Current Hepatology Reports (2025) 24:27
https://doi.org/10.1007/s11901-025-00694-7

REVIEW

Role of Tips in Acute Variceal Bleeding

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Accepted: 14 May 2025

Abstract

Purpose of review We aimed to review the role of TIPS in acute variceal bleeding (AVB), focusing on preemptive-TIPS (p-TIPS) as discrepant data suggest room for refinement.

Recent findings Salvage-TIPS can effectively control ongoing AVB despite first-line therapy, but mortality is high. Placing a p-TIPS to prevent failure in high-risk patients may improve survival. This is related to its effect decreasing the overall risk of a further decompensation (FD), not just rebleeding but also ascites and derived complications.

Summary FD is closely related to death risk after AVB. The risk of FD and death concentrates in patients presenting with ascites ± HE in addition to AVB. p-TIPS improve survival, not only by decreasing rebleeding risk, but mainly FD overall. This review suggests potential improvements to optimize p-TIPS, such as improving risk stratification, restricting the indication to patients with AVB and ascites ± HE, or selectively identifying those at high-risk of failure (10%-15% cases) for an early placement. Research on these issues is warranted.

Keywords Acute variceal bleeding · Salvage TIPS · Preemptive TIPS · Elective TIPS · Decompensated cirrhosis · Further decompensation · Stages of cirrhosis

Abbreviations

ACLD	Advanced chronic liver disease
ACLF	Acute-on-chronic liver failure
AVB	Acute variceal bleeding
cACLD	Compensated advanced chronic liver disease
CLIF-C	Chronic Liver Failure Consortium
dACLD	Decompensated advanced chronic liver disease
EVL	Endoscopic variceal ligation
GV	Gastric fundal varices
IPD-MA	Individual patient data meta-analysis
HE	Hepatic encephalopathy
HVPG	Hepatic venous pressure gradient
MA	Meta-analysis
NSBBs	Non-selective β-blockers
PCG	Portacaval pressure gradient
PTFE	Polytetrafluoroethylene
p-TIPS	Preemptive TIPS
RCTs	Randomized controlled trials
RTO	Retrograde transvenous obliteration
SOC	Standard of care
TIPS	Transjugular intrahepatic portosystemic shunt

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Introduction

Acute variceal bleeding (AVB) is an emergency associated with high short-term mortality, therefore requiring urgent management that may involve transjugular intrahepatic portosystemic shunt (TIPS).[1] Bleeding results from variceal wall rupture due to an increased wall tension, which is mainly related to portal hypertension.[2] Mortality occurring within the first six-weeks of admission is considered bleeding related and constitutes the current primary endpoint of trials according to guidelines.[3, 4] Such mortality has markedly declined, from 40% of cases 3–4 decades ago

Published online: 26 July 2025

to 15%−20% at present, which is still non-negligible.[5, 6] Herein we will review and discuss the role of TIPS in AVB.

Substages of Variceal Bleeding

Cirrhosis is an advanced chronic liver disease (ACLD) involving two well-differentiated stages, one compensated (cACLD) and the other decompensated (dACLD). [7] The transition to the decompensated stage determines a marked decline in life expectancy.[7–9] Portal hypertension is the main disturbance leading to decompensation, [10, 11] which is defined by the development of events, such as ascites, AVB and hepatic encephalopathy (HE). [4] Patients with dACLD can be differentiated according to the acute or non-acute development of decompensation, with acute decompensation carrying worse prognosis. [12, 13].

AVB constitutes a well-characterized stage within dACLD. It is an acute decompensating event determining a still high mortality. [1, 2] Two substages with different prognosis can be distinguished in patients with AVB, according to whether bleeding occurs with or without other decompensating events, among which ascites is the most frequent (Fig. 1). [14, 15] AVB presenting without any other decompensating event is an acute decompensation occurring in patients with cACLD. [14] When AVB presents with ascites ± HE, frequently constitutes a further decompensating event occurring in patients with dACLD (i.e. with previous ascites). [15] However, sometimes both bleeding and ascites are concomitant first decompensating events occurring in patients with cACLD. [14, 15] In patients with AVB plus ascites, portal pressure is greater and hyperdynamic circulation is much more developed than in those presenting with bleeding alone, while prognosis is worse. [15, 16] Indeed, both the risk of further decompensation and the risk of death are significantly higher (more than double) in patients with AVB plus ascites than in those with AVB alone (Fig. 1). [15, 16] Patients with previous ascites (before bleeding) have worse survival than those presenting first ascites concomitantly with bleeding. [15] However, both further decompensation and death, occur much less frequently in patients presenting only with bleeding than in those who also have ascites, whether it is first presenting or had occurred before. [14, 15] In addition, among patients with AVB plus ascites the risk of death is significantly higher in those who in

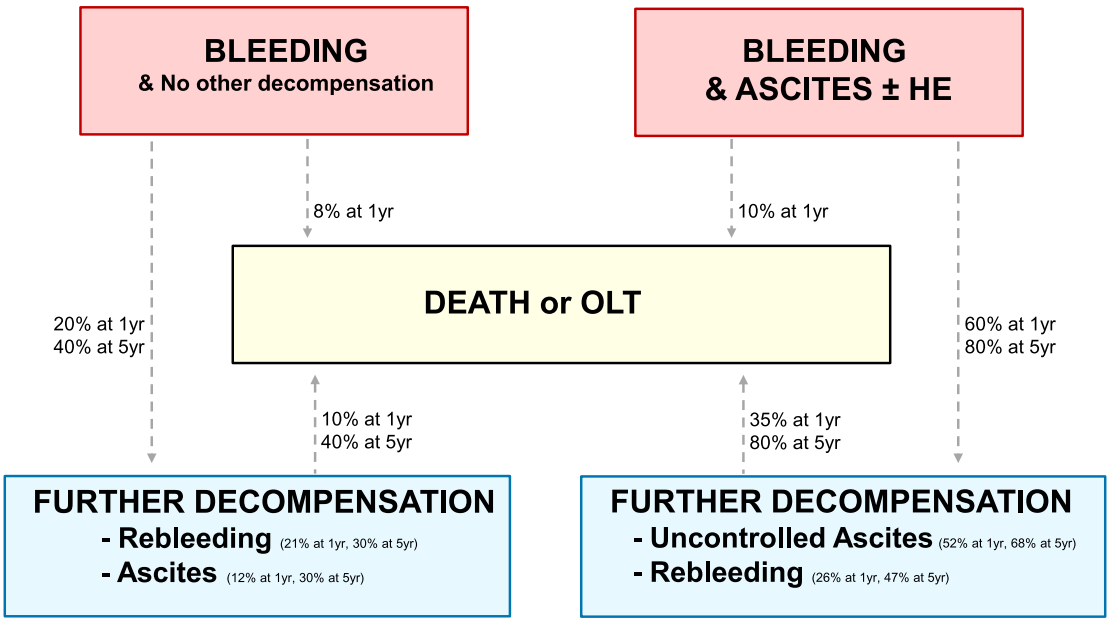

Fig. 1 Substages in patients with acute variceal bleeding (AVB). Two substages with different prognosis can de differentiated in patients with AVB, according to whether bleeding occurs alone or with other decompensating events, i.e. ascites ± hepatic encephalopathy (HE). Patients without any other decompensating event have much better prognosis. In patients with AVB plus ascites, portal pressure is greater and hyperdynamic circulation is more developed than in those presenting with bleeding alone. The risk of further decompensation and the risk of death are significantly higher in patients with AVB plus ascites ± HE. Occasionally, patients in both substages may progress directly to death. Much more often they develop further decompensation and the risk of death markedly increase afterwards. Death risk after further decompensation is significantly higher in patients presenting with AVB plus ascites ± HE. Among patients with AVB plus ascites the risk of death is significantly higher in those who in addition have HE. AVB presenting with HE but without ascites is less frequent and may be related to particular pathophysiologic mechanisms, such as the presence of portal-systemic collaterals. Numbers in the figure are from ref.15

addition have HE. [15, 16] In each substage of AVB, the risk of death significantly increases with the development of further decompensation and is three times greater in these patients than in those without further decompensation. [15, 17] AVB presenting with HE but without ascites, is rare and may be related to particular pathophysiologic mechanisms, such as the presence of portal-systemic collaterals.

First-Line Therapy of Avb

Successful treatment of AVB requires the permanent control of the acute bleeding episode. This includes the initial control of active bleeding but also the prevention of further bleeding within the first few days, which is common without therapy. [1, 2] Once controlled the acute episode, elective therapy should be instituted to prevent recurrent bleeding, particularly early rebleeding (i.e. that occurring during the first 6-weeks) that markedly increases death risk. [1, 18] With current first-line treatment, failure to control acute bleeding only occurs in 10%−15% of patients. [2, 6] However, improving survival is the final therapeutic goal and mortality frequently develops despite achieving the permanent control of bleeding. [19–21] This is due to additional decompensating events besides bleeding leading to liver failure, or to bleeding-related complications such as bacterial infections or development of acute-on-chronic liver failure (ACLF). Early rebleeding (within 6-weeks) markedly worsens prognosis, but with current first-line therapy it occurs in < 15% of cases. [18] Other decompensating events such as uncontrolled ascites or its related complications occur more frequently, mainly in patients presenting with ascites ± HE on top of AVB, greatly impacting prognosis. [15, 17] Thus, in order to improve survival therapy should be addressed to prevent not just rebleeding but further decompensation as a whole.

The mainstay treatment of acute bleeding episode includes vasoactive drugs, prophylactic antibiotics, a restrictive blood transfusion policy and performing early endoscopy with endoscopic variceal ligation (EVL) when esophageal AVB is confirmed. [1–6] In patients not undergoing TIPS during the index AVB, the standard of care (SOC) therapy to prevent recurrent bleeding at long-term combines non-selective β-blockers (NSBBs) and repeated sessions of EVL until variceal eradication. [6, 22] NSBBs are essential part of combined therapy, since the meta-analysis of randomized controlled trials (RCTs) shows that while the addition of EVL to drug therapy provides a marginal benefit, the addition of NSBBs to EVL significantly increases the efficacy to prevent rebleeding also improving survival, particularly in patients with Child–Pugh class B/C (i.e. with ascites ± HE in addition to bleeding). [23] TIPS is mostly recommended as second-line therapy to prevent recurrent variceal bleeding, since trials have shown that despite first-line TIPS effectively prevent rebleeding, it also increases the risk of HE and does not improve survival significantly. [24–27] TIPS can be considered as first-line therapy to prevent recurrent bleeding in patients with other indication, such as recurrent ascites. [6, 26] Several studies suggest that TIPS may also be preferred in patients with portal vein thrombosis. [27].

TIPS implantation in AVB can be considered for uncontrolled acute bleeding as salvage therapy, in patients developing early rebleeding as rescue therapy and also as a preemptive therapy for patients at high risk of failure with SOC (Table 1). [24–27] TIPS is not indicated for primary prophylaxis of AVB, since the risks of complications outweigh its potential benefits in this setting. [6, 24, 26] However, when TIPS is performed due to other indications, such as recurrent ascites, further therapy to prevent variceal bleeding may not be required. TIPS should not be performed in compensated cirrhosis as it could lead to liver dysfunction and decompensation by diverting blood flow away from the liver. [6, 26].

Contraindications for TIPS include congestive heart failure, severe pulmonary arterial hypertension, uncontrolled encephalopathy and systemic infection or sepsis. [24–27] In patients with advanced liver dysfunction (Child–Pugh > 13 points) and in those over 75 years old, TIPS are rarely performed due to the high risk of complications. [28–30] Untreated biliary obstruction and uncorrectable severe coagulopathy are relative contraindications. [24–27].

Pathophysiological Effects of Tips and Hemodynamic Targets

TIPS is an endovascular shunt placed under radiographic guidance that creates an intrahepatic portocaval derivation, very effectively inducing an immediate reduction in portal pressure (of around 50%) by decompressing the hypertensive portal system. [31, 32] In addition, the portal-systemic blood derivation induced by TIPS is associated to a rapid increase in effective blood volume improving extrahepatic circulatory derangements. [31, 32] The effect markedly decreasing portal pressure allows the efficient correction of complications related to portal hypertension, such as variceal bleeding or ascites. [32, 33] Ideally, TIPS should achieve these positive goals while also avoiding complications potentially related to the procedure. Such related complications may include a worsening in liver function consequence of a decreased portal liver perfusion, or the development of HE, which is induced by portal systemic blood derivation and may affect up to 30%−50% patients. [34–37] Systemic circulatory overload may occur in up to 20% of cases. It develops as a consequence of an increased blood inflow, and may induce pulmonary hypertension or heart failure. [30–35] Procedure-related

complications currently occur in < 5% of cases. Although it can be severe (such as intraperitoneal bleeding, arterial injury, liver infarct, capsular puncture or hemobilia), the procedure-related death is < 1%. [24–26] Indeed, given the efficiency of TIPS in achieving portal system decompression, the low risk of complications and very low associated mortality, TIPS has replaced surgical portal-systemic shunts.

Therefore, TIPS aims to efficiently reduce the portacaval pressure gradient (PCG) in order to correct to portal hypertension-related complications, while maintaining enough portal liver perfusion to avoid worsening liver dysfunction. Ideally, TIPS can be calibrated to create the smallest-necessary caliber shunt to achieve these therapeutic goals. [33] To do that, the introduction of polytetrafluoroethylene (PTFE)-covered stents has been a major breakthrough. PTFE-covered stents, have dramatically improved the procedure by drastically reducing the risk of TIPS dysfunction, which was frequent using bare stents. [38] In addition, to properly calibrate the shunt, some issues should be taken into account. Several studies indicate that, compared with 10-mm stents, 8-mm covered-stents may prevent variceal rebleeding with similar efficacy but decreasing the risk of HE and might even improve survival. [39, 40] Thus, to maximize the benefit, PTFE-covered-stents of fixed diameter can be under-dilated (to 6–7 mm) with additional stent dilation when required (up to 10 mm). [41] However, it is difficult to rely on the diameter achieved by this procedure as self-expanding stents can continue to expand when under-dilated until achieving their nominal diameter. The recently introduced "controlled expansion" stent-grafts can also be used. [42] This allows a range of operator-determined shunt diameters with a single shunt (between 8–10 mm).

TIPS induce a reduction in portal pressure that should decrease to a level allowing the control of portal hypertension-related complications. Both, variceal bleeding and ascites, mainly occur with PCG > 12 mmHg. [43–46] Accordingly, current guidelines recommend a target goal of achieving a PCG ≤ 12 mmHg. [24–27] On the other hand, the risk of developing severe encephalopathy after TIPS increases with PCG below 10 mmHg. [35] Therefore, the target post-TIPS PCG is narrow and not always easy to reach. [33] As commented, this can be achieved by a gradual dilatation of PTFE-covered stents, starting with under-dilated

Table 1 Role of TIPS in patients with varices according to clinical setting

	Varices without previous bleeding	Acute variceal bleeding	Prevention of rebleeding
First-line therapy (SOC)	NSBBs/EVL *	Vasoactive drugs + EVL + prophylactic antibiotics + restrictive transfusion	NSBBs + EVL
Role of tips according to the stage of cirrhosis			
Compensated	- NSBBs (carvedilol) preferred over EVL - No role for TIPS †	- Salvage/Rescue-TIPS if failure of SOC §	- Elective-TIPS if failure of SOC ‖
Decompensated	- NSBBs/EVL - Elective-TIPS: ‡ Consider according to events such as recurrent or refractory ascites, hydrotorax	- p-TIPS if high-risk ¶ - Salvage/Rescue-TIPS if failure of SOC §	- Elective-TIPS if failure of SOC ‖ - First-line TIPS: ** Consider according to events such as recurrent or refractory ascites, hydrotorax

EVL endoscopic variceal ligation, *NSBBs* non-selective β-blockers, *p-TIPS* preemptive TIPS, *SOC* standard of care

* NSBBs are preferred over EVL in patients with compensated cirrhosis, as may prevent the development of ascites, which is the most frequent decompensating event in these patients

† TIPS should not be performed in compensated cirrhosis as could lead to liver dysfunction and decompensation by diverting portal blood flow away from the liver

‡ In primary prophylaxis the risk of complications related to TIPS outweigh the potential benefits. Thus, TIPS should only be considered when indicated for other reasons in decompensated patients

§ In patients with acute variceal bleeding (AVB), salvage/rescue TIPS can be life-saving. Salvage TIPS should be considered to manage ongoing/uncontrolled variceal bleeding despite SOC. Rescue TIPS should be considered in patients presenting early rebleeding after initial control of AVB

¶ Current guidelines recommend considering p-TIPS in patients with AVB and Child–Pugh class B > 7 plus active bleeding at endoscopy despite vasoactive drug, or with Child–Pugh class C < 14. We suggest an alternative approach and consider p-TIPS in patients with ascites ± encephalopathy in addition to bleeding, aiming to prevent rebleeding but also further decompensation. In these patients, p-TIPS could be considered according to MELD, in those with a score > 12 mainly if > 18 (only exceptionally if ≥ 30 given the high mortality). The value of this alternative approach requires appropriate investigation

‖ Rescue TIPS should be considered when SOC to prevent rebleeding fails

** When indicated for other reasons such as recurrent ascites, TIPS can be considered as first-line therapy to prevent recurrent bleeding, as well as further decompensation overall

stents, or more confidently using "controlled-expansion" stents. The optimal procedure has yet to be defined by properly designed studies. Such studies should also precisely define the optimal PCG after TIPS, as currently used targets were obtained using bare stents and could be suboptimal. [33] In fact, PCG may vary according to the indication. A PCG ≤ 12 mmHg may be required when TIPS is placed for uncontrolled acute variceal bleeding, but a PCG ≤ 16 mmHg may be enough when it is placed to prevent recurrent bleeding as rebleeding risk concentrates in patients with PCG > 16 mmHg. [16] Achieving a PCG ≤ 16 mmHg might be enough particularly when this represent a substantial delta decrease from the baseline value. Strong evidence indicates that an hepatic venous pressure gradient (HVPG) reduction > 20% from baseline under drug therapy is associated with a significant decrease in the risk of rebleeding or other decompensating events and significantly improves survival, [44, 46] while a 50% reduction was suggested as a good response to prevent rebleeding with uncovered TIPS. [33, 35] Optimal PCG-target reductions can differ when placing TIPS for other indications such as ascites. Therefore, further specific investigation is required to define the optimal hemodynamic response using covered-stents.

Salvage and Resue Tips in Avb

Salvage TIPS is used as an emergency to manage ongoing/uncontrolled variceal bleeding despite SOC (Table 1). Rescue TIPS is used when, after an initial control of AVB, early rebleeding occurs despite first-line therapy. In addition, elective TIPS is placed in stable patients as therapy of choice to prevent rebleeding or recurrent or complicated ascites.

In patients with uncontrolled AVB, self-expandable esophageal covered metallic stents or balloon tamponade may be necessary as a bridge therapy before placing salvage TIPS. A small trial suggests that self-expandable esophageal stents may be more effective and safer than tamponade. [47] Rescue/Salvage TIPS can be a life-saving procedure in AVB. However, the evidence supporting its value is limited, coming from observational and uncontrolled studies and frequently using suboptimal therapies, such as sclerotherapy for endoscopic treatment or bare stents for TIPS. [48–50] In these studies, salvage TIPS achieved high rates of success controlling bleeding (over 90% of cases) but, despite this, it was associated with high mortality (35–40% at 6-weeks and > 50% at 1-year). Survival with salvage TIPS has not improved in recent series using covered stents. [51–53] In these patients, death is usually due to factors such as organ failures or infections. [51–55] Indeed, ACLF is an important determinant of mortality in patients with AVB. [51] Therapeutic alternatives are frequently unavailable and futility use to be the main factor limiting the use of rescue/salvage TIPS, [24–27] while a recent cohort study suggests that TIPS may be effective even in patients with ACLF. [51] Child–Pugh class C with score > 13, Lactate ≥ 12 mmol/L or MELD score ≥ 30 are associated with very high mortality rates (> 90% of cases), suggesting futility of salvage/rescue TIPS in these cases. [51–53] In these patients, indication of salvage/rescue TIPS should be better decided on case by case basis, considering if TIPS can be a successful bridge to short-term liver transplantation.

Evidence of Efficacy Favoring P-Tips in Avb: The Facts

Therapeutic failure with current SOC occurs in up to 10%–15% of patients with AVB within the first 5-days. [6, 56] Patients at high-risk of failure can be considered for preemptive TIPS (p-TIPS), which consists in placing a TIPS before they fail to prevent further bleeding and the associated risk of death. Current guidelines recommend placing p-TIPS shortly after admission, within the first 72-h. [3, 6, 25–27].

Different RCTs and observational studies have shown a significant survival benefit favoring p-TIPS (Table 2), [57–64] although some failed to show such gain. [65, 66] An individual patient data meta-analysis (IPD-MA), including RCTs (but not the last negative trial) and cohort studies, suggested survival benefit at 6-weeks and at 1-year favoring p-TIPS in patients with Child–Pugh class C (score < 14) or class B with active bleeding. [67] A subsequent meta-analysis and trial sequential analysis including all the RCTs performed suggests that benefit was more apparent in cohort studies. [68] An updated IPD-MA, involving 1389 patients (342 treated with p-TIPS and 1047 with SOC), has shown a significant reduction in mortality, which was halved favoring p-TIPS (HR = 0·43, 95% CI: 0.32–0.60, p < 0.001). [69].

The studies performed have consistently shown a very marked reduction on the risk of further bleeding favoring p-TIPS, with an incidence < 10% of cases. [57–66] p-TIPS induces a marked decrease in portal pressure, which in addition to efficiently prevent rebleeding favors the control of ascites. [58, 59] Indeed, the impact of p-TIPS on the likelihood of developing new or worsening ascites has been documented by the updated IPD-MA, showing a risk reduction of almost 70% (sHR = 0.32, 95%CI = 0.17 to 0.59). [69] Such positive effect is not a minor issue, since ascites is the most common and severe decompensating event, even in patients with AVB and particularly in those already presenting with ascites in addition to AVB. [15–17] Regarding the risk of encephalopathy post-TIPS, RCTs suggest that in patients treated by p-TIPS such risk may be outweighed by the beneficial effect on further bleeding and ascites. [69].

Table 2 Summary of studies assessing the efficacy of early p-tips in high risk patients with acute variceal bleeding

Autor/Ref	Design	Inclusion Criteria	Treatments*, *N*	Child-Pugh Class *N* (%)	MELD Score median or mean (IQR or SD)	Previous decompensation *N* (%)	Follow-up median or mean (IQR or SD), months	Rebleeding *N* (%)	Ascites *N* (%)	HE *N* (%)	Death *N* (%)	Liver trasplant *N* (%)
Monescillo A, Hepatology 2004 [57]	RCT Muticenter 2 centers in Spain	Cirrhosis AVB HVPG ≥ 20mmHg	N 52 SOC 26 (included sclerotherapy instead EVL) pTIPS 26 (using bare stents)	SOC A 4 (15) B 10 (38) C 12 (46) pTIPS A 3 (11) B 11 (42) C 12 (46)	SOC NI pTIPS NI	SOC Bleed 4 (16) Ascadm 15 (58) EH 4 (15) pTIPS Bleed 7 (27) Ascadm 14 (54) EH 2 (8)	Up to 12 m	SOC 13 (50) vs pTIPS 3 (12) $P < 0.01$	NI	SOC 9 (35) vs pTIPS 8 (31) P NS	SOC 17 (65) vs pTIPS 8 (31) $P = 0.01$	NI
Garcia-Pagan JC, N Engl J Med 2010 [58]	RCT Multicenter 9 centers in Europe	Cirrhosis AVB CP C < 14p CP B 7–9 + AB	N 63 SOC 31 pTIPS 32	SOC A 0 B 16 (51) C 15 (48) pTIPS A 0 B 16 (50) C 16 (50)	SOC 16.9 ± 6.3 pTIPS 15.5 ± 5	SOC Bleed 5 (16) Ascadm 18 (58) EH 0 pTIPS Bleed 11 (34) Ascadm 19 (59) EH 6 (18)	SOC 10.6 ± 9.9 pTIPS 14.6 ± 8.4	SOC 14 (45) vs pTIPS 1 (3) $P = 0.001$	SOC 9 (29) vs pTIPS 5 (15) P NS	SOC 12 (39) vs pTIPS 8 (25) P NS	SOC 12 (39) vs pTIPS 4 (12) $P = 0.001$	SOC 2 (6) vs pTIPS 4 (12) P NS
Lv Y, Lancet 2019 [59]	RCT 1 center in China	Cirrhosis AVB CP C < 14p CP B ± AB	N 132 SOC 45 pTIPS 84	SOC A 0 B 35 (78) C 10 (22) pTIPS A 0 B 65 (77) C 19 (23)	SOC 13.4 (12–16) pTIPS 14 (12–16)	SOC Bleed NI Ascadm 40 (89) EH 0 pTIPS Bleed NI Ascadm 74 (88) EH 3 (4)	SOC 24 (9–24) pTIPS 18 (1–24)	SOC 17 (38) vs pTIPS 11 (13) $P < 0.001$	SOC 20 (44) vs pTIPS 14 (17) $P < 0.001$	SOC 16 (36) vs pTIPS 29 (35) P NS	SOC 15 (33) vs pTIPS 15 (18) $P = 0.04$	SOC 1 (2) vs pTIPS 2 (2) P NS
Dune PJ, Aliiment Pharmacol Ther 2020 [65]	RCT Multicenter 2 UK centers	Cirrhosis AVB CP > 8 < 13	N 58 SOC 29 pTIPS 29	SOC A 0 B 12 (41) C 17 (59) pTIPS A 0 B 13 (45) C 16 (55)	SOC 17 ± 3.8 pTIPS 17 ± 3.4	SOC Bleed NI Ascadm 17 (58) EH 1 (3) pTIPS Bleed NI Ascadm 20 (68) EH 3 (10)	Up to 12m	SOC 10 (34) vs pTIPS 7 (24) P NS	SOC 3 (10) vs pTIPS 4 (13) P NS	SOC 5 (17) vs pTPIS 12 (41) $P = 0.05$	SOC 7 (24) vs pTPIS 6 (20) P NS	SOC 1 (4) vs pTPIS 0 P NS

Table 2 (continued)

Autor/Ref	Design	Inclusion Criteria	Treatments*, *N*	Child-Pugh Class *N* (%)	MELD Score median or mean (IQR or SD)	Previous decompensation *N* (%)	Follow-up median or mean (IQR or SD), months	Rebleeding *N* (%)	Ascites *N* (%)	HE *N* (%)	Death *N* (%)	Liver trasplant *N* (%)
Garcia-Pagan JC, J Hepatol 2013 [60]	Observational retrospective Multicenter 9 centers in Europe	Cirrhosis AVB CP C < 14p CP B 7–9 + AB	N 75 SOC 30 pTIPS 45	SOC A 0 B 10 (33) C 20 (67) pTIPS A 0 B 18 (40) C 27 (60)	SOC 18 ± 6 pTIPS 17 ± 5	SOC Bleed 8 (27) Ascadm 26 (87) EH 3 (10) pTIPS Bleed 8 (18) Ascadm 34 (76) EH 2 (4)	SOC 14.6 ± 12 pTIPS 13.1 ± 12	SOC 15 (50) vs pTIPS 3 (7) $P < 0.001$	SOC 13 (43) vs pTIPS 5 (11) $P < 0.01$	SOC 15 (50) vs pTIPS 23 (51) P NS	SOC 10 (33) vs pTIPS 6 (13) $P = 0.048$	SOC 3 (10) vs pTIPS 8 (17) P NS
Rudler M, Aliment Pharmacol Ther 2014 [66]	Observational Propsective 1 center in France	Cirrhosis AVB CP C < 14p CP B 7–9 + AB	N 62 SOC 31 pTIPS 31	SOC A 0 B 4 C 4 pTIPS A 2 B 10 C11	SOC 22 ± 7 pTIPS 21 ± 7	SOC Bleed 5 (16) Ascadm 27 (87) EH 17 (55) pTIPS Bleed 11 (35) Ascadm 22 (71) EH 14 (45)	7.8 (0.3–12)	SOC 12 (39) vs pTIPS 1 (3) $P < 0.001$	NI	SOC 16 (52) vs pTIPS 14 (45) P NS	SOC 8 (26) vs pTIPS 9 (29) P NS	SOC 4 (13) vs pTIPS 7 (23) P NS
Thabut D, JHepatol 2018 [62]	Observational prospective Multicenter 58 centers in France	Cirrhosis + AVB	N 326 SOC 304 pTIPS 22 (25)	SOC A NI B NI C NI pTIPS A 8 (10) B 32 (38) C 44 (52)	SOC 19 (18–20) pTIPS 16 (13–19)	SOC Bleed NI Ascadm 170 (57) EH 105 (35) pTIPS Bleed NI Ascadm 9 (41) EH 3 (15)	Up to 12 m	NI	NI	NI	SOC 190 (62) vs pTIPS 5 (22) $P = 0.04$	NI

Table 2 (continued)

Autor/Ref	Design	Inclusion Criteria	Treatments*, *N*	Child-Pugh Class *N* (%)	MELD Score median or mean (IQR or SD)	Previous decompensation *N* (%)	Follow-up median or mean (IQR or SD), months	Rebleeding *N* (%)	Ascites *N* (%)	HE *N* (%)	Death *N* (%)	Liver trasplant *N* (%)
Lv Y, Gut 2018 [64]	Observational retrsopective Multicenter 12 centers in China	Cirrhosis + AVB	N 1425 SOC 1219 pTIPS 206	SOC A 455 (37) B 654 (54) C 88 (7) pTIPS A 40 (19) B 131 (63) C 33 (16)	SOC 12 ± 4 pTIPS 13 ± 4	SOC Bleed 608 (50) Ascadm 532 (44) EH 52 (4) pTIPS Bleed 109 (53) Ascadm 137 (66) EH 13 (6)	SOC 23.4 ± 18.2 pTIPS 22.9 ± 16.3	SOC 490 (40) vs pTIPS 22 (11) $P < 0.001$	SOC 116 (12) vs pTIPS 9 (4) $P = 0.021$	SOC 333 (27) vs pTIPS 77 (37) P NS	SOC 211 (17) vs pTIPS 29 (14) $P < 0.001$ (adjusted for confounders)	SOC 78 (7) vs pTIPS 15 (7) P NS
Hernández-Gea V, Hepatology 2019 [63]	Observational Propsective Multicenter 33 centers in Europe + 1 center Canada	Cirrhosis AVB CP C < 14p CP B 7–9 +AB	N 671 SOC 605 pTIPS 66	SOC A 0 B 218 (36) C 387 (64) pTIPS A 0 B 19 (29) C 47 (71)	SOC 16 ± 7 pTIPS 15 ± 6	SOC Bleed 190 (31) Ascadm NI EH NI pTIPS Bleed 17(25) Ascadm NI EH NI	Up to 12 m	SOC 141 (23) vs pTIPS 3 (5) $P = 0.002$	SOC 288 (47) vs pTIPS 6 (9) $P < 0.001$	SOC 228 (38) vs pTIPS 28 (42) P NS	SOC 228 (35) vs pTIPS 12 (18) $P = 0.014$	SOC 19 (5) vs pTIPS 6 (13) P NS

AB, Active bleeding; *Asc* adm, ascites at admission; *AVB*, Acute variceal bleeding; *Bleed*, previous bleeding; *CP*, Child Pugh; *ET*, Endoscopic treatment (ligation o sclerotherapy); *EVL*, endoscopic variceal ligation; *HE* (or *EH*), hepàtic encephalopathy; *HVPG*, Hepatic venosu pressure gradient; *ISMN*, Isorbide-5-mononitrate; *MELD*, Model for End-stage Liver Disease; *NI*, No information ; *NSBBs*, non-selective β-blockers; *p-TIPS*, preemptive TIPS; *PVT*, Portal vein thrombosis; *RCT*, randomized controlled trial; *SOC*, Standard of care treatment; *TIPS*, Transjugular Porto Sistemic shunt

*TIPS using covered stents and Elective SOC with NSBBs plus EVL, except where indicated

It should be noted that studies evaluating p-TIPS frequently excluded patients at risk of unfavorable outcomes with TIPS such as those oldest (usually > 75 years), with highest Child–Pugh score (> 13), with nonearly stage hepatocellular carcinoma or with severe kidney disease, among others. [57–66] On the other hand, data from observational studies suggest that some events carrying risk of unfavorable outcomes after elective TIPS, such as acute HE, hyperbilirubinemia or ACLF, when presenting at the time of bleeding should not be considered absolute contraindications for p-TIPS. [51, 54, 55].

Reconstructing P-Tips: Keys Leading to Improved Survival

As commented above, numerous studies show that p-TIPS can provide a significant survival improvement in patients with AVB. [69] To maximize the potential benefit, a thorough analysis may be timely and may help to determine how p-TIPS can provide such survival gain and who is most likely to take advantage.

To prevent recurrent variceal bleeding, old trials comparing NSBBs or endoscopic sclerotherapy vs a control arm, not receiving active therapy, showed lower rebleeding with active therapy and often showed survival improvement over the high death rates observed in controls (up to 50% of cases). [70, 71] However, subsequent trials using an effective therapy in the control arm, rarely have shown survival improvement favoring the new experimental treatment, even when they were effective reducing rebleeding risk. This has been the case in RCTs comparing EVL vs sclerotherapy, EVL vs NSBBs, or endoscopic therapy plus NSBBs vs either monotherapy. [70–72] Similarly, using elective uncovered TIPS as first-line therapy to prevent rebleeding, RCTs comparing such TIPS vs endoscopic therapy (either sclerotherapy or EVL), or vs endoscopic therapy plus NSBBs, or vs NSBBs plus nitrates, have shown lower rebleeding favoring TIPS without survival benefit. [73–76] Covered stents improve the efficacy of TIPS by preventing the dysfunction frequently associated with bare stents. [38, 77] However, even using covered stents no significant survival improvement has been observed in trials comparing TIPS vs SOC as elective first-line therapy for secondary prophylaxis, despite lower rebleeding risk favoring TIPS. [78, 79] All these data suggest that the impact achieved by preventing rebleeding to improve the survival achieved with current SOC may be limited, while other factors affecting the risk of death may be involved in addition to recurrent bleeding. Certainly, with the low mortality rates of current SOC, demonstrating a slight improvement would require very large sample sizes. [80] Nevertheless, using p-TIPS most RCTs have shown survival gain despite not recruiting large sample sizes and using as control arm the current SOC combining NSBBs plus EVL, associated with death rates of around 20–25% at 1-year. [69] The benefit on survival favoring p-TIPS can be likely (and mainly) related to other additional factors besides the effect decreasing rebleeding risk. Elucidating how p-TIPS achieves that improvement may optimize the benefit.

The effect of p-TIPS preventing recurrent bleeding is relevant as rebleeding, and particularly early rebleeding, increases the risk of death. [18] However, the impact on overall survival is probably limited since with current SOC few patients (< 15%) develop early rebleeding. [18] Moreover, in most cases death occurs despite successful bleeding control, after developing other decompensating events such as uncontrolled ascites, since complications of ascites (such as spontaneous bacterial peritonitis, acute kidney injury or recurrent/refractory ascites) lead to a marked worsening in prognosis. [81] Indeed, it is important to remark that p-TIPS can efficiently prevent not just rebleeding, but also uncontrolled ascites and its related complications. [58, 59, 63, 64, 69] Furthermore, by markedly reducing portal pressure TIPS improves portal hypertension but also induces a rapid decrease in bacterial translocation and systemic inflammation with the potential to prevent (or improve) organ failures related to AVB such as ACLF, a strong predictor of death after AVB.[32, 40, 54].

Current evidence strongly suggests that the survival improvement favoring p-TIPS is due not just to the impact on a single decompensating event, but to the effect decreasing the overall risk of further decompensation. [69] Concordantly, another recent IPD-MA shows that TIPS effectively prevents further decompensation in cirrhosis, [82] which in the last Baveno-VII conference was defined as a second or a recurrent or complicated decompensating event. [4] This is a key point, since as previously commented further decompensation very markedly increases the risk of death. [15, 17] Certainly, death can occur after AVB without developing further decompensation, but this happens in few cases (< 10% at 1-year). [17] The majority of patients (almost 80% at 5-y), develop further decompensation after AVB markedly increasing then the risk of death. [15, 17] In patients with AVB who develop further decompensation, mortality at 2-years reaches 50% of cases among those presenting with bleeding-plus-ascites and is bellow 30% in those who only have bleeding. [15, 16] At 5-years these figures reach the 80% and 40% of cases, respectively. [15] Therefore, it seems likely that the effect of p-TIPS effectively preventing the overall risk of further decompensation is what largely determines the improvement in survival. [82, 83].

Stratifying Risk: the Ideal Candidate For Tips

In contrast to what happens with p-TIPS, RCTs assessing elective first-line therapy with TIPS vs SOC to prevent variceal rebleeding did not show survival improvement, despite decreasing rebleeding risk with TIPS and even using only covered stents. [78, 79] No risk stratification was used in these trials. By contrast, the studies assessing p-TIPS selected only high-risk patients to be treated with p-TIPS. Dealing with patients at high-risk of death likely contributed to obtain a survival gain, since TIPS can be useful but can also induce undesirable effects. Adequately selecting candidates who may benefit the most from p-TIPS, while avoiding it when offers no clear benefit or may even harm, is crucial to achieve a maximal gain.

The first RCT investigating p-TIPS selected high-risk patients based on HVPG, since previous studies had shown that the risk of death was much higher when HVPG was ≥ 20 mmHg. [84] However, such measurements are not widely available, especially under emergency conditions. Subsequent studies selected high-risk patients based on clinical parameters, involving patients with Child–Pugh class C (but score < 14) or class B patients with active bleeding at endoscopy, as these criteria had been associated with poor outcomes. [85, 86] However, relevant drawbacks should be noted. Using active bleeding at endoscopy has raised concern, since it is subjective and has non-negligible interobserver variability. [87, 88] Furthermore, although it may reflect rebleeding risk, is unclear whether it captures the risk of liver dysfunction or that of other events related to death risk, such as ascites. Moreover, recent studies have shown that while death risk is very high in patients with Child–Pugh class C, it is much lower in those with class B. [21, 62, 87, 88] Refinement of risk stratification has been proposed by using a recalibrated MELD or other models, such as the CLIF-C acute decompensation score or combining Child–Pugh class C and creatinine level ≥ 1 mg/dL. [21, 87–90] By reassessing risk in Child–Pugh class B patients, it has been suggested that only those with scores > 7 benefit from p-TIPS, along with class C patients.[69] The majority of patients with Child–Pugh class C or B (with score > 7) have dACLD with ascites and/or HE. [91] In fact, most patients with AVB (around 60%) also have ascites ± HE in addition to bleeding and, as previously commented, they are those at higher risk of both further decompensation and death. [15–17] Therefore, it is likely that risk stratification may improve by taking this issue into account, i.e. by differentiating whether patients with AVB present with bleeding alone or whether they also have ascites ± encephalopathy. [83] Patients with ascites ± HE on top of bleeding and with a Child–Pugh score > 7, are those at higher risk and thus they are most likely to benefit from p-TIPS. [15–17, 69] On the other hand, patients presenting with bleeding alone have much lower risk of both further decompensation and death, and have lower mortality in case of rebleeding. [15, 16] It is possible that rescue TIPS may be as effective as p-TIPS in these patients. However, this requires specific investigation.

Data from several studies suggest that recalibrated-MELD may be more appropriate than Child–Pugh as a decision tool for p-TIPS. [87–90] Indeed, the use of MELD may avoid the subjectivity of clinical variables in Child–Pugh and, unlike it, does not categorize continuous variables, which may improve accuracy. [92] In addition, first considering whether patients have ascites ± HE on top of bleeding may cover the information provided by clinical variables in Child–Pugh, further suggesting improvement by subsequently using MELD score. Figure 2 shows an alternative approach to select suitable candidates to benefit the most from p-TIPS, suggesting potential to improve risk stratification by first considering the substage of cirrhosis in bleeding patients and considering MELD score subsequently. Nevertheless, specific research would be required to clarify if this suggested approach may actually improve outcomes.

Regarding this suggested approach to stratify risk (Fig. 2), the potential value of p-TIPS is unclear in several circumstances that would require particular investigation. This is the case of patients presenting with first ascitic decompensation at the time of bleeding, since it is unclear to what extend they have worse prognosis than patients presenting with bleeding alone. [15, 17] The potential utility of p-TIPS is also doubtful in patients presenting with encephalopathy but not ascites in addition to bleeding, since spontaneous portal-systemic shunting may play a relevant role in such cases. [93] The value of p-TIPS should also be clarified in patients with bleeding and no other decompensating events, even among those with Child–Pugh > 7 or MELD > 19. Such high scores may reflect advanced liver dysfunction which might even worsen with p-TIPS.

Certainly, HVPG is not widely accessible in clinical practice, although the availability can be greater in centers providing p-TIPS. HVPG may greatly improve risk stratification in patients with AVB and can clearly help to identify those who may benefit the most from p-TIPS. [94] Many studies and meta-analyses have consistently shown that HVPG provides valuable prognostic information to stratify risk in this setting. [44, 46, 94] An HVPG ≥ 20 mm Hg, measured early after admission for AVB, is a strong predictor of early rebleeding and death. [84] In addition, several studies have shown that a baseline HVPG over 16 mm Hg identifies patients with reduced survival. [16] Furthermore, many studies have also consistently shown that an HVPG reduction ≥ 20% of baseline or to values < 12 mmHg when treated with NSBBs, is associated to a reduced risk of rebleeding and also of further decompensation overall and to significantly improved survival. [44, 46, 94] Ideally, such

HVPG response can be assessed in a single baseline hemodynamic study by testing acute response to NSBBs. [95] Certainly, the majority of patients with ascites ± HE on top of AVB have an HVPG > 16 mmHg (around 90%) and have an HVPG decrease < 20% under NSBBs (around 70%). [15, 16] However, patients with baseline HVPG < 16 mmHg, or those with an HVPG decrease > 20% under NSBBs, have very good prognosis under treatment with NSBBs plus EVL and are unlikely to benefit from p-TIPS.

Optimal Timing For P-Tips: When Early Placement Is Really Worth

In most studies dealing with p-TIPS, the procedure was performed early (within the first 72 h) to avoid early rebleeding and the related mortality. However, such an early insertion of p-TIPS faces some challenges in real-world clinical practice. Furthermore, caution is required when considering to what extend the efficacy of p-TIPS relays on its prompt implementation. Early p-TIPS will be helpful in patients at high-risk of failure to control AVB (i.e. at risk of early rebleeding within the first few days despite firs-line therapy). With current SOC this occurs only in 10% to 15% of cases, but it is associated with high mortality. [19, 85] Moreover, although any death occurring within 6 weeks from admission is considered related to AVB, in < 20% of such cases death occurs because uncontrolled bleeding, while is much more frequently due to liver failure or to associated complications such as infections or ACLF. [1, 2, 19, 54, 96] Prompt implementation of p-TIPS will benefit the 10–15% who will develop failure if the procedure is delayed, whereas most patients would not require such early implantation. Thus, adequately identifying risk of failure to control AVB might allow to properly apply early p-TIPS, as soon as possible within the first 72-h, only to patients at high-risk. Currently used criteria (i.e. Child–Pugh class C (< 14) or class B (> 7) with active bleeding), focuses on identifying risk of death. Selectively identifying patients at risk of failure to control AVB would be preferable. This might allow the early placement of p-TIPS only when required, also adapting to feasibility in real-world clinical practice.

According to available studies, failure to control bleeding is more likely in patients presenting with a severe bleeding

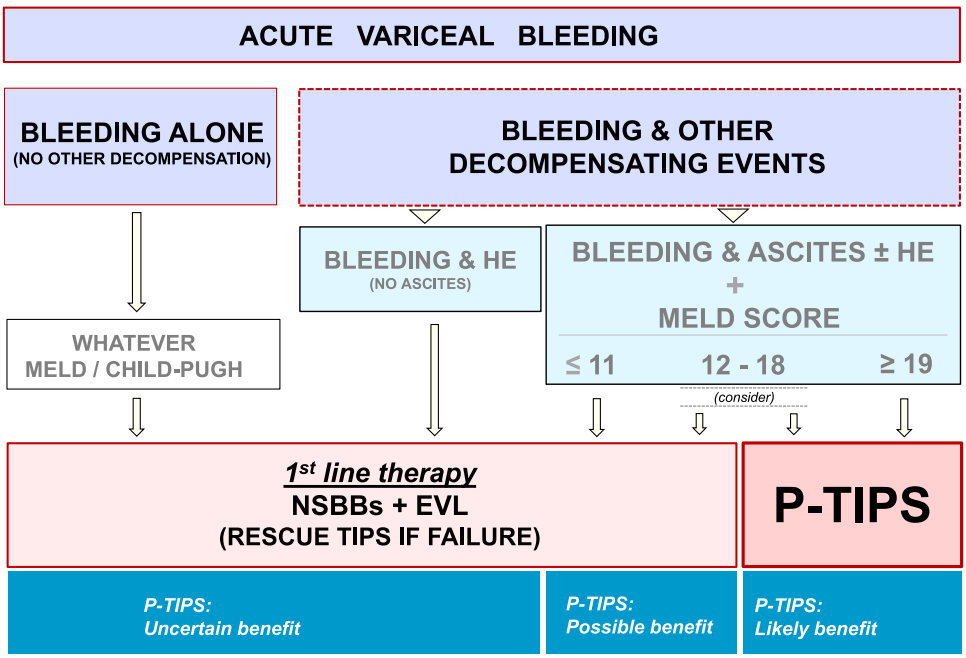

Fig. 2 Elective therapy after acute variceal bleeding (AVB) according to a suggested alternative approach for risk-stratification. Patients with AVB presenting without any other decompensating event have good prognosis and benefit with p-TIPS is uncertain. This is also the case in patients presenting with bleeding and encephalopathy but not ascites, in who spontaneous portal-systemic shunting may play a relevant role. In patients with AVB presenting with ascites ± encephalopathy, p-TIPS should be considered if MELD score ≥ 19 as risk of mortality is high and benefit from the procedure is likely. [21, 64, 87] Given the high mortality of patients with MELD score ≥ 30, [53] p-TIPS should be very carefully considered in such cases. p-TIPS should also be considered with MELD scores between 12 and 18 and non-negligible risk, particularly among those with higher scores. [21, 64, 87] p-TIPS will be rarely indicated in patients with MELD score ≤ 11 as they have good prognosis. Benefit is uncertain in patients with AVB presenting with ascites for the first time, as although prognosis is worse than in those who only have bleeding, it is also much better than in those with previous ascites. [15]. Specific research will be required to assess if this potential approach to select high-risk candidates for p-TIPS may be more beneficial than the currently used criteria

episode. Thus, 5-days failure has been related to factors such as presence of hypovolemic shock at admission (or low systolic blood pressure), low values of hemoglobin or hematocrit or high transfusion requirement. [19, 85, 97–99] Failure has also been related to the presence of active bleeding at endoscopy under treatment with vasoactive drugs. [100, 101] Further bleeding has been related to higher values of HVPG, i.e. HVPG > 16 mmHg and particularly > 20 mmHg. [16, 84] Therefore, although a specific model to accurately identify such patients at high-risk is still an unmet need, patients with AVB who also have ascites ± HE and who have signs of a severe bleeding (including shock, low Hb despite transfusion and presence of active bleeding at endoscopy) probably are those most likely to benefit from an early implementation of p-TIPS. Nevertheless, further investigation is warranted to selectively identify such high-risk patients who may benefit from early placement of p-TIPS. Large RCT on p-TIPS are currently ongoing. [102].

Role Of Tips To Manage Gastrofundal Varices

Around 20% of patients with cirrhosis have gastric varices. Varices extending into the lesser curvature of the stomach are the most common. They have similar behavior to esophageal varices and are treated similarly. [4, 6] Varices extending along the greater curvature and isolated fundal varices are frequently referred to as gastro-fundal varices (GV). Prevalence and bleeding risk from GV are lower than those of esophageal varices. Bleeding GV had been associated with higher rates of treatment failure and mortality, although differences are becoming closer with current SOC. [103, 104] GV are more common in prehepatic portal hypertension.

GV are supplied by left-gastric, short- gastric or posterior-gastric veins. Although GV may drain into the gastroesophageal venous system, more frequently drain through the gastro-phrenic venous system into the left renal vein. The accompanying gastro-renal shunts can be large and provide an opportunity for other interventional radiology endovascular techniques besides TIPS, such as retrograde transvenous obliteration (RTO), to close portal-systemic shunt and GV. [26, 103, 104] Both TIPS and RTO have shown efficacy managing GV. [105–108] Choosing between one or the other may be difficult given the absence of RCTs comparing both techniques. A comprehensive imaging workup to define vascular anatomy can help to determine the optimal approach. [25–27] Reducing the risk of HE and preserving liver function are the main potential advantages of RTO over TIPS. However, RTO may increase portal pressure once closed the shunt and may worsen esophageal varices, ascites or hydrothorax. Therefore, the presence of such complications may favor TIPS. When performing TIPS, the concurrent obliteration of GV may improve the efficacy to prevent rebleeding. [25, 26].

At present, TIPS are not recommended for primary prophylaxis of GV bleeding. [4, 6, 25–27] Salvage/rescue TIPS have similar efficacy than for esophageal varices. [6, 26] A recent small RCT suggests superiority of p-TIPS over cyanoacrylate injection plus NSBBs in patients with acute GV bleeding and Child–Pugh class B or C. [108] According to current guidelines, either TIPS, RTO or cyanoacrylate injection plus NSBBs can be used as first-line therapy to prevent GV rebleeding. [4, 6, 26] Recent data suggest greater benefit favoring interventional radiology endovascular techniques. [106–108] Nevertheless, the endoscopic approach may improve by using ultrasound-guided injection (with cyanoacrylate glue) combined with coils embolization, which may allow successful targeting and obliteration of GV. [109] Therefore, further investigation will be required to clarify the best role for each of these option (or combination of techniques) in different clinical settings.

Conclusions

Risk of death after AVB is closely related to the development of further decompensation, i.e. not just rebleeding but also ascites ± HE. Patients with AVB may require a salvage/rescue TIPS or a p-TIPS. In patients with uncontrolled bleeding despite first-line therapy, salvage-TIPS can effectively control bleeding but carries high mortality. Conversely, placing a p-TIPS to prevent failure in high-risk patients can improve survival. TIPS induce a rapid and marked decrease in portal pressure, allowing to efficiently manage decompensating events related to portal hypertension. Indeed, the survival gain favoring p-TIPS is achieved by decreasing rebleeding risk, but also by reducing the risk of developing ascites and its related complications, i.e. by preventing the overall risk of further decompensation. This review suggests potential improvements to optimize p-TIPS, which would deserve investigation. First, the efficacy of p-TIPS might be enhanced by improving risk stratification to identify patients at high-risk of further decompensation, who are at highest risk of death and who may benefit the most from p-TIPS. Since risk of further decompensation concentrates in patients with ascites ± HE in addition to AVB, this should be considered to select candidates for p-TIPS. Among these patients, those with worse liver function (Child–Pugh score > 7 or MELD > 12) and high mortality risk are most likely to benefit from p-TIPS. Furthermore, most patients might not require an early placement of p-TIPS (within the first 72 h), which despite being frequently recommended faces challenges in practice. Early p-TIPS mainly benefit patients at high-risk of failure with first-line therapy (which occurs in < 15% of cases). Selectively identifying such patents can also be helpful.

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Author Contribution All authors reviewed the bibliography. CV wrote a first manuscript draft. MGG prepared a first draft of tables. AH prepared a frist draft of figures. All authors reviewed and discussed each section until the final verion of the complete manuscript

Funding Open Access Funding provided by Universitat Autonoma de Barcelona.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Financial Support This study has been supported in part by grants from the Instituto de Salud Carlos III (PI14/00876, PI15/00066). The CIBERehd is funded by the Instituto de Salud Carlos III (ISCiii).

Competing interest The authors declare no competing interests.

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