TIPS: 25 years later

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Summary

In the 25 years since the first TIPS intervention has been performed, technical standards, indications, and contraindications have been set up. The previous considerable problem of shunt failure by thrombosis or intimal proliferation in the stent or in the draining hepatic vein has been reduced considerably by the availability of polytetrafluoroethylene (PTFE)-covered stents resulting in reduced rebleeding and improved survival. Unfortunately, most clinical studies have been performed prior to the release of the covered stent and, therefore, do not represent the present state of the art. In spite of this, TIPS has gained increasing acceptance in the treatment of the various complications of portal hypertension and vascular diseases of the liver.

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Introduction and history of TIPS

In 1969 already, Joseph Rösch et al. first described an interventional technique to establish a transjugular intrahepatic portosystemic shunt in dogs by implanting a silicone-coated spring coil to achieve patency for as long as 2 weeks [1,2]. These early experiments were continued by creation of a TIPS in cirrhotic livers and in cadavers [3]. In the late ’70s, Burgener and Gutierrez [4] constructed shunt tracts in dogs with portal hypertension by balloon dilatation of the parenchymal track that normalized the elevated portal pressure, but occluded within 1 week. In 1982, Colapinto and Gordon were the first to apply this technique clinically in more than 20 patients [5,6]. The long-term results were, however, not encouraging and most patients rebled and 9 died within a month.

With the introduction of expandable metallic stents in the mid-1980s by Palmaz, high long-term patency rates were achieved by implanting such stents in cirrhotic livers of dogs [7,8]. Based on own experiences in hepatic vein catheterization and transjugular liver biopsies, the Freiburg TIPS project was started in 1987 after its approval by the local ethics committee. With the help of J. Palmaz, the first TIPS procedure with implantation of a metallic Palmaz-stent was performed in Freiburg in 1988 and 9 more procedures followed in the same year [9–13]. Of the 10 patients who were intended to treat, TIPS could be implanted successfully in 7. Two of these 7 patients died early. Interventions lasted an average of 8 hours and consisted of a transjugular as well as a percutaneous transcostal approach to place a metallic target (Dormia bascet) in the right branch of the portal vein. Due to complications and technical difficulties in establishing the TIPS, the project was discontinued until spring 1990 when Jean Marc Perarnau from Metz, France, joined our group. With his improved puncture technique including sonographic targeting of the portal vein, we were able to perform the procedure in its present form within 1 to 2 hours with a considerably reduced complication rate [14]. This was the start of a series of about 50 patients treated within 1990 and 500 patients treated until 1995 in Freiburg. A summary of the early results of the 2 leading centers at this time, Freiburg and San Francisco, was published in 1993 [15].

The last decade of the millennium was devoted to technical problems solving and to performing numerous randomized clinical studies [16]. Finally, patients’ selection and the definition of the best indications have been worked out and discussed in consensus conferences [17,18]. Steady adaptation of this process is necessary to include new results obtained with increasing experience and new technical facilities such as covered stents.

The present review concentrates on specific technical aspects and clinical implications based on former and actual study results.

Technical considerations

Pre-interventional measures

Before TIPS implantation, hepatic functional insufficiency and clinically overt hepatic encephalopathy should be excluded. A duplex examination should exclude portal and hepatic arterial abnormalities. Road mapping by CT or MRI is not routinely necessary but may help facilitate the anatomical orientation. In patients with suspected or known cardiac disease, an echocardiography should be performed to exclude significant diastolic or systolic cardiac failure. In patients with refractory ascites or hydrothorax, paracentesis and/or thoracentesis should be performed. This may reposition the liver from a more transversal into a more frontal posture, facilitating the portal puncture. It also improves the quality of the fluoroscopic picture and reduces

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the radiogenic exposure of the patient and physician. In addition, the respiratory function improves and facilitates sedation.

Intervention

The technical performance of the TIPS procedure may be somewhat different in the US and Europe where not only Radiologists but also Gastroenterologists have given their input. Thus, many centers in Europe use sedation with midazolam, piritramide, and propofol while in the US general anesthesia with endotracheal intubation is preferred [19]. In addition, sonographic targeting is commonly performed by Gastroenterologists while Radiologists often trust preinterventional imaging [17]. For the creation of the TIPS procedure, two puncture sets are presently in use: the modified open Colapinto or Ross needle with an adapted multipurpose catheter and a closed coaxial system where a stylette is advanced through a canula. The open needle is relatively expensive and allows rapid execution of the puncture. With its use, complete TIPS procedures have been performed in less than 20 min. The closed coaxial needle set is more expensive, more complex, and time consuming, but may be less invasive. Studies comparing the two equipments have not been performed so far.

After an appropriate branch of the intrahepatic portal vein has been punctured, a guidewire followed by a pigtail catheter is introduced into the splenic vein and portal venography and pressure measurements are performed. If present and indicated, collaterals are now occluded using bucylate, coils or Amplatz plug. The parenchymal track is then dilated and a stent is placed. To avoid shunt related complications, stents with a nominal diameter of 10 mm should be employed but dilated only to 8 mm. This may result in a more limited pressure reduction, not always achieving the recommended threshold of 12 mmHg [19–22], but possibly reducing the rate of TIPS-induced hepatic encephalopathy [22,23]. In case of insufficient response, further pressure reduction can be achieved by a second intervention. However, no studies are available showing that the presently preferred self-expandable stents with a nominal diameter of 10 mm keep the reduced diameter over time. This certainly depends on the radial forces of the stent and compliance of the cirrhotic liver, both may differ to a great extent. Stents with low radial forces (e.g., Viatorr) may be preferred.

A final portography and pressure measurement in the main portal vein and the right atrium are performed. In contrast to the measurements of the pressure gradients performed and published in studies investigating the effect of drugs, the free hepatic vein pressure measurement is usually replaced by the measurement in the right atrium. Measurement in the hepatic vein after TIPS is compromised by the stent and the high flow in the hepatic vein. Instead, measurement in the inferior caval vein at the level of the hepatic veins has been suggested [24]. However, the location of the tip of the catheter straight below the right atrium is often difficult and distinction between the upper part of the caval vein and the right atrium is not always possible. Therefore, in the setting of TIPS, most investigators measure the porto-atrial gradient which is slightly higher than the gradients obtained between the portal vein and the hepatic or inferior caval veins.

Should anticoagulation or antibiotics be provided during or after the TIPS procedure? This is an open question which has often been discussed. The advantage of platelet aggregation inhibitors has been demonstrated for bare stents [16,25]. Our present approach is to treat patients with bare stents and with higher platelet count (e.g., >100 000/µl) with acetylic salicylic acid (100 mg/day). Whether this strategy can also be recommended for covered stents is not investigated so far. Their introduction led to marked decrease in shunt dysfunction [15% vs. 44%], and a lower rate of clinical relapse [10% vs. 29%] [26,27]. However, it should be noticed that the advantage diminishes with time to require shunt revision of about 50% after a 5-year follow-up [28]. Post-interventional infection has been observed in up to 20% of patients and prophylactic antibiotic with Ceftriaxone [29], but not with Cefotiam [30], has been suggested. In addition, infection of the stent lumen, named “endotipsitis”, has been described with a calculated incidence of 1.3% [31,32]. It can be assumed that, in the meanwhile, the incidence of post-interventional infection decreased by better technical skills (fewer catheter exchanges), questioning the usefulness of prophylactic antibiotics. However, complicated procedures requiring many changes of catheters and sheaths may have a higher rate of infection, justifying prophylactic antibiotic treatment.

The early post-procedural setting consists of monitoring of the blood pressure, haemoglobin/hematocrit and maybe urine volume during 24 hours. With few exceptions, intensive care is not necessary. In general, in patients with variceal bleeding, ß-blockers are withdrawn and in patients with refractory ascites, diuretic medication is reduced by half. A Duplex-sonographic examination is performed before patient’s discharge.

The “direct” TIPS

In patients with a Budd-Chiari syndrome, the catheterization of a hepatic vein may not be possible. In these as well as in the rare patients with unaccessible hepatic veins, a direct puncture through the inferior caval vein may be inevitable. A series of 40 patients with direct TIPS (DIPS) using intravascular ultrasound has been reported showing a high success and patency rate [33,34]. Another technique of a direct TIPS, which was applied to 11 patients with Budd-Chiari syndrome, used a percutaneous transabdominal approach to the left portal branch which was then extended to the inferior caval vein [35].

Technical complications

Unfortunately, prospective studies investigating the technical complications are not available. Perforation of the liver capsule without or with intraperitoneal hemorrhage has been described in 33 and 1–2% of the procedures, respectively [19]. However, in centers using sonography during the puncture process, these complications are almost abolished. The same is true for clinically significant hemobilia or hemolysis, complications which have been seen more frequently at the beginning of the TIPS era [16]. With the use of modern stents, stent misplacement or migration is also very rare. Frequencies of 20% proximal or distal displacement given in a recent review [20] are, in our experience, unusual. In particular, the Viatorr stent is designed to be placed with great accuracy and misplacement is almost impossible (Fig. 1).

Long-term follow-up

Doppler ultrasound is the most valuable means to estimate shunt function. The parameters which should be evaluated before and after TIPS implantation are summarized in Table 1. In general, the pre-procedural low-flow velocity in the portal vein (Vmax: 10–20 cm/sec) increases by TIPS by a factor of 2–4 to
40–60 cm/sec [36–41]. A post-TIPS portal vein flow velocity of less than 30 cm/sec suggests shunt insufficiency. The flow velocity in the stent is expected to be between 80 and 160 cm/sec shortly after TIPS. Values below 60 or above 180 cm/sec indicate shunt insufficiency. In particular, any value lower than 40 or higher than 200 cm/sec clearly indicates shunt malfunction [41]. It should be emphasized that measurements in the stent-shunt or in the draining hepatic vein are only reliable in cases of simple stenoses (Figs. 2 and 3). In cases with a complex structure of the intimal proliferation in the stent or in the draining hepatic vein, the measurements are not reliable and normal values cannot exclude stenosis (Figs. 2 and 4). Therefore, in case of normal values within the stent, the findings in the portal vein define whether shunt function is sufficient or not. In addition, a change in flow direction of the intrahepatic portal branches from retrograde shortly after TIPS to prograde may also be a good qualitative indicator of shunt malfunction [37]. If simple stenosis is seen, the Bernoulli equation ($\Delta p = 4 v^2$) can be applied to calculate the pressure gradient $\Delta p$ (in mmHg) across the stenosis from the flow velocity measured in the stenosis ($V_{\text{max}}$ in m/sec).

Accordingly, a flow velocity ($V_{\text{max}}$) of 180 cm/sec (1.8 m/sec) indicates a pressure gradient across the stenosis of 13 mmHg. It could be demonstrated that calculated gradients using the Bernoulli equation closely correlate with gradients determined by catheter measurement ($r = 0.84$) [41].

When TIPS dysfunction is suspected, revision is not generally indicated in the absence of clinical symptoms. In patients with previous variceal bleeding, the decision should be based on the endoscopic verification of significant varices. Certainly, revision should not be performed in patients who developed severe liver failure or hepatic encephalopathy at the time of TIPS patency. If the original TIPS was created using a bare-metal stent, a covered stent should now be implanted [42].

### Major adverse events, limitations, and contraindications

#### Hepatic function

Due to the diversion of portal venous flow, an increase in bilirubin concentration is frequent due to decreased liver perfusion while albumin or INR is not affected [43–45]. A small study including 15 patients investigated the effect of TIPS on aminopyrin breath test, monoethylglycinexylidide test (MEGX), bilirubin, albumin, and PT-time. Compared to values obtained before TIPS, no significant changes were seen 1, 3, and 6 months after TIPS [45]. Nevertheless, few patients develop severe liver failure characterized by a rapid increase in bilirubin concentration. They require immediate TIPS occlusion to prevent death. Fortunately, the loss or reduction of the portal perfusion by TIPS induces an immediate rise in the arterial blood flow which is known as the arterial buffer response [46]. This explains why TIPS-induced hypoxic damage of the liver is a rare exception. Thus, endoluminal flow measurements showed an immediate increase in the arterial liver perfusion from 599 ± 100 ml/min to 749 ± 161 ml/min when the TIPS is opened [47].

#### Hepatic encephalopathy (HE)

The incidence of HE after TIPS varies from 15% to 48% [48–55]. In controlled trials comparing TIPS with medical treatment for

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### Table 1. Duplex-sonographic findings obtained from the literature [36–41] before and after TIPS and values indicating shunt failure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before TIPS</th>
<th>Patent shunt</th>
<th>Shunt failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Portal vein</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow velocity ($V_{\text{max}}$, cm/sec)</td>
<td>15</td>
<td>40</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Direction of intrahepatic flow</td>
<td>Hepatopedal (90%)</td>
<td>Hepatofugal (90%)</td>
<td>Hepatopedal</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Flow (ml/min)</td>
<td>800</td>
<td>1800</td>
<td>&lt;1200</td>
</tr>
<tr>
<td><strong>Stent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow velocity ($V_{\text{max}}$, cm/sec)</td>
<td>110</td>
<td>&lt;50, &gt;180</td>
<td></td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow (ml/min)</td>
<td>1600</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic vein</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow velocity ($V_{\text{max}}$, cm/sec)</td>
<td>&gt;180</td>
<td></td>
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</table>
variceal bleeding, the incidence of HE was always greater in patients who received a TIPS [56–58]. In patients with ascites, a recent meta-analysis of individual patient data showed that the cumulative probability of developing a first episode of HE during follow-up was not different between TIPS and paracentesis groups \((p = 0.36)\) [59]. However, patients allocated to TIPS had significantly more episodes of HE with regard to both total number of episodes \((1.13 \pm 1.93 \text{ vs. } 0.63 \pm 1.18, p = 0.006)\) and number of severe episodes \((0.68 \pm 1.0 \text{ vs. } 0.24 \pm 0.50, p = 0.008)\). It should be pointed out that most studies were not designed to investigate HE [60]. Longitudinal cohort studies may be biased by comparing a retrospective evaluation before TIPS (past history of HE together with the assessment at index hospitalization) with a prospective evaluation after TIPS. In addition, evaluation of HE was performed by subjective measures (e.g., New Haven criteria) and unblinded investigators, a fact which may have influenced the result. The study by Kircheis et al. using the critical flicker frequency test [61] showed a stable HE-severity in the control group (no TIPS) while patients with TIPS showed no change in HE-severity in 44%, deterioration in 35%, and improvement in 21% of the patients. Thus, while controls remained stable, TIPS had a considerable potential to deteriorate HE but also a chance for its improvement.

Prediction of HE is difficult since many variables are involved. Most often, increased age, advanced liver failure (expressed by elevated bilirubin), a history of encephalopathy before TIPS insertion, and low serum sodium concentration have been found to predict HE [49–51,53]. In patients with an acute bleed, predictors other than biometrical ones have limited value since the bleeding may affect psycho-neurological performance.

While primary factors (liver function and blood flow) inducing HE are expected to be worsened by the shunt, the shunt may improve some secondary factors such as the mean arterial pressure, serum sodium concentration, renal function, and nutrition [62,63]. In contrast to serial paracentesis, TIPS leads to a significant improvement of these parameters including total body nitrogen and total body protein [64–66], muscle mass, and albumin concentration [67].

For prevention of HE, attempts have been made to limit shunting by reducing the diameter of the shunt. As demonstrated recently, 25 out of 27 patients who developed HE after TIPS implantation had a pressure gradient of <12 mmHg [22]. Thus, in patients with a higher risk of HE (and/or poor liver function), the portosystemic pressure gradient should be decreased with great caution by implantation of small stents. Surprisingly, a study comparing 8 vs. 10 mm diameter covered-stent TIPS could not show a difference in HE between groups although the pressure gradient was higher in the 8 than in the 10 mm group (8.9 vs. 6.5 mmHg) [68]. The study was discontinued preterm because of unsatisfactory efficiency of the 8 mm TIPS and did, therefore, not reach a sample size necessary to assess differences in HE. Prevention with drugs was studied recently showing no effect of lactitol or rifaximin vs. no treatment [69].

Treatment of HE is medical including ornithin-aspartate, branched chain amino acids, lactulose, and xifaxan [70]. In patients receiving diuretics, exsiccosis is frequent and should be ruled out. In refractory cases, shunt reduction by placement of an hourglass-shaped ePTFE covered reducing stent led to an immediate increase in the pressure gradient and to long-term improvement of HE in all patients [71]. A more sophisticated and variable approach has been reported recently [72]. Two stents were released within the original stent-shunt. One of the stents is a covered stent which remains patent. The other stent is bare and short and placed besides the covered stent. The final flow volume through the covered stent can be adjusted by expansion of the bare stent. In view of the encouraging results with the...
of 18 or less [79–81]. However, as shown in patients with refractory ascites, a MELD score above 18 predicts a significantly higher mortality [59]. In patients with MELD scores between 10 and 20, the estimated mortality was always better in the TIPS than paracentesis groups [59]. With MELD scores between 10 and 20, the estimated mortality was always better in the TIPS than paracentesis groups [59].

hourglass-stent and a potential risk of stent migration, the need and advantage of this latter procedure seem to be questionable.

Limitations and contraindications

Older age, pre-TIPS HE and bilirubin >3 mg/dl are the most significant predictors of outcome and may be used as relative contraindications [16,43,73–76]. In addition, a number of scores predicting outcome after TIPS have been investigated [77–81]. Thereby, the MELD score [77] including bilirubin, creatinine and INR, was found to be superior to the Child-Pugh score at predicting post-TIPS mortality [78,80], or the Emory score [79]. A MELD score above 18 predicts a significantly higher mortality 3 months after TIPS, compared with patients with MELD scores of 18 or less [79–81]. However, as shown in patients with refractory ascites, a strong correlation between mortality and MELD-score was also found in paracentesis patients [59]. In patients with MELD scores between 10 and 20, the estimated mortality was always better in the TIPS than paracentesis groups [59]. Therefore, the MELD score cannot reliably guide the decision for or against TIPS treatment in patients with refractory ascites.

Cardiac disease and moderate to severe pulmonary hypertension are also regarded as contraindications for TIPS. Recently, the E/A ratio, an indicator for diastolic dysfunction, has been found to predict survival after TIPS [82]. A pre-TIPS reduced E/A ratio was correlated with reduced ascites clearance after TIPS (HR 7.3, p <0.021) and increased post-TIPS mortality (HR 4.7, p <0.035) [83]. The presence of diastolic dysfunction (E/A ratio <1) 28 days after TIPS was associated with poor survival (HR 8.9, p <0.005) [84]. Thus, cardiac failure contributes to mortality after TIPS implantation and, therefore, the determination of the E/A ratio before and after TIPS insertion may be recommended to better adjust its indication and post-TIPS surveillance. In this context, the pro-brain natriuretic peptide (proBNP) and BNP concent-

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centrations may also be of diagnostic value [85], but are not sufficiently assessed as predictors of response and mortality in TIPS patients so far.

Irrespective of the predictors used, they are not suitable to decide pro or contra TIPS or continuation of the standard treatment. They can only be used to advise the patient about the expected outcomes and to decide on the urgency for liver transplantation. In any case, adverse events and contraindications are rarely absolute and they need always to be balanced against the urgency of treatment escalation.

Key Points 1

• Improvement of skills and stents reduced complications and improved patency
• Hepatic encephalopathy is still the major problem of TIPS. To further reduce its incidence, small shunts (8 mm) using covered stents with a nominal diameter of 10 mm are recommended and further dilatation should be delayed until needed. More studies are needed to further support this recommendation
• TIPS has gained an advanced position in the treatment of patients with acute variceal bleeding with high risk of early rebleeding. Variceal embolization together with TIPS implantation may be recommended in patients bleeding with low pressure gradients, but additional studies are necessary
• The role of covered-stent TIPS in the secondary prophylaxis of variceal bleeding needs to be investigated. Until then, TIPS is a second line treatment after medical treatment failed

Indications for TIPS

TIPS has been used to treat most of the complications of portal hypertension. Randomized controlled trials are available for variceal bleeding and refractory ascites, whereas other indications have been evaluated in uncontrolled studies only.

Bleeding indications

Acute esophageal variceal bleeding

Two recent randomized studies and one retrospective surveillance study compared TIPS with medical treatment for acute bleeding [Fig. 5] [86–88]. The first study by Monesello et al. [86] included high risk patients with a pressure gradient above 20 mmHg measured within 24 hours after admission to receive an early bare-stent TIPS (n = 26) or medical treatment (n = 26). Compared with the medical group, the TIPS group had a significantly better outcome with respect to treatment failure, transfusions, need for intensive care, and in-hospital and 1-year mortality. In spite of the clear result of this study and possibly due to lack of respective facilities, consensus statements were not adapted and everyday clinical practice was not influenced.

The second study by García-Pagán et al. [87] used a more clinical approach for patients’ selection. High-risk patients with Child-Pugh class B and acute variceal bleeding at index endoscopy or class C were randomized within 72 h after admission to
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receive a covered stent TIPS or medical treatment using B-blocker plus nitrate or endoscopic band ligation if unresponsive to drugs. The early TIPS group had a significantly lower rebleeding rate (3% vs. 45%) and better survival (1-year: 87.5% vs. 61.3%) (Fig. 5). Surprisingly, the incidence of HE was lower in the TIPS group possibly due to the lower rate of rebleedings. The results of the study were confirmed by a post-RCT surveillance study [88] (Fig. 5). In addition, a recent economic modelling of early TIPS in high risk patients with acute variceal bleeding showed cost effectiveness of the TIPS procedure compared to standard therapy [89]. Consequently, the Baveno V conference in 2010 recommended considering early TIPS (within 72 h) in patients with high risk of treatment failure [90].

Prophylaxis of rebleeding

Most randomized studies comparing TIPS with medical treatment for prevention of rebleeding were performed in the 1990s using bare metal stents. A total of 13 RCTs including 948 patients were published and analysed. Rebleeding was reduced after insertion of TIPS (9–40.6%) compared to medical therapy (20.5–60.6%) [56–58]. However, there was a more than twofold increase in the rate of development of hepatic encephalopathy after a TIPS procedure. Mortality was comparable between the TIPS and endoscopic/medical therapy groups. Since HE was considered to have a greater negative impact than rebleeding on quality of life, medical treatment was regarded as first line treatment in the prevention of variceal rebleeding [18,90]. It should be emphasised that, at this time, bare stents were used exclusively and dilated to up to 12 mm.

Variceal embolization

A prospective study found that embolization together with TIPS implantation significantly reduced rebleeding during a 4-year follow-up (29% vs. 47%) although patients receiving additional embolization had higher post-TIPS pressure gradients [91]. A controlled study confirmed these findings with 1-year rebleeding rates of 19.5% in the TIPS plus embolization group compared to 41.5% in the TIPS group [92]. Both studies show unusually high rebleeding rates questioning their quality with respect to the shunt as well as the follow-up. Thus, additional studies are necessary before variceal embolization can be recommended as a valuable adjunct to TIPS treatment. To avoid reflux of bucrylate into the portal vein, embolization with bucrylate should be performed prior to implantation of the stent. After embolization, the patient may exhibit upper abdominal pain probably due to phlebitis.

Gastric variceal bleeding

Bleeding from gastric varices often occurs with a low portal pressure gradient [93]. In these patients, the rationale for a decompression alone may not be given and TIPS alone without embolization may not be the optimal solution. This is confirmed by the finding that TIPS improved mortality only in patients with pre-TIPS pressure gradients above 12 mmHg [93]. Nevertheless, TIPS was superior to endoscopic embolization as demonstrated in a controlled study [94].

Rare bleeding indications

Rare bleeding sites are ectopic varices, portal hypertensive gastropathy, stomas or conduits or hemorrhoidal bleeding. Local treatments are often impossible and inefficient. Therefore, the transjugular approach can be used to embolize the feeding vessel and to implant a small diameter TIPS to facilitate reintervention in case of rebleeding [95,96]. The use of TIPS for bleeding from portal hypertensive gastropathy is not proven but case reports suggest that TIPS may control bleeding in these patients [97]. In contrast, chronic bleeding from gastric antral vascular ectasia (GAVE) could not be successfully managed by TIPS [98].

Ascites and related complications

The treatment of refractory or recidivant and tense ascites and its associated complications has changed considerably during recent years. Large volume paracentesis (LVP) has been shown to be safe, easy to perform, and has the advantages of immediate relief of complaints and reduced duration of hospitalization [99]. It has, however, a negative effect on systemic hemodynamics and renal function [100] which often limits its use as a long-term treatment. In contrast, TIPS offers a treatment option which even improves renal function and systemic hemodynamics as well. As summarized in a recent review [73], within 4 weeks after TIPS, urinary sodium excretion and serum creatinine improve significantly and can normalize within 6–12 months. This is associated with an increase in serum sodium concentration, urinary volume, and glomerular filtration rate together with a normalization of plasma renin activity, aldosterone, and noradrenaline concentrations during 4–6 months of follow-up (Fig. 6). In addition, 6 studies showed normalization of renal hemodynamics during a 12-month follow-up after TIPS [101–106]. These findings strongly suggest that TIPS reverses the hyperdynamic circulation and ameliorates central underfilling. Most likely, this is due to redistribution of local resistances allowing the renal resistance to decrease.

The effect of TIPS on redistribution of local resistances is shown in Table 2. The values for total, splanchnic, hepatic/portal, and renal resistances are calculated from variables (pressure gradients ΔP, and flow volumes F) obtained from the literature [101,106–111]. The splanchnic and hepatic/portal resistances have a serial arrangement while peripheral, renal, and splanchnic/hepatic resistances are arranged in parallel. The inverse value (1/R) [Table 3] represents the conductance (C = F/ΔP) which is, in contrast to the resistance, additive in parallel. As shown in Fig. 7, TIPS has a great influence on local conductances. The total vascular conductance markedly increases (i.e., decreasing resistance), shortly after opening of the TIPS, due to an almost unrestricted flow through the splanchnic bed. With time, the splanchnic/ hepatic conductance decreases (increasing resistance) but remains above the pre-TIPS level. The peripheral conductance decreases allowing the renal conductance to increase. Thus, circulatory dysfunction gradually resolves by portal decompression as it arose by portal hypertension.

Efficacy

A recent analysis of the literature on TIPS for refractory ascites including 16 studies showed a complete response in 51% and a complete and partial response not requiring paracenteses in 68% of the patients [112]. Analysing the individual data of 4 randomized studies [43,113–115], the mean response to TIPS was 76% [59]. Recurrence of tense ascites occurred in 42% of patients allocated to TIPS and 89% of patients allocated to paracentesis (p <0.0001). Recurrence is mostly due to shunt insufficiency and can be effectively treated by TIPS revision. Accordingly, the
The average number of paracenteses-per-patient was significantly lower in patients allocated to TIPS (1.6 ± 3.5 vs. 7.1 ± 8.8; p < 0.0001). With respect to other complications related to portal hypertension (gastrointestinal bleeding, SBP and HRS), the overall rate of these complications was significantly lower in the TIPS group than in the paracentesis group (15% vs. 28%; p = 0.005) [59].

Survival
With respect to survival, the 6 randomized studies from France [102], Germany [43], Spain/USA [113], USA/Canada [114], Italy [115], and Japan [116] show inconsistent results [73]. The last study published in 2011 has not been included in the numerous meta-analyses [59,117–120]. Three of the 5 meta-analyses [118–120] disregarded heterogeneity. One meta-analysis [120] incorporated incorrect data from the Italian publication by mixing "patients in study" and "percentages died" [121]. Only the meta-analysis performed by D’Amico et al. [117] eliminated heterogeneity by identifying the French study as its source. Actuarial rates of survival became now different between groups favoring TIPS (POR 0.74). The meta-analysis of individual patients’ data by Salerno et al. [59] showed that TIPS patients lived significantly longer than patients treated with paracentesis. TIPS also seems to improve the estimated transplant free survival in patients with MELD scores between 10 and 20, suggesting that even patients with severe disease may benefit from TIPS. In a multivariate analysis, factors predicting mortality were older age (p = 0.015), high bilirubin levels (p = 0.022), low sodium concentration (p = 0.03), and TIPS (HR 0.61, 95% CI 0.41–0.91, p = 0.015).

By considering the 2 relevant meta-analyses [59,117], the German guidelines recommend TIPS as first line treatment in patients with cirrhosis and refractory ascites [122].

**Hepatorenal syndrome [HRS]**
As shown above, TIPS improves renal function and hemodynamic variables. Even patients with cirrhosis and parenchymal kidney disease may benefit from TIPS [123]. Many patients with HRS type 1, however, suffer from advanced hepatocellular...
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**Fig. 7. Conductances (1/R) of local vascular beds before, 5 min, and 1 year after TIPS implantation.** The renal conductance increases (decreasing resistance) as a result of a decrease in the peripheral conductance (increased resistance).

insufficiency with serum bilirubin concentrations exceeding 5 mg/dl, a clear contraindication for TIPS. As summarized recently [73], a total of 61 patients with HRS receiving a TIPS have been included in a number of small studies [104,124–126]. In the largest study, 31 non-transplantable patients (14 type 1 and 17 type 2) were included [124]. Their renal function improved after TIPS and the 1 and 2-year survival rates were 20% for type 1 and 70% and 45%, respectively, for type 2 HRS. Liver failure was one of the most frequent causes of death following TIPS. TIPS may also have a role in maintaining patients who initially respond to vasoconstrictor treatment [125] and awaiting transplantation [126].

**Hepatic hydrothorax**

Hepatic hydrothorax is due to direct passage of peritoneal fluid via diaphragmatic leaks. The treatment modalities including TIPS have been summarized and discussed recently [73,127,128]. Overall, 198 patients (predominantly Child-Pugh B and C) receiving a TIPS were included in 6 studies [129–134]. The mean complete and partial (not requiring thoracenteses) response rates were 65 and 15%, respectively. The average 30-day survival was around 80%. The 1-year survival, given in 2 studies [131,134], was 64 and 48%, respectively. Survival was correlated with response, age <60 to 65 years, and the MELD score [73]. Compared with other treatment options, TIPS seems to provide a high rate of response and a rather good long-term survival. In addition, TIPS is the only treatment option which also treats the refractory ascites, the source of the hepatic hydrothorax.

**Vascular abnormalities indicating TIPS**

**Budd-Chiari syndrome (BCS)**

The BCS may present as a fulminant/acute, subacute, or chronic disease depending on the velocity and extent of the thrombosis formation [135]. This and accompanying complications, such as portal vein thrombosis, thrombosis of inferior caval vein, or renal failure are the relevant parameters determining outcome. In patients with acute disease, anticoagulation together with supportive treatment (volume, antibiotics, diuretics) is given to bridge the time until sufficient collaterals have been developed [136]. In patients with subacute or chronic BCS, the complications of portal hypertension dominate the clinical picture. Irrespective of the course of the disease, a side-to-side shunt or liver transplantation is an option if medical treatment fails [137,138].

The rationale for a side-to-side shunt is to improve hepatic blood flow and function by creation of an artificial outflow via the portal vein bed [138]. In addition, the shunt reduces portal hypertension and relieves from splanchnic congestion. As demonstrated by numerous case reports and by cohort studies [139,140], this can be achieved not only by a surgical shunt but also by TIPS. The latter may have a lower “operative” risk and is not compromised by the characteristic inferior caval vein obstruction which is due to the enlarged liver. It is the reason why portacaval shunting is often impossible or ineffective, requiring a cavo-atrial shunt in addition [138]. Moreover, liver transplantation, an option in some of these patients, remains untouched by the transjugular shunt.

In a minority of patients, one or more hepatic veins are stenosed or occluded over a short segment only. This short segment Budd-Chiari syndrome may ideally be treated by angioplasty with or without stenting as described previously [141–143]. This leads to a reconstruction of the natural vascular bed and blood flow and has, therefore, priority over the shunt treatment as long as cirrhosis has not developed.

The major obstacle of TIPS treatment in patients with BCS is the difficulty to catheterize the occluded hepatic vein. This is, however, overcome by the technique of direct, transcaval puncture of the liver parenchyma with subsequent implantation of a covered stent [139]. The latter has been shown to improve short and long-term patency considerably [144,145]. In contrast to patients receiving a transjugular shunt for variceal bleeding, where a graded reduction of the portal pressure may be advisable [23], in BCS patients a larger diameter of the shunt may be recommended to allow decompression of both the sinusoidal and splanchnic beds and to facilitate arterial perfusion [139]. During and after the transjugular shunt intervention, patients should receive anticoagulation and/or platelet aggregation inhibitors. Physicians should be aware of the high incidence of heparin induced thrombosis in patients with BCS (about 30%) [139] and, therefore, heparin should be given with caution or replaced. In case of portal or inferior caval thrombosis, local thrombolytic treatment seems to be safe and effective [139].

With respect to survival, favourable results with a 90% 5-year and 80% 10-year survival can now be expected, irrespective of whether the course of the disease was acute or even fulminant [136,139,140]. With the availability of TIPS, liver transplantation has become a rare exception.

**Sinusoidal obstruction syndrome/veno-occlusive disease (VOD)**

The sinusoidal obstruction syndrome is almost always seen in the setting of bone marrow transplantation. Several case reports were published showing beneficial effects of TIPS on liver disease but not on survival [146,147]. The data, however, is very limited and, therefore, the role of TIPS remains undetermined [136,148,149].

**Portal vein thrombosis**

Portal vein thrombosis occurs in up to 28% of patients with cirrhosis with a cumulative incidence of 12.8%, 20%, and 38.7% at 1, 5, and 8–10 years of follow-up, respectively, and had little influence on prognosis [150,151]. A hypercoagulative state is an exception [152,153] suggesting that hemodynamic factors play the dominant role. Warfarin treatment resulted in complete
resolution of the thrombus in 39%, partial resolution in 43% and no change in 18% [152]. Anticoagulation using low molecular weight heparin for 6 months has also been recommended after exclusion of esophageal or gastric varices [154]. A recent study investigated the effect of TIPS on portal vein thrombosis in cirrhosis [155]. 87% of patients improved with a complete recanalisation in 57%. Long-term outcome was excellent with a 24-month survival of 81%. It should be mentioned that additional anticoagulation during or after the TIPS procedure was not applied. Considering the positive results, several factors argue in favour of TIPS: first, portal perfusion is already abolished or limited by thrombosis and TIPS may not exert its known negative effects. Second, if complications of portal hypertension are present, TIPS implantation may be beneficial for their treatment. Third, later use of TIPS in case of its urgent indication may be more difficult due to aging of the thrombus or extension into intrahepatic branches. However, the findings that portal vein thrombosis does not affect outcome [150,151] argue against any treatment. Randomized studies are required to confirm recent findings and to more properly select patients which may benefit from treatment. TIPS treatment has also been applied to patients with cirrhotic or non-cirrhotic portal vein thrombosis with cavernomatous transformation. In patients with a relevant communication between an intrahepatic portal branch and the extrahepatic collaterals, TIPS may be effective in draining the varices and prevent bleeding. Four studies including 85 patients with portal cavernoma successfully implanted a TIPS in 73%, 83%, 35%, and 63%, respectively [156–159]. Rebleeding was significantly reduced in patients without cirrhosis [158], but not in cirrhosis [159].

### Key Points 2

- TIPS improves circulatory dysfunction by redistribution of local vascular resistances favoring renal perfusion
- TIPS improves survival and reduces portal hypertensive complications in patients with refractory ascites
- In patients with Budd-Chiari syndrome not responding rapidly to medical therapy, TIPS is the treatment of choice. The transplant-free 10-year survival of 80% reduces the need for liver transplantation to a great extent
- Cirrhotic or non-cirrhotic portal vein thrombosis is no more a contraindication for TIPS. Its effect on mortality remains to be determined

### Conclusions

Technical advancements in skills and stents have reduced complications and improved patency of TIPS. The major obstacle remains hepatic encephalopathy, which requires proper selection of patients and smaller shunts. In patients with acute varical bleeding and high risk of early rebleeding, recent studies showed improved survival recommending early TIPS implantation. With respect to the prevention of rebleeding (secondary prophylaxis), TIPS remains the second-line treatment unless new studies with covered stents demonstrate its superiority over standard medical therapy. As demonstrated in 2 relevant meta-analyses, TIPS improves survival in patients with refractory ascites, justifying its earlier application. It clearly reverses the circulatory dysfunction which leads to normalization of the renal function. With a 10-year survival rate of 80%, TIPS is the preferred treatment in patients with Budd-Chiari syndrome who do not respond sufficiently to medical treatment.

### Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

### References


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