TIPS: Is Early Intervention Helpful?

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Faculty Disclosure

• No financial disclosures
Objectives

• Define role of TIPS in the treatment of patients with acute variceal bleeding

• Define role of TIPS in the treatment of patients with refractory ascites

• Discuss risk stratification and prognostic parameters in patients with complications of cirrhosis prior to TIPS

• Discuss evaluation of patients prior to TIPS
TIPS VS. ENDOCSOPIC THERAPY for variceal bleeding

- Significantly lower rates of rebleeding in TIPS patients
- Higher rate of encephalopathy in TIPS patients
- No significant difference in survival
- 12-30% of patients in endoscopic arm required TIPS rescue
- No difference in duration of hospitalization

Risk stratification during index bleeding:

- Early study tried stratification based on HPVG measured within 24 hours
  - HPVG > 20 mm Hg considered high risk for medical failure
  - Randomized to TIPS (n=26) or standard therapy (n=25)

<table>
<thead>
<tr>
<th></th>
<th>TIPS group</th>
<th>Non TIPS group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>12%</td>
<td>50%</td>
</tr>
<tr>
<td>In hospital mortality</td>
<td>11%</td>
<td>38%</td>
</tr>
</tbody>
</table>
Early Use of TIPS in Patients with Cirrhosis and Variceal Bleeding

Juan Carlos García-Pagán, M.D., Karel Caca, M.D., Christophe Bureau, M.D., Wim Laleman, M.D., Beate Appenrodt, M.D., Angelo Luca, M.D., Juan G. Abraldes, M.D., Frederik Nevens, M.D., Jean Pierre Vinel, M.D., Joachim Mössner, M.D., and Jaime Bosch, M.D., for the Early TIPS (Transjugular Intrahepatic Portosystemic Shunt) Cooperative Study Group

NEJM 2010; 362:25: 2370-2379
Study design

Patients with cirrhosis and acute variceal bleeding. Child-Pugh class C or class B with active bleeding seen on Endoscopy

Pharmacotherapy + Endoscopic band ligation (EBL) (n=31)

Early TIPS group within 72 hours (n=32)
## Results:

<table>
<thead>
<tr>
<th></th>
<th>Pharmacotherapy + EBL</th>
<th>Early TIPS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding or failure to control bleeding</td>
<td>14</td>
<td>1</td>
<td>0.001</td>
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<tr>
<td>1 year bleeding free actuarial probability</td>
<td>50%</td>
<td>97%</td>
<td>&lt;0.001</td>
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<tr>
<td>Mortality rate</td>
<td>12</td>
<td>4</td>
<td>0.01</td>
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<tr>
<td>1 Year actuarial survival</td>
<td>61%</td>
<td>86%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU stay and total in hospital stay length</td>
<td>7 received rescue TIPS</td>
<td>4 died despite TIPS</td>
<td></td>
</tr>
<tr>
<td>1 year actuarial probability of hepatic encephalopathy</td>
<td>28%</td>
<td>40%</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Use of early-TIPS for high-risk variceal bleeding: Results of a post-RCT surveillance study

- early-TIPS (n = 45) or drugs + endoscopic therapy (ET) (n = 30)
- 1-year survival 86% vs. 70% respectively; p = 0.056
Conclusion

• Baveno V conference in 2010 recommended considering early TIPS (within 72 h) in patients with high risk of treatment failure

• Definition: Child-Pugh score B with active bleeding at endoscopy, or Child-Pugh score C with less than 14 points in the early TIPS-situation (within 72 h after bleeding)

J Hepatol 2015;63:743–752
J Hepatol 2013;58:45–50
Premature closure?

Early-TIPSS placement prevents rebleeding in high-risk patients with variceal bleeding, without improving survival

- 31/128 patients with cirrhosis (MELD score 20.9 ± 6.9, Child–Pugh C: 77.4%)
- matched to 31 historical patients
- 1-year probability of being free of rebleeding was higher in the TIPSS+ group (97% vs. 51%, $P < 0.001$)
- 1-year survival was not different between the two groups (66.8 ± 9.4% vs. 74.2 ± 7.8%, $P = 0.78$)
- Acute cardiac failure occurred more frequently in the TIPSS+ group (25.8% vs. 6.4%, $P = 0.03$).

Rudler et al, Aliment Pharmacol Ther 2014;40:1074–1080
Covered Transjugular Intrahepatic Portosystemic Shunt Versus Endoscopic Therapy + b-blocker for Prevention of Variceal Rebleeding

- 72 patients, first or second episode of gastric and/or esophageal variceal bleeding
- follow-up of 23 months
- Variceal rebleeding: 29% in the endoscopy vs 0% patients in the TIPS group (P = 0.001)
- Mortality: TIPS 32% vs. endoscopy 26%; P = 0.418
- Early hepatic encephalopathy (within 1 year) 35% TIPS vs. 14% endoscopy; P = 0.035
- During long-term follow-up this difference diminished (38% vs. 23%; P = 0.121).

Holster et al, Hepatology 2016
Covered Transjugular Intrahepatic Portosystemic Shunt Versus Endoscopic Therapy + β-blocker for Prevention of Variceal Rebleeding
### Early transjugular intrahepatic portosystemic shunt in cirrhotic patients with acute variceal bleeding: a systematic review and meta-analysis of controlled trials

#### References

<table>
<thead>
<tr>
<th>Subgroup within study</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-value</th>
<th>P-value</th>
<th>Events / total</th>
<th>Odds ratio and 95% CI</th>
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<tr>
<td>Garcia-Pagán et al. [14] Death</td>
<td>0.308</td>
<td>0.098</td>
<td>0.969</td>
<td>-2.015</td>
<td>0.044</td>
<td>Early TIPSS 6 / 45, Medical 10 / 30</td>
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<td>Garcia-Pagán et al. [13] Death</td>
<td>0.228</td>
<td>0.063</td>
<td>0.808</td>
<td>-2.289</td>
<td>0.022</td>
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<td>Monescillo et al. [12] Death</td>
<td>0.235</td>
<td>0.074</td>
<td>0.751</td>
<td>-2.444</td>
<td>0.015</td>
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<td>Rudler et al. [15] Death</td>
<td>1.176</td>
<td>0.385</td>
<td>3.595</td>
<td>0.285</td>
<td>0.776</td>
<td>Early TIPSS 9 / 31, Medical 8 / 31</td>
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#### Odds ratio and 95% CI

Favours early TIPSS Favours controls

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<table>
<thead>
<tr>
<th>Subgroup within study</th>
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<tr>
<td>Garcia-Pagán et al. [14] Composite endpoint</td>
<td>0.071</td>
<td>0.018</td>
<td>0.282</td>
<td>-3.768</td>
<td>0.000</td>
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<td>Garcia-Pagán et al. [13] Composite endpoint</td>
<td>0.039</td>
<td>0.005</td>
<td>0.324</td>
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<td>0.003</td>
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<td>Monescillo et al. [12] Composite endpoint</td>
<td>0.133</td>
<td>0.039</td>
<td>0.459</td>
<td>-3.197</td>
<td>0.001</td>
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<td>Rudler et al. [15] Composite endpoint</td>
<td>0.046</td>
<td>0.006</td>
<td>0.383</td>
<td>-2.849</td>
<td>0.004</td>
<td>Early TIPSS 1 / 31, Medical 13 / 31</td>
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</table>

Favours early TIPSS Favours controls

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TIPS in refractory ascites:

• Refractory ascites:
  • Unresponsive to salt restriction and high dose diuretics
  • Recurs rapidly after therapeutic paracentesis

• About 10% of patients with cirrhosis and ascites develop refractory ascites

• Portends poor prognosis
  • 21% mortality rate by 6 months
  • 70% mortality rate by 2 years
• Within weeks after TIPS:
  • urinary sodium excretion and serum creatinine improve significantly and can normalize within 6–12 months
  • decrease in bacterial translocation and systemic inflammation

• complete response in 51%
• partial response in 68%
• recurrence of tense ascites occurred in 42%

Gastroenterology 2007;133:825–834.
Two-year survival rates of randomized studies comparing transjugular intrahepatic portosystemic shunt (TIPS) and paracentesis

<table>
<thead>
<tr>
<th>Author, year (Ref)</th>
<th>n</th>
<th>TIPS</th>
<th>Paracentesis</th>
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<tr>
<td>Lebreck 1996</td>
<td>25</td>
<td>29</td>
<td>60</td>
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<td>Rössle 2000</td>
<td>60</td>
<td>58</td>
<td>32</td>
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<td>Gines 2002</td>
<td>70</td>
<td>26</td>
<td>30</td>
<td>0.51</td>
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<td>Sanyal 2003</td>
<td>109</td>
<td>62</td>
<td>62</td>
<td>NS</td>
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<td>Salerno 2004</td>
<td>66</td>
<td>79</td>
<td>29</td>
<td>0.021</td>
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</table>
Transjugular Intrahepatic Portosystemic Shunt for Refractory Ascites: A Meta-analysis of Individual Patient Data

Salerno et al. Gastroenterology 2007;133:825–834
Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites

- 62 patients with cirrhosis and at least 2 large-volume paracenteses within a period of at least 3 weeks
- TIPS (n = 29) or large-volume paracenteses and albumin as necessary (LVP+A, n = 33)
- primary study end point- survival without a liver transplant for 1 year after the procedure: TIPS group 93%, LVP+A group 52% (P=0.003)
- 1-year probability of remaining free of encephalopathy was 65% for each group

Long-term clinical outcome of patients with cirrhosis and refractory ascites treated with transjugular intrahepatic portosystemic shunt insertion

Survival benefit of TIPS versus serial paracentesis in patients with refractory ascites: a single institution case-control propensity score analysis

Gaba et al. Clin Radiol 2015;70:e51–e57
Transjugular intrahepatic portosystemic shunt (TIPS) for the treatment of hepatic hydrothorax

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>n</th>
<th>Response (%)</th>
<th>30-day mortality (%)</th>
<th>1-year probability of survival (%)</th>
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<tr>
<td>Gordon 1997</td>
<td>24</td>
<td>79</td>
<td>21*</td>
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<td>Jeffries 1998</td>
<td>12</td>
<td>58</td>
<td>25</td>
<td></td>
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<tr>
<td>Siegerstetter 2001</td>
<td>40</td>
<td>82</td>
<td>5</td>
<td>64</td>
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<td>Spencer 2002</td>
<td>21</td>
<td>74</td>
<td>29</td>
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<td>Wilputte 2007</td>
<td>28</td>
<td>68</td>
<td>14</td>
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<tr>
<td>Dhanasekaran 2009</td>
<td>73</td>
<td>75</td>
<td>19</td>
<td>48</td>
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<tr>
<td>Total/range</td>
<td>198</td>
<td>58–82</td>
<td>5–25</td>
<td>48–64</td>
</tr>
</tbody>
</table>
Association Between Transjugular Intrahepatic Portosystemic Shunt and Survival in Patients With Cirrhosis

- United Network for Organ Sharing registries from 2002 to 2013
- cohort of transplant-naive adults with cirrhosis (N = 97,063) from the time of transplant listing until the time of death or transplantation
- patients with a TIPS had a lower risk of
  - death (adjusted sub-hazard ratio, 0.95; 95% CI, 0.9-0.99),
  - transplantation (adjusted sub-hazard ratio, 0.92, 95% CI, 0.88-0.95),
  - or the combined outcome of death or transplantation (adjusted hazard ratio, 0.85; 95% CI, 0.83-0.88).

Berry et al, Clin Gastroenterol Hepatol 2015
Portosystemic Shunts: Stable Utilization and Improved Outcomes, Two Decades After the Transjugular Intrahepatic Portosystemic Shunt

- Retrospective analysis of patients undergoing surgical portal decompression and TIPS procedures
- TIPS procedures represented 86% of all procedures in 2013
- In-hospital mortality decreased by 42% (P < .05)
- Length of stay decreased by 20% (P < .05)

Perry et al, J Am Coll Radiol 2015
Prognostic indicators: Emory model

- Bilirubin >3.0 mg/dL (1 point), ALT >100 IU/L (1 point), pre-TIPS encephalopathy (1 point) and urgency of TIPS (2 points)
  - high risk, 4–5 points; medium risk, 1–3 points; low risk, 0 points

*Chalasani et al, Gastroenterology 2000*
MELD score:

- 475 patients underwent elective TIPS over a 10-year period
  - MELD score ≤ 18
    - 3-month mortality 10%
  - MELD score > 18 (17 patients)
    - 3-month mortality 60%
  - P=0.002

- Independent predictors of death: creatinine level, bilirubin level, age, and refractory ascites.
- Renal function strongest independent predictor of survival.

• General consensus:
  • Child-Pugh class C patient with a score of 13 or higher is at a very high risk of early death after TIPS
<table>
<thead>
<tr>
<th></th>
<th>MELD (95% CI)</th>
<th>Child-Pugh (95% CI)</th>
<th>Emory (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-mo mortality</td>
<td>0.71 (0.56–0.86)</td>
<td>0.72 (0.60–0.84)</td>
<td>0.69 (0.57–0.81)</td>
</tr>
<tr>
<td>12-mo mortality</td>
<td>0.73* (0.64–0.82)</td>
<td>0.67 (0.57–0.76)</td>
<td>0.60 (0.52–0.68)</td>
</tr>
<tr>
<td>36-mo mortality</td>
<td>0.74† (0.64–0.84)</td>
<td>0.73‡ (0.63–0.84)</td>
<td>0.64 (0.55–0.72)</td>
</tr>
</tbody>
</table>

* $p = 0.012$ vs Emory.
† $p = 0.065$ vs Emory.
‡ $p = 0.038$ vs Emory.

• elevated pre-TIPS bilirubin level is a powerful independent predictor of 30-day mortality after TIPS creation with a 40% increased risk of death for each 1-mg/dL increase above 3.0 mg/dL.

  • Rajan et al, J Vasc Interv Radiol 2002

• Serum bilirubin was found to be an independent predictor of survival. Bilirubin concentration above 3 mg/dl can be regarded as a relative contraindication for TIPS in patients with refractory ascites

  • Gerbes A, Hepatology 2005
Serum bilirubin and platelet count: A simple predictive model for survival in patients with refractory ascites treated by TIPS

Bureau et al. J Hepatol 2011;54:901–907

![Survival curves for different combinations of serum bilirubin and platelet count](image-url)
One answer for all?

- Prognostic markers vary also with the indication for TIPS
- Bilirubin levels of around 5 mg/dl might be tolerated in patients with bleeding
- TIPS might be dangerous in patients with refractory ascites with bilirubin levels higher than 3 mg/dl
- Median survival for the ascites group 29 mo compared to > 60 mo for the bleeding group (P = 0.009).


Trebicka, Journal of Hepatology 2017 vol. 66 j 442–450
Diastolic dysfunction is associated with poor survival in patients with cirrhosis with transjugular intrahepatic portosystemic shunt

- Echo with Doppler before and 28 days after TIPS
- 32 patients (2 patients MELD >18)
- Diastolic dysfunction identified as an independent predictor of death (RR 8.9, 95% CI 1.9 to 41.5, p = 0.005)
- During the first year of follow-up, six out of 10 patients with an E/A ratio ≤1 died, whereas all 22 patients with E/A ratio ≥1 survived.

Cazzaniga et al., Gut 2007;56:869–875.
Right atrial pressure may impact early survival of patients undergoing transjugular intrahepatic portosystemic shunt creation

- 90 day mortality in variceal hemorrhage patients based on RA pressures (baseline and final)

Hepatic encephalopathy

- Incidence of new or worsening encephalopathy following TIPS is 20-31%
- In controlled trials comparing TIPS to alternative forms of therapy the incidence of encephalopathy is always greater in those who received a TIPS
- Most studies were not designed to investigate HE
- Subjective measures

Study by Kircheis et al (Eur J Gastroenterol Hepatol. 2009)
  - critical flicker frequency test
  - no change in severity in 44%
  - deterioration in 35%
  - improvement in 21%
• **Sauerbruch** 8mm cTIPS: no difference between patients with portal pressure gradients less than or greater than 12 mm Hg after TIPS placement (P = .939)

• **Holster** cTIPS initial dilation to 8 mm, if necessary additional dilation to 10 mm:
  • Early hepatic encephalopathy (within 1 year) 35% TIPS group vs. 14% in endoscopy group; P=0.035), but during long-term follow-up this difference disappeared (38% vs. 23%;P=0.121)

Riggio randomized to receive 8- or 10-mm cTIPS
Probability of remaining free of HE 42.6% in 8 mm stent group vs 46.7% in 10 mm stent group (P=0.48)
Early Liver Failure after Transjugular Intrahepatic Portosystemic Shunt in Patients with Cirrhosis with Model for End-Stage Liver Disease Score of 12 or Less: Incidence, Outcome, and Prognostic Factors

Luca et al. Radiology 2016;280:622–629
Cardiac volume overload and pulmonary hypertension in long-term follow-up of patients with a transjugular intrahepatic portosystemic shunt

- 1–5 years after TIPSS
- median left atrial diameter (LAD) increased from 37 mm [interquartile range (IQR): 33–43] to 40 mm (IQR: 37–47, P = 0.001)
- Left ventricular end-diastolic diameter (LV-EDD) increased from 45 mm (range: 41–49) to 48 mm (IQR: 45–52, P < 0.001)
- pulmonary artery systolic pressure (PASP) increased from 25 mmHg (IQR: 22–33) to 30 mmHg (IQR: 25–36, P = 0.038)

In Summary

• TIPS is efficient in treating complications of portal hypertension, especially variceal bleeding and refractory ascites.

• Special care is required in the selection of patients eligible for TIPS.

• Persistent need for diagnostic and prognostic biomarkers.
Thank You
SECTION 3