Role of Beta-Blockers in Decompensated Cirrhosis

Guadalupe García-Tsao, MD, FAAASLD
Professor of Medicine
Yale University
Chief, Digestive Diseases Section
VA-CT Healthcare System

Postgraduate Course:
Challenges in Management of Common Liver Diseases
Case # 1

55 year-old male with chronic hepatitis C cirrhosis with ascites found to have large esophageal varices on screening upper endoscopy. Has never had gastrointestinal hemorrhage.
Key Questions

- Should beta blockers be recommended in patients with ascites?
- How to titrate dose of beta-blockers?
Cirrhosis is classified in at least two different prognostic entities

Chronic liver disease

- Compensated cirrhosis
  - No varices
  - Median survival >12 years

- Decompensated cirrhosis
  - Varices
  - Median survival ~2 years

Death

- Variceal hemorrhage
- Ascites
- Encephalopathy
HVPG $\geq 10$ mmHg is an independent predictor of decompensation in patients with *compensated* cirrhosis.

Probability of decompensation (ascites, variceal hemorrhage, hepatic encephalopathy)

Log rank test: $P<0.01$
HR $3.95$ (2.29–6.83)

Also predictive of varices and HCC

Clinically-significant portal hypertension (CSPH)

Mild portal hypertension

Management of varices and variceal hemorrhage must be considered in the context of other complications of cirrhosis.

- **Compensated cirrhosis**
  - Mild PH
  - CSPH
    - No varices
    - Varices

- **Decompensated cirrhosis**
  - Variceal hemorrhage
  - Ascites
  - HE

- **Further decompensation**
  - Recurrent VH
    - Refractory ascites, HypoNa, HRS
    - Recurrent HE
    - Jaundice

- **Death**

Mild portal hypertension (PH) = HVPG >5 but <10 mmHg
CSPH= clinically significant portal hypertension = HVPG ≥ 10 mmHg

VH=variceal hemorrhage; HE = hepatic encephalopathy; HRS=hepatorenal syndrome
In patients with CSPH and varices the objective is to prevent variceal hemorrhage and decompensation.

Compensated cirrhosis:
- Mild PH
- CSPH
  - No varices
  - Varices

Decompensated cirrhosis:
- Variceal hemorrhage
  - Ascites
  - HE

Further decompensation:
- Recurrent VH
  - Refractory ascites, Hyponatremia, HRS
  - Recurrent HE
  - Jaundice

Death

Mild portal hypertension (PH) = HVPG >5 but <10 mmHg
CSPH = clinically significant portal hypertension = HVPG ≥ 10 mmHg

VH = variceal hemorrhage; HE = hepatic encephalopathy; HRS = hepatorenal syndrome
Varices at a high risk of hemorrhage

- Medium/large varices
- Any size varices with red wale marks
- Any size varices in a Child C patient

If they have not bled, high-risk varices require prophylactic therapy to prevent first episode of variceal hemorrhage

Portal hypertension in cirrhosis is due to an increase in intrahepatic resistance and an increase in portal flow.
Portal hypertension in cirrhosis is due to an increase in intrahepatic resistance and an increase in portal flow.

- Increased resistance
- Splanchnic vasodilatation
- Increased flow
- Effective hypovolemia
- Activation neurohumoral systems
- Increased cardiac output
- Sodium and water retention
- Hypervolemia

NSBB (propranolol, nadolol)

- β-2 blockade
- β-1 blockade
There is no correlation between the decrease in HVPG and decrease in HR induced by NSBB.

NSBB prevent first variceal hemorrhage in both compensated and decompensated patients


NSBB = nonselective beta-blockers
Two treatments reduce the risk of first variceal hemorrhage in pts with medium/large varices

- Beta-blockers (19 trials)
- Ligation (19 trials)

In good quality trials (n=7), no significant differences in bleeding between EVL (17%) and BB (19%)

D’Amico et al., Sem Liv Dis 1999; 19:475


* Significantly lower
Baveno VI recommendations for pts with medium / large varices that have not bled

- Either NSBB or endoscopic variceal ligation is recommended in primary prophylaxis.

- The choice of treatment should be based on local resources and expertise, patient preference and characteristics, side effects, and contra-indications.
In patients with large varices that have not bled, a decrease in HVPG >10% improves outcomes.


How to enhance response?
Portal hypertension in cirrhosis is due to an increase in intrahepatic resistance and an increase in portal flow.
Carvedilol has a higher rate of hemodynamic responders* compared to traditional NSBB

* HVPG decrease to < 12 mmHg or >20% from baseline

25-30 mg/day associated with decrease in MAP and fluid retention

NSBB = propranolol and nadolol

Miñano and Garcia-Tsao, Gastro Clin N Am 2010;39:681
Carvedilol (non-selective, vasodilating β-blocker) was more effective than ligation (EVL) in preventing first variceal hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>EVL</th>
<th>Carvedilol*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>75</td>
<td>77</td>
<td>p</td>
</tr>
<tr>
<td>Median follow-up (mos)</td>
<td>25.5</td>
<td>26.2</td>
<td>ns</td>
</tr>
<tr>
<td>First variceal hemorrhage</td>
<td>23%</td>
<td>10%</td>
<td>0.04</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>37%</td>
<td>35%</td>
<td>ns</td>
</tr>
<tr>
<td>Bleeding-related mortality</td>
<td>2%</td>
<td>3%</td>
<td>ns</td>
</tr>
<tr>
<td>Treatment discontinuation due to intolerance</td>
<td>12%</td>
<td>16%</td>
<td>ns</td>
</tr>
</tbody>
</table>

*12.5 mg/day

Tripathi et al. Hepatology 2009;50(3):825-33
Propranolol and carvedilol hemodynamic responders* have a lower probability of variceal bleeding and decompensation than EVL

* HVPG decrease to < 12 mmHg or >20% from baseline

Carvedilol is associated with a larger decrease in mean arterial pressure (MAP) than propranolol

**Propranolol**

- Banares (1999): -4.00 (-12.32, 4.32)
- De, acute (2002): -3.60 (-14.41, 7.21)
- Banares (2002): -4.80 (-15.51, 5.91)
- De, chronic (2002): -5.70 (-15.32, 3.92)
- Lin (2004): -9.00 (-17.32, -0.68)
- Hobolth (2012): -8.00 (-14.47, -1.53)
- Overall (I² = 0.0%, P = 0.936): -6.35 (-9.86, -2.83)

**Carvedilol**

- Banares (1999): -16.00 (-25.80, -6.20)
- De, acute (2002): -10.50 (-18.26, -2.74)
- Banares (2002): -10.20 (-17.56, -2.84)
- De, chronic (2002): -15.10 (-24.12, -6.08)
- Lin (2004): -8.00 (-22.13, 6.13)
- Hobolth (2012): -5.00 (-12.28, 2.28)
- Overall (I² = 0.0%, P = 0.477): -10.40 (-13.90, -6.90)

Progressive alterations in systemic hemodynamics are associated with increased inflammatory markers.

Turco L et al. EASL 2016

Decreases in MAP should be avoided in patients with cirrhosis and ascites.
Prevention of First Variceal Hemorrhage

- **Should beta blockers be recommended in patients with ascites?**
  - In patients with high-risk varices *with and without ascites* traditional NSBB (propranolol or nadolol) are valid first line therapy to prevent first hemorrhage
  - Carvedilol should be used cautiously or not at all in patients with ascites
  - If patient not candidate or intolerant to NSBB → ligation

- **How to titrate dose of beta-blockers?**
  - Propranolol or nadolol: maximal tolerated dose or heart rate 50-55 bpm - maximum dose: **160 mg** (BID for propranolol, QD for nadolol)
  - In pts with ascites - maximum dose: **80 mg** (BID for propranolol, QD for nadolol)
  - Reduce or discontinue if systolic BP <90 mmHg
  - Carvedilol titrated at 6.25 -12.5 mg/day
Case #2

55 year old male with chronic hepatitis C cirrhosis with refractory ascites, Child B, has just recovered from an episode of variceal hemorrhage.
Key Questions

- What is recommended therapy for prevention of rebleeding?
- Should beta blockers be recommended in patients with refractory ascites?
If variceal hemorrhage occurs in the absence of other decompensating events, endpoint of treatment is prevention of rebleeding/other complications.

- Compensated cirrhosis
  - Mild PH
  - CSPH
    - No varices
    - Varices
- Decompensated cirrhosis
  - Variceal hemorrhage
    - Ascites
    - HE
- Further decompensation
  - Recurrent VH
    - Refractory ascites, HypoNa, HRS
    - Recurrent HE
    - Jaundice
- Death

VH=variceal hemorrhage; HE = hepatic encephalopathy; HRS=hepatorenal syndrome
The combination of NSBB + ligation is associated with lower rebleeding rates

*non-selective β-blockers (NSBB) ± nitrates

The essential component of combination therapy (EVL+NSBB) is the NSBB

Puente et al. Liver Int 2014;34:823-33
Individual patient meta-analysis stratifying response by Child class (A vs. B/C) shows key role of NSBB

**EVL + NSBB vs. NSBB**
- Added effect of EVL (to NSBB alone) is marginal
- Combo prevents rebleeding in Child A patients

**NSBB + EVL vs. EVL**
- Added effect of NSBB (to EVL alone) leads to less rebleeding and death, particularly in Child B/C pts

*Albillos et al.* AASLD 2015.
Individual patient meta-analysis shows a higher mortality with EVL alone in Child B/C patients.

**EVL + BB vs. BB**

**BB + EVL vs. EVL**

Albillos
Bleeding and death are significantly lower in patients on NSBB who are HVPG responders*

HVPG responders also have a lower incidence of other complications of cirrhosis (ascites, SBP, HE)

Abraaldes et al. Hepatology 2003

D’Amico et al. Gastroenterology 2006;131:1611–1624
If variceal hemorrhage occurs in addition to other complications, endpoint of therapies is prevention of death.

Compensated cirrhosis
- Mild PH
- CSPH
  - No varices
  - Varices

Decompensated cirrhosis
- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

Further decompensation

Death

VH=variceal hemorrhage; HE = hepatic encephalopathy; HRS=hepatorenal syndrome
In a prospective cohort study, patients with refractory ascites on propranolol had a poorer survival than those not on NSBB.

On multivariate analysis, propranolol use remained an independent predictor of death. Patients on propranolol had a significantly lower systolic blood pressure than those not on NSBB (103 vs. 123 mmHg).
Studies showing a higher mortality with NSBB also showed a lower blood pressure at baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Patient population</th>
<th>BB Dose</th>
<th>Baseline MELD</th>
<th>Baseline MAP</th>
<th>Follow-up (months)</th>
<th>Adjusted HR for mortality associated with BB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serste (2010)</td>
<td>151</td>
<td>Refractory ascites</td>
<td>80</td>
<td>18.8</td>
<td>18.9</td>
<td>8</td>
<td>2.61 (1.63-4.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BB No BB</td>
<td>BB No BB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandorfer (2014)</td>
<td>182</td>
<td>Spontaneous bacterial peritonitis</td>
<td>80</td>
<td>20.0</td>
<td>21.6</td>
<td>~9.6</td>
<td>1.64 (1.1-2.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BB No BB</td>
<td>BB No BB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leithead (2015)</td>
<td>322</td>
<td>Ascites on transplant list</td>
<td>80</td>
<td>16</td>
<td>17</td>
<td>2.4</td>
<td>0.35 (0.14 to 0.86)</td>
</tr>
<tr>
<td></td>
<td>(208</td>
<td>matched)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bossen (2016)</td>
<td>1,188</td>
<td>Ascites in RCT of satavaptan/placebo</td>
<td>&lt;80</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>1.02 (0.74-1.40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mookerjee (2016)</td>
<td>349</td>
<td>Acute-on-chronic liver failure</td>
<td>40</td>
<td>29</td>
<td>27</td>
<td>1</td>
<td>0.60 (0.36-0.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Garcia-Tsao G, J Hepatol 2016

*systolic blood pressure
In a propensity adjusted study in patients with refractory ascites, propranolol was associated with a reduced mortality for doses lower than 160 mg/day.

Bang et al. Liv Int 2016 [ePub ahead of print]
Prevention of Re-Bleeding

- **What is recommended therapy?**
  - First line therapy for all patients is the combination of NSBB (propranolol or nadolol) + EVL
  - NSBB is the key element of combination therapy
  - Carvedilol is not recommended in secondary prophylaxis

- **Should NSBB be used in patients with refractory ascites?**
  - In patients with cirrhosis and ascites NSBB (propranolol, nadolol) should be used cautiously
  - Maximal dose: **80 mg** (BID propranolol, QD nadolol)
  - NSBB should be reduced/discontinued if a patient with refractory ascites develops systolic BP <90 mmHg, hyponatremia or acute kidney injury