Esophageal Varices
Beta-Blockers or Band Ligation

Cesar Yaghi MD
Hotel-Dieu de France University Hospital
Universite Saint Joseph
Esophageal Varices
Beta-Blockers or Band Ligation?

• Risk of esophageal variceal bleeding:
  – Large varices
  – Presence of red spot signs.
  – Liver failure
  – Degree of portal hypertension (HVPG)

• Despite advances in the management of acute variceal bleeding the 6 weeks mortality is still as high as 20%.

• Our Aim:
  – Preventing bleeding
  – Achieving hemostasis
  – Preventing rebleeding

• Multiple question marks remaining in the guidelines.
All Cirrhotics Should Have Initial Screening Endoscopy

Child-Pugh ≤ 7

- No varices at screening: EGD in 2–3 yr
- Small varices at screening: EGD in 1 yr

Child-Pugh > 7

- Large varices at screening: Band ligation or beta blocker
- No or small varices at screening: EGD in 1 yr
Surveillance of oesophageal varices in compensated patients (changed from Baveno V)

- No varices at screening endoscopy and ongoing liver injury (e.g. active drinking in alcoholics, lack of SVR in HCV):
  - Surveillance endoscopy should be repeated at 2 year intervals (5;D).
- No varices at screening endoscopy in whom the etiological factor has been removed (e.g. achievement of SVR in HCV; long-lasting abstinence in alcoholics) and who have no co-factors (e.g. obesity)
  - Surveillance endoscopy should be repeated at 3 year intervals (5;D).
- Small varices and with ongoing liver injury (e.g. active drinking in alcoholics, lack of SVR in HCV)
  - Surveillance endoscopy should be repeated at 1 year intervals (5;D).
- Small varices at screening endoscopy in whom the etiological factor has been removed
  - Surveillance endoscopy should be repeated at two year intervals (5;D).

De Franchis, Journal of Hepatology, 63, (3) September 2015, Pages 743-752
Non-Selective Beta-Blockers

• Patients with no varices or small varices (unchanged)
  – No indication to beta blockers to prevent the formation of varices (1b;A).
• Patients with small varices without signs of increased risk
  – May be treated with NSBB to prevent bleeding (1b;A). Further studies are required to confirm their benefit.
• Patients with small varices with red wale marks or ChildPugh C class have an increased risk of bleeding (1b;A)
  – Should be treated with (NSBB) (5;D).
• Patients with medium-large varices (unchanged)
  – Either NSBB or endoscopic band ligation is recommended for the prevention of the first variceal bleeding of medium or large varices (1a;A).
  – The choice of treatment should be based on local resources and expertise, patient preference and characteristics, contraindications and adverse events (5;D).

De Franchis, Journal of Hepatology, 63, (3) September 2015, Pages 743-752
Primary Prophylaxis against Variceal Hemorrhage.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Goal</th>
<th>Duration</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Starting dose of 20 mg given orally twice a day</td>
<td>Increase to maximally tolerated dose or until heart rate is approximately 55 beats/min</td>
<td>Indefinite</td>
<td>Ensure heart-rate goals met at each clinic visit; no need for follow-up endoscopy</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Starting dose of 40 mg given orally once a day</td>
<td>Increase to maximally tolerated dose or until heart rate is approximately 55 beats/min</td>
<td>Indefinite</td>
<td>Ensure heart-rate goals met at each clinic visit; no need for follow-up endoscopy</td>
</tr>
<tr>
<td>Endoscopic variceal ligation</td>
<td>Every 2–4 weeks</td>
<td>Obliterate varices</td>
<td>Until variceal obliteration achieved (usually 2–4 sessions)</td>
<td>Perform first surveillance endoscopy 1–3 mo after obliteration, then every 6–12 mo indefinitely</td>
</tr>
</tbody>
</table>

* Therapies that should not be used as prophylaxis include nitrates alone, endoscopic variceal sclerotherapy, shunt therapy (either transjugular intrahepatic portosystemic shunt or surgical shunt), nonselective beta-blockers plus endoscopic variceal ligation, and nonselective beta-blockers plus nitrates.

† Only one of the three regimens should be used.
Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Response Rate</th>
<th>HVPG Decrease</th>
<th>2 years Bleeding Rate</th>
<th>Hepatic Decompensation</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>80-160 mg/d</td>
<td>36% (37/104)</td>
<td>$-12 \pm 11%$ (p&lt;0.001)</td>
<td>11%*</td>
<td>38% #</td>
<td>14%</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>6.25-50 mg/day</td>
<td>56% (38/67)</td>
<td>$-19 \pm 10%$ versus $-12 \pm 11%$ (p&lt;0.001)</td>
<td>5%*</td>
<td>25% #</td>
<td>11%</td>
</tr>
<tr>
<td>EBL</td>
<td></td>
<td>44% (29/67)</td>
<td></td>
<td>25%*</td>
<td>55% #</td>
<td>31%</td>
</tr>
</tbody>
</table>

- Carvedilol leads to a significantly greater decrease in HVPG than propranolol.
- Using carvedilol for primary prophylaxis, a substantial proportion of non-responders to propranolol can achieve a hemodynamic response, which is associated with improved outcome with regard to prevention of variceal bleeding, hepatic decompensation and death.

In hemodynamic responders compared to the EBL group.
* P = 0.0429
# p=0.0789
p=0.0455

NSBB
Carvedilol (changed from Baveno V)

• Traditional NSBB (propranolol, nadolol) (1a;A) and carvedilol (1b;A) are valid first line treatments.

• Carvedilol is more effective than traditional NSBB in reducing HVPG (1a;A) but has not been adequately compared head-to-head to traditional NSBB in clinical trials.
Prophylaxis of Variceal Hemorrhage

Diagnosis of Cirrhosis

Endoscopy

No Varices

Small Varices

Medium/Large Varices
Child’s C or Stigmata

Follow-up EGD in 2-3 years*

Follow-up EGD in 1-2 years*

Beta-blocker therapy

*EGD every year in decompensated cirrhosis

• Stepwise increase until maximally tolerated dose
• Continue beta-blocker (life-long)
• No role for repeated endoscopy!!

No Contraindications

Contraindications or Beta-blocker intolerance

Endoscopic Variceal Band Ligation

No role for sclerotherapy or nitrates
NSBB VS EBL for primary prophylaxis of esophageal variceal bleeding:

Overall Bleeding

<table>
<thead>
<tr>
<th>Study name</th>
<th>BB</th>
<th>EVBL</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 1999</td>
<td>2/30</td>
<td>1/26</td>
<td>1.727</td>
<td>0.171</td>
<td>17.422</td>
<td>0.463</td>
<td>0.643</td>
</tr>
<tr>
<td>De, 1999</td>
<td>1/15</td>
<td>2/15</td>
<td>0.489</td>
<td>0.047</td>
<td>5.101</td>
<td>-0.598</td>
<td>0.550</td>
</tr>
<tr>
<td>Sarin, 1999</td>
<td>12/44</td>
<td>4/45</td>
<td>3.431</td>
<td>1.170</td>
<td>10.062</td>
<td>2.245</td>
<td>0.025</td>
</tr>
<tr>
<td>Song, 2000</td>
<td>7/30</td>
<td>6/31</td>
<td>1.263</td>
<td>0.374</td>
<td>4.259</td>
<td>0.376</td>
<td>0.707</td>
</tr>
<tr>
<td>Lopez-Acosta, 2002</td>
<td>3/28</td>
<td>2/28</td>
<td>1.539</td>
<td>0.249</td>
<td>9.505</td>
<td>0.464</td>
<td>0.642</td>
</tr>
<tr>
<td>Gheorghe, 2002</td>
<td>13/28</td>
<td>3/25</td>
<td>4.967</td>
<td>1.551</td>
<td>15.902</td>
<td>2.700</td>
<td>0.007</td>
</tr>
<tr>
<td>Lui, 2002</td>
<td>9/66</td>
<td>3/44</td>
<td>2.004</td>
<td>0.593</td>
<td>6.775</td>
<td>1.119</td>
<td>0.263</td>
</tr>
<tr>
<td>Abulfutah, 2003</td>
<td>10/66</td>
<td>4/44</td>
<td>1.717</td>
<td>0.550</td>
<td>5.366</td>
<td>0.930</td>
<td>0.352</td>
</tr>
<tr>
<td>Lo, 2004</td>
<td>13/50</td>
<td>7/50</td>
<td>2.101</td>
<td>0.792</td>
<td>5.571</td>
<td>1.492</td>
<td>0.136</td>
</tr>
<tr>
<td>Schepeke, 2004</td>
<td>22/77</td>
<td>19/75</td>
<td>1.777</td>
<td>0.577</td>
<td>2.405</td>
<td>0.448</td>
<td>0.654</td>
</tr>
<tr>
<td>Thukuvath, 2005</td>
<td>1/15</td>
<td>2/16</td>
<td>0.524</td>
<td>0.050</td>
<td>5.463</td>
<td>-0.540</td>
<td>0.589</td>
</tr>
<tr>
<td>Jutabha, 2005</td>
<td>4/31</td>
<td>0/31</td>
<td>0.194</td>
<td>1.068</td>
<td>61.158</td>
<td>2.051</td>
<td>0.040</td>
</tr>
<tr>
<td>Psilopoulos, 2005</td>
<td>9/30</td>
<td>2/30</td>
<td>4.680</td>
<td>1.266</td>
<td>16.535</td>
<td>2.316</td>
<td>0.021</td>
</tr>
<tr>
<td>Drastich, 2011</td>
<td>2/33</td>
<td>2/40</td>
<td>1.224</td>
<td>0.164</td>
<td>9.146</td>
<td>0.197</td>
<td>0.844</td>
</tr>
<tr>
<td>Lay, 2006</td>
<td>9/50</td>
<td>5/50</td>
<td>1.793</td>
<td>0.627</td>
<td>5.941</td>
<td>1.147</td>
<td>0.251</td>
</tr>
<tr>
<td>Abdelfattah, 2006</td>
<td>13/52</td>
<td>4/51</td>
<td>3.431</td>
<td>1.218</td>
<td>9.663</td>
<td>2.334</td>
<td>0.020</td>
</tr>
<tr>
<td>Gil, 2006</td>
<td>13/50</td>
<td>6/50</td>
<td>2.641</td>
<td>0.911</td>
<td>7.651</td>
<td>1.775</td>
<td>0.076</td>
</tr>
<tr>
<td>Norberto, 2007</td>
<td>3/31</td>
<td>3/31</td>
<td>1.000</td>
<td>0.188</td>
<td>5.313</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Perez-Ayuso, 2010</td>
<td>9/36</td>
<td>5/39</td>
<td>2.207</td>
<td>0.695</td>
<td>7.003</td>
<td>1.343</td>
<td>0.179</td>
</tr>
</tbody>
</table>

Odds ratio and 95% CI

Favors BB  Favors EVBL

NSBB VS EBL for primary prophylaxis of esophageal variceal bleeding:
Risk of Bleeding at 18 months

NSBB VS EBL for primary prophylaxis of esophageal variceal bleeding: Overall Mortality

NSBB VS EBL for primary prophylaxis of esophageal variceal bleeding: Bleeding-related Mortality

Management of the acute variceal bleeding

• Blood volume restitution
  – Preserve tissue perfusion: restore and maintain hemodynamic stability.
  – Packed red blood cells transfusion conservatively
    • target haemoglobin level between 7 and 8 g/dl,
    • transfusion policy in individual patients should also consider other factors such as cardiovascular disorders, age, hemodynamic status and ongoing bleeding (1b;A).

De Franchis, Journal of Hepatology, 63, (3) September 2015, Pages 743-752
Endoscopy in patients with upper GI bleeding and features suggesting cirrhosis

- Following hemodynamic resuscitation, esophagogastroduodenoscopy within 12 h of presentation (5;D).
- In the absence of contraindications (QT prolongation), pre-endoscopy infusion of erythromycin (250 mg IV 30-120 min before endoscopy (1b;A).
- ICU or other well monitored units (5;D).
- Protection of the airway In patients with altered consciousness (5;D).
- Ligation is the recommended form of endoscopic therapy for acute esophageal variceal bleeding (1b;A).

De Franchis, Journal of Hepatology, 63, (3) September 2015, Pages 743-752
Management of the acute variceal bleeding

- Antibiotic prophylaxis (partly changed from Baveno V)
  - Antibiotic prophylaxis is an integral part of therapy for patients with cirrhosis presenting with upper gastrointestinal (GI) bleeding and should be instituted from admission (1a;A).
  - The risk of bacterial infection and mortality are very low in patients with Child-Pugh A cirrhosis (2b;B),
  - Consider individual patient risk characteristics and local antimicrobial susceptibility patterns (5;D).

- Intravenous ceftriaxone 1 g/24 h should be considered in patients with advanced cirrhosis (1b;A), in hospital settings with high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis (5;D).

De Franchis, Journal of Hepatology, 63, (3) September 2015, Pages 743-752
Management of the acute variceal bleeding
Prevention of hepatic encephalopathy

• Recent studies suggest that either lactulose or rifaximin may prevent hepatic encephalopathy in patients with cirrhosis and upper GI bleeding (1b;A).

• Although, there are no specific studies in acute variceal bleeding, it is recommended to adopt the recent EASL/AASLD HE guidelines
  – Episodic HE should be treated with lactulose (25 ml q 12 h until 2-3 soft bowel movements are produced, followed by dose titration to maintain 2-3 soft bowel movements per day) (5;D).

De Franchis, Journal of Hepatology, 63, (3) September 2015, Pages 743-752
Prognosis of acute variceal bleeding: is being on beta-blockers an aggravating factor? A short-term survival analysis.

- The estimated association between NSBB with both 5-day failure and 6-week mortality was homogenous across all MELD spectrums.
- Prophylactic NSBB treatment is not a negative prognostic indicator for the short-term survival of cirrhotic patients admitted with AVB

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>NSBB</th>
<th>control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>142</td>
<td>49</td>
<td>93</td>
</tr>
<tr>
<td>5-day failure</td>
<td></td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td>probability of survival at 6 weeks</td>
<td></td>
<td>96%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Similar severity of bleeding in both groups
Higher proportion of alcoholic etiology and active alcoholism (37% vs. 10%), higher platelets count and lower hematocrit at admission in the control group

Management of the acute variceal bleeding
Assessment of prognosis

• variables most consistently found to predict six week mortality
  – Child-Pugh class C
  – Updated MELD score
  – Failure to achieve primary hemostasis are the (2b;B).

• Pharmacological treatment (partly changed from Baveno V) In suspected variceal bleeding, vasoactive drugs should be started as soon as possible, before endoscopy (1b;A).

• Vasoactive drugs (terlipressin, somatostatin, octreotide) should be used in combination with endoscopic therapy and continued for up to five days (1a;A).

De Franchis, Journal of Hepatology, 63, (3) September 2015, Pages 743-752
SUMMARY OF MANAGEMENT OF VARICES AND VARICEAL HEMORRHAGE

**Evolution of Varices**

- Cirrhosis with no varices
  - Small varices
    - No hemorrhage
  - Medium / large varices, No hemorrhage
- Variceal hemorrhage
  - Recurrent variceal hemorrhage

**Level of Intervention**

- Pre-primary prophylaxis
- Primary prophylaxis
- Secondary prophylaxis

**Management Recommendations**

- Repeat Endoscopy in 2-3 years
  - No specific therapy
- Repeat endoscopy in 1-2 years
  - No specific therapy
  - Beta blockers or EVL for large varices?
  - Beta-blocker to prevent enlargement?
- Antibiotics in all patients
  - Endoscopic/pharmacologic therapy
  - TIPS or shunt surgery as rescue therapy
- Beta-blockers + EVL?
  - Beta-blockers + nitrates or EVL
  - TIPS or shunt surgery as rescue therapy
Drugs plus ligation to prevent rebleeding in cirrhosis: Effect on rebleeding. Drugs ? EVL? Drugs + EVL?

Drugs plus ligation to prevent rebleeding in cirrhosis: Effect on Mortality.

Drugs ? EVL? Drugs + EVL?

### Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>EVL + Drugs Events</th>
<th>Total</th>
<th>EVL Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009 Ahmad</td>
<td>7</td>
<td>37</td>
<td>6</td>
<td>35</td>
<td>10.2%</td>
<td>1.10 [0.41, 2.96]</td>
</tr>
<tr>
<td>2009 Garcia Pagán</td>
<td>16</td>
<td>80</td>
<td>15</td>
<td>78</td>
<td>25.0%</td>
<td>1.04 [0.55, 1.96]</td>
</tr>
<tr>
<td>2009 Lo</td>
<td>16</td>
<td>60</td>
<td>13</td>
<td>60</td>
<td>24.5%</td>
<td>1.23 [0.65, 2.33]</td>
</tr>
<tr>
<td>2009 Villanueva</td>
<td>18</td>
<td>29</td>
<td>13</td>
<td>30</td>
<td>40.2%</td>
<td>1.43 [0.87, 2.36]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>206</strong></td>
<td><strong>47</strong></td>
<td><strong>203</strong></td>
<td><strong>100.0%</strong></td>
<td>1.24 [0.90, 1.70]</td>
<td></td>
</tr>
</tbody>
</table>

- **Heterogeneity:** $X^2 = 0.70$, df = 3 ($P = 0.87$); $I^2 = 0$
- **Test for overall effect:** $Z = 1.34$ ($P = 0.18$)

### Additional Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>EVL + Drugs Events</th>
<th>Total</th>
<th>EVL Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 Lo</td>
<td>10</td>
<td>60</td>
<td>20</td>
<td>62</td>
<td>52.8%</td>
<td>0.42 [0.18, 1.00]</td>
</tr>
<tr>
<td>2004 Sollano</td>
<td>0</td>
<td>16</td>
<td>1</td>
<td>15</td>
<td>4.8%</td>
<td>0.29 [0.01, 7.76]</td>
</tr>
<tr>
<td>2005 De la Peña</td>
<td>5</td>
<td>43</td>
<td>4</td>
<td>37</td>
<td>12.2%</td>
<td>1.09 [0.27, 4.38]</td>
</tr>
<tr>
<td>2009 Ahmad</td>
<td>7</td>
<td>37</td>
<td>8</td>
<td>39</td>
<td>20.4%</td>
<td>0.90 [0.29, 2.80]</td>
</tr>
<tr>
<td>2009 Kumar *</td>
<td>1</td>
<td>72</td>
<td>3</td>
<td>69</td>
<td>9.7%</td>
<td>0.31 [0.03, 3.05]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>228</strong></td>
<td><strong>36</strong></td>
<td><strong>222</strong></td>
<td><strong>100.0%</strong></td>
<td>0.58 [0.33, 1.03]</td>
<td></td>
</tr>
</tbody>
</table>

- **Heterogeneity:** $X^2 = 2.36$, df = 4 ($P = 0.67$); $I^2 = 0$
- **Test for overall effect:** $Z = 1.84$ ($P = 0.07$)
Risk factors for band-induced ulcer bleeding after prophylactic and therapeutic endoscopic variceal band ligation.

140 for acute hemorrhage

749 episodes of EVBL

609 prophylactic procedures

EVBL-induced ulcer bleeding 2.8%

Death: 28%

EVBL-induced ulcer bleeding 1.5%,

22% mortality.

Acute variceal hemorrhage = only significant predictor of EVBL-induced ulcer bleeding [OR =6.25 (2.57-15.14), P<0.0001

Higher MELD score reflux esophagitis associated with EVBL-induced ulcer bleeding [OR 25.53 (2.14-303.26), P=0.010 and OR 1.07 (1.01-1.13), P=0.019,

Vaughan R. Eur J Gastroenterol Hepatol 2015 Aug; Vol. 27 (8), pp. 928-32
Take Home messages

• Beta Blockers for medium sized varices as a primary prophylaxis
• Carvedilol is superior to propranolol for decreasing HVPG and decreasing the risk of bleeding.
• For larger varices, EVL = Beta blockers in terms of mortality
• EVL seems better than Beta blockers for primary prophylaxis
• EVL + Beta-blockers seems better than EVL or Beta-blockers alone for prevention of secondary esophageal bleeding.
**Evolution of Varices**

- Cirrhosis with no varices
  - Small varices, No hemorrhage
    - Medium / large varices, No hemorrhage
      - Variceal hemorrhage
        - Recurrent variceal hemorrhage

**Level of Intervention**

- Pre-primary prophylaxis
- Primary prophylaxis
- Secondary prophylaxis

**Management Recommendations**

- Repeat Endoscopy in 2-3 years
  - No specific therapy

- Repeat endoscopy in 1-2 years
  - No specific therapy
  - Beta-blockers or EVL for primary prophylaxis for large varices especially in advanced liver disease

- Antibiotics in all patients
  - Endoscopic/pharmacologic therapy
  - No added risk with beta blockers
  - TIPS or shunt surgery as rescue therapy

- Beta-blockers + EVL
  - Beta-blockers + nitrates or EVL
  - TIPS or shunt surgery as rescue therapy