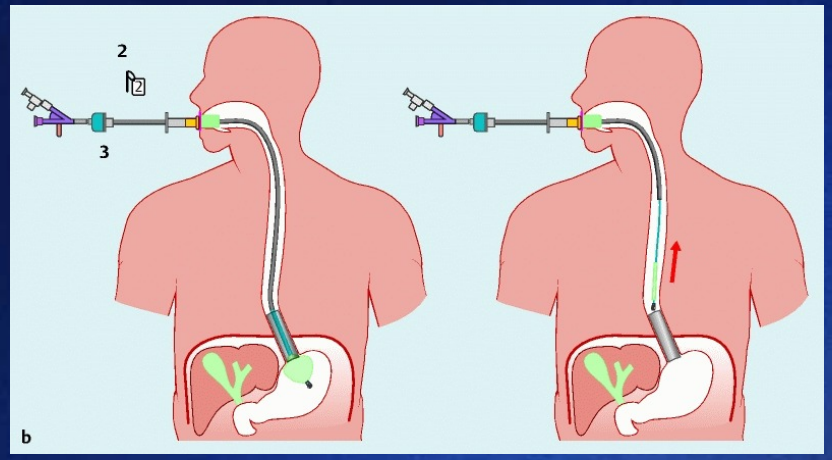


Patient intubated and tube with 0.5-1 Kg traction
Bleeding Control 80%, complication rate 14%, mortality 20%
BRIDGE TO OTHER THERAPY FOR </= 24 HOURS

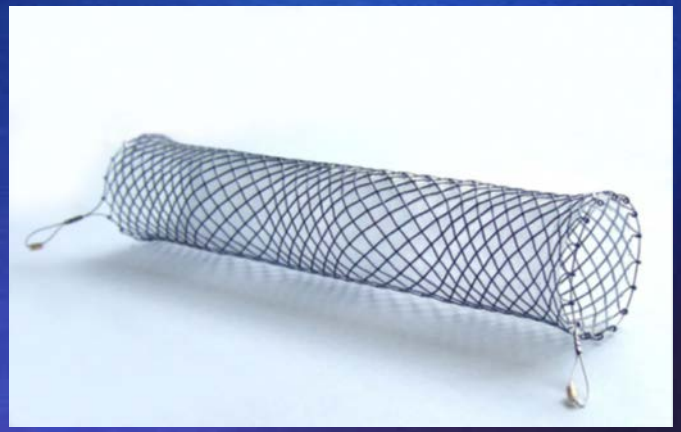
Direct Pressure Technique

Self-Expandable Stents in Esophageal Variceal Hemorrhage

- Approximately 60 case series: 100% bleed control.
- Used mostly as “bridge therapy” to TIPS; removed after 9-11 days. (Hubmann R et al. Endoscopy 2006;38:896-901)
- There is an ongoing prospective study comparing with balloon tamponade.
- Supported by BavenoVI (potentially as efficacious and safer than balloon tamponade) (de Franchis R.; J of Hepatol 2015;DOI:http://dx.doi.org/10.1016/j.jhep.2015.05.022)
- Has been used as “definitive treatment” in a few (up to 214 days) (Holster IL et al.Endoscopy 2013;45:485-488)



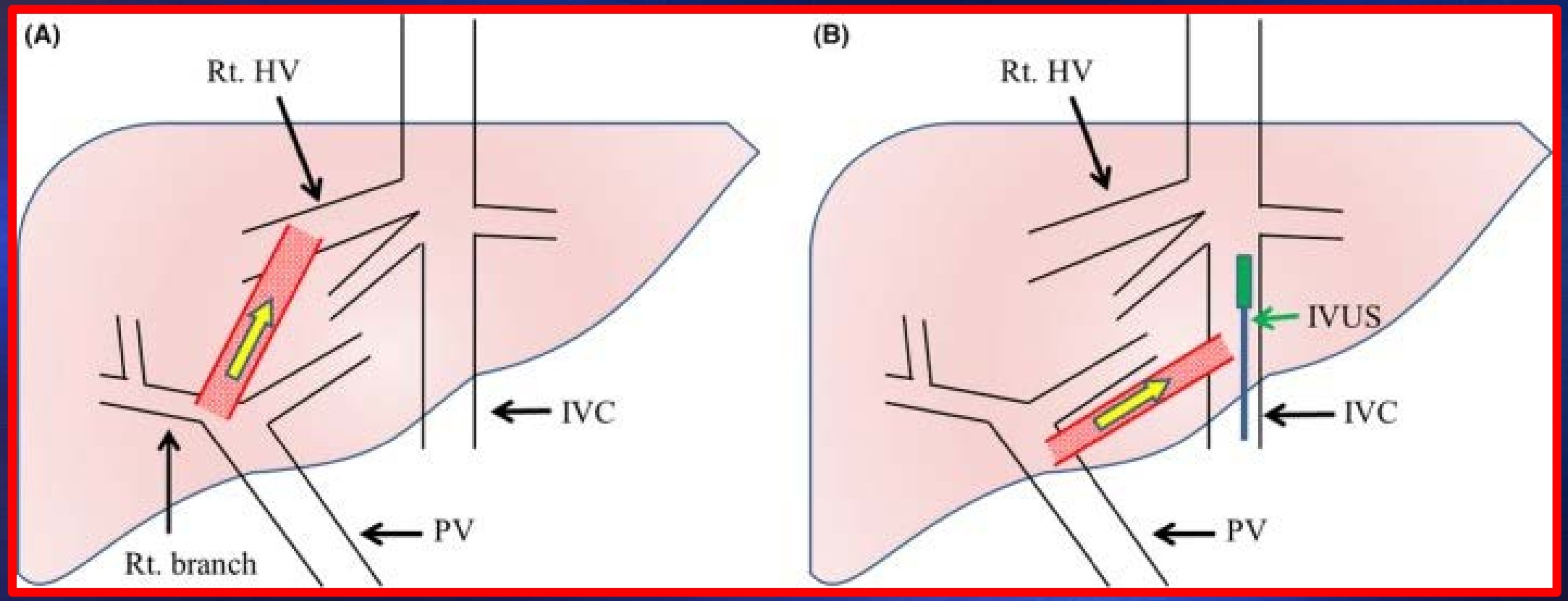
SX-Ella Stent Danis 135 mm x 25 mm
Nitinol cubierto con lamina de poliuretano



TIPSS as Salvage Treatment

- Bleeding Control: 90%
- Re-bleeding Rate: 16-30%
- Mortality: 20-30%
- 30-day survival is 67% when rescuing endoscopic + medical therapy failure.
- Predictors of poor post-TIPS survival:
  - Age > 60
  - Emergency TIPS
  - ALT > 100 U/L
  - Bilirubin > 4 mg/dL increases mortality
  - Pre-TIPSS encephalopathy not related to bleed
  - Pre-TIPSS MELD Score (> 15-18 has high mortality; done only if there are no other options)

TIPS and DIPS



Contraindications for TIPSS

ABSOLUTE

- Severe CHF
- Severe Pulmonary HTN (45 mm Hg)
- Polycystic liver disease
- Severe hepatic failure
- Portal V thrombosis with cavernoma
- Severe tricuspid regurgitation

RELATIVE

- Active infection
- Poorly controlled PSE
- Hypervascular liver tumor
- Portal V thrombosis without cavernoma
- Biliary obstruction

Management of Acute Esophageal Varices Hemorrhage

- Vasoactive drugs (SMT or its analogue, octreotide; VP or its analogue, terlipressin) should be initiated as soon as VH is suspected.
- PRBC transfusion should be done conservatively, starting to transfuse when the hemoglobin reaches a threshold of around 7 g/dL with the goal of maintaining it between 7 and 9 g/dL.
- Short-term (maximum 7 days) antibiotic prophylaxis should be instituted in any patient with cirrhosis and GI hemorrhage.
- Intravenous ceftriaxone 1 g/24 h is the antibiotic of choice and should be used for a maximum of 7 days.
  - consider discontinuing when hemorrhage has resolved and vasoactive drugs discontinued.

Management of Acute Esophageal Varices Hemorrhage

- EGD should be performed within 12 hours of admission and once the patient is hemodynamically stable.
- If a variceal source is confirmed/suspected, EVL should be performed.
- In patients at high risk of failure or rebleeding (CTP class C cirrhosis or CTP class B with active bleeding on endoscopy) who have no contraindications for TIPS, an “early” (preemptive) TIPS within 72 hours from EGD/EVL may benefit selected patients.
- For patients in whom an early TIPS is not performed, intravenous vasoactive drugs should be continued for 2-5 days and NSBBs initiated once vasoactive drugs are discontinued.
  - Rescue TIPS is indicated in these patients if hemorrhage cannot be controlled or if bleeding recurs despite vasoactive drugs+EVL.
- In patients in whom TIPS is performed successfully, intravenous vasoactive drugs can be discontinued.

Practical Approach
Suspected or Proven Variceal Bleed

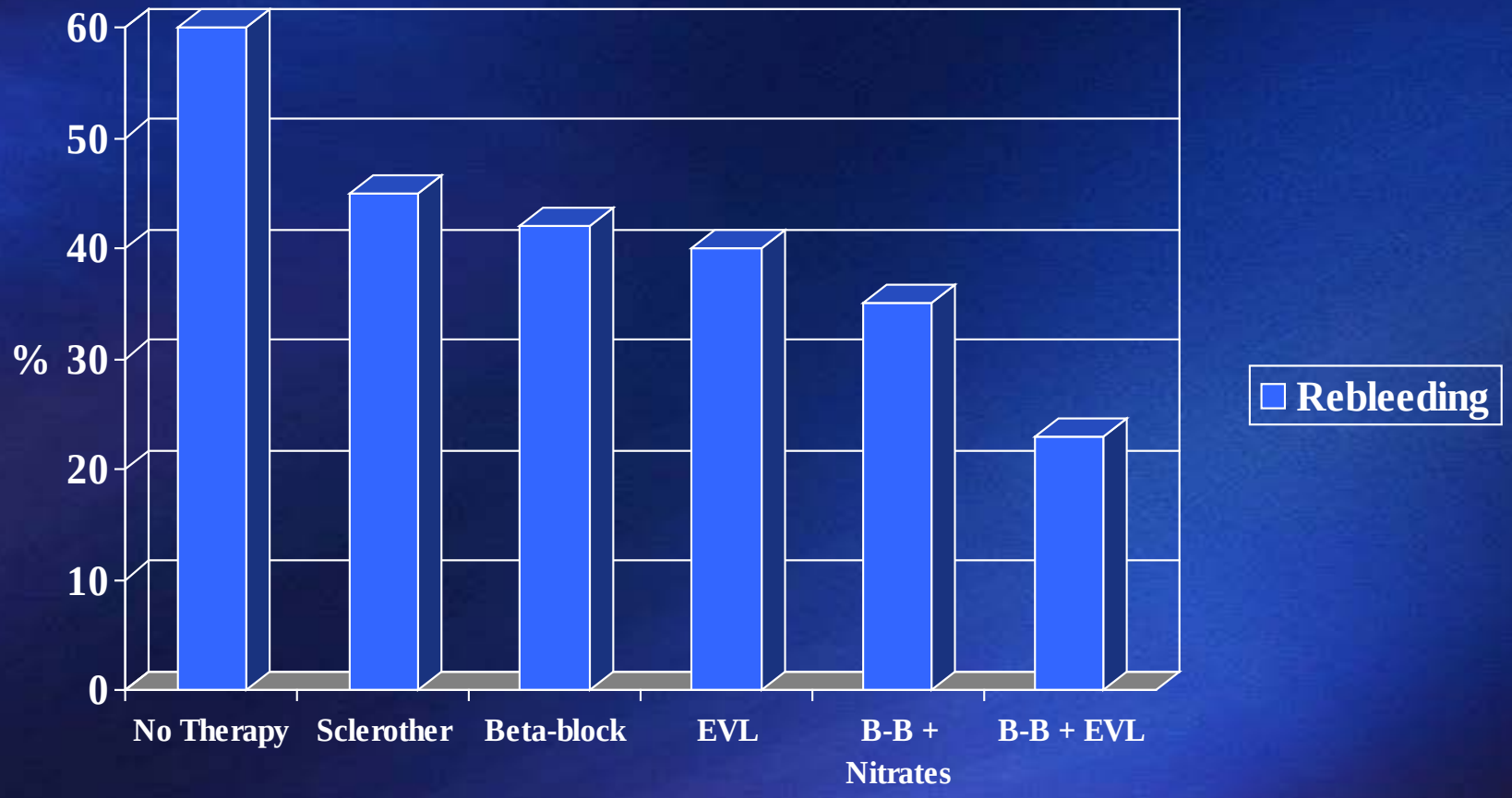
- Start empirical Terlipressin 2 mg q 4h IV or Octreotide 50 mcg bolus + 50 mcg/hour, at arrival, x 5 days.
- Antibiotic prophylaxis with ceftriaxone x 7 days; start at arrival.
- Esophageal variceal bleed: Banding at arrival, then
  - Banding q 2 weeks until obliteration if Child A, Child B without active bleeding at EGD, or MELD score 19 or higher.
  - Early TIPS (</= 72 hours) with PTFE stent, if MELD score </= 18 **and** Child B actively bleeding at EGD, or Child C with score 10-13.
  - Consider early TIPS if HPVG > 20 mm Hg (within 24 hours from bleed).
- Gastric variceal bleed: Cyanoacrylate with sequential injections q 3-4 weeks until obliteration (or acute sclerotherapy or banding, followed by urgent TIPSS, or BRTO +/- TIPSS)
  - splenectomy in splenic vein thrombosis with isolated gastric varices
- Add Nadolol or Propranolol long term (only in esophageal varices).
- Liver Transplant evaluation.

Variceal Rebleed

LONG TERM PROPHYLAXIS

LONG TERM Rebleeding Risk

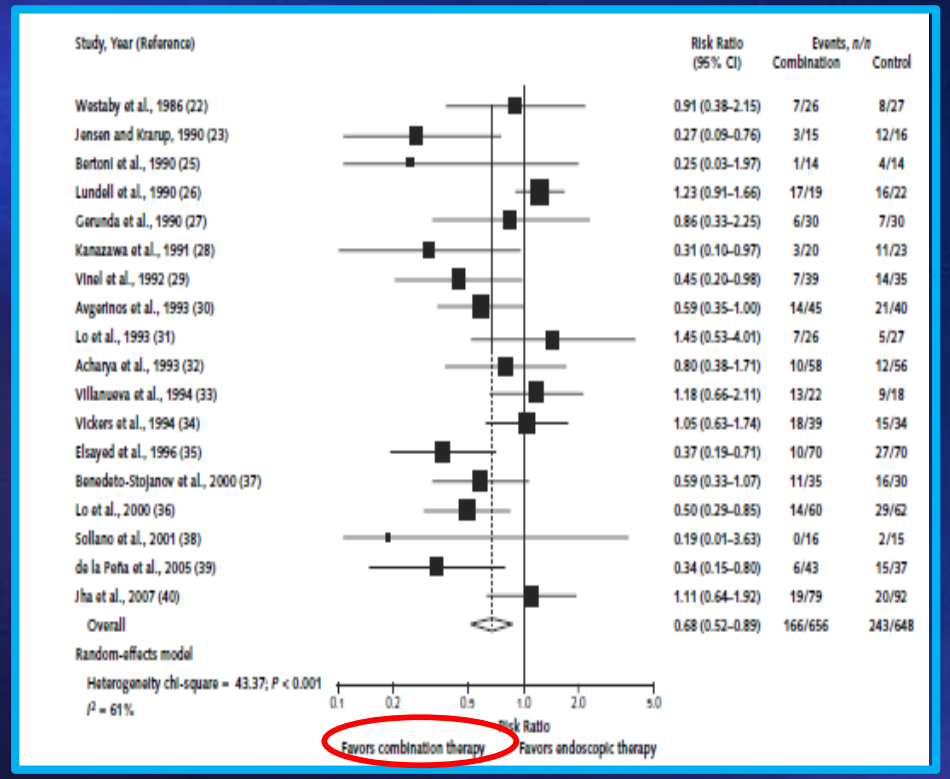
Different Prophylaxis



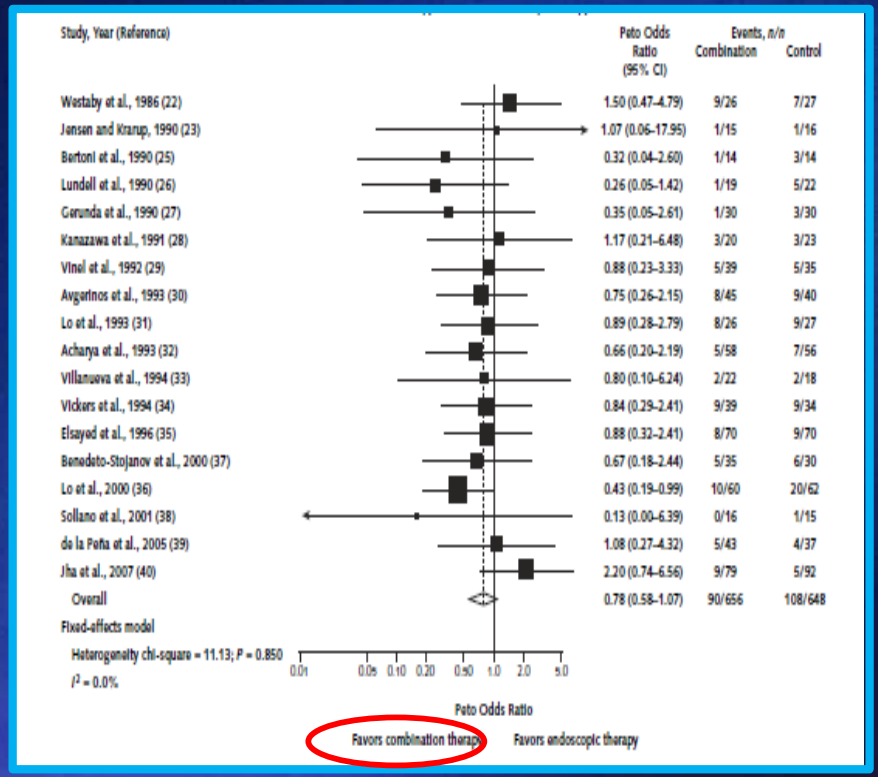
Meta-Analysis of [Endoscopy + Drug therapy] vs Drug-Therapy to Prevent Variceal Re-bleeding

Gonzalez R et al. Ann Intern Med 2008;149:109-122

Re-Bleeding Rate



Mortality



The combination of Beta-blocker + Endoscopy is superior to endoscopy alone in decreasing re-bleeding rate and mortality.

Secondary Prophylaxis for Esophageal Variceal Hemorrhage

EVL + NSBB

Therapy	Recommended Dose	Therapy Goals	Maintenance/Follow-up
Propranolol	•With EVL. •20-40 mg orally *twice* a day •Adjust every 2-3 days until treatment goal is achieved •Maximal daily dose: • 320 mg/day in patients without ascites • 160 mg/day in patients with ascites	•Resting heart rate of 55-60 beats per minute •Systolic blood pressure should not decrease <90 mm Hg	•At every outpatient visit make sure that heart rate is on target •Continue indefinitely
Nadolol	•With EVL. •20-40 mg orally *once* a day •Adjust every 2-3 days until treatment goal is achieved •Maximal daily dose: • 160 mg/day in patients without ascites • 80 mg/day in patients with ascites	•Resting heart rate of 55-60 beats per minute •Systolic blood pressure should not decrease <90 mm Hg	•At every outpatient visit make sure that heart rate is on target •Continue indefinitely
EVL	•With NSBB. •Every 1-4 weeks until the eradication of varices	•Variceal eradication (no further ligation possible)	•First EGD performed 3-6 months after eradication and every 6-12 months thereafter

NSBB is the main component of the therapy. If intolerant to NSBB, consider TIPS
Carvedilol has not been studied well for secondary prophylaxis.

Discontinuation of Beta-blockers as Secondary Prophylaxis (Baveno VI)

- Until randomized trials are available NSBB should be reduced/discontinued if a patient with refractory ascites develops any of the following events:
  - Systolic blood pressure <90 mmHg
  - Hypo-Natremia < 130
  - Acute Kidney Injury
- If there was a clear precipitant for these events (e.g. spontaneous bacterial peritonitis, hemorrhage), re-initiation of NSBB should be considered after these abnormal parameters return to baseline values after resolution of the precipitant
  - If reinitiating NSBBs, dose should be re-titrated, starting at the lowest dose
  - If the patient continues to be intolerant to NSBB and is an appropriate TIPS candidate, covered TIPS placement may be considered

Practical Approach to Prevent Variceal Bleed

PREVENT 1st BLEED

- Cirrhotic: EGD to R/O varices
- No varices: re-scope
  - q 1 y (decompensated) or
  - q 2y (compensated & active)
  - q 3 y (compensated & inactive)
- F-1 and Child A without red-wale: re-scope
  - q 1 y (decompensated or compensated & active)
  - q2 y (compensated & inactive).
- F-1 (</= 5 mm) + Child B/C or red-wale = B-blocker
- F-2 varices Child A, no red-wale: Beta-blocker
- F-2 + Child B/C or red-wale: Beta-blocker or EVL
- F-3 varices : Beta-blocker or EVL

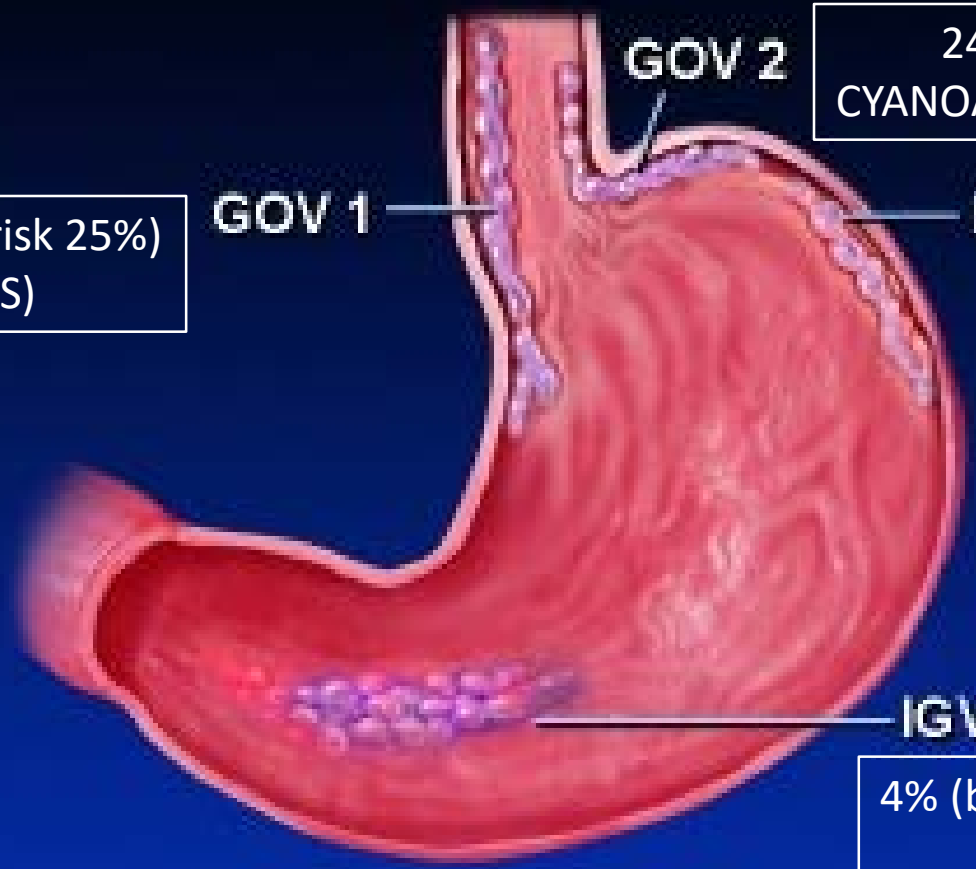
PREVENT RE-BLEED

- *Liver Transplant eval.*
- Early TIPS if Child B + actively bleeding, or Child C 10-13, & MELD < 19
- Early TIPS if HVPG >/= 20 mmHg, & MELD < 19.
- Banding + Beta-blocker
- Banding in BB intolerant
- TIPS rescue in re-bleed

Thank you for your attention

Gastric Variceal Bleed

Classification of Gastric Varices



24% (bleeding risk 60%)
CYANOACRYLATE +/- TIPS +/- BRTO

70% (bleeding risk 25%)
EVL (or ES)

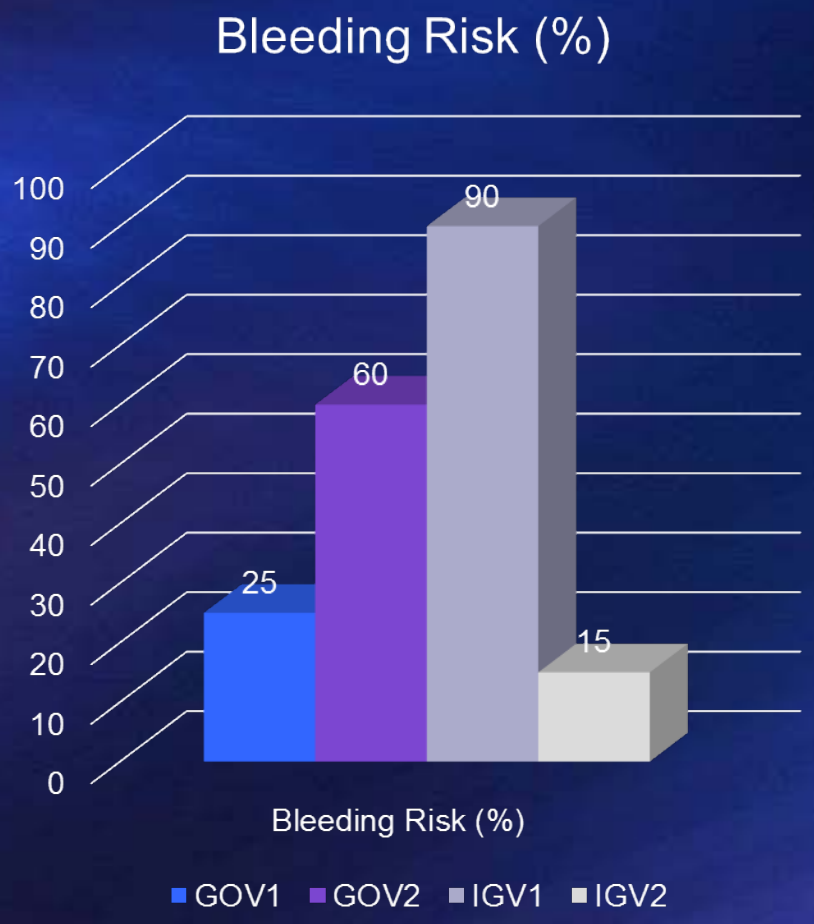
2% (bleeding risk 90%)
TIPS +/- BRTO or SPLENECTOMY

4% (bleeding risk 15%)
EVL or ES

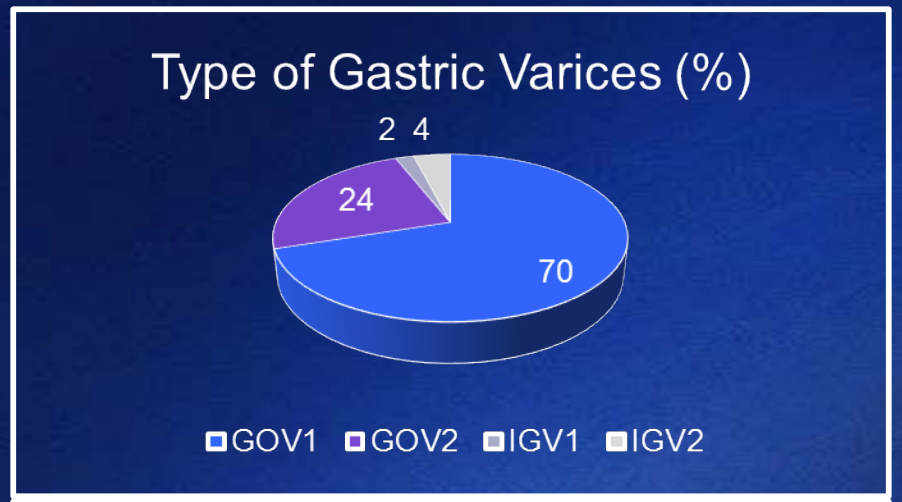
Sarin et al, Am J Gastro 1989; 84:1244

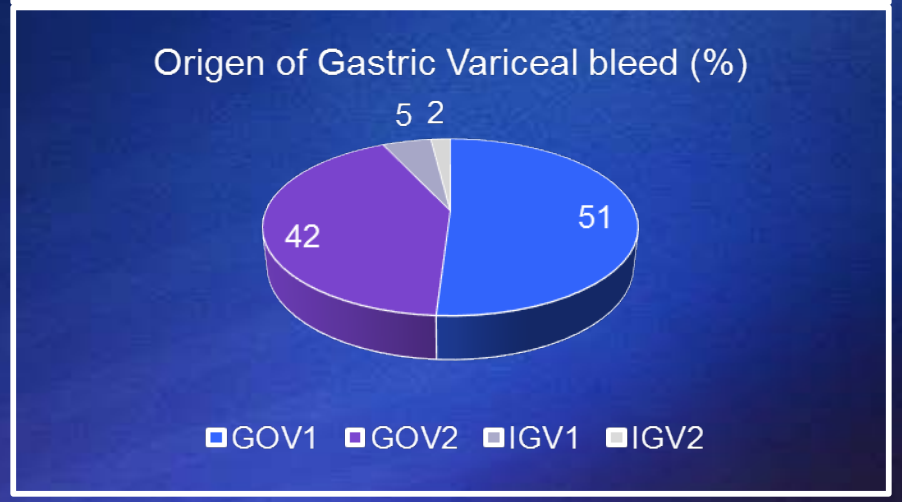
Gastric Variceal Bleed

Risk, Frequency & Origen



Lifetime Risk of Bleeding





Primary Prophylaxis for Gastric Variceal Hemorrhage

- Prevention of first bleeding from GOV1 varices may follow the recommendations for EV.
- For prevention of first VH from GOV2 or IGV1, NSBBs can be used, although the data are not as strong as for EV.
- Neither TIPS nor BRTO are recommended to prevent first hemorrhage in patients with fundal varices that have not bled.

Effect of Primary Prophylaxis in Gastric Variceal Bleed

Mishra SR et al. J Hepatol 2011; 54: 1161-1167

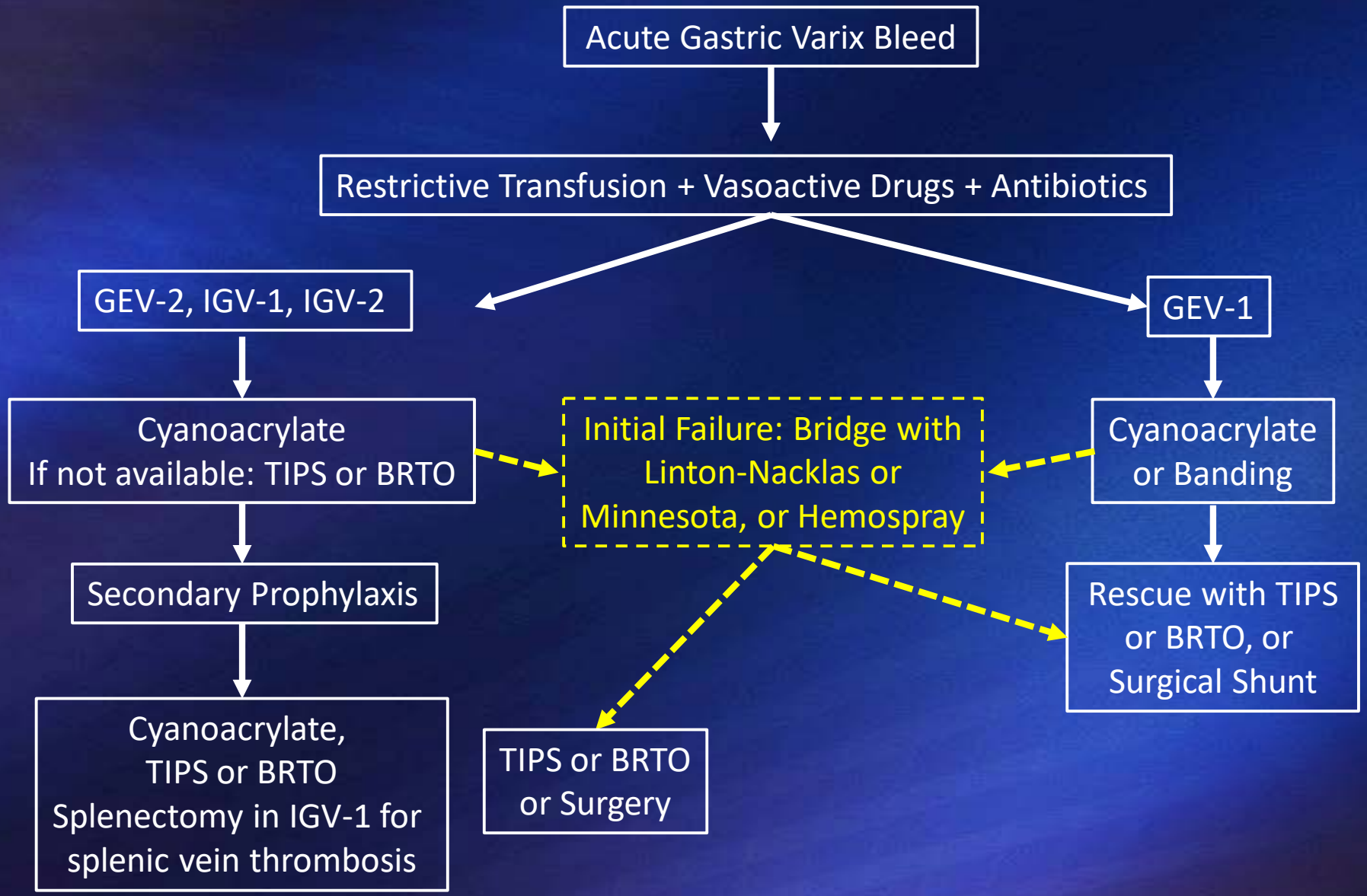
	Cyanoacrylate	Propranolol	No therapy	p
Bleeding	10	38	53	0.003
Bleeding Mortality	0	10	24	0.034
Total Mortality	7	17	26	0.113
Complications	3	3	7	1

We lack confirmatory studies of the effectiveness of Cyanoacrylate.
Carvedilol is superior to Propranolol for Primary Prophylaxis.
RECOMMENDATION: Use Carvedilol or Propranolol

Treatment of Gastric Variceal Hemorrhage

- Patients with acute bleeding from GV should be initially managed in a similar fashion to those bleeding from EV
  - using a restrictive transfusion policy, vasoactive drug infusion, and antibiotic prophylaxis.
- **GOV1 varices:** either EVL (if technically feasible) or cyanoacrylate glue injection, if available, are the recommended endoscopic treatments.
- **GOV2 or IGV1 varices:** TIPS is the treatment of choice in the control of bleeding from cardio-fundal varices. If not a TIPS candidate, then BRTO + partial splenic embolization is a good choice. If IGV1 is due to Splenic vein thrombosis, then the treatment is splenectomy.
  - Cyanoacrylate glue injection is an option for cases in which TIPS is not technically feasible, but it is not approved for treatment of GV in the United States and should be performed only in centers where the expertise is available.

Acute Gastric Varix Hemorrhage



Gastric Variceal Bleed (GOV2)

- 10-15% of all esophageal + gastric variceal bleeds.
- Bleeding Risk:
  - At 1 year, 2 years, 3 year, and 5 years, the bleeding risk is 16%, 25%, 36%, and 44% (Kim T et al. Hepatology 1997;25:307-12). Lifetime risk is 60%. Mean bleed 4.8 units.
  - Increases by size (> 10 mm, vs 5-10 mm, vs < 5 mm) and
  - Increases by Child Class (C>B>A);
    - Annual bleeding rate is 65% in Child C with large varix + red signs;
    - Annual bleeding rate is 4% in Child A with small varix without red markings.
- Mortality: 30-52%
- Re-bleeding Rate: 30%
- Gastric varix (GV) is usually a single large vessel; difficult to band or loop ligate.
- TIPS does not decrease diameter nor thickness of varix wall, and GV bleed at lower portal pressures.
- Re-bleeding rate post TIPS monotherapy is 20%.

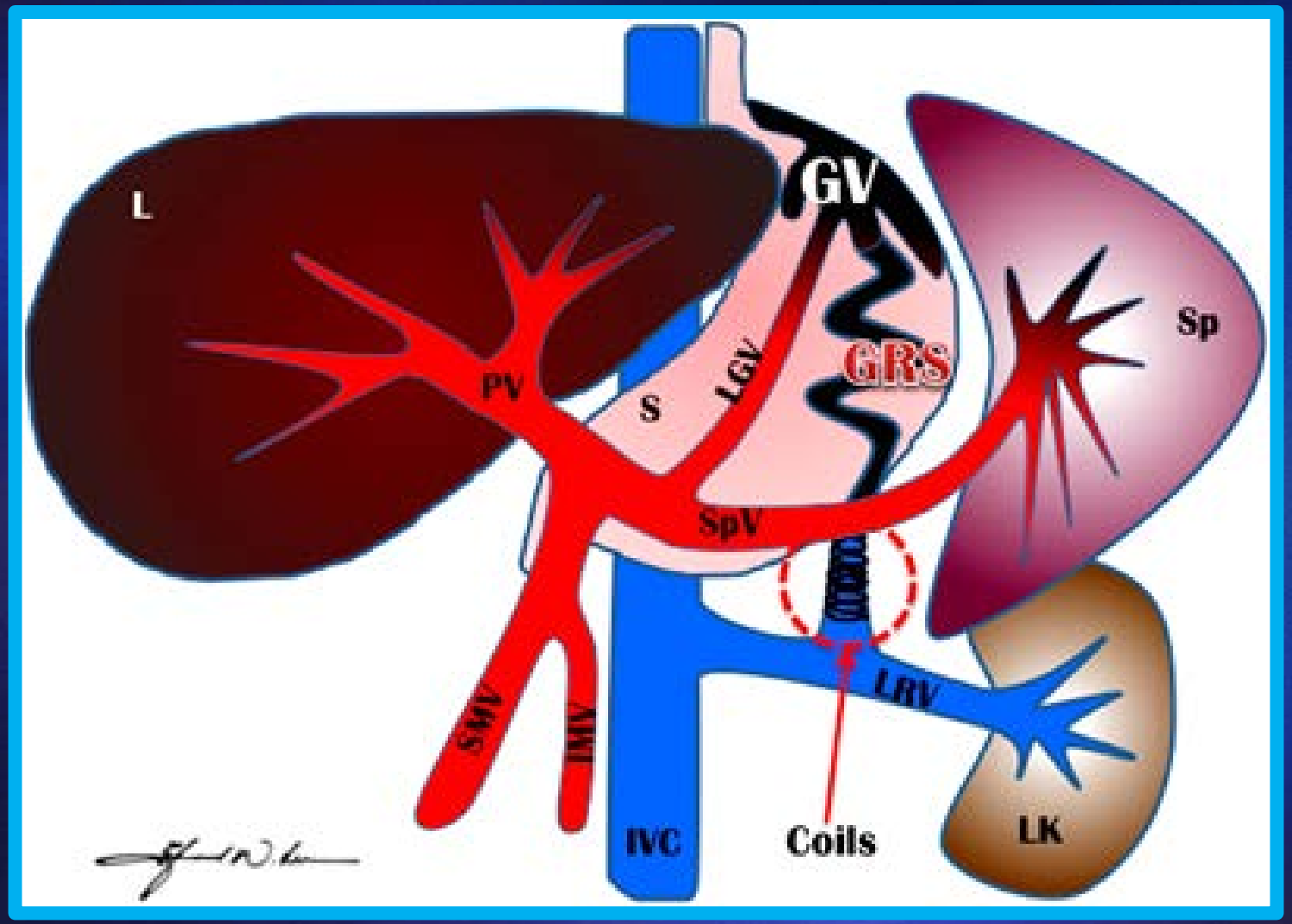
Cyanoacrylate vs TIPS in Gastric Variceal Bleed

- Acute hemostasis: 90-95%
- Re-bleeding: 15%
- Follow-up: Repeat at 4 weeks to confirm effect or re-treat; then q 6 months.
- Is superior to Banding and to Endoscopic sclerotherapy.
- Addition of beta-blockers does not help
- More cost-effective than TIPS.
- TIPS compared with cyanoacrylate for prevention of recurrent bleeding
  - re-bleeding 11-25% in TIPS versus 10% in Cyanoacrylate (38% if not eradicated) ;
  - survival is similar and
  - encephalopathy 26% in TIPS versus 3% in cyanoacrylate.

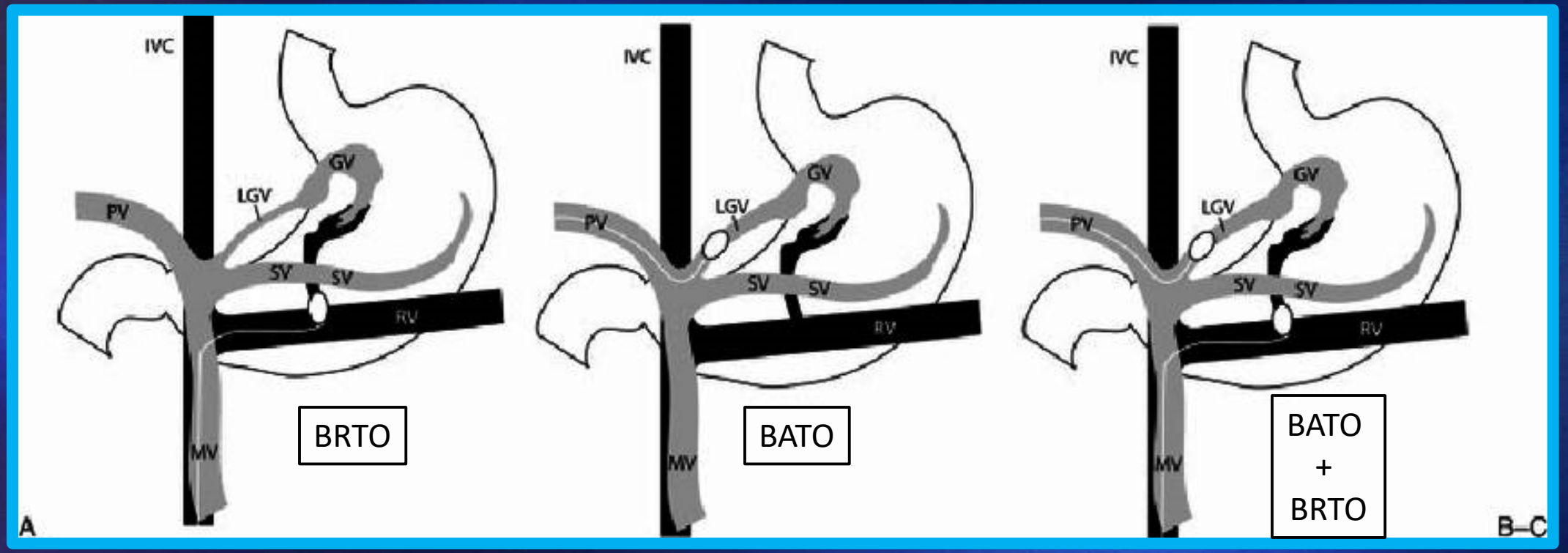
Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

- BRTO needs a Gastro-Renal Shunt (present in 85% of GV patients).
- Technique: instillation of sclerosant or foam into the GV via a balloon-occluding catheter placed through the Gastro-Renal Shunt.
- Indication: GVB who have failed endoscopic therapy and are poor candidates for TIPS.
  - In Japan: prevention of initial bleed and secondary prophylaxis of GVB.
- Initial control of bleeding > 90%,
- Re-bleeding rates 0%-9%,
- Variceal eradication rates 75%-100%,
- Adverse effects: fever, ascites, pleural effusions, and development of Esophageal Varices in up to two-thirds of patients.
- Partial splenic embolization preceding BRTO reduces incidence of Esophageal Varices compared with BRTO alone (9% versus 45%) by reducing blood inflow into the portal vein.

Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)



Balloon-occluded Retrograde Trans-venous Obliteration (BRTO) and Balloon Occluded Antegrade Transvenous Obliteration (BATO)



(A) BRTO: The balloon-occlusion catheter is advanced from a transfemoral approach and positioned and inflated in the gastro-renal shunt near its base at the left renal vein (RV).

(B) BATO (Balloon-occluded Antegrade Trans-venous Obliteration) or PTO (Percutaneous Transhepatic Obliteration): The balloon-occlusion catheter is advanced from a transhepatic (portal venous) approach and positioned and inflated in the left gastric vein (LGV) or coronary vein near its base at the main portal vein (PV). PTO is a subtype of BATO; the other subtype is the trans-TIPS BATO approach.

(C) Combined BATO and BRTO: Uses two balloon-occlusion catheters for a combined transhepatic BATO (PTO) and BRTO procedure.

IVC, Inferior vena cava; MV, mesenteric vein; SV, splenic vein; GV, gastric varix.

Treatment of Acute Gastric Variceal Bleed

- Intra-variceal Cyanoacrylate injection (**Hystoacryl**, Dermabond) q 3-4 weeks until obliteration:
  - hemostasis in 90%;
  - embolization 0.7%;
  - re-bleeding at 3 d, 3 month and 1 year: 6.9%, 10.6%, and 10.0%.
- TIPSS:
  - controls 90% of bleeds (goal HVPG pressure =/< 8 mmHg);
  - re-bleeding at 3 d, 3 month and 1 year: 9.5%, 20.7%, and 25% (Procaccini NJ et al. Gastrointestinal Endoscopy 2009;70:881-7)
- Vasoactive drugs + antibiotics (used but not studied).
- BRTO (Balloon-Occluded Retrograde Trans-venous Obliteration)
- BRTO + TIPS: less ascites, hydrothorax, esophageal varices and re-bleeding.
- Balloon (Linton-Nacklas or modified Minnesota) as bridge to TIPS

Secondary Prophylaxis of Gastric Variceal Hemorrhage

- In patients who have recovered from a GOV1 hemorrhage:
  - the combination of NSBBs and endoscopic variceal therapy (EVL or cyanoacrylate injection) is the first-line therapy.
- In patients who have recovered from GOV2 or IGV1 hemorrhage:
  - TIPS or BRTO are first-line treatments.
  - Cyanoacrylate glue injection is an option for cases in which TIPS or BRTO are not technically feasible, but it is not approved for the treatment of GV in the United States and should be performed only in centers where the expertise is available.

PROPHYLAXIS

- SECONDARY PROPHYLAXIS: comparison of beta blockade vs n-BCA (at time 0, 2, and 6 months) obliteration gives (Mishra SR et al. Gut 2010;59:729-35):
  - Re-bleeding at 26 weeks: 55% in BB vs 15% with n-BCA
  - Mortality at 26 weeks: 25% in BB vs 3% with n-BCA
  - Addition of beta-blocker to serial cyanoacrylate obliteration does no change re-bleeding rate nor mortality. (Hung HH et al. Journal of Hepatology 2012;56:1025-32).

- PRIMARY PROPHYLAXIS: In mostly GOV2 (some IGV1); first bleeding rate after 26 weeks of follow up:
  - No treatment = 45% vs
  - Propranolol = 28%, vs
  - Cyanoacrylate (n-BCA) = 13%