Gastric Variceal Bleed

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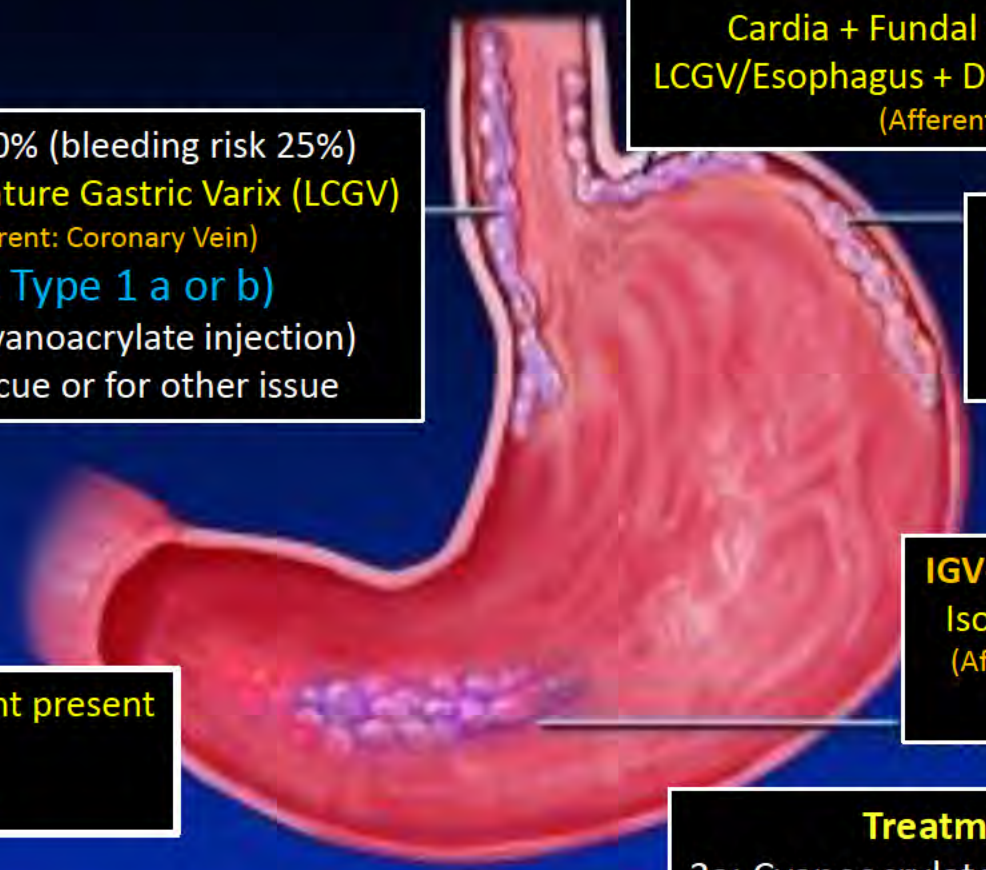
Classification of Gastric Varices

Sarin (Endoscopic) and Saad-Caldwell (S-C) (Hemodynamic)

GOV-2: 24% (bleeding risk 60%)
Cardia + Fundal Gastric Varix (S-C Type 2 a/b or 3 a/b)
LCGV/Esophagus + Distal Gastric Varix (S-C Type 2 a/b or 3 a/b)
(Afferent: Multiple equally dominant Veins)

GOV-1: 70% (bleeding risk 25%)
Lesser Curvature Gastric Varix (LCGV)
(Afferent: Coronary Vein)
(S-C Type 1 a or b)
EVL (or Cyanoacrylate injection)
TIPS Rescue or for other issue

IGV-1: 2% (bleeding risk 90%)
Isolated Fundal Gastric Varix
(Afferent: Short Gastric Veins)
(S-C Type 2 a or b)



IGV-2: 4% (bleeding risk 15%)
Isolated Distal Gastric Varix
(Afferent: Posterior Gastric Vein)
(S-C Type 2 a/b)

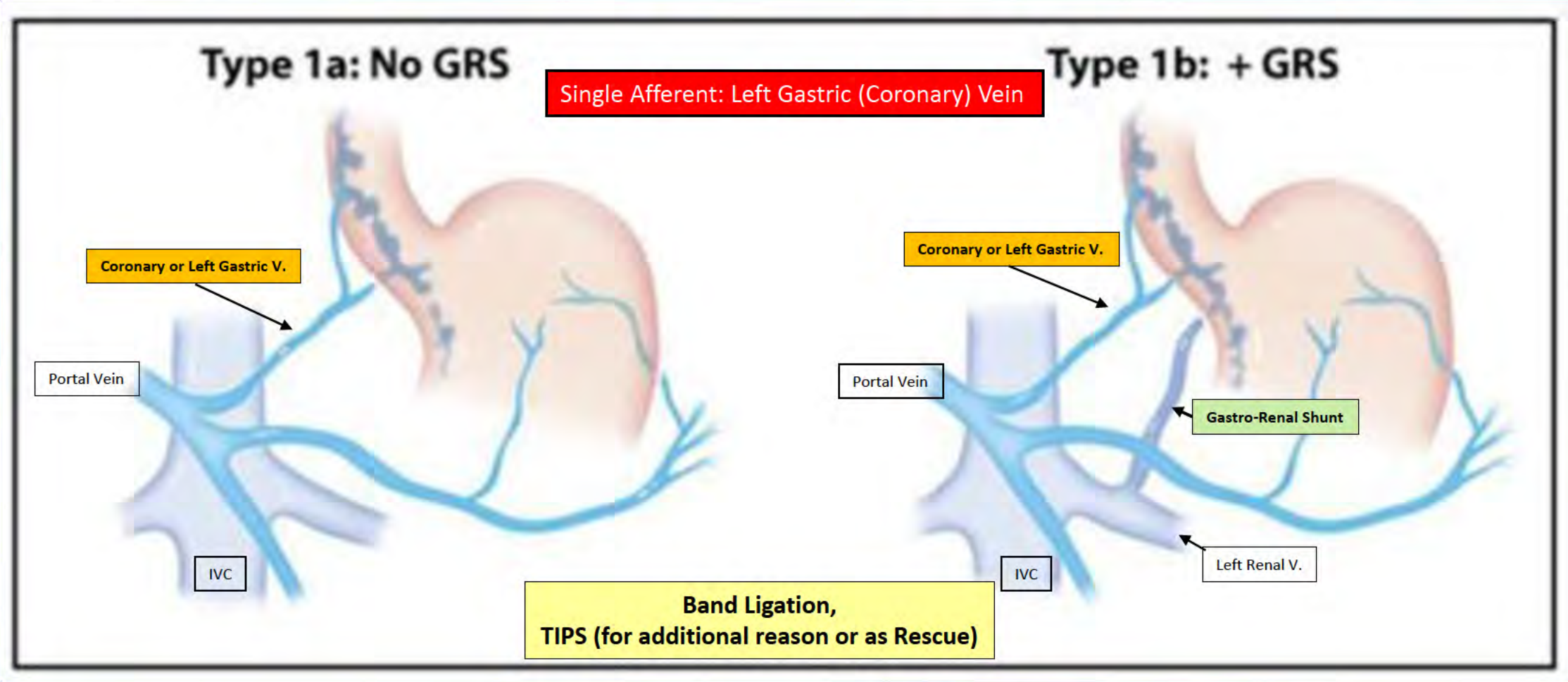
Gastro-Renal Shunt present
a: NO
b: YES

Treatment by Saad-Caldwell (S-C) Type
2a: Cyanoacrylate, or Splenectomy in Splenic V. thrombosis
2b: BRTO
3a: TIPS + Embolization, or Cyanoacrylate
3b: BRTO + EVL of cardia +/- TIPS

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

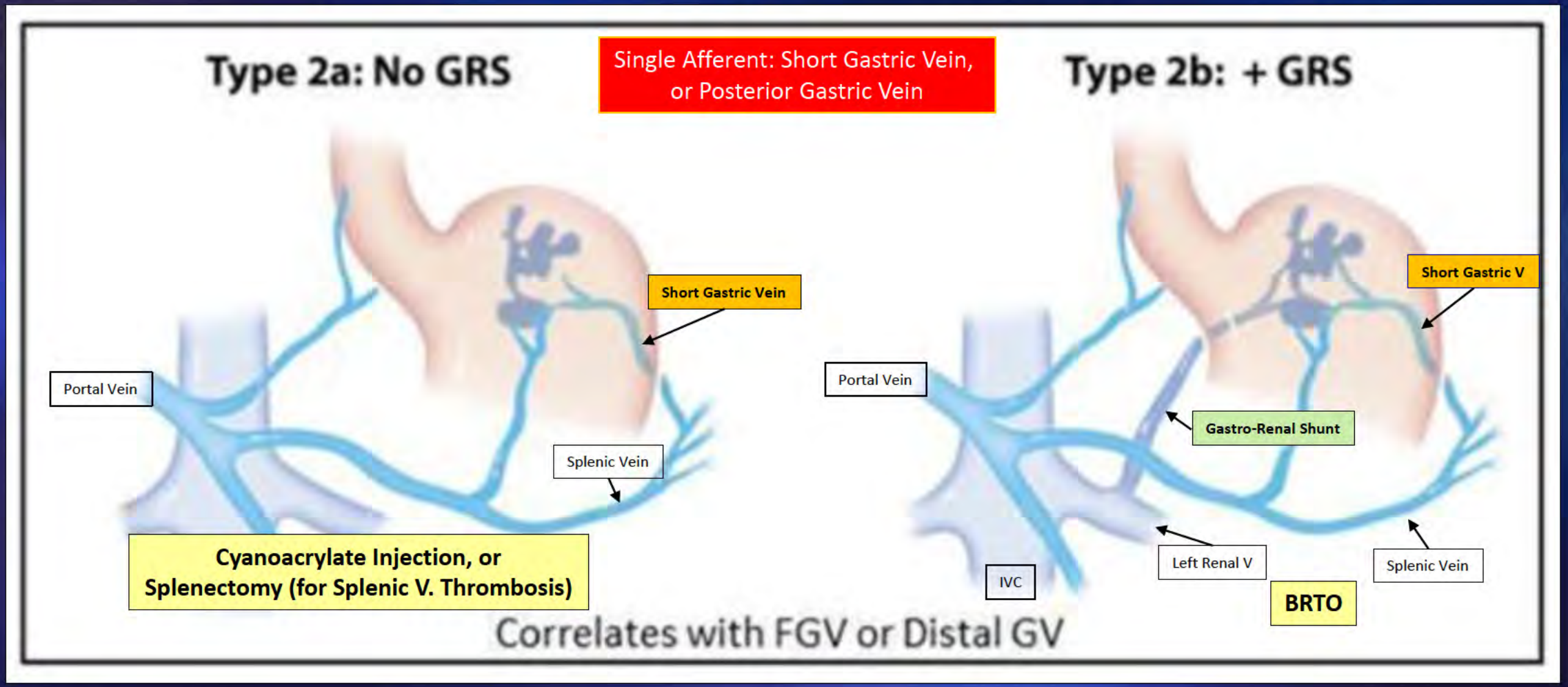
S-C Type 1 Gastric Varices

Lesser Curvature Gastric Varices (LCGV) – **GOV-1**



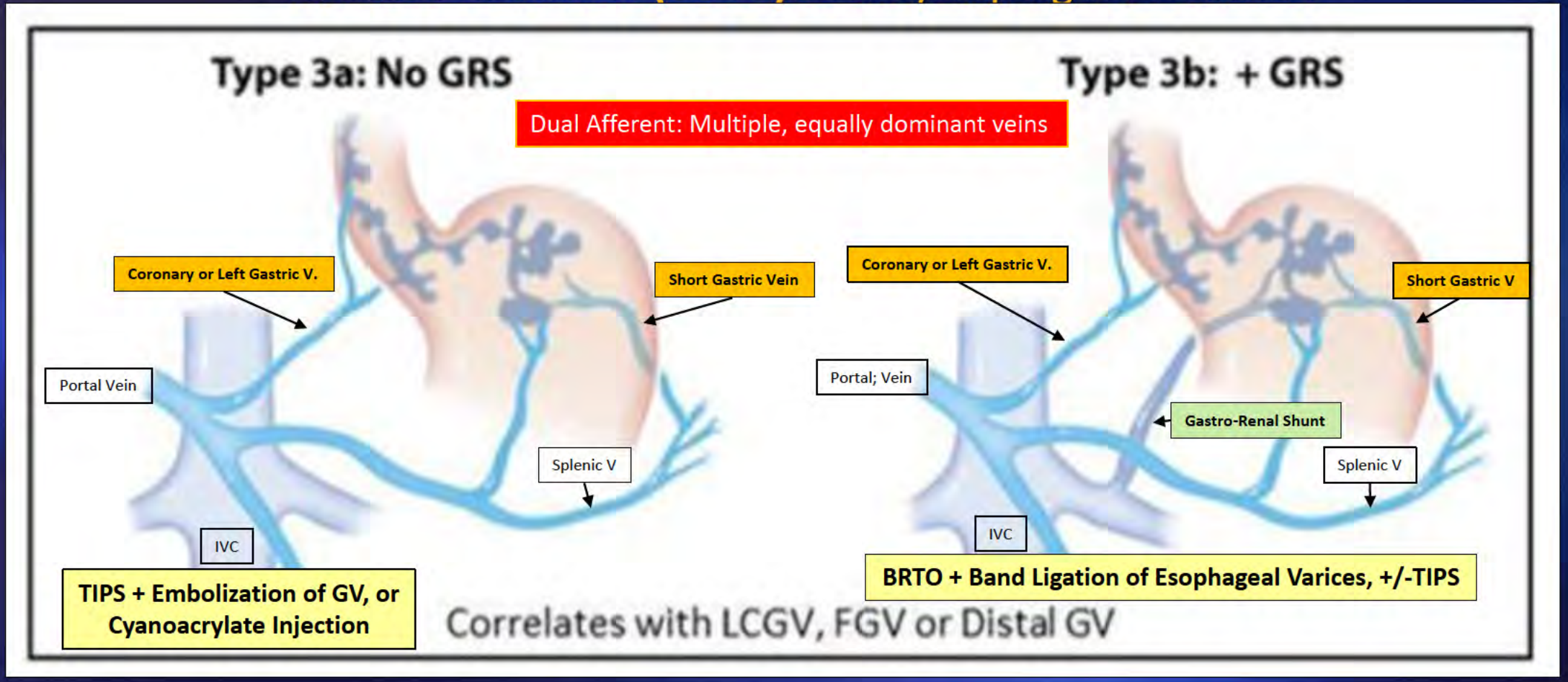
S-C Type 2 Gastric Varices

Isolated Fundal Gastric Varices **(IGV-1)** or Isolated Distal Gastric Varices **(IGV-2)**



S-C Type 3 Gastric Varices

Cardia GV + Fundal GV **(GOV-2)** or LCGV/Esophagus V + Distal GV



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

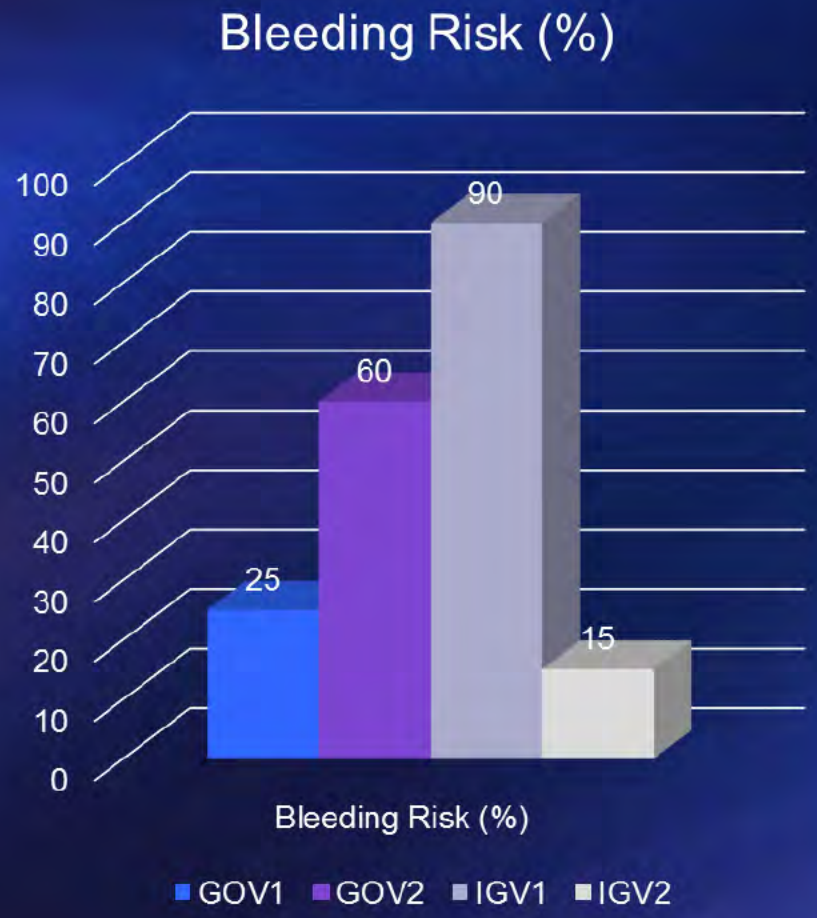
Mishra SR et al. J Hepatol 2011; 54: 1161-1167

	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

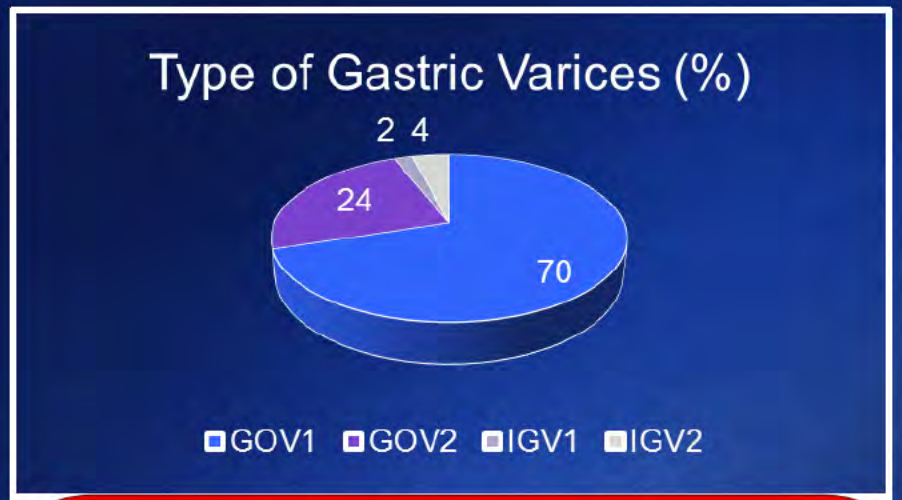
We lack confirmatory studies of the effectiveness of Cyanoacrylate.
Carvedilol is superior to Propranolol for Primary Prophylaxis.
RECOMMENDATION: Use Carvedilol or Propranolol

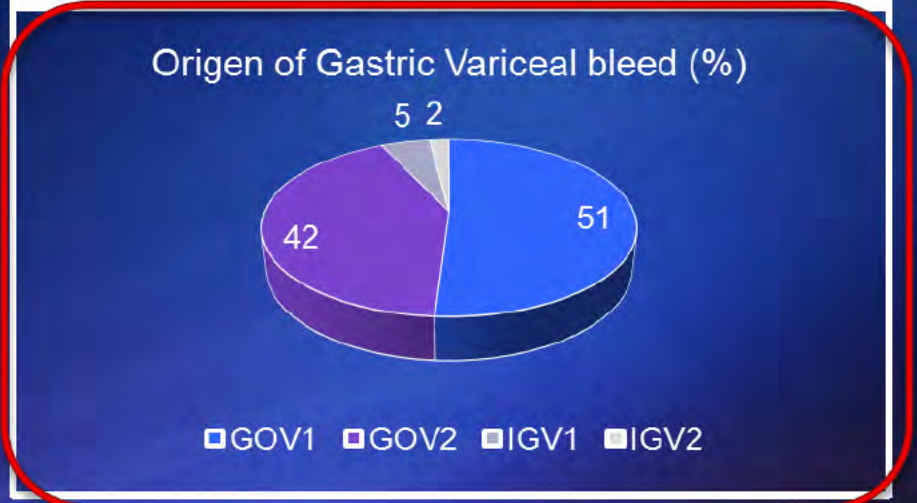
Gastric Variceal Bleed

Risk, Frequency & Origen



Lifetime Risk of Bleeding



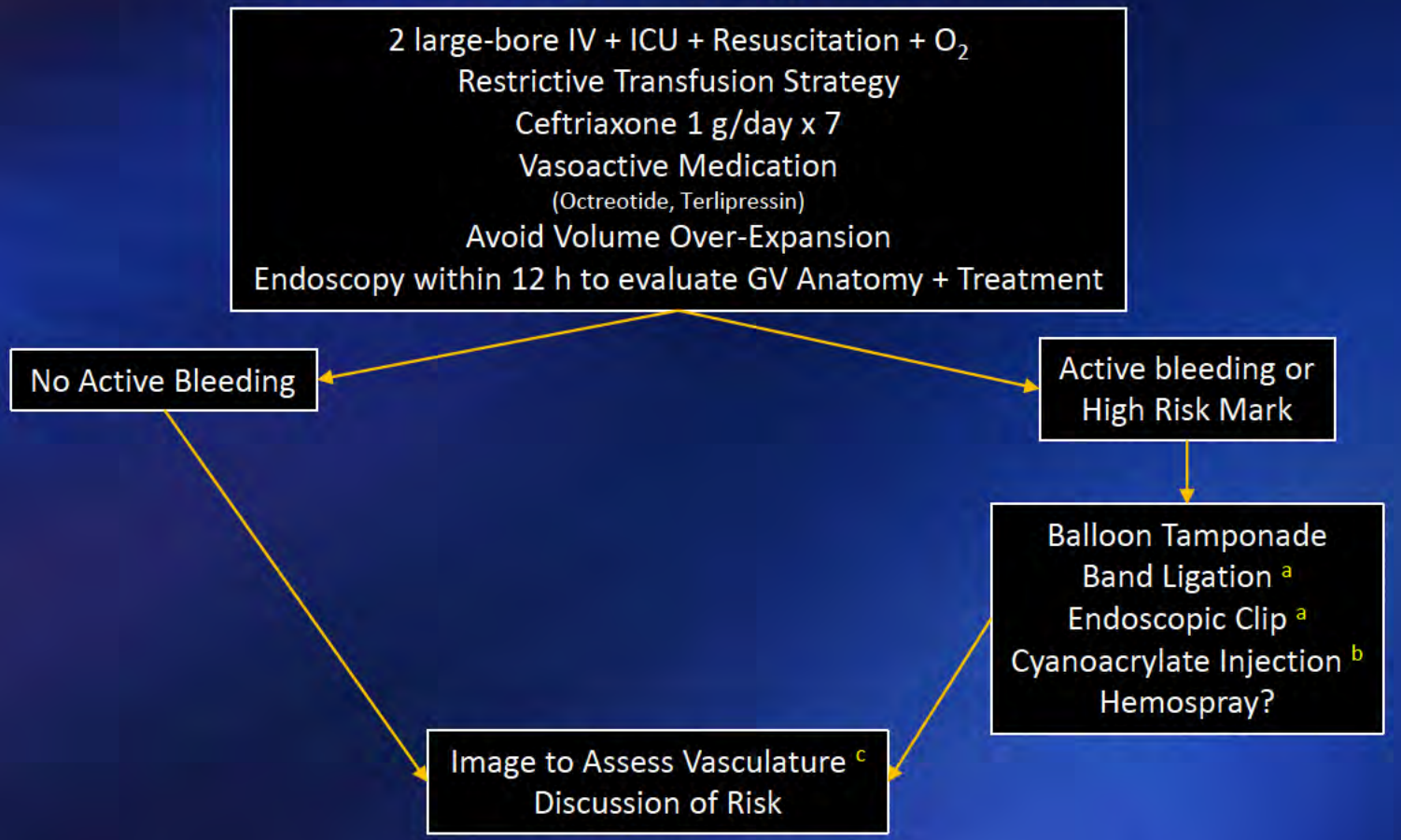


Gastric Variceal Bleed (GOV2)

- 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; additional Embolization of Fundal Varix is recommended.
- Re-bleeding rate post TIPS monotherapy is 20%.

Initial Evaluation and Management of Gastric Varices Bleed

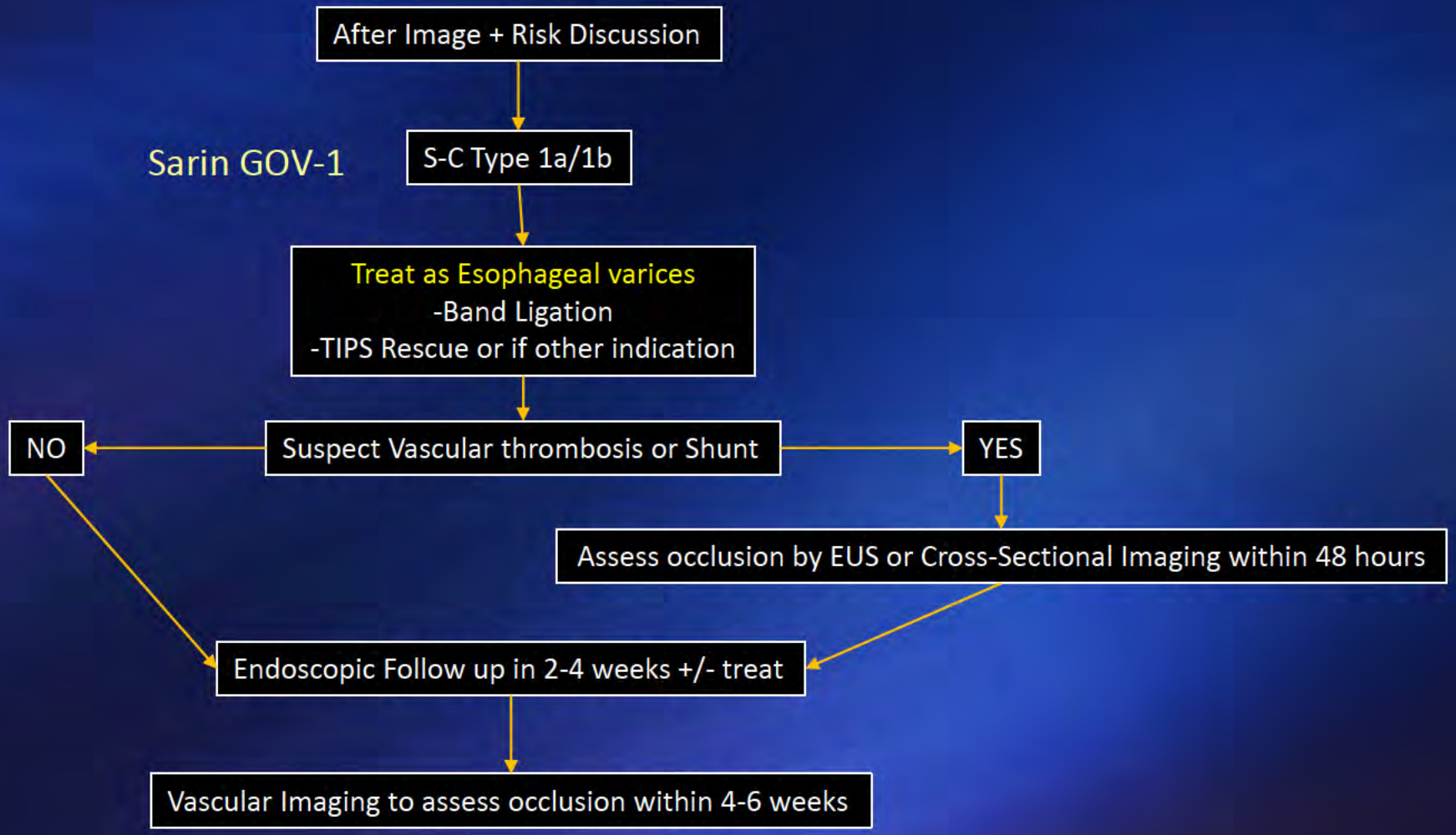
Clinical Gastroenterology and Hepatology 2021;19:1098–1107



a Temporizing options should be chosen based on local expertise and available resources; **Sclerotherapy with Ethanolamine is not recommended**.
b Cyanoacrylate injection is often not feasible in the acute setting and is more safely used as definitive treatment once imaging has been obtained.

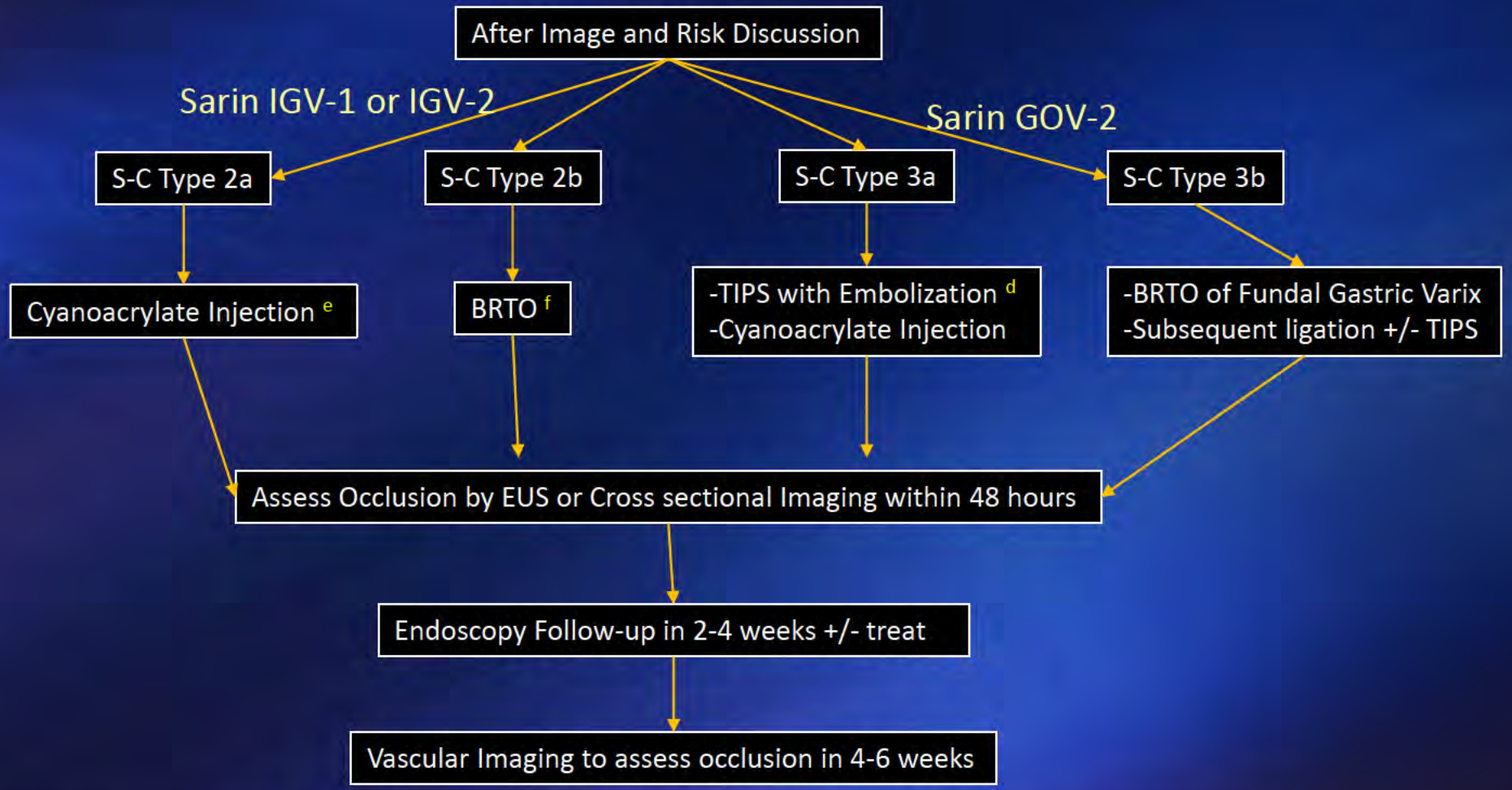
Definitive Therapy of Lesser Curvature Gastric Varices

Type 1 are only in lesser curvature (LCGV) + Esophagus (Coronary Vein)



Definitive Therapy of Cardio-Fundal Gastric Varices

Type 2 do not have any Esophageal/LCGV (Short Gastric Vein or Posterior Gastric Vein); Type 3 are combined (Multiple co-dominant veins)



d: TIPS alone is often insufficient to control bleeding from cardio-fundal GV and should be combined with direct embolization.
e: In the absence of a GRS cyanoacrylate injection is the best option for managing cardio-fundal GV.
f: In the presence of a GRS, BRTO is the best option for managing cardio-fundal GV absent severe complications of pHTN.

Treatment of Acute Gastric Variceal Bleed

- Vasoactive drugs + antibiotics (used but not studied).
- Intra-variceal Cyanoacrylate injection (**Hystoacryl**, Dermabond) q 3-4 weeks until obliteration:
  - hemostasis in 90%;
  - embolization 0.7% with Pulmonary embolus or stroke; rarely impaction of the needle, exacerbation of bleeding, portal or splenic vein thrombosis, and infection.
  - re-bleeding at 3 d, 3 month and 1 year: 6.9%, 10.6%, and 10.0%.
- Bridge: Balloon (Linton-Nacklas or modified Minnesota), Hemoclip, Variceal Ligation.
- TIPS:
  - 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)
- BRTO (Balloon-Occluded Retrograde Trans-venous Obliteration)
- BRTO + TIPS: less ascites, hydrothorax, esophageal varices and re-bleeding.

Factors Affecting Treatment Choice

	FAVOR	DISFAVOR
TIPS	Ascites, Hydrothorax, Risky esophageal varices, No Gastro-Renal Shunt	MELD > 18*, Creatinine > 3, Bili > 3*, Past Hepatic Encephalopathy, Pulmonary HTN, CHF Gastro-Renal shunt
BRTO	Gastro-Renal Shunt, Past Hepatic Encephalopathy, MELD > 18, Bili > 3, Creatinine > 3, Contraindication for TIPS	Ascites, hydrothorax, Risky esophageal varices, Bland Portal Vein clot
Cyanoacrylate Injection	No Gastro-Renal Shunt, Lower cost, S-C Type 2a	Esophageal varices (but can be banded), Gastro-Renal Shunt, Medico-Legal risk (no FDA approved).

*TIPS improves survival up to MELD 29, ACLF-3a and Bili > 10

If not a TIPS candidate but with comorbidities from portal HTN, then BRTO + partial splenic embolization is a reasonable choice.

Endoscopic Cyanoacrylate Injection

Cyanoacrylate for Gastric Varices

Use Sterile Water
(DO NOT use Saline)

Place Syringes on Ice

Preparation

1. Draw 15–20cc neutral oil (such as olive oil) in 60cc slip tip syringe
2. Connect endoscopic injector needle (19–23g) to 3-way stop cock[A]
3. Draw up 5cc sterile water into a 5–10cc syringe (prepare 2–4 syringes)[B]
4. Connect sterile water to side port of stop cock
5. Draw up 2mL cyanoacrylate (CA) into a 5–10cc syringe (prepare 2–4 syringes)[C]
6. Cap syringes and place on ice to prevent polymerization of CA[D]

Endoscopy

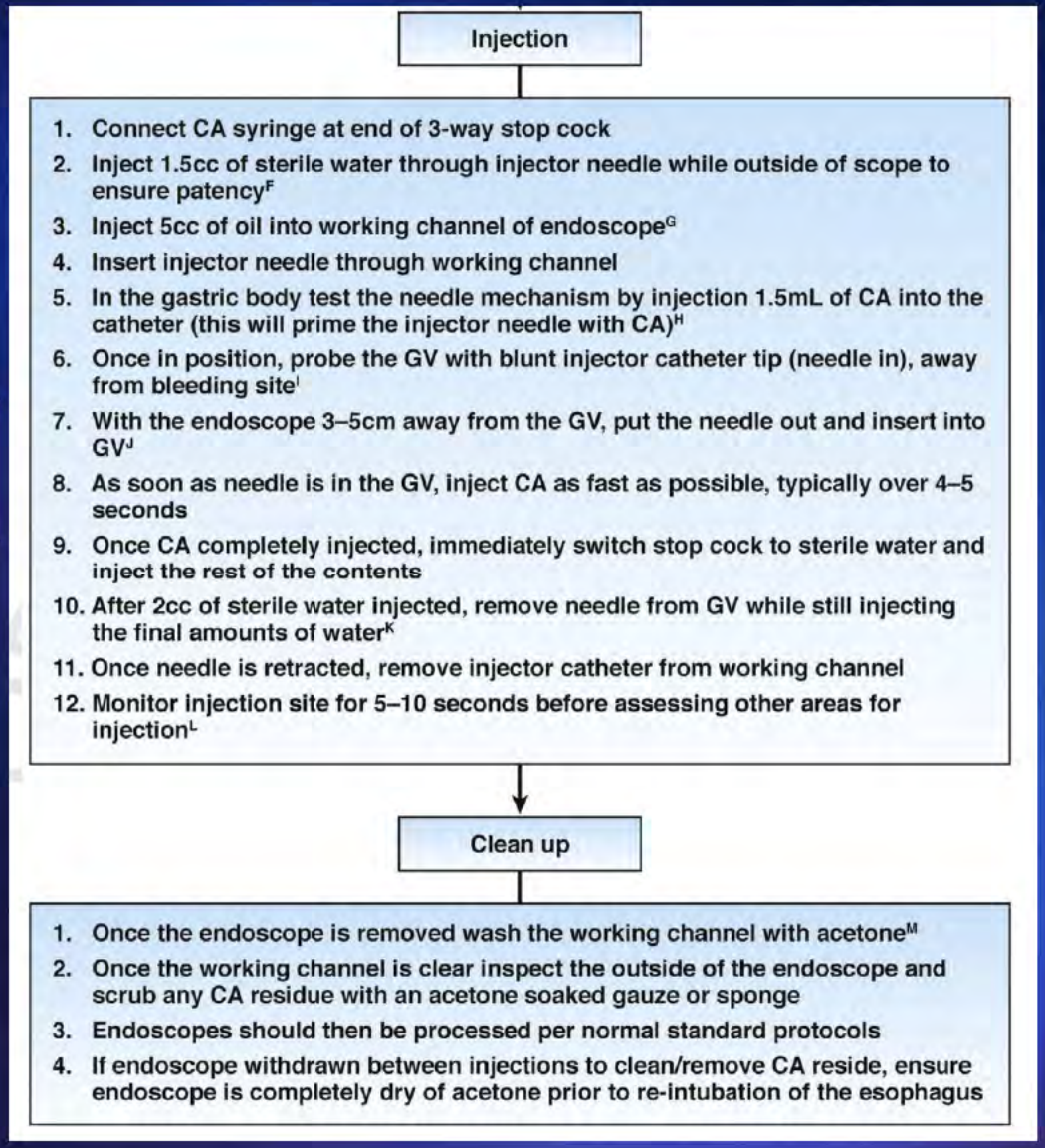
1. Use of standard gastroscope may be sufficient, but consider using a sigmoidoscope for increased flexibility needed in the cardia/fundus[E]
2. Best approach for cardiofundal varices is via retroflexion; for lesser curve or distal GV a forward view may be best

HISTOACRYL (0.5 mL/amp) N-butyl-2-cyanoacrylate

Cyanoacrylate for Gastric Varices

Injection needle should be 23 G or larger (19-23 G)

Use Sterile Water (DO NOT use Saline)



Injection

1. Connect CA syringe at end of 3-way stop cock
2. Inject 1.5cc of sterile water through injector needle while outside of scope to ensure patency[F]
3. Inject 5cc of oil into working channel of endoscope[G]
4. Insert injector needle through working channel
5. In the gastric body test the needle mechanism by injection 1.5mL of CA into the catheter (this will prime the injector needle with CA)[H]
6. Once in position, probe the GV with blunt injector catheter tip (needle in), away from bleeding site[I]
7. With the endoscope 3–5cm away from the GV, put the needle out and insert into GV[J]
8. As soon as needle is in the GV, inject CA as fast as possible, typically over 4–5 seconds
9. Once CA completely injected, immediately switch stop cock to sterile water and inject the rest of the contents
10. After 2cc of sterile water injected, remove needle from GV while still injecting the final amounts of water[K]
11. Once needle is retracted, remove injector catheter from working channel
12. Monitor injection site for 5–10 seconds before assessing other areas for injection[L]

Clean up

1. Once the endoscope is removed wash the working channel with acetone[M]
2. Once the working channel is clear inspect the outside of the endoscope and scrub any CA residue with an acetone soaked gauze or sponge
3. Endoscopes should then be processed per normal standard protocols
4. If endoscope withdrawn between injections to clean/remove CA reside, ensure endoscope is completely dry of acetone prior to re-intubation of the esophagus

Repeat EGD q 2-4 weeks to re-treat until obliteration. Then in 6 moths, and yearly thereafter.
Repeat CT or MRI yearly.

BRTO

Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

- BRTO needs a Gastro-Renal Shunt (present in 85% of GV patients).
- Indication: GVB with anatomy Saad-Caldwell type 2b or 3b.
- Technique: instillation of sclerosant, coils, or foam into the GV via a balloon-occluding catheter placed through the Gastro-Renal Shunt.
- Initial control of bleeding: > 90%,
- Re-bleeding rates: 5%-9% at 1 year,

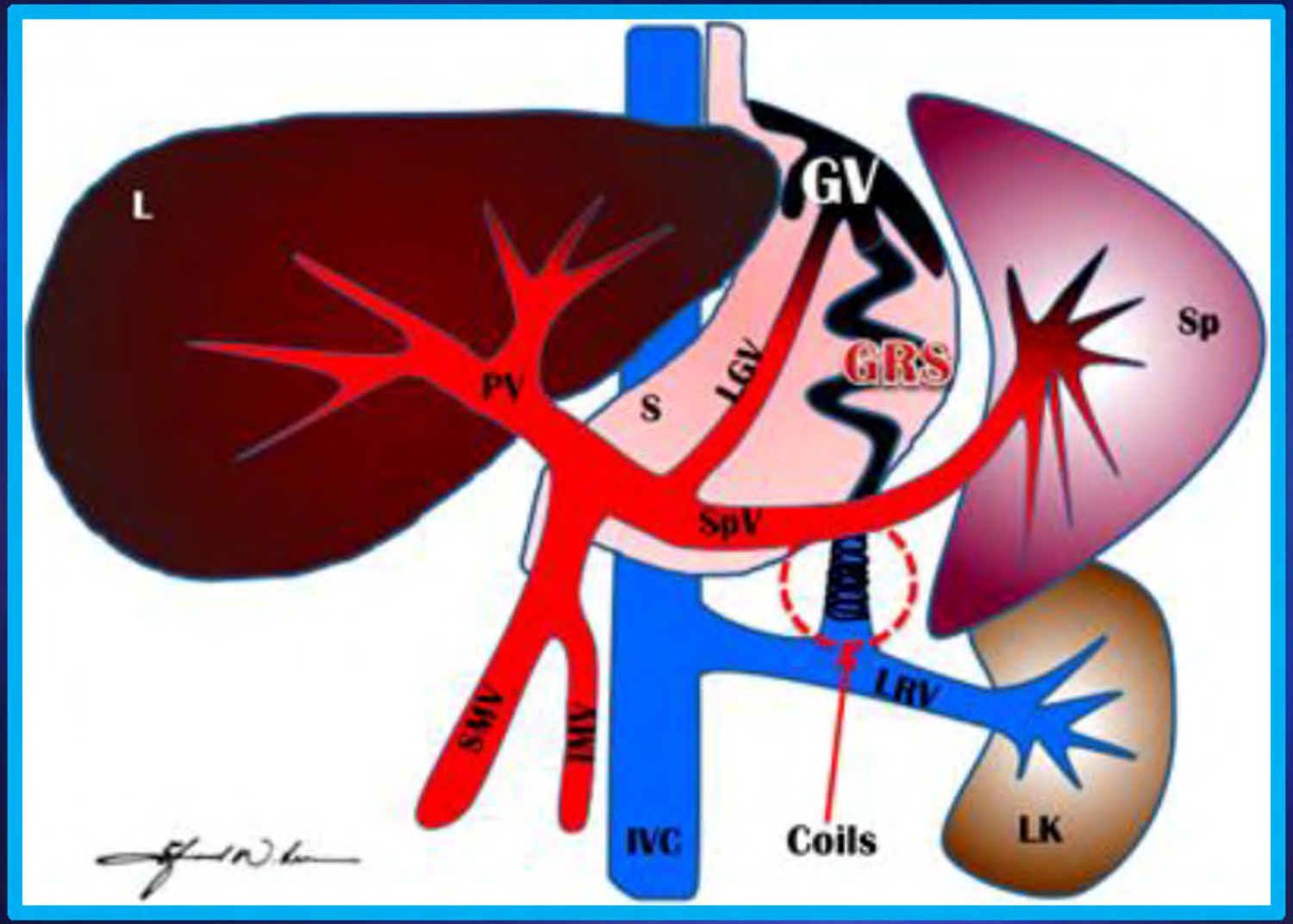
In Japan: BRTO is used for prevention of initial bleed and secondary prophylaxis of GVB.

Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

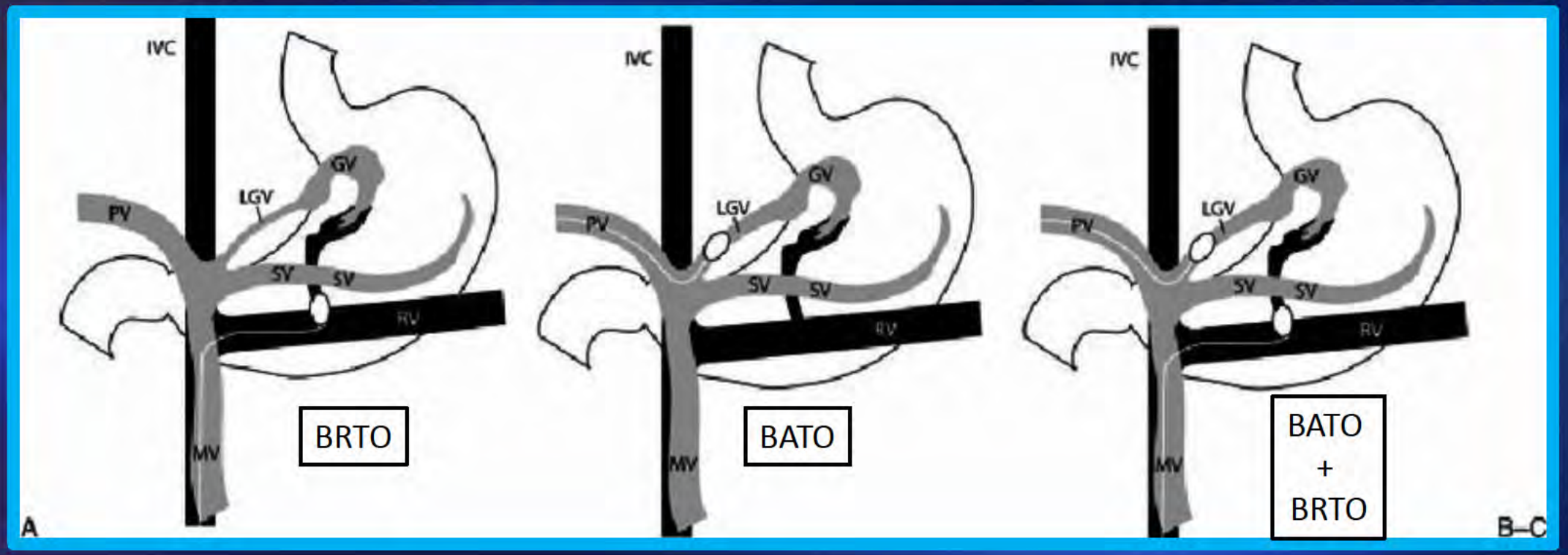
- Variceal eradication rates: 75%-100%,
- Adverse effects: fever, ascites, pleural effusions, and development of Esophageal Varices in up to two-thirds of patients.
  - 30%–35% of Esophageal Varices will progress in size after BRTO.
  - Symptomatic ascites or hydrothorax requiring an intervention occur in 15% of patents within a year after BRTO and are present in up to 35%–40% of patients by imaging.
- 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.

In Japan: BRTO is used for prevention of initial bleed and secondary prophylaxis of GVB.

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.

Management after BRTO

- EUS within 48 hours after BRTO to confirm obliteration of GV, evaluate for exacerbation of EV, and obtain a new baseline after the procedure.

- Upper endoscopy +/- Banding
  - High Risk E-V: within 2 weeks after BRTO
  - Low-Risk E-V: within 4–6 weeks after BRTO

- Multiphase MRI or CT Scan within 4-6 weeks after BRTO to evaluate for new shunts, and identify complications such as splenic vein thrombosis, portal vein thrombosis, or compromise of the left renal vein from hardware or sclerosant. Repeat again 3-6 month later.

TIPS

Contraindications for Elective TIPS

ABSOLUTE

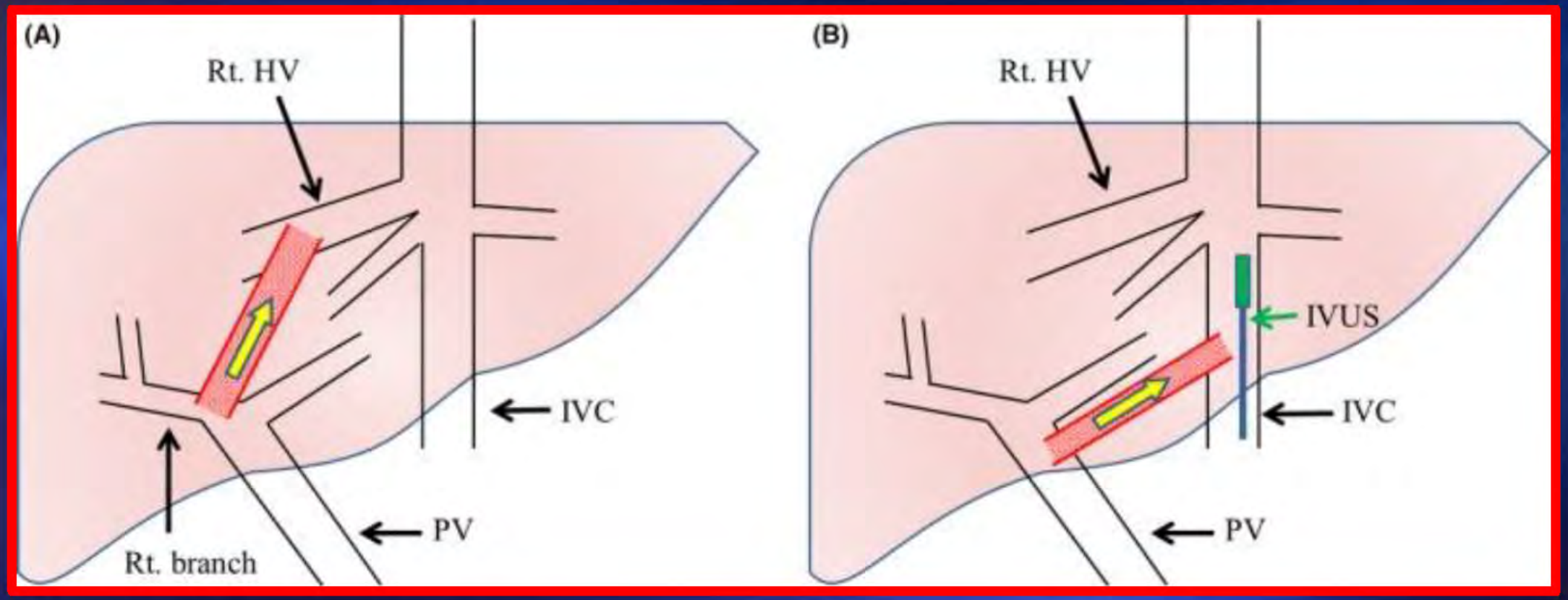
- Severe hepatic failure (does not apply in variceal bleed)
- Severe congestive heart failure (ACC/AHA stage C or D HF)
- Severe untreated valvular heart disease (AHA/ACC stage C or D VHD)
- Severe tricuspid regurgitation
- Severe pulmonary HTN with PAPm >/= 45 mm Hg despite medical optimization
- Uncontrolled systemic infection
- Refractory overt HE
- Unrelieved biliary obstruction
- Lesions (eg, cysts) or tumors in the liver parenchyma that preclude TIPS creation

Stage C HF: Structural heart disease with symptoms of heart failure
Stage D HF: Refractory heart failure requiring specialized interventions
Stage C VHD: Asymptomatic patients who have the criteria for severe VHD
Stage D VHD: Symptomatic VHD

RELATIVE

- Active infection - Controlled
- Poorly controlled PSE
- Portal V thrombosis with or without cavernoma
- If RVSP > 45 mm Hg or TAPSE < 1.6 cm, consult cardiology for right heart catheterization (RHC) to evaluate for RV dysfunction and pulmonary hypertension before TIPS creation.
- Avoid elective TIPS in LVEF < 50% or grade III diastolic dysfunction.
- Moderate or severe POPH on treatment PAPm > 35 mm Hg, pulmonary vascular resistance > 3 wood units) has risk of RV failure.
- If pre-TIPS RA pressure > 14 mm Hg, do RHC to R/O and measure Pulmonary HTN. (Pre-TIPS RAP > 14.5 and post-TIPS > 21.5 increases mortality)

TIPS and DIPS in Gastric Variceal Bleed



In Gastric Variceal bleed: Goal HVPG of </= 8 mm Hg

ECHO Evaluation Pre-TIPS

Left ventricular function assessment	Right ventricular function assessment
Systolic function o Ejection fraction (normal: >50%) o Global longitudinal strain (normal: absolute value ≥18%) Diastolic function[a] o Early diastolic transmitral flow to early diastolic mitral annular tissue velocity (E/e′) ratio (normal: ≤14 cm/s) o Septal e′ velocity (normal: ≥7 cm/s) o Left atrial volume index (normal: ≤34 mL/m^2) o Tricuspid regurgitation velocity (normal: ≤2.8 m/s)	Right ventricular systolic pressure (normal: age-dependent, up to 45 mm Hg) Tricuspid annular plane systolic excursion (normal: >1.6 cm)

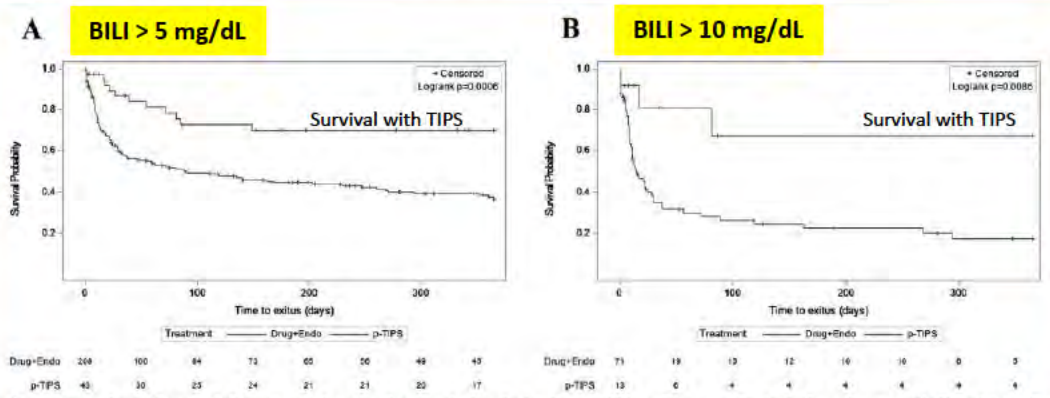
[a]Two or more abnormalities are needed to make the diagnosis of diastolic dysfunction. The degree of diastolic dysfunction is to be determined by the cardiologist depending on additional measures such as early to late diastolic transmitral flow velocity (E/A) ratio (at rest or during Valsalva), left atrial strain, and left ventricular strain. Guidance is adapted from the American Society for Echocardiography guidelines and the Cirrhotic Cardiomyopathy Consortium practice guidance.[114,115]

Grade III Diastolic Dysfunction: E/A ≥2, DT <160 ms, IVRT >60 ms, mitral A flow duration shorter than Ar duration, and average E/e' ratio >13 (or septal E/e' >15 and lateral E/e' >12).

Meta-Analysis of Individual Patient Data

Nicoara-Farcau, O et al. Gastroenterology 2021;160:193–205

Early TIPS improves Survival even if Bili > 10 mg/dL



Supplementary Figure 7. Survival at 1 year of patients treated with p-TIPS vs Drugs + Endo in A. patients with Bilirubin > 5 mg/dL and B. patients with Bilirubin > 10 mg/dL.

Early TIPS is Beneficial even with Multiple Risk Factors

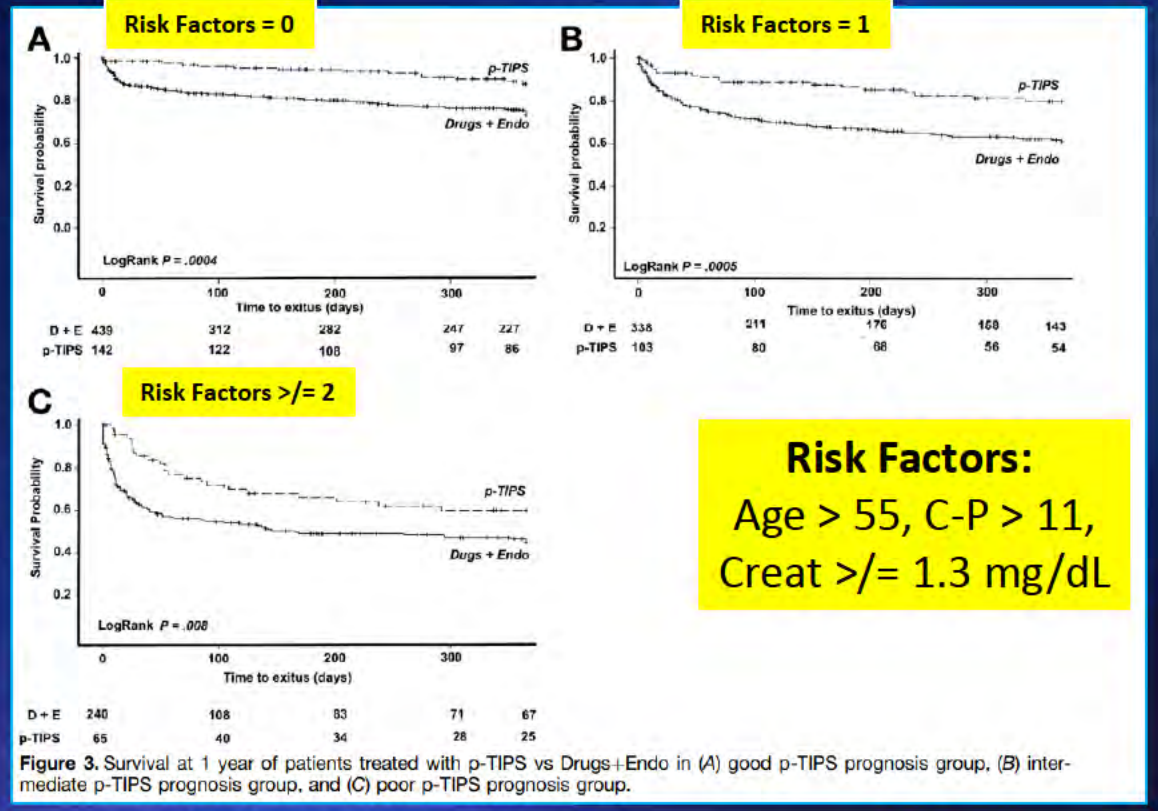


Figure 3. Survival at 1 year of patients treated with p-TIPS vs Drugs+Endo in (*A*) good p-TIPS prognosis group, (*B*) intermediate p-TIPS prognosis group, and (*C*) poor p-TIPS prognosis group.

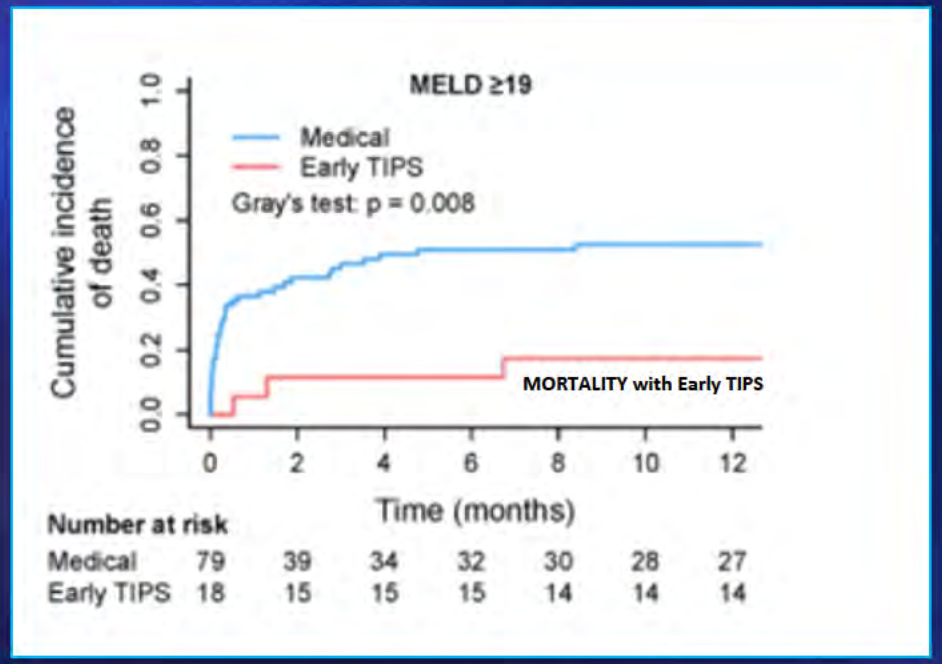
Risk Factors:
Age > 55, C-P > 11,
Creat >/= 1.3 mg/dL

Extrapolation from Esophageal Varix Bleed

Early TIPS in High MELD and in ACLF

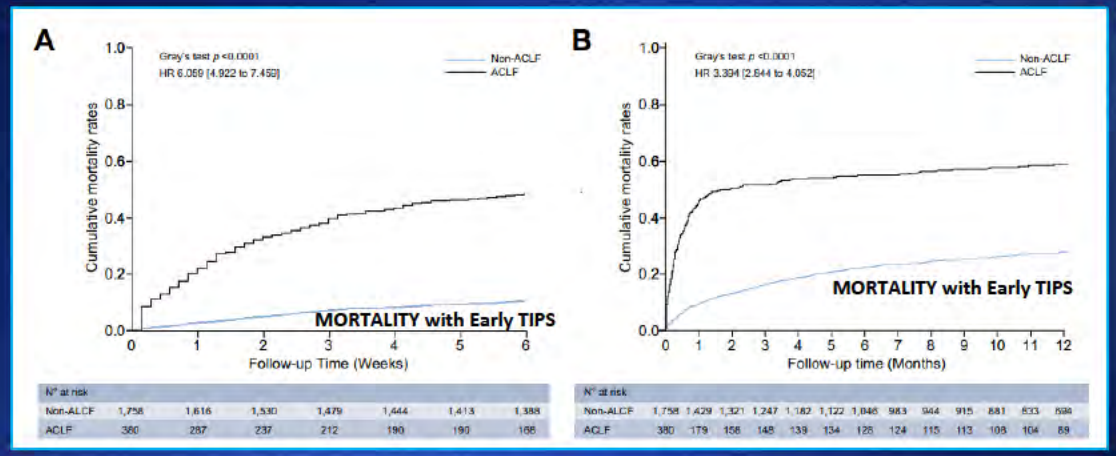
Early TIPS in High MELD

Lv Y, et al. Gut 2019;68:1297–1310



Early TIPS in ACLF

Trebicka J et al. Journal of Hepatology 2020 vol. 73: 1082–1091



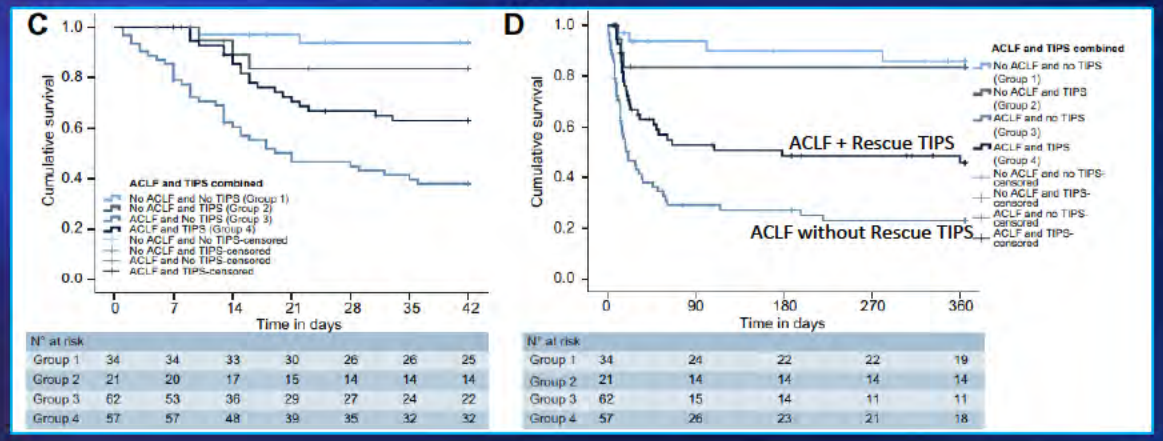
Early TIPS Decreases Mortality even in High MELD and in ACLF

Extrapolation from Esophageal Varix Bleed, Child-Pugh B with bleeding and Child-Pugh up to 13

Rescue TIPS Improves Survival in ACLF

1-Year Survival with Rescue TIPS in ACLF

Kumar R et al. Journal of Hepatology 2021 vol. 74: 66–79



6-week Survival with Rescue TIPS by Grade

Walter A et al. Hepatology, VOL. 74, NO. 4: 2085-2101, 2021

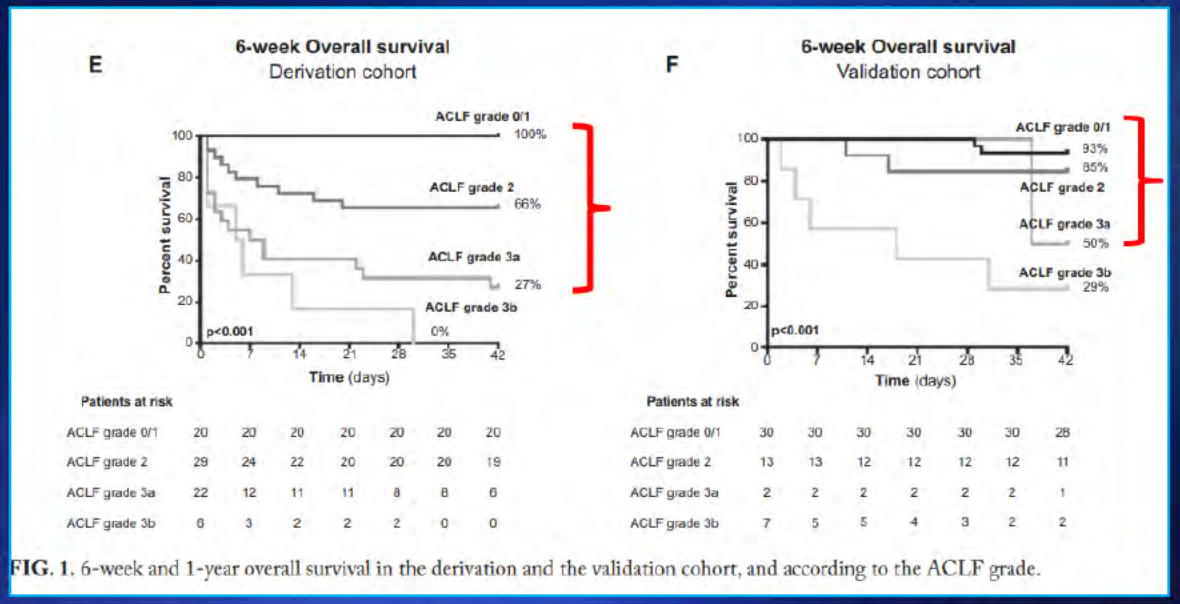


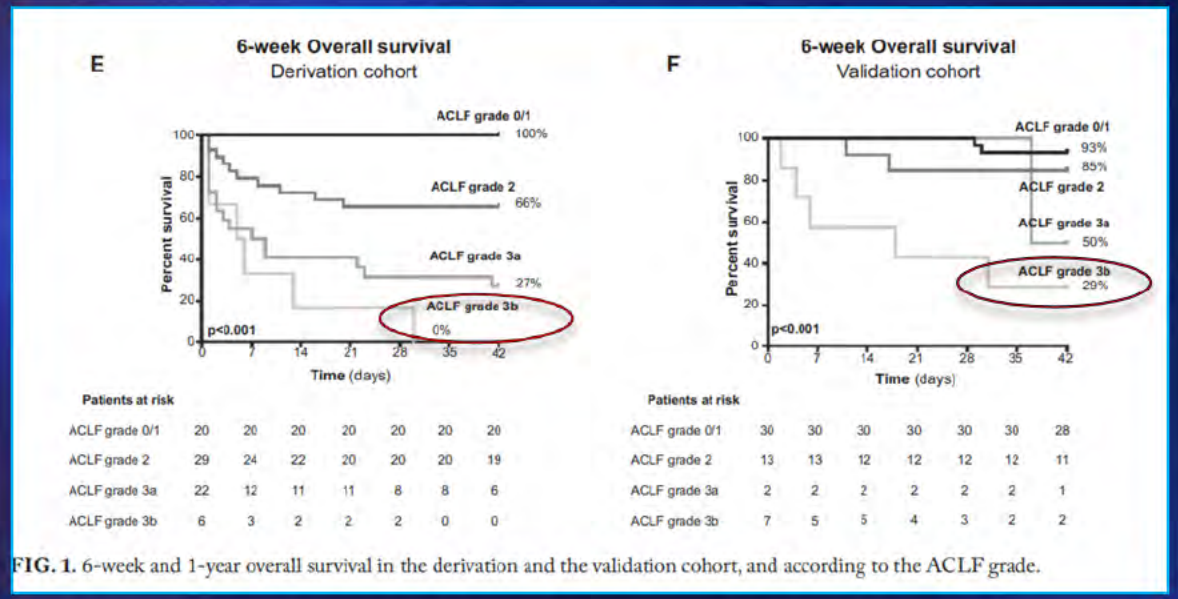
FIG. 1. 6-week and 1-year overall survival in the derivation and the validation cohort, and according to the ACLF grade.

Rescue TIPS Improves Survival in ACLF with up to 3 organ failures

Point of Futility for Rescue / Salvage TIPS

Walter A et al. Hepatology, VOL. 74, NO. 4: 2085-2101, 2021

TIPS is Futile in ACLF with >/= 4 Organ Failures (3b)



Patients at risk

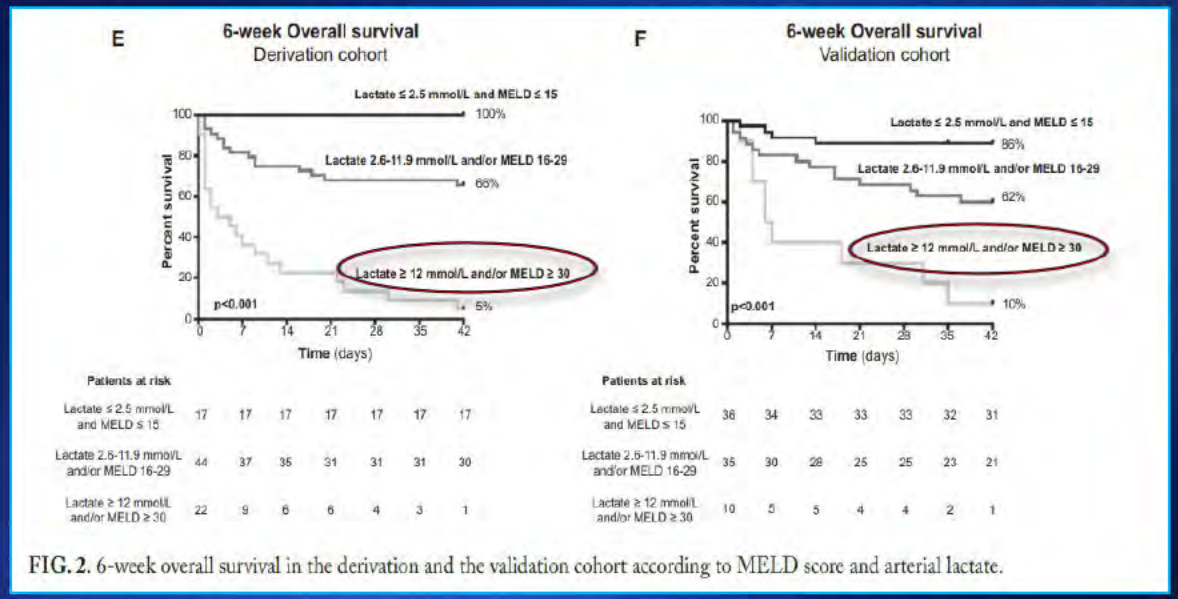
ACLF grade 0/1	20	20	20	20	20	20	20
ACLF grade 2	29	24	22	20	20	20	19
ACLF grade 3a	22	12	11	11	8	8	6
ACLF grade 3b	6	3	2	2	2	0	0

Patients at risk

ACLF grade 0/1	30	30	30	30	30	30	28
ACLF grade 2	13	13	12	12	12	12	11
ACLF grade 3a	2	2	2	2	2	2	1
ACLF grade 3b	7	5	5	4	3	2	2

FIG. 1. 6-week and 1-year overall survival in the derivation and the validation cohort, and according to the ACLF grade.

TIPS is Futile if Lactate is >/= 12 mmol/L or MELD >/= 30



Patients at risk

Lactate ≤ 2.5 mmol/L and MELD ≤ 15	17	17	17	17	17	17	17
Lactate 2.6-11.9 mmol/L and/or MELD 16-29	44	37	35	31	31	31	30
Lactate ≥ 12 mmol/L and/or MELD ≥ 30	22	9	6	6	4	3	1

Patients at risk

Lactate ≤ 2.5 mmol/L and MELD ≤ 15	36	34	33	33	33	32	31
Lactate 2.6-11.9 mmol/L and/or MELD 16-29	35	30	28	25	25	23	21
Lactate ≥ 12 mmol/L and/or MELD ≥ 30	10	5	5	4	4	2	1

FIG. 2. 6-week overall survival in the derivation and the validation cohort according to MELD score and arterial lactate.

Do all patients have the same benefit?: CP-C

- Child C patients <14 points: Survival benefit in all studies
- Child C 14-15 : always futile?

Transplant International ISSN 0934-0874

LETTER TO THE EDITORS

Salvage transjugular intrahepatic portosystemic shunt followed by early transplantation in patients with Child C14-15 cirrhosis and refractory variceal bleeding: a strategy improving survival

Rudler, Rousseau & Thabut. Transplant International 2013

Salvage TIPS followed by rapid LT in patients with CP-C 14-15
MELD score at the time of listing for LT ranged from 29 to 40.
The median delay between TIPS and LT was 8 days (range 3–17 d)
The 6-month survival was 100% (TIPS+LT) vs 0% (TIPS) ($P < 10^{-4}$).

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Management after TIPS

- TIPS without GV obliteration: EGD 1 month after for shrinking or resolution of the GV.
  - Stable or enlarging cardio-fundal GV merit subsequent through TIPS embolization (BATO), BRTO, or Endoscopic Cyanoacrylate Injection (ECI).
  - Following TIPS, therapy with Endoscopic Cyanoacrylate Injection (ECI) carries an increased risk for glue embolization or portal vein thrombosis.
- TIPS with obliteration of GV: EGD after 1-month with through-the-scope audible Doppler probe or EUS to evaluate for persistent flow in the GV.
  - Endoscopic Cyanoacrylate Injection (ECI) or BATO can be performed to "complete" therapy with subsequent endoscopic follow-up q 2-4 weeks until obliteration, and than in 6 months and then yearly.
- In case of re-bleed:
  - BRTO is favored, or
  - Direct GV embolization (BATO) through the patent TIPS is an alternative.
- If lesser curve GV persist after TIPS, then subsequent band ligation should be performed until eradication.

Secondary Prophylaxis of Gastric Variceal Hemorrhage

- After Recovery from a GOV1 hemorrhage:
  - the combination of NSBBs and endoscopic variceal therapy (EVL or cyanoacrylate injection) is the first-line therapy. TIPS Rescue.
- After Recovery from GOV2, IGV1 or IGV2 hemorrhage:
  - TIPS with Embolization or BRTO (only for S-C Type 2b or 3b) are first-line treatments.
    - The Injection of Cyanoacrylate in S-C Type 2b and 3b Gastric Varices is highly effective.

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.

Thank you for your attention

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 5%-9% at 1 year,
- Variceal eradication rates 75%-100%,

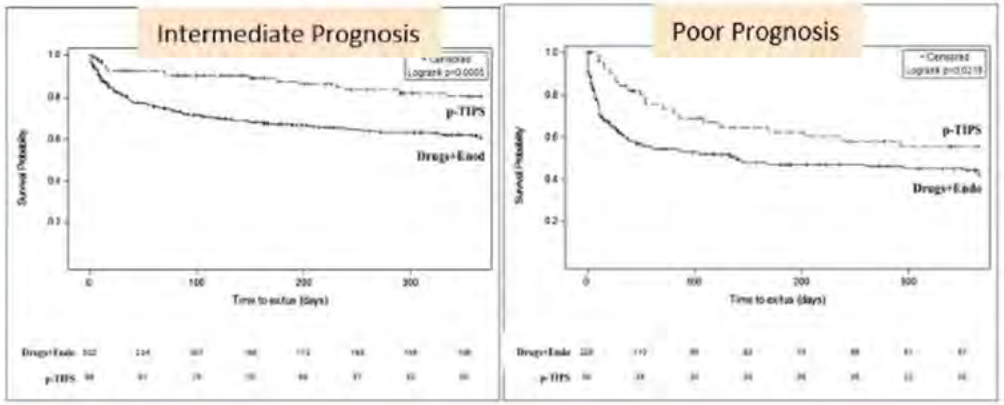
Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

- Adverse effects: fever, ascites, pleural effusions, and development of Esophageal Varices in up to two-thirds of patients.
  - 30%–35% of EV will progress in size after BRTO.
  - Symptomatic ascites or hydrothorax requiring an intervention occur in 15% of patents within a year after BRTO and are present in up to 35%–40% of patients by imaging.
- 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.

Can we identify futility criteria among high risk patients?

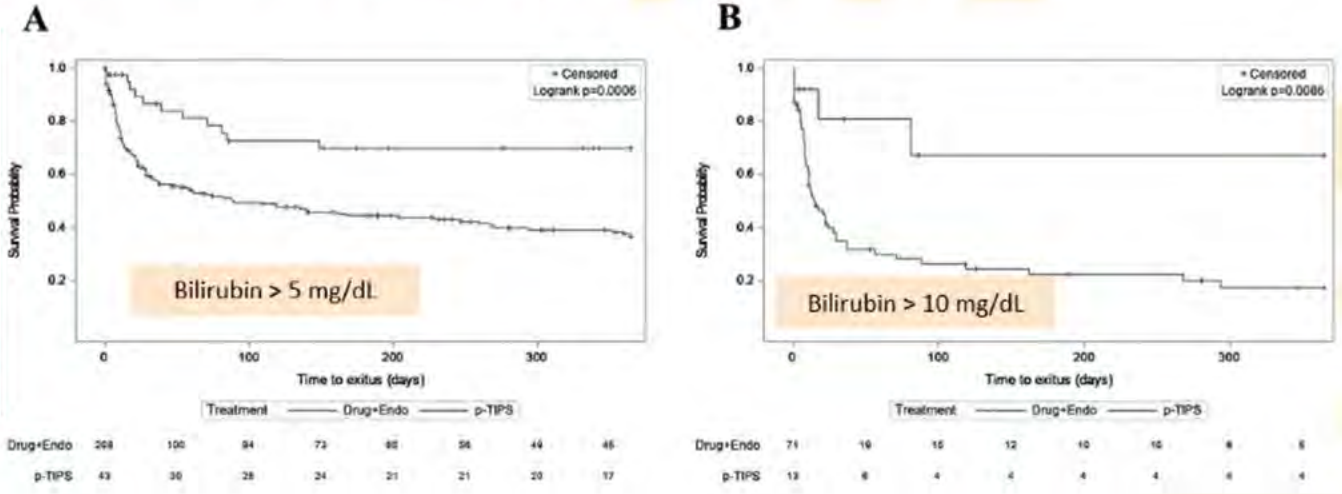
Patient's characteristics	Points to be assigned
Age > 55 years	2.5 points
Child – Pugh > 11 points	3 points
Creatinine ≥ 1.3 mg/dL	2.5 points

Classes of risk of death	
Good prognosis	0 points
Intermediate prognosis	2.5 points
Poor prognosis	>2.5 points

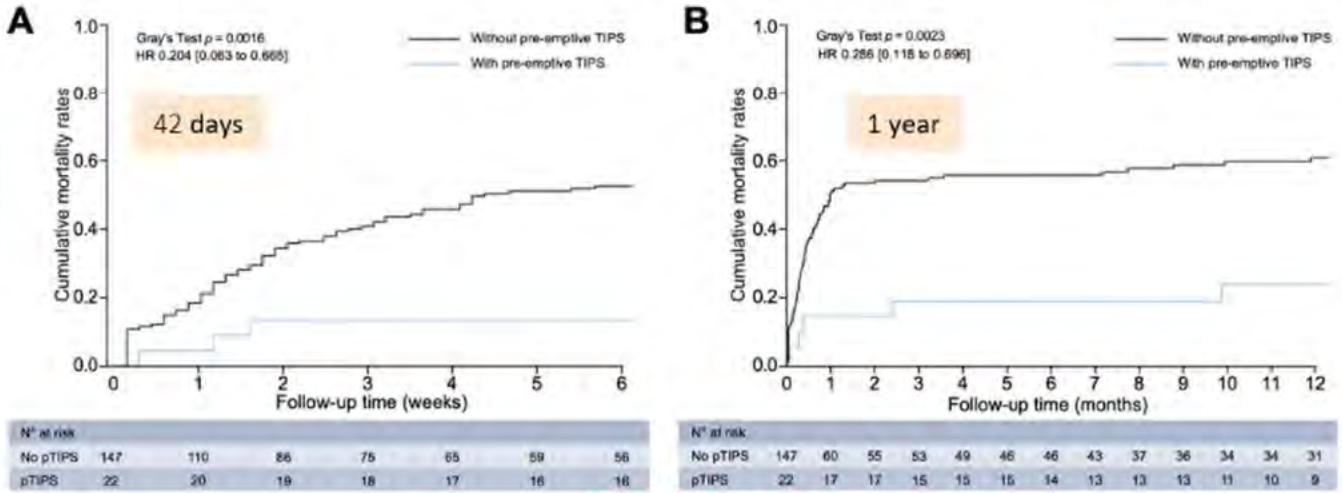


Benefit of early TIPS still present in "poor prognosis", high Bili > 10 and ACLF

Hyperbilirrubinemia



ACLF



Nicoară-Farcău O et al. Gastroenterology 2021; Trebicka J, Gu W et al. J Hepatol 2020

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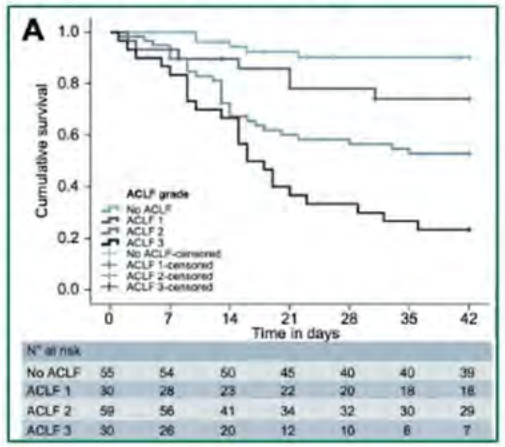
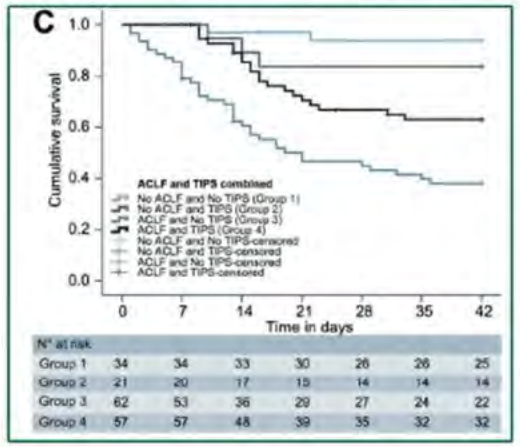
Are all patients candidates to Recue TIPS?

6 week mortality

According to ACLF grade



According to ACLF &TIPS status

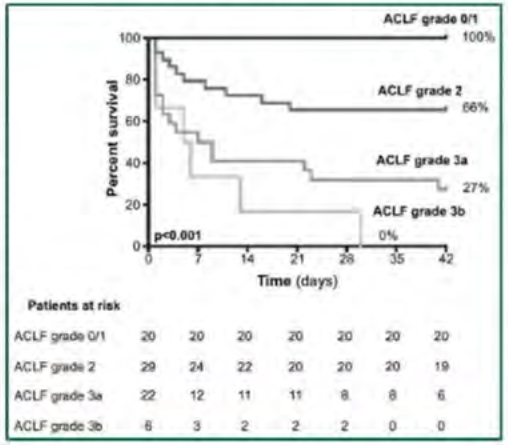


*Age, CLIF-C OF score and TIPS status were independent predictors of mortality

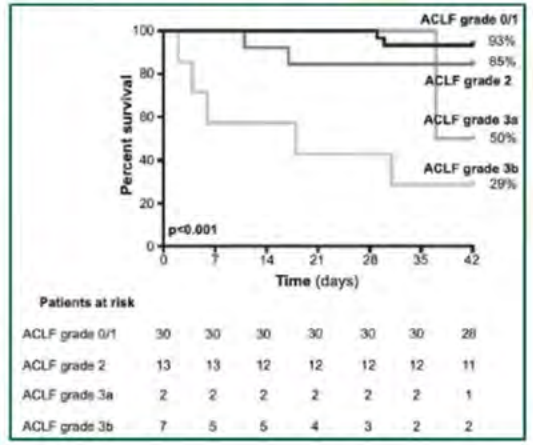
Kumar R et al. J Hepatol 2020

6 week mortality

Study cohort (France)



Validation cohort (Spain)



ACLF-3b grade may appear as indicative of futile prognosis for salvage TIPS

Walter A et al. Hepatology 2021

ACLF-3b: >/= 4 Organ Failures
TIPS Futile as “Rescue”

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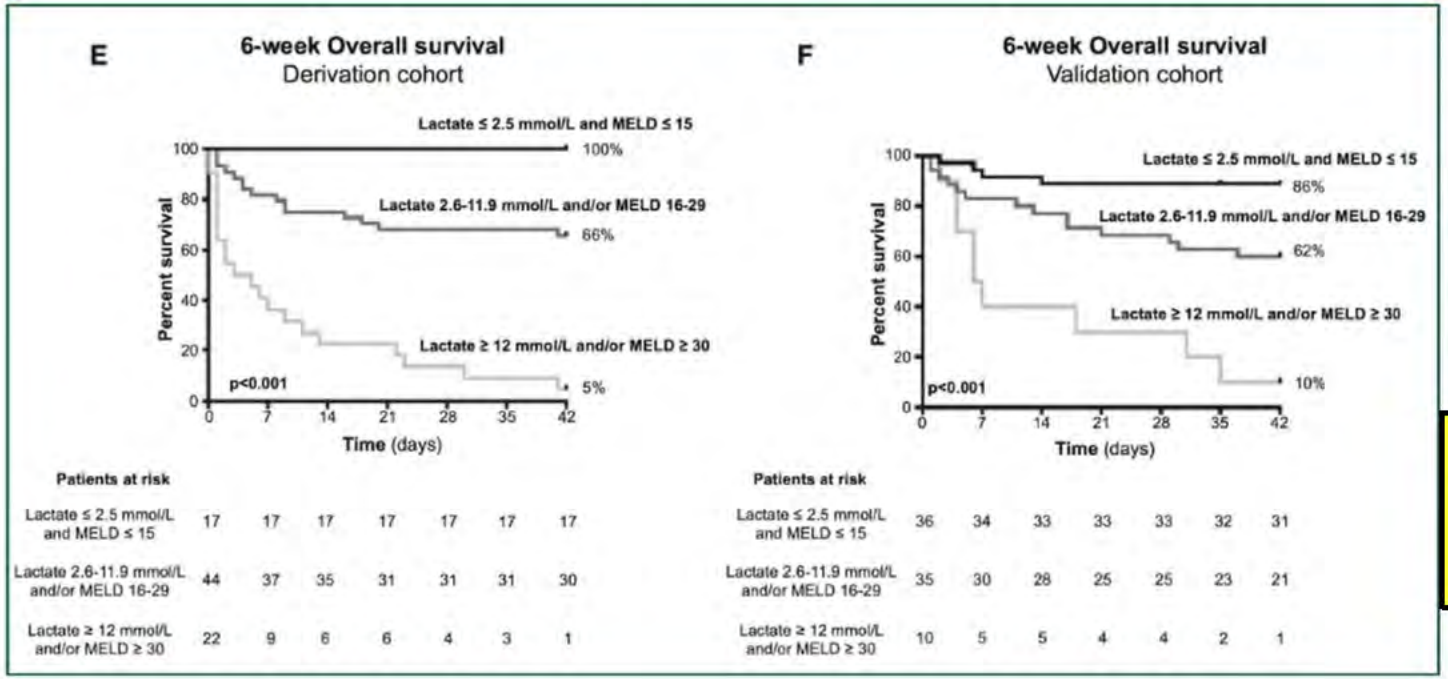
Are all patients candidates to Recue TIPS?

Low risk of death (**lactate ≤ 2.5mmol/L and MELD ≤ 15**)
6-week OS: 100.0% - 86.0%
High risk of death (lactate ≥ 12mmol/L and/or a MELD ≥ 30)
6-week OS: 5.0% - 10.0%



Walter A et al. Hepatology 2021

Six-week survival rate after salvage TIPS for refractory bleeding was 58%

Rescue TIPS has very Poor Survival if Lactate >/= 12 mmol/L, or MELD >/= 30

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