Do we need to update the Baveno V guideline for high risk variceal bleeding patients?

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The Leipzig Interventional Course (LINC)
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“An early TIPS within 72 hours (ideally ≤ 24 hours) should be considered in patients at high-risk of treatment failure (e.g. Child-Pugh class C <14 points or Child class B with active bleeding) after initial pharmacological and endoscopic therapy.” (1b;A)
Early TIPS Improves Prognosis in High-Risk Patients (HVPG>20 mmHg)

What new evidence do we have since then?
Early PTFE-TIPS vs Conventional Therapy in Patients at High-Risk of Failure. A Multicenter European RCT

Primary end-point

![Graph showing time to failure to control bleeding or rebleeding (months)]

- Standard Therapy
- Early TIPS

\[ p < 0.0001 \]

Survival

![Graph showing cumulative incidence of death (months)]

- Early TIPS

\[ p < 0.001 \]

*7 patients in the STD group were treated with TIPS as rescue therapy: 4 (57%) died early after (all Child C)

Results confirmed in a Post-RCT Observational Study performed in the same centers participating in the RCT and including 75 pts (45 early-TIPS and 30 Drug+EBL)

Garcia-Pagán et al. J Hepatol 2012
Post-RCT Surveillance Study

Death

García-Pagán et al. J Hepatol 2012
**Meta-analysis. Bleeding according to Child-Pugh**

**Child-Pugh class B patients**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Early TIPS n/N</th>
<th>Non TIPS n/N</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monescillo (Hepatol)</td>
<td>1/11</td>
<td>4/10</td>
<td>0.15 [0.01, 1.68]</td>
</tr>
<tr>
<td>Garcia-Pagan (NEJM)</td>
<td>0/16</td>
<td>5/16</td>
<td>0.06 [0.00, 1.26]</td>
</tr>
<tr>
<td>Garcia-Pagan (J Hep)</td>
<td>2/18</td>
<td>5/10</td>
<td>0.13 [0.02, 0.86]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>45</td>
<td>36</td>
<td>0.11 [0.03, 0.42]</td>
</tr>
</tbody>
</table>

Total events: 3 (Early TIPS), 14 (Non TIPS).
Test for heterogeneity: Chi² = 0.21, df = 2 (P = 0.90), I² = 0%
Test for overall effect: Z = 3.23 (P = 0.001)

**Child-Pugh class C patients**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Early TIPS n/N</th>
<th>Non TIPS n/N</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monescillo (Hepatol)</td>
<td>2/12</td>
<td>9/12</td>
<td>0.07 [0.01, 0.49]</td>
</tr>
<tr>
<td>Garcia-Pagan (NEJM)</td>
<td>1/16</td>
<td>9/15</td>
<td>0.04 [0.00, 0.43]</td>
</tr>
<tr>
<td>Garcia-Pagan (J Hep)</td>
<td>1/27</td>
<td>10/20</td>
<td>0.04 [0.00, 0.34]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>55</td>
<td>47</td>
<td>0.05 [0.01, 0.17]</td>
</tr>
</tbody>
</table>

Total events: 4 (Early TIPS), 28 (Non TIPS).
Test for heterogeneity: Chi² = 0.15, df = 2 (P = 0.93), I² = 0%
Test for overall effect: Z = 4.82 (P < 0.00001)
### Meta-analysis. Survival according to Child-Pugh

#### B. Mortality in Child-Pugh class B patients

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Early TIPS n/N</th>
<th>Non TIPS n/N</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monescillo (Hepatol)</td>
<td>1/11</td>
<td>3/10</td>
<td>0.23 [0.02, 2.73]</td>
</tr>
<tr>
<td>Garcia-Pagan (NEJM)</td>
<td>1/16</td>
<td>2/16</td>
<td>0.47 [0.04, 5.73]</td>
</tr>
<tr>
<td>Garcia-Pagan (J Hep)</td>
<td>0/18</td>
<td>3/10</td>
<td>0.06 [0.00, 1.26]</td>
</tr>
</tbody>
</table>

Total (95% CI): 45 (Early TIPS) 36 (Non TIPS)
Test for heterogeneity: Chi² = 1.08, df = 2 (P = 0.58), I² = 0%
Test for overall effect: Z = 2.17 (P = 0.03)

#### C. Mortality in Child-Pugh class C patients

<table>
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<tr>
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<tbody>
<tr>
<td>Monescillo (Hepatol)</td>
<td>3/12</td>
<td>7/12</td>
<td>0.24 [0.04, 1.36]</td>
</tr>
<tr>
<td>Garcia-Pagan (NEJM)</td>
<td>3/16</td>
<td>10/15</td>
<td>0.12 [0.02, 0.60]</td>
</tr>
<tr>
<td>Garcia-Pagan (J Hep)</td>
<td>6/27</td>
<td>7/20</td>
<td>0.53 [0.15, 1.93]</td>
</tr>
</tbody>
</table>

Total (95% CI): 55 (Early TIPS) 47 (Non TIPS)
Test for heterogeneity: Chi² = 2.08, df = 2 (P = 0.35), I² = 3.9%
Test for overall effect: Z = 2.93 (P = 0.003)
Hierarchy of evidence

Studies at the Top of the Pyramid

- 2 RCTs (2004; 2010)
- 1 observational (2012)
Early-TIPSS placement prevents rebleeding in high-risk patients with variceal bleeding, without improving survival

31 pts Early-TIPS matched vs 31 Historical Controls (TIPS only as rescue)

**Failure bleeding/rebleeding**

<table>
<thead>
<tr>
<th></th>
<th>N° at risk</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIPSS – group</td>
<td>31 18 16 15 15 15</td>
<td></td>
</tr>
<tr>
<td>TIPSS + group</td>
<td>31 23 20 13 11 11</td>
<td></td>
</tr>
</tbody>
</table>

**Survival**

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<tr>
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<td></td>
</tr>
</tbody>
</table>

Very different periods of time (2011-2013 vs 2008-2011)

Although NS (probably because low sample size) baseline differences of the 2 cohorts of patients

Rudler et al. Aliment Pharmacol Ther 2014
Hierarchy of evidence

- Randomized Controlled Studies
- Cohort Studies
- Case Control Studies
- Case Series
- Case Reports
- Ideas, Editorials, Opinions
- Animal research
- In vitro ('test tube') research
- Meta-analysis
“An early TIPS within 72 hours (ideally ≤ 24 hours) should be considered in patients at high-risk of treatment failure (e.g. Child-Pugh class C <14 points or Child class B with active bleeding) after initial pharmacological and endoscopic therapy.” (1b;A)
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Variceal Bleeding

General Management
- Antibiotics
- Careful replacement of volemia

Early Drug Rx
- Terlipressin
- Somatostatin and analogues

Endoscopy EBL / EIS

Patient at High-Risk of Rx Failure?
- Child B + Active bleeding (oozing or jet over a varix) or Child C (<14)
- HVPG > 20 mmHg
- Others?

YES
Early-PTFE Covered TIPS
- Rx acute bleeding
- Preventing Rebleeding
Variceal Bleeding

General Management
- Antibiotics
- Careful replacement of volemia

Early Drug Rx
- Terlipressin
- Somatostatin and analogues

Endoscopy

Patient at High-Risk of Rx Failure?
- Child B + Active bleeding (oozing or jet over a varix) or Child C (<14)
- HVPG > 20 mmHg
- Others?

NO

- Keep on Drugs for 2-5 days
- Then, secondary prophylaxis to prevent rebleeding
Do we need to update the Baveno V guideline for high risk variceal bleeding patients?

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