Review

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Where does TIPS fit in the management of patients with cirrhosis?

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Summary

In this review, we summarise the current knowledge on the indications and contraindications of transjugular intrahepatic portosystemic shunt (TIPS) placement for the treatment of the complications of portal hypertension in cirrhosis, specifically variceal haemorrhage and ascites. Moreover, we discuss the role of TIPS for the treatment of portal vein thrombosis (PVT) and the prevention of complications after extrahepatic surgery ('preoperative TIPS') in patients with cirrhosis. The position of TIPS in the treatment hierarchy depends on the clinical setting and on patient characteristics. In acute variceal haemorrhage, preemptive TIPS is indicated in patients at a high risk of failing standard therapy, that is those with a Child-Pugh score of 10–13 points or Child-Pugh B with active bleeding at endoscopy, although the survival benefit in the latter group still remains to be established. Non-preemptive TIPS is a second-line therapy for the prevention of recurrent variceal haemorrhage and for the treatment of ascites. Of note, TIPS may also improve sarcopenia. Contraindications to TIPS placement, independent of clinical setting, include very advanced disease (Child-Pugh >13 points), episodes of recurrent overt hepatic encephalopathy without an identifiable precipitating factor, heart failure, and pulmonary hypertension. In patients with PVT, TIPS placement not only controls complications of portal hypertension, but also promotes portal vein recanalisation. Although the severity of portal hypertension correlates with poor outcomes after extrahepatic surgery, there is no evidence to recommend preoperative TIPS placement.

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Introduction: Complications of portal hypertension

With the progression of chronic liver disease (CLD) to compensated advanced chronic liver disease (a term that subsumes advanced liver fibrosis and cirrhosis), the hepatic venous pressure gradient (HVPG) rises due to increases in intrahepatic resistance.[1] This initial increase in portal pressure induces splanchnic and peripheral vasodilatation that leads to increased portal venous inflow and a hyperdynamic circulatory state that further increases portal pressure to values ≥10 mmHg.[2] At this stage, termed clinically significant portal hypertension (CSPH), patients may develop gastroesophageal varices and/or other portosystemic collaterals, but even more importantly, hepatic decompensation.[3] First hepatic decompensation (most commonly, the development of ascites, followed by acute variceal bleeding (AVB) and hepatic encephalopathy (HE)[4]) denotes the transition from the compensated to the decompensated state and confers a dramatic increase in mortality risk (from 14% to 93% at 20 years[5]). In decompensated cirrhosis, treatment strategies primarily aim at decreasing the risk of mortality by preventing further decompensation and acute-on-chronic liver failure (ACLF).[6]

Bleeding

Portal hypertensive bleeding, particularly AVB, is associated with considerable short-term mortality (~15%), which, among other factors, is determined by the degree of hepatic dysfunction.[7] Regarding the short-term outcome of AVB, 2 important endpoints have been defined[8]: failure to control bleeding (*i.e.*, treatment failure or death within 5 days) and bleeding-related mortality (*i.e.*, death within 6 weeks – the recommended primary endpoint for clinical trials). The adoption of 6-week mortality as the primary endpoint emphasises that, in addition to controlling the bleeding itself (as reflected by failure to control bleeding), prevention of bleeding-related complications such as bacterial infections and the development of ACLF[9] is of critical importance for improving outcomes. Vasoactive drugs, prophylactic antibiotics, a restrictive blood transfusion policy, as well as early endoscopy are the mainstays of treatment for bleeding episodes. In general, this treatment strategy is highly effective, but in some patients, particularly in those

with severely impaired liver function, these measures result in poor outcomes.

AVB also impacts long-term prognosis. Indeed, it increases the risk of developing another AVB (rebleeding) and mortality, as indicated by the transition from the stage of compensated cirrhosis with CSPH (5-year mortality: 10%) to the stage of portal hypertensive bleeding (5-year mortality: 20%). In previously decompensated patients who develop a second decompensation event (*e.g.*, AVB), 5-year mortality increases to 88%.

Ascites

Ascites is the most common first hepatic decompensation, impacting nearly half of patients with compensated cirrhosis within the first 10 years of diagnosis.[10,11] Hepatic sinusoidal pressure is the main driver of ascites formation. Patients with ascites have been shown to have a sinusoidal or a portosystemic gradient of at least 12 mmHg.[12,13] Reducing portal pressure (as determined by the HVPG) prevents the development of ascites in patients with compensated cirrhosis.[14] Furthermore, in patients with ascites in whom HVPG is reduced, mostly in response to therapy with non-selective beta-blockers (NSBBs), *i.e.*, 'HVPG responders',[15] the probabilities of developing complications, such as refractory ascites (RA) and hepatorenal syndrome (HRS), are significantly reduced.[16] In addition to sinusoidal portal hypertension, these complications result from vasodilatation and increased renal vasoconstriction resulting from systemic inflammation.[17,18] While 1-year survival in patients who develop ascites is approximately 85%, survival decreases to 32% in the subset with RA.[19] Ascites also predisposes patients to 2 other complications of cirrhosis that are linked to poor outcomes: spontaneous bacterial peritonitis (SBP), which commonly triggers the acute form of HRS or HRS-AKI (formerly known as HRS-1)[18]. SBP impacts approximately 3.5% of asymptomatic non-hospitalised patients and about 10–30% of hospitalised patients with a mortality rate of about 30% per episode and, by inducing inflammation, is a major risk factor for the development of HRS-AKI.[18,20] HRS-AKI occurs in 20% of patients within the first year of ascites development, with a cumulative incidence rising to 40% at 5 years, and median survival ranges from 2 weeks to 6 months.[21]

Although uncomplicated ascites, RA, SBP, and HRS are distinct clinical entities, in reality, these conditions occur along a spectrum. Therapy for ascites is predominantly aimed at reducing the volume of ascites, and thus, the need for paracentesis (thereby improving quality of life) but should be also aimed at removing risk factors for SBP and HRS and, ultimately, improving survival.

Portal vein thrombosis

Non-malignant portal vein thrombosis (PVT) is a frequent complication in patients with cirrhosis. It is commonly found in asymptomatic patients during routine imaging studies for hepatocellular carcinoma (HCC) screening, but its diagnosis may also coincide with an aggravation of portal hypertension. In this latter situation, it is not entirely clear whether PVT is the cause or the consequence.[22]

Several classifications have been proposed to stage the extension of PVT. A frequently used classification was developed by Yerdel *et al.*[23] and is based on the degree of occlusion and the number of affected vessels. According to this classification, grade 1 and grade 2 refer to non-occlusive and occlusive involvement of the portal trunk, respectively. In grade 3, the thrombosis extends to the porto-spleno-mesenteric confluence while in grade 4, there is extensive involvement of the superior mesenteric vein. Even grade 3 and 4 PVT rarely induce intestinal ischaemia in patients with cirrhosis, which is probably due to the pre-existence of portal hypertension and portosystemic collaterals that decompress the system.

While the potential causal relationship between PVT and deterioration of liver function is still under debate,[24] PVT has repeatedly been linked to poor outcomes in patients with AVB.[25] Moreover, extensive PVT has been shown to worsen liver transplant outcomes in an analysis based on the OPTN/UNOS data,[26] and may even preclude liver transplantation. Accordingly, maintaining patency of the portal vein (PV) is particularly relevant in the liver transplant waiting list setting.

Key points

- Preemptive TIPS has become the standard of care in patients with high-risk acute variceal bleeding (*i.e.*, Child-Pugh B plus active bleeding on endoscopy or C with 10–13 points).
- Further efforts are needed to implement preemptive TIPS in clinical practice.
- Persistent bleeding and severe rebleeding within 5 days should be managed by rescue/salvage TIPS.
- TIPS should not be used as a first-line treatment to prevent rebleeding.
- In selected patients with ascites requiring repeated large-volume paracentesis, TIPS using polytetrafluoroethylene-covered stents leads to improved control of ascites and lowers mortality.
- In patients with portal vein thrombosis (PVT), TIPS placement not only controls complications of portal hypertension, but also promotes portal vein recanalisation.
- TIPS placement ±recanalisation of the porto-spleno-mesenteric axis may enable liver transplantation in patients with extensive chronic PVT/cavernoma and decreases the need for surgical reconstruction at the time of liver transplantation.

Role of TIPS in patients with cirrhosis

The combination of a relatively low invasiveness (compared to surgery), leading to a favourable safety profile even in vulnerable patient groups, and the profound amelioration of portal (sinusoidal) hypertension, are unique characteristics of TIPS. These features make it an ideal therapy in the management of portal hypertensive bleeding and to prevent its recurrence, as well as to treat ascites, particularly when other less invasive management approaches have failed. Moreover, because reduced PV flow velocity[27] – due to increased intrahepatic resistance and the development of spontaneous portosystemic shunts[28] – contributes to the development of PVT,[22] TIPS placement can also promote PV recanalisation by decreasing transhepatic resistance and redirecting flow to the PV. Moreover, it allows direct access to the porto-spleno-mesenteric axis, enabling additional endovascular therapies to be performed.

In addition to portal hypertension due to cirrhosis (±PVT), TIPS is a well-established treatment option for other vascular diseases of the liver,[25] such as Budd-Chiari syndrome, which have recently been reviewed elsewhere[29] and are not discussed in this review article.

TIPS for bleeding

Pre-primary and primary prophylaxis for oesophageal varices

Considering the comparatively low risk of AVB in patients who have not bled,[5] the risks of TIPS placement clearly outweigh its

potential benefits, and thus, TIPS is not indicated for pre-primary and primary prophylaxis, *i.e.*, prevention of varices or first bleeding episode. However, if TIPS is performed for another indication (*i.e.*, ascites), prophylaxis of variceal haemorrhage is no longer necessary and should be discontinued as long as the TIPS is functional.

Preemptive TIPS for bleeding from oesophageal varices

The concept of 'preemptive TIPS' describes the early (within 24 h[30] or within 72 h[31,32] of admission), but most importantly, the preventive insertion of a TIPS in patients at high risk of uncontrolled bleeding and bleeding-related mortality. This concept is based on a body of evidence indicating that TIPS is highly effective in controlling AVB/preventing rebleeding as well as the assumption that a profound reduction in portal pressure may prevent subsequent organ failures/ACLF, and thus, reduce bleeding-related mortality.

Several randomised controlled trials (RCTs) evaluated the safety and efficacy of a timely TIPS placement in patients with AVB.[33] Although the populations investigated in these studies comprised a variable proportion of preemptive TIPS patients, they also included patients in whom conventional secondary prophylaxis had failed, who did not meet high-risk criteria, or who actually required rescue/salvage TIPS. As these studies may be confused with/included in the term 'early TIPS', the term has been substituted by 'preemptive TIPS' which puts emphasis on the indication for undergoing TIPS, rather than the timeframe.

The safety and efficacy of preemptive TIPS has been evaluated in a series of RCTs, which are summarised in Table 1. To begin with, the preemptive TIPS strategy requires the definition of a high-risk population, *i.e.*, the target population for this intervention. A HVPG ≥20 mmHg has repeatedly been associated with a substantially (*e.g.*, more than 5-fold[34]) increased risk of poor bleeding control/failure to control bleeding[34,35]; and, in line with the prognostic value of HVPG in general, HVPG ≥20 mmHg identifies patients at increased risk of in-hospital mortality,[30] bleeding-related mortality[30] and 1-year mortality.[35] Based on these findings, Monescillo *et al.*[30] randomised 52 patients (Child-Pugh B: 40%, C: 46%; active bleeding: 35%; 22% with previous AVB) with HVPG ≥20 mmHg who had undergone a single session of sclerotherapy to receive an uncovered TIPS or conventional therapy (Table 1). Interestingly, TIPS decreased the probability of in-hospital (absolute risk reduction [ARR]: 20%) and 1-year (ARR: 27%) mortality, while the decrease in bleeding-related mortality did not reach statistical significance despite an ARR of 19%. Although this study provided important evidence supporting the preemptive use of TIPS, its results have to be interpreted/extrapolated with caution, as both the TIPS technique (uncovered *vs.* polytetrafluoroethylene [PTFE]-covered stents[36–38]) and conventional therapy (sclerotherapy *vs.* endoscopic variceal ligation [EVL]) have changed since the conduct of the study. Moreover, the use of HVPG for risk stratification and treatment assignment (*i.e.*, personalised therapy) has important limitations, since its assessment is challenging in the context of AVB (as evidenced by 5 patients not undergoing HVPG), and most importantly, its availability is restricted to large centres. Moreover, in another study, 5-day mortality appeared to be more strongly determined by the severity of underlying hepatic impairment (*i.e.*, Child-Pugh and model for end-stage liver disease [MELD] score) than by HVPG ≥20 mmHg.[34]

In order to confirm the concept of 'preemptive TIPS' and to establish its role in the management of AVB outside of centres with sufficient expertise to measure HVPG, a European multicentre RCT applied the following high-risk criteria for preemptive TIPS placement: Child-Pugh B plus active bleeding on endoscopy (about half of patients) or Child-Pugh C with 10–13 points.[31] Moreover, a series of criteria aiming to exclude patients with negative prognostic factors/conditions that are not improved or unlikely to be improved by TIPS were applied, which led to a highly selected patient population. However, even

Table 1. Randomised controlled trials on 'preemptive TIPS'.

Author	Sample size; Intervention and comparator	Main inclusion criteria	Main exclusion criteria	Safety	Efficacy
Monescillo *et al.*[30]	134 consecutive patients; 116 screened by HVPG measurement; 52 patients randomised 1:1	HVPG ≥20 mmHg	Age <18/>75 years; HCC; PVT; Previous TIPS; HIV; Cardiac/chronic renal failure; n = 5 too instable for HVPG	No increase in *de novo* PSE; n = 5 severe complications likely related to TIPS	Failure to control bleeding: decreased, favouring TIPS; In-hospital mortality: 11% *vs.* 31%, favouring TIPS; Bleeding-related mortality: 19% *vs.* 38% (n.s.); Mortality at 1 year: 38% *vs.* 65%, favouring TIPS
García-Pagán *et al.*[31]	359 consecutive patients; 63 patients randomised 1:1	Child-Pugh B plus active bleeding (51%) or Child-Pugh C ≤13 points (49%)	Age <18/>75 years; HCC out of Milan criteria; Occlusive PVT; Previous TIPS; Failure of NSBB plus EVL; Bleeding from IGV/ectopic varices; Serum creatinine >3 mg/dl; Heart failure	No increase in PSE during hospitalisation or follow-up; n = 5 severe complications likely related to TIPS	Failure to control bleeding or rebleeding at 1 year: 3% *vs.* 50%, favouring TIPS; Mortality at 1 year: 14% *vs.* 39%, favouring TIPS; *De novo* or worsening of ascites: trend towards decrease
Lv *et al.*[32]	373 consecutive patients; 132 patients randomised 2:1	Child-Pugh B (57% without and 21% with active bleeding) and C ≤13 points (22%)	Similar to García-Pagán *et al.*[31] plus recurrent overt HE without precipitating factor	No increase in overt PSE	Failure to control bleeding or rebleeding at 1 year: 11% *vs.* 34%, favouring TIPS; Mortality at 1 year: 38% *vs.* 65%, favouring TIPS; *De novo* or worsening of ascites: 11% *vs.* 43%, favouring TIPS

EVL, endoscopic variceal ligation; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; IGV, isolated gastric varices; NSBB, non-selective beta blocker; PVT, portal vein thrombosis; PSE, portosystemic encephalopathy; RCT, randomised controlled trial; TIPS, transjugular intrahepatic portosystemic shunt.

when using the current standard of care (NSBB plus EVL) as a comparator, the 1-year probability of failure to control bleeding or rebleeding (ARR: 47%), and most importantly, mortality at 1 year (ARR: 25%) were substantially decreased with TIPS. These excellent outcomes with preemptive TIPS have been confirmed by 5 (but not all) subsequent observational studies, 4 of them[39–42] using similar clinical high-risk and exclusion criteria as the European multicentre RCT. The fifth and most recent observational study was a Chinese single centre analysis, including mostly patients with cirrhosis due to hepatitis B who were subjected to antiviral therapy[43]; while the majority of inclusion and exclusion criteria were similar to the previous ones, preemptive TIPS was also offered to Child-Pugh A patients and Child-Pugh B patients without active bleeding. Importantly, a survival benefit was observed in patients fulfilling the high-risk criteria used in the multicentre European multicentre RCT, but not in patients with Child-Pugh A or Child-Pugh B without active bleeding.

Finally, a Chinese single centre RCT[32] in patients with Child-Pugh B (57% without and 21% with active bleeding) and Child-Pugh C (10–13 points [22%]) confirmed that preemptive TIPS is effective in reducing bleeding-related mortality and decreasing 1-year transplant-free mortality, however, the ARR (13%) appeared to be lower than in the European studies.[30,31] This may be explained by the inclusion of patients who are possibly at lower risk of failure to control bleeding or rebleeding (*i.e.*, patients with Child-Pugh B without active bleeding and patients with hepatitis B on antiviral therapy[44]) and the low proportion of patients with Child-Pugh C, who are assumed to benefit the most from this intervention.[43] Accordingly, the probability of transplant-free survival at 1 year in the control arm tended to be considerably higher in the Chinese (73%) than the European (61%) RCT,[32] thereby attenuating the ARR, despite similarly encouraging results in the TIPS arm. Interestingly, preemptive TIPS tended to decrease mortality throughout all strata (Child-Pugh B with or our without active bleeding and Child-Pugh C) and Child-Pugh stage (*i.e.*, B *vs.* C) did not seem to modify the impact of preemptive TIPS on transplant-free survival. However, limited sample size/statistical power does not allow for definitive conclusions regarding subgroups.

In summary, there is evidence from 3 RCTs (including 2 RCTs with a state-of-the-art comparator) demonstrating that preemptive TIPS placement improves survival in high-risk patients (Table 1), thus providing a strong rationale for its application in clinical practice. This is supported by most,[40–43] but not all[39,45] observational studies. Of note, the observational studies not reporting a survival benefit had limited sample size[39] or used non-contemporaneous controls.[45] Moreover, it cannot be ruled out that some of the patients included in the observational studies actually underwent 'early' rescue/salvage TIPS instead of preemptive TIPS, which, in addition to confounding by indication, substantially limits their significance.

However, there is still some uncertainty and an ongoing controversy regarding the optimal identification/definition of high-risk patients who should be subjected to preemptive TIPS. Several observational studies attempted to address this question, with the largest series of patients being investigated by Lv *et al.*[43] In this Chinese observational multicentre study, the therapeutic benefit of early (*i.e.*, not strictly preemptive) TIPS was pronounced among patients with Child-Pugh B and active bleeding, Child-Pugh C, or MELD ≥19.[31] In contrast, in patients with Child-Pugh B without active bleeding, as well as in patients with Child-Pugh A or MELD ≤11 points, mortality was low regardless of treatment arm.

Taken together, current evidence and clinical practice recommendations[8,46] support the use of preemptive TIPS in patients with Child-Pugh C or Child-Pugh B plus active bleeding, but not in patients with Child-Pugh B without active bleeding, or patients with Child-Pugh A. However, results in patients with Child-Pugh B were less consistent/convincing, compared to results in those with Child-Pugh C. Accordingly, individual patient data meta-analyses of available RCTs, as well as additional RCTs powered to detect clinically meaningful differences in survival in patients with Child-Pugh B (±active bleeding at endoscopy), are needed to confirm the survival benefit in this subgroup.

Importantly, preemptive TIPS did not increase the risk of portosystemic encephalopathy (PSE) and decreased the incidence/worsening of ascites in the more recent RCT,[31,32] as well as in observational studies,[42,43] providing a further argument for considering patients with Child-Pugh B and active bleeding for preemptive TIPS, until more data regarding the survival benefit become available.

As outlined above, a major therapeutic goal behind preemptive TIPS placement in AVB is the prevention of subsequent organ failures/ACLF, which raises the question of whether preemptive TIPS is still indicated in patients who have already developed ACLF at the time of decision making. Although this population has not been specifically investigated in an RCT, a recent analysis of prospectively collected data from the International Variceal Bleeding Observational Study Group of the Baveno Cooperation established ACLF as an independent risk factor for bleeding-related mortality and rebleeding; they linked preemptive TIPS placement to improved outcomes in patients with ACLF.[47] Accordingly, preemptive TIPS should not be deferred because of ACLF and eligibility should be evaluated based on the number and severity of organ dysfunctions.

Although preemptive TIPS has already been recommended in the Baveno V consensus published in 2010,[48] a prospective French survey conducted from 4/2012 to 5/2013 revealed that only 7% of eligible patients underwent preemptive TIPS, despite good outcomes under real-world conditions.[41] Similarly, in a large prospective observational multicentre study that recruited patients from high-volume centres between 2011 and 2015,[42] preemptive TIPS was placed in only 13% of high-risk patients. These figures indicate a substantial underutilisation of preemptive TIPS in clinical practice. This is concerning, considering its profound effect on patient outcomes: For instance, the number needed to treat (NNT) of preemptive TIPS was 4 (long-term mortality; *vs.* conventional therapy; calculation based on[31]), which compares favourably to interventions in other fields of medicine, *e.g.*, primary percutaneous coronary intervention (PCI) for myocardial infarction (NNT: 31.8; long-term mortality; *vs.* lysis; calculation based on[49]), which are far better implemented. Accordingly, further efforts are needed to lower the bar for the use of preemptive TIPS in clinical practice.

Rescue/salvage TIPS for bleeding from oesophageal varices

It is conceivable that the wide-spread application of treatment individualisation in the form of preemptive TIPS will substantially affect both the frequency and the outcomes of rescue/salvage TIPS. Accordingly, the findings of previous studies on rescue/salvage TIPS will have limited applicability, as the patients who would now be considered candidates for rescue/salvage TIPS would be enriched with patient groups that are not

candidates for preemptive TIPS: a) low-risk patients who may have even better outcomes with standard non-TIPS therapy and b) patients with a very poor prognosis who would have a very high mortality with TIPS and who were excluded from studies on preemptive TIPS due to very advanced disease (*i.e.*, Child-Pugh C >13 points) or other negative prognostic factors.

While less severe cases of rebleeding after the initial endoscopy may be managed by a second endoscopic attempt to achieve haemostasis, persistent bleeding and severe rebleeding within 5 days should be managed by rescue/salvage TIPS.[8,46] Current clinical practice guidelines recommend self-expandable metallic stent (SEMS), or if not available, balloon tamponade as a bridge to definite treatment. SEMS seem to be more effective and safe[50] and have a longer dwell time, however, we would like to emphasise that they should not be removed before placement of a functional rescue/salvage TIPS due to the high risk of rebleeding.[50] Of note, the studies which established the value of TIPS as a rescue/salvage therapy were uncontrolled (due to the lack of an adequate comparator), still used sclerotherapy/uncovered stents, and indicated considerable short- and long-term mortality despite high rates of bleeding control.[51–54] Although uncovered TIPS have been found to be non-superior to surgical distal splenorenal shunts for patients with Child-Pugh A and B, with failure of secondary prophylaxis,[55] surgical expertise is lacking these days and mortality rates have been exceedingly high in rescue/salvage settings or in patients with poor liver function. Considering the lack of therapeutic alternatives, the main factor limiting the use of rescue/salvage TIPS is therapeutic futility, which should be evaluated in the light of the number and severity of organ dysfunctions and the patients' eligibility for liver transplantation. Of note, studies investigating prognostic factors/potential indicators of therapeutic futility (as reviewed in detail by Bouzbib *et al.*[56]) are rather old, and thus, they have to be redefined based on more recent cohorts.

Secondary prophylaxis after bleeding from oesophageal varices

Initially, 2 RCTs investigated the use of TIPS (*vs.* propranolol plus isosorbide mononitrate [ISMN] plus EVL[57] or propranolol monotherapy[58]) for secondary prophylaxis. Although 1 study reported a decrease in rebleeding and *de novo* or worsening of ascites,[57] there were no differences in mortality (Table 2). Importantly, the rates of TIPS dysfunction and PSE were comparatively high, which is explained by the use of uncovered stents.[36,37]

More recently , the role of TIPS in the prevention of rebleeding has been re-evaluated in 2 RCTs using PFTE-covered stents. In the first RCT by Sauerbruch *et al.*,[59] TIPS using 8 mm PFTE-covered stents was superior in preventing rebleeding compared to HVPG-guided therapy - propranolol plus ISMN were used to treat HVPG responders,[15] while non-responders were treated with EVL monotherapy. However, there was no difference in survival. Of note, a considerable proportion of patients were enrolled

Table 2. Randomised controlled trials on the use of TIPS for secondary prophylaxis of AVB.

Author	Sample size; Intervention and comparator	Main inclusion criteria	Main exclusion criteria	Safety	Efficacy
Escorsell *et al.*[57]	91 patients randomised 1:1; Uncovered 10 mm dilated to 8-10 mm *vs.* propranolol plus ISMN plus EVL	Within 2 weeks of AVB controlled with vasoactive drugs plus endoscopy (preferably EVL); Child-Pugh B/C	Age <18/>75 years; HCC; Occlusive PVT; Previous TIPS; Chronic renal failure; Alcoholic hepatitis; Bilirubin >10 mg/dl; Prothrombin index <30%; PLT <20 G/L	70% required TIPS revision; Increase in *de novo* PSE during follow-up in the TIPS group; Trend towards increase in hospital admissions due to PSE in the TIPS group	Rebleeding at 2 years: 13% *vs.* 49%, favouring TIPS; Mortality at 2 years: 28% *vs.* 28% (n.s.); *De novo* or worsening of ascites: 7% *vs.* 21%, favouring TIPS; Similar quality of life
Sauer *et al.*[58]	85 patients randomised 1:1; Uncovered dilated to 8-12 mm *vs.* propranolol	Within 3 days of control of AVB with vasoactive drugs plus endoscopy (sclerotherapy)	Gastric varices; Previous endoscopic or surgical therapies; PVT; Grade 3/4 HE; Severe extrahepatic comorbidities	89% required TIPS revision; Increase in PSE during follow-up in the TIPS group	Failure to control bleeding or all-cause rebleeding at 5 years: 31.1% *vs.* 38.9% (n.s.); Failure to control bleeding or rebleeding from varices at 5 years: 19.4% *vs.* 29.9% (n.s.); Mortality at 5 years: 24.1% *vs.* 17.8% (n.s.)
Sauerbruch *et al.*[59]	185 patients randomised 1:1; PFTE-covered 8 mm dilated to 8 mm *vs.* HVPG-guided therapy: propranolol plus ISMN or EVL monotherapy	Within 21 (56%) or after >21 days (44%) of AVB controlled with vasoactive drugs plus endoscopy (EVL)	Age <18/>75 years; Child-Pugh ≥12 points; MELD >30 points; Previous NSBB treatment; Previous TIPS; Bilirubin >3 mg/dl; Prothrombin index <30%; PLT <30 G/L	Increase in PSE during follow-up in the TIPS group	Rebleeding at 2 years: 7% *vs.* 26%, favouring TIPS - driven by stratum I; Mortality at 2 years: similar; Similar quality of life
Holster *et al.* [62]	72 patients randomised 1:1; PFTE-covered 10 mm dilated to 8-10 mm *vs.* propranolol plus EVL or cyanoacrylate	At a median of 4 days after a first or second AVB controlled with vasoactive drugs plus endoscopy (EVL or cyanoacrylate)	Age <18/>75 years; Grade 3/4 HE; Heart failure NYHA III/IV; PVT; Previous TIPS; Advanced HCC; Child-Pugh >13 points; Sepsis and/or ACLF	Increase in PSE at 1 year in TIPS group, but during long-term follow-up, this difference diminished	Rebleeding: 0% *vs.* 29%, favouring TIPS; Mortality: 32% *vs.* 26% (n.s.)

AVB, acute variceal bleeding; ACLF, acute-on-chronic liver failure; EVL, endoscopic variceal ligation; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; ISMN, isosorbide mononitrate; MELD, model for end-stage liver disease; NSBB, non-selective betablocker; PLT, platelet count; PFTE, polytetrafluoroethylene; PSE, portosystemic encephalopathy; PVT, portal vein thrombosis; RCT, randomised controlled trials; TIPS, transjugular intrahepatic portosystemic shunt.

more than 21 days after the index bleed, which may have led to the inclusion of patients with a comparatively low rebleeding and mortality risk, regardless of treatment assignment.[60] Additionally, a recent individual patient-based meta-analysis showed that, in patients with Child-Pugh B/C, EVL monotherapy is associated with a higher mortality rate than combination therapy with EVL and NSBB,[61] although this may not be entirely comparable to the study by Sauerbruch *et al.*[59] in which EVL monotherapy was only used in HVPG non-responders, *i.e.*, patients who are less likely to benefit from NSBB treatment. In the second RCT by Holster *et al.*,[62] 10 mm (dilated to 8-10 mm) PFTE-covered TIPS stents were compared to NSBB (mostly long-acting propranolol) plus endoscopic therapy (EVL or cyanoacrylate). In both studies, patients in the TIPS arms had a lower rate of rebleeding, but a higher incidence of PSE. Importantly, survival was not improved by PFTE-covered TIPS in any of these studies. However, both included a spectrum of patients with a very heterogeneous rebleeding and mortality risk and the inclusion of patients at low risk of death could have limited their ability to detect a survival benefit. Accordingly, whether TIPS placement improves outcomes in selected patients who do not meet the preemptive TIPS criteria or require salvage TIPS, but who are still at high risk of mortality despite the current standard of care, requires further study. This would require reliable risk stratification systems for this specific clinical setting, which are still to be established. Recently, an analysis of the International Variceal Bleeding Observational Study Group of the Baveno Cooperation found ascites and mild hyponatremia/renal function impairment to be the main determinants of mortality,[63] suggesting that these factors may identify the target population for an RCT comparing TIPS to standard therapy. Such refinements may facilitate the design of trials aiming to provide a definitive answer to the question of whether a subgroup of non-high-risk patients with AVB or patients who did not undergo preemptive TIPS for logistical reasons may benefit from a timely TIPS placement for secondary prophylaxis. Finally, the use of adjunctive treatments, *e.g.*, prophylactic rifaximin to prevent post-TIPS PSE,[64] may further improve the safety profile of TIPS in the future, and thus, could affect the risk/benefit assessment. Until then, TIPS should not be used as a first-line treatment to prevent rebleeding.

Similar to rescue/salvage TIPS, the spectrum of patients who will be candidates for secondary prophylaxis is likely to see profound changes following the broad use of preemptive TIPS.

Finally, if secondary prophylaxis with NSBB plus EVL fails, there is a broad consensus that these patients should undergo TIPS placement, as the risk of an additional episode of AVB is very high.[8,46]

Management of GOV-1, GOV-2, IGV, and ectopic varices

In general, treatment strategies for these types of varices are less well-established, given the low number of RCTs, which mostly suffered from small sample sizes. TIPS is not indicated for primary prophylaxis, as both NSBB or cyanoacrylate are sufficiently effective.[8,46] Except for the possibility of cyanoacrylate injection, gastroesophageal varices type 1 (GOV-1: according to the classification by Sarin *et al.*[65]) are treated very similarly to oesophageal varices, and accordingly, the role of TIPS in the treatment of GOV-1 is similar to oesophageal varices.[8,46] However, TIPS is the preferred treatment for AVB from gastroesophageal varices type 2 (GOV-2) and isolated gastric varices (IGV) according to the AASLD clinical practice guidelines, which is partly explained by the lack of FDA approval for cyanoacrylate for this indication.[46] In contrast, Baveno VI recommends NSBB plus endoscopic treatment by cyanoacrylate injection as the first-line treatment strategy for secondary prophylaxis.[8]

Importantly, the previously mentioned considerations regarding preemptive TIPS also apply to patients with GOV-1 and GOV-2, who have been included in the García-Pagán *et al.* trial,[31] while patients with IGV (who seem to be at particularly high risk of bleeding and, possibly, rebleeding[66]) were excluded from this study. However, it is likely that the preemptive TIPS concept may also apply to bleeding IGV.

In patients with bleeding from GOV-2 and IGV type 1 (IGV-1) who have a gastrorenal shunt (or, in experienced centres, even alternative vessels), balloon-occluded retrograde transvenous obliteration (BRTO) may be a therapeutic alternative. Of note, while TIPS is a shunting procedure which may induce/worsen PSE, BRTO closes a shunt, and thus, may aggravate portal hypertension. In line with these pathophysiological considerations, BRTO showed lower rates of HE/PSE (*vs.* TIPS) in the most recent meta-analysis.[67] Interestingly, BRTO was also associated with lower rates of failure to control bleeding and rebleeding.[68] However, except for a small RCT, all of the included studies were observational, some of them showing surprisingly high rates of rebleeding in the TIPS group, which are not in line with the findings of a trial demonstrating the superiority of TIPS *vs.* cyanoacrylate injection in secondary prophylaxis.[69] Although BRTO is recommended for secondary prophylaxis in patients who bled from GOV-2 or IGV according to the AASLD clinical practice guidelines,[46] there is still a need for high-quality studies confirming that BRTO is more effective than cyanoacrylate injection and as effective as TIPS in patients in whom all treatment modalities would be feasible. Nevertheless, BRTO may be a good option for patients considered to be at high risk of post-TIPS PSE or heart failure.[68]

Low-quality evidence indicates that TIPS is effective in controlling bleeding/preventing rebleeding in patients with ectopic varices.[70,71] However, uncontrolled bleeding/rebleeding may occur despite adequate portal pressure reduction and may be managed by embolisation.[70,72] Importantly, treatment decisions in these patients (cyanoacrylate injections *vs.* TIPS *vs.* BRTO) are highly dependent on bleeding site and vascular anatomy and should be individualised based on interdisciplinary discussion.[46]

Portal hypertensive gastropathy

Based on the observations of uncontrolled studies that TIPS placement improves portal hypertensive gastropathy and reduces blood transfusion requirements in the majority of patients,[73] TIPS is considered a good treatment option for patients with significant blood transfusion requirements despite pharmacological (vasoactive drugs for acute and NSBB for chronic bleeding) and endoscopic (most commonly, argon plasma coagulation) treatment.[8]

TIPS for ascites

The mainstay of therapy for uncomplicated ascites is salt restriction and diuretics (a mineralocorticoid-receptor antagonist with or without a loop diuretic).[74] However, this therapy acts downstream of the pathogenic cascade. While it may relieve ascites temporarily, the response to diuretics eventually ceases and ascites becomes 'refractory' requiring repeated large-volume paracenteses (LVP) for comfort. The definition of 'refractory ascites' per the International Club of Ascites (ICA)[75] is quite stringent, defining it as lack of response (weight loss <0.8 kg over

4 days and a sodium output lower than sodium intake) in patients who are on intensive diuretic therapy (spironolactone 400 mg/d and furosemide 160 mg/d) for at least 1 week and salt restriction of <90 mmol (*i.e.*, 5.2 g of salt)/day. It is primarily in these patients that TIPS placement has been explored.

However, there may be intermediate stages between diuretic-responsive ascites and RA. In a recent RCT performed in patients with 'persistent uncomplicated ascites despite ongoing diuretic treatment' that excluded patients with RA, long-term albumin infusions (40 g twice weekly, followed by 20 g weekly) reduced the need for LVP and improved survival.[76] Albumin, through an anti-inflammatory and a volume expansion effect, acts upstream of the pathogenic cascade proving that earlier treatment with a strategy that acts on important pathogenic mechanisms can prevent the development of RA.[77]

Serial LVP is first-line therapy for the treatment of RA.[74,75] With each LVP, concomitant administration of albumin is recommended to prevent paracentesis-induced circulatory dysfunction, an entity associated with faster ascites recurrence, renal dysfunction and higher mortality.[78,79] However, LVP acts even further downstream than diuretics in the pathogenic cascade and therefore recurrence of ascites is the rule.

Besides LVP with albumin (LVP+A), options for the management of RA include TIPS, peritoneo-venous shunting, placement of chronic indwelling peritoneal catheters or catheters connected to the bladder. Of these, TIPS is the one that acts on the pathogenesis of ascites, first by decompressing the hepatic sinusoids and second by expanding effective arterial blood volume by transferring blood from the congested splanchnic circulation to the systemic circulation. In fact, TIPS is currently considered second-line therapy for RA.[74,75]

To date, 7 RCTs have investigated the use of TIPS *vs.* LVP+A for RA (Table 3). The first 6 RCTs[80–85] used uncovered stents, while the most recent study[86] used PFTE-covered stents. Characteristics from these trials were somewhat heterogeneous as shown in Table 3, particularly regarding the results. Although TIPS was associated with improved control of ascites in all RCTs, a survival benefit was demonstrated in only 4 of the 7 RCTs, with the earliest study[80] suggesting that TIPS was associated with increased mortality.

Meta-analysis and/or systematic reviews of the 5 initial RCTs (all of which used uncovered TIPS stents), while showing a decrease in recurrent tense ascites, failed to demonstrate a survival benefit in favour of TIPS and showed an increase in PSE.[87–90] In one of these meta-analyses,[88] meta-regression analysis showed that bilirubin levels and successful TIPS placement rates were associated with survival and identified an outlier trial.[80]

A subsequent individual patient data-based meta-analysis[91] that included individual data from 4 of the trials, excluding the outlier trial, and a more recent meta-analysis including all 6 RCTs that used uncovered TIPS stents[92] showed a survival benefit in favour of TIPS, with improvement in ascites recurrence but with worsening PSE.

Notably, the studies that showed a survival benefit for TIPS were those that included patients with a lower severity of cirrhosis/ascites who did not meet the stringent ICA criteria (Table 3), having included a significant percentage of patients with only 'recurrent'[81] or 'recidivant'[84] ascites – defined in both studies as tense ascites that recurred on at least 3 occasions within a 12-month period despite standard treatment (*i.e.*, not RA as defined by ICA criteria) – or having limited inclusion to patients with Child-Pugh B.[85]

The study by Bureau *et al.*[86] is particularly notable because it is the only RCT to date that has used PFTE-covered stents and included patients who did not meet the strict definition of RA. They included patients with 'recurrent tense ascites' defined as requiring 2 LVP within a minimum interval of 3 weeks and excluded those who had required >6 LVP within the previous 3 months. Results of the study show a significantly better 1-year survival (93%) in the TIPS group compared to the LVP+A group (52%), even considering that almost half of the patients allocated to the LVP+A group had a TIPS placed because of failure of LVP+A. Importantly, it not only showed a decrease in the incidence of treatment failure (requirement of >6 LVP within 3 months) but it also showed no differences in the incidence of PSE, as the 1-year probability of remaining free of PSE was 65% in both groups. It should be mentioned that about half of the patients considered for the trial had to be excluded mainly because of age (>70 years), Child-Pugh score >12 points, or requiring >6 LVP in the previous 3 months. The median MELD in patients included in the study was 12, similar to the median MELD in the long-term albumin RCT.[76] These characteristics should be taken into account when considering TIPS placement for ascites.

Therefore, it would appear that careful selection of patients with ascites that is difficult to treat (but does not necessarily meet ICA criteria for RA) is instrumental in making a decision regarding TIPS placement for ascites.

The main problems associated with TIPS, particularly when placed for the management of ascites, have been shunt dysfunction and the development of PSE. These issues have been ameliorated by addressing stent-related technical issues.

Firstly, the issue of shunt dysfunction has been substantially improved by using stents with a PTFE-coating. Two RCTs have shown improved shunt patency, reduced rates of clinical relapse, and possibly increased survival with PTFE-covered stents in comparison to uncovered stents.[36,37] A third RCT confirmed that PTFE-covered stents are associated with lower rates of shunt dysfunction; however, unlike the others, showed that early post-TIPS complications and mortality were unchanged.[38] Because of a significantly lower rate of shunt dysfunction, PTFE-covered stents are now considered the standard of care and were used in the RCT by Bureau *et al.*[86] In this study only 1 patient had thrombosis of the stent and the 1-year survival rate was 93%, which is higher than the 1-year survival rate of ~80% observed in the TIPS groups of the 2 most recent RCTs that used uncovered stents.[84,85] TIPS dysfunction rates were in the order of 6–23% in these 2 studies. Thus, in addition to better patient selection, the use of covered stents was also a determinant of the observed improvement in outcomes in the study by Bureau *et al.*[86]

Stent diameter also plays a fundamental role in the efficacy and safety of TIPS. Although older studies[93,94] advocated for larger diameter PFTE-covered stents (10 mm), pathophysiologically, the larger the shunt, the greater the probability of developing PSE, a complication that may have an even more profound impact on quality of life than ascites. In a more recent non-randomised prospective study, PSE developed in a significantly lower proportion of patients with TIPS stents that had been under-dilated to a diameter as low as 6 mm (27%) compared to controls who had TIPS stents dilated to nominal diameter (8–10 mm; 54%), without differences in the rate of recurrent variceal bleeding or ascites and without development of stent thrombosis.[95] Similarly, a large RCT[96] recently reported that 8 mm PFTE-covered stents had similar efficacy in preventing variceal

Table 3. Randomised controlled trials of TIPS *vs.* LVP+A for recurrent/RA.

Author	Sample size	Main inclusion criteria	Main exclusion criteria	Safety	Efficacy
Lebrec[80]	25 patients randomised 1:1	Cirrhosis and RA defined by no response to maximal diuretic therapy for 5 days during hospitalisation or 2 or more episodes of tense ascites requiring hospitalisation over the prior 4 months	Age >70 years; HE ≥grade 2; PVT; Biliary obstruction; Serum creatinine >1.7 mg/dl; HCC; Active bacterial infection; Severe non-hepatic disease; Pulmonary hypertension	Increased incidence of PSE in the uncovered TIPS group	2-year OS: 29% *vs.* 56%, favouring LVPs
Rossle[81]	155 consecutive patients evaluated; 60 patients randomised 1:1	Cirrhosis and RA as defined by ICA criteria (55%) or patients with recurrent ascites (45%)	HE ≥grade 2; PVT; Bilirubin >5 mg/dl; Serum creatinine >3 mg/dl; Advanced HCC; Hepatic hydrothorax; Technical failure of paracentesis	No difference in the incidence of PSE	1- and 2-year TFS: 69% and 58% *vs.* 52% and 32% (n.s.), favouring uncovered TIPS; 61% *vs.* 18% had no ascites at 3 months, favouring uncovered TIPS
Gines[82]	119 consecutive patients; 70 patients randomised 1:1	Cirrhosis and RA as defined by ICA criteria	Age <18/>75 years; HE ≥grade 2; PVT; Bilirubin >10 mg/dl; Serum Creatinine >3 mg/dl; Prothrombin index <40%, PLT <40 G/L; CHF; HCC; Parenchymal kidney disease	No difference in the incidence of PSE but more episodes of severe PSE, favouring LVP	1- and 2-year TFS: 41% and 26% *vs.* 35% and 30% in the uncovered TIPS *vs.* LVP groups, respectively (n.s.); Median time to recurrence of ascites of 171 days *vs.* 20 days, favouring uncovered TIPS
Sanyal[83]	525 consecutive patients; 109 patients randomised 1:1	Cirrhosis and RA as defined by ICA criteria; Serum creatinine <1.5 mg/dl	HE ≥grade 2, PVT; Bilirubin >5 mg/dl; INR >2; HCC; Bacterial infection; Alcoholic hepatitis; Cardiopulmonary failure; Pulmonary hypertension; Parenchymal kidney disease; Recent gastrointestinal bleeding; Life-limiting non-hepatic disease	Incidence of moderate to severe PSE: 38% *vs.* 21%, favouring LVP	TFS: 19.6 *vs.* 12.4 months, favouring uncovered TIPS; Lower rate of recurrent ascites in the uncovered TIPS group
Salerno[84]	137 consecutive patients; 66 patients randomised 1:1	Cirrhosis and RA as defined by ICA criteria (68%) or patients with 'recidivant' ascites (32%)	Age >72 years; HE ≥grade 2; Occlusive PVT; Child-Pugh >11 points; Bilirubin >6 mg/dl; Serum creatinine >3 mg/dl; Advanced HCC; Bacterial infection; Cardiopulmonary failure; Recent GI bleeding	Incidence of PSE: 61% *vs.* 39% (n.s.); Greater number of severe episodes per patient, favouring LVP	1- and 2-year TFS: 77% and 59% *vs.* 52% and 29%, favouring uncovered TIPS; Lower rate of treatment failure in the uncovered TIPS group
Narahara[85]	78 consecutive patients; 60 patients randomised 1:1	Cirrhosis and RA as defined by ICA criteria; Child-Pugh <11 points; Bilirubin <3 mg/dl; Serum creatinine <1.9 mg/dl	Age >70 years; Episodes of HE; PV cavernoma; HCC or other malignancy; Active infection; Active severe cardiac or pulmonary disease; Organic kidney disease	Increased incidence of PSE and severe PSE in the uncovered TIPS group	1- and 2-year OS: 80% and 64% *vs.* 49% and 35%, favouring uncovered TIPS; Improved control of ascites and less treatment failure, favouring uncovered TIPS
Bureau[86]	137 consecutive patients; 62 patients randomised 1:1	Cirrhosis; Age >18/<70 years; Recurrent tense ascites requiring at least 2 LVP within the prior 3 weeks	>6 LVPs within the previous 3 months; Expected to receive transplant within the next 6 months or on waiting list; Recurrent overt HE; Occlusive PVT, Child-Pugh >12 points; Bilirubin >5.8 mg/dl; Serum Creatinine >2.8 mg/dl; HCC; CHF; pulmonary hypertension	No difference in rates of overt PSE	1-year TFS: 93% *vs.* 52%, favouring PFTE-covered TIPS; Free of treatment failure: 89% *vs.* 29%, favouring PFTE-covered TIPS

CHF, chronic heart failure; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; IAC, International Ascites Club; INR, international normalised ratio; LVP+A, large-volume paracentesis with albumin; OS, overall survival; PFTE, polytetrafluoroethylene; PLT, platelet count; PSE, portosystemic encephalopathy; PVT, portal vein thrombosis; RA, refractory ascites; RCT, randomised controlled trials; TFS, transplant-free survival; TIPS, transjugular intrahepatic portosystemic shunt.

haemorrhage as 10 mm stents, while decreasing post-TIPS PSE independent of the post-TIPS portosystemic pressure gradient. Furthermore, a recent propensity score-matched study demonstrated improved survival in patients with RA who had PFTE-covered 8 mm stents placed *vs.* those who had 10 mm stents, regardless of under-dilation (or not) to 8 mm.[97] This brings up the issue of whether under-dilated stents expand with time to their nominal diameter. This is also controversial as a study reported that PFTE-covered stents without a controlled expansion sleeve do not dilate to nominal diameter after a mean follow-up time of 8.4 months,[95] while other studies including uncovered stents, with longer follow-up times of 12.7[98] and 26.2 months,[99] found that stents eventually dilate to nominal diameter. Although time could play a role, a prospective study based on

2- and 3-dimensional ultrasound investigations (which were validated against radiographic images) of PFTE-covered stents indicated that 8 mm stents dilate to nominal diameter within 6 weeks of placement.[100]

In conclusion, TIPS is a pathophysiological approach to the treatment of difficult-to-treat ascites that appears to not only ameliorate ascites but also to improve survival, particularly when using PFTE-covered stents.

In light of recent findings, TIPS placement for the management of difficult-to-treat ascites (not necessarily refractory per ICA criteria) is strongly supported when taking into account appropriate patient factors, *e.g.*, an MELD score of around 12.[86] Further studies exploring the use of stents of smaller nominal diameter or under-dilated controlled expansion PFTE-TIPS stents to minimise PSE are eagerly awaited. In the meantime, it would appear advisable to avoid the use of large (≥10 mm) stents for this indication.

TIPS for PVT

In the absence of intestinal ischaemia, anticoagulation is the recommended initial treatment strategy for PVT in patients with cirrhosis, although there is no consensus regarding the exact indication for anticoagulation. This is explained by uncertainties regarding the impact of PV recanalisation on clinical evolution, the high rates of spontaneous recanalisation, and the limited efficacy of anticoagulation. In a recent meta-analysis on the efficacy of anticoagulation in patients with cirrhosis and PVT, PVT progression was observed in 9% of treated patients compared to 33% of untreated patients.[101] Conversely, PV recanalisation occurred in 42% of untreated patients, while the PV recanalisation rate with anticoagulation was 71%. However, the efficacy of anticoagulation substantially decreases in patients with chronic PVT or those who have already developed PV cavernoma.[22] Accordingly, a considerable proportion of patients require add-on/alternative treatments to prevent the progression of PVT and/or to achieve PV recanalisation.

In the setting of acute/recent non-malignant PVT, TIPS is indicated in patients with contraindications for or progressive PVT despite anticoagulation,[25] especially if the patient is a transplant candidate.[24] In addition, patients with chronic PVT who have complications of portal hypertension that are refractory to medical treatment may be evaluated for TIPS placement ±recanalisation of the porto-spleno-mesenteric axis. Performing TIPS in the setting of acute/recent PVT is usually not a major technical challenge and is associated with high success rates. However, the situation changes in the setting of chronic PVT. Nevertheless, a recent meta-analysis by Rodrigues *et al.*,[102] in which 92% of included patients had cirrhosis, 87% had chronic PVT, and 17% had PV cavernoma, found that TIPS (±additional endovascular therapies ± anticoagulation) was technically feasible in 95% of patients, resulting in a PV recanalisation rate of 79% at 12 months. However, in most studies included in this meta-analysis, PVT itself was not the indication for TIPS. In this context, it is important to note that the number of patients with chronic PVT who were not even considered for TIPS and in whom the technical success rate may have been substantially lower, remains unknown. The presence of a PV cavernoma or chronic thrombosis of the intrahepatic PV branches is linked to low technical success of TIPS placement,[102] however, a single centre experience from the United States indicated excellent results using a PV recanalisation technique[103] that included transsplenic, and in rare cases, percutaneous transhepatic punctures.[104,105] The final cohort comprised 66 patients of whom 80% and 20% had Yerdel grade 2 and 3 PVT, respectively, and 48% had a PV cavernoma.[106] The technical success rate was 98% and TIPS/PV patency was maintained in 92% of patients, at a median follow-up of 19.2 months. This series indicates that, even in technically challenging cases, excellent results are achievable in highly specialised centres. Since end-to-end anastomosis was feasible in 96% of patients who underwent liver transplantation in the latter series, this report also suggests that pre-transplant recanalisation of the porto-spleno-mesenteric axis may decrease the need for surgical recanalisation or non-physiological PV reconstruction at the time of liver transplantation,[107] and thus, may even improve post-transplant outcomes.

Moreover, TIPS may be indicated for the treatment of complications of portal hypertension. Two RCTs[108,109] compared the efficacy of TIPS with propranolol plus EVL for the secondary prophylaxis of AVB in patients with PVT. In both studies, patients who were randomised to the TIPS arm had lower rates of rebleeding and a higher PV recanalisation rate, without increasing the risk of HE. However, like secondary prophylaxis studies conducted in patients without PVT, TIPS did not improve survival, although both studies observed numerically lower mortality rates in the TIPS arm.

TIPS prior to extrahepatic surgery ('preoperative TIPS')

Surgery, particularly major surgery, is one of the precipitants of acute decompensation and ACLF in cirrhosis and postoperative mortality correlates with severity of liver disease. This relationship was first described by Child and Turcotte in 1964 in the setting of portocaval shunt surgery.[110] To this day the Child-Turcotte classification modified by Pugh (substituting nutritional status with international normalised ratio) is one of the most commonly used scoring systems in the assessment of surgical risk.[111] Portal hypertension, specifically CSPH, has been associated with increased rates of hepatic decompensation after hepatic resection for HCC.[112] In a recent prospective study, HVPG was an independent predictor of mortality at 1 year after extrahepatic surgery in 140 patients with cirrhosis, with HVPG values ≥16 mmHg indicating a high surgical risk.[113] Even though increasing portal pressure is an indicator of cirrhosis severity, it has been proposed that preoperative TIPS placement, by lowering portal pressure, would result in better postoperative outcomes. This would appear rational in intra-abdominal or oesophageal surgery where there would be a higher surgical risk of bleeding in the presence of portal hypertension. Unfortunately, no prospective trials have been performed in this setting. Recent reviews of mostly uncontrolled studies suggest that preoperative TIPS is safe.[114,115] The largest comparative study, not included in these reviews, comprised 134 patients (56 preoperative TIPS, 68 no TIPS) among 4 centres in France.[116] In this study, the only difference in outcomes was a lower incidence of postoperative ascites in the TIPS group, although patients who received TIPS had more advanced cirrhosis than controls. The rates of severe complications and 90-day mortality were similar. No study has shown a survival benefit in favour of preoperative TIPS, but prospective studies with risk-matched controls are required before conclusions can be made regarding the role of TIPS in the preoperative setting.

Further risks/benefits of TIPS in cirrhosis

In addition to procedure-related complications and hepatic failure, the main post-TIPS risks are PSE and cardiac decompensation. It is important to mention that recent RCTs of preemptive TIPS[31,32] or TIPS for difficult-to-treat ascites[86] have excluded patients older than 70–75 years, with Child-Pugh score >12–13 points, recurrent overt HE without precipitating factors, heart failure, pulmonary hypertension, serum creatinine above ~3 g/dl, HCC, sepsis and occlusive PVT. Current clinical practice guidelines[74] recommend against TIPS placement for ascites in patients with HE ≥grade 2 (*i.e.*, overt HE[117]) or patients with 'chronic HE', which is in line with most RCTs in the context of secondary prophylaxis or ascites. However, the term 'chronic HE' leaves some room for interpretation. In our practice, we usually do not consider patients with a history of recurrent overt HE episodes without an identifiable precipitating factor for elective TIPS placement. Poor liver function is the main determinant of post-TIPS PSE and vulnerable patients may benefit the most from the avoidance of aggressive portal pressure gradient reduction,[118] and possibly, the use of low-diameter or under-dilated stents (see the 'TIPS for ascites' section). Importantly, more specific predictors of post-TIPS PSE than indicators of liver function would be desirable to facilitate risk stratification/patient selection, and thus, personalised therapy. Critical flicker frequency[119] and other tests for covert HE[120] have been shown to predict post-TIPS PSE, however, generally agreed criteria are lacking. Another approach to lower the burden of post-TIPS PSE is to offer preventive treatment. Although a small (n = 65) RCT by Riggio and colleagues[118] observed similar rates of post-TIPS PSE in patients receiving lactulose, rifaximin, or placebo, a more appropriately powered RCT, recently presented by Bureau *et al.*,[64] found that rifaximin prevented the occurrence of post-TIPS PSE (39.3% *vs.* 65.8%) within 6 months after TIPS placement. Interestingly, the use of rifaximin even increased survival in the latter study. However, the results of this study, which reported a strikingly high incidence of post-TIPS PSE, have yet to be fully published. Sarcopenia has been identified as a risk factor in the development of post-TIPS PSE.[121] Interestingly, one of the benefits of TIPS that goes beyond variceal haemorrhage or ascites is a significant improvement in skeletal muscle area or mass.[122–124] In turn, patients who experience a significant improvement in muscle mass after TIPS are less prone to develop PSE[125] and even show increased survival.[126]

Another important, albeit, poorly defined complication is cardiac decompensation post-TIPS. As a consequence of the profound haemodynamic changes occurring directly after the intervention (increases in cardiac output and right heart pressures[127]), elective TIPS placement is contraindicated in patients with severe systolic or diastolic dysfunction, or pulmonary hypertension.[128] Although challenging, cardiac assessment is important because a relevant proportion of patients with decompensated cirrhosis have cirrhotic cardiomyopathy, as defined by a blunted contractile response to stress and an altered diastolic relaxation.[128] Specifically, diastolic dysfunction is highly prevalent and has repeatedly been linked to poor outcomes after TIPS,[129,130] although this has not been confirmed in another study.[131] Recently, Billey *et al.*[132] developed the 'Toulouse algorithm' for predicting post-TIPS cardiac decompensation based on a cohort of prospectively characterised patients who underwent a detailed cardiac evaluation (measurement of brain natriuretic peptide (BNP) and the N-terminal fragment of its prohormone (NT-proBNP), electrocardiogram, and echocardiography) before undergoing elective TIPS placement. Overall, 20 out of 100 patients developed cardiac decompensation within 1 year of follow-up, which translated into decreased survival. While patients with BNP/NT-proBNP values <40 pg/ml/<125 pg/ml, normal left ventricular systolic function, and no evidence of pulmonary hypertension or aortic stenosis (31% of the study population) were not at risk of developing cardiac decompensation, patients with elevated enzymes and echocardiographic indicators of moderate/severe diastolic dysfunction (37% of the study population) showed a high risk (19 out of 37 patients developed cardiac decompensation). Moreover, patients with aortic stenosis had a particularly high risk, raising the question of whether TIPS should be deferred in these patients, or whether they should undergo transcatheter aortic valve replacement prior to elective TIPS placement.[132]

In conclusion, even in patients without contraindications for elective TIPS placement, post-TIPS PSE and cardiac decompensation remain important safety concerns. Accordingly, there is an unmet need for well-validated risk stratification systems for both outcomes and multicentre studies which prospectively characterise patients who undergo a standardised evaluation, procedure, and follow-up.

Abbreviations

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ARR, absolute risk reduction; AVB, acute variceal bleeding; BNP, brain natriuretic peptide; BRTO, balloon-occluded retrograde transvenous obliteration; CHF, chronic heart failure; CLD, chronic liver disease; CSPH, clinically significant portal hypertension; EVL, endoscopic variceal ligation; GOV, gastro-oesophageal varices; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; ICA, International Club of Ascites; IGV, isolated gastric varices; INR, international normalised ratio; ISMN, isosorbide mononitrate; LVP, large-volume paracenteses; LVP+A, LVP with albumin; MELD, model for end-stage liver disease; NNT, number needed to treat; NSBB, non-selective beta blocker; OS, overall survival; PCI, percutaneous coronary intervention; PFTE, polytetrafluoroethylene; PLT, platelet count; PSE, portosystemic encephalopathy; PV, portal vein; PVT, portal vein thrombosis; RA, refractory ascites; RCTs, randomised controlled trials; SBP, spontaneous bacterial peritonitis; SEMS, self-expandable metallic stent; TFS, transplant-free survival; TIPS, transjugular intrahepatic portosystemic shunt.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Review concept: J.C.G.-P. and G.G.-T; Drafting of the key points as well as the introduction, bleeding, portal vein thrombosis, and risk/benefit chapters: M.M.; Drafting of the summary as well as the introduction, ascites, and preoperative transjugular intrahepatic portosystemic shunt chapters: S.S.; Revision: all authors; Approval of the final version: all authors.

Supplementary data

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Author names in bold designate shared co-first authorship

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