

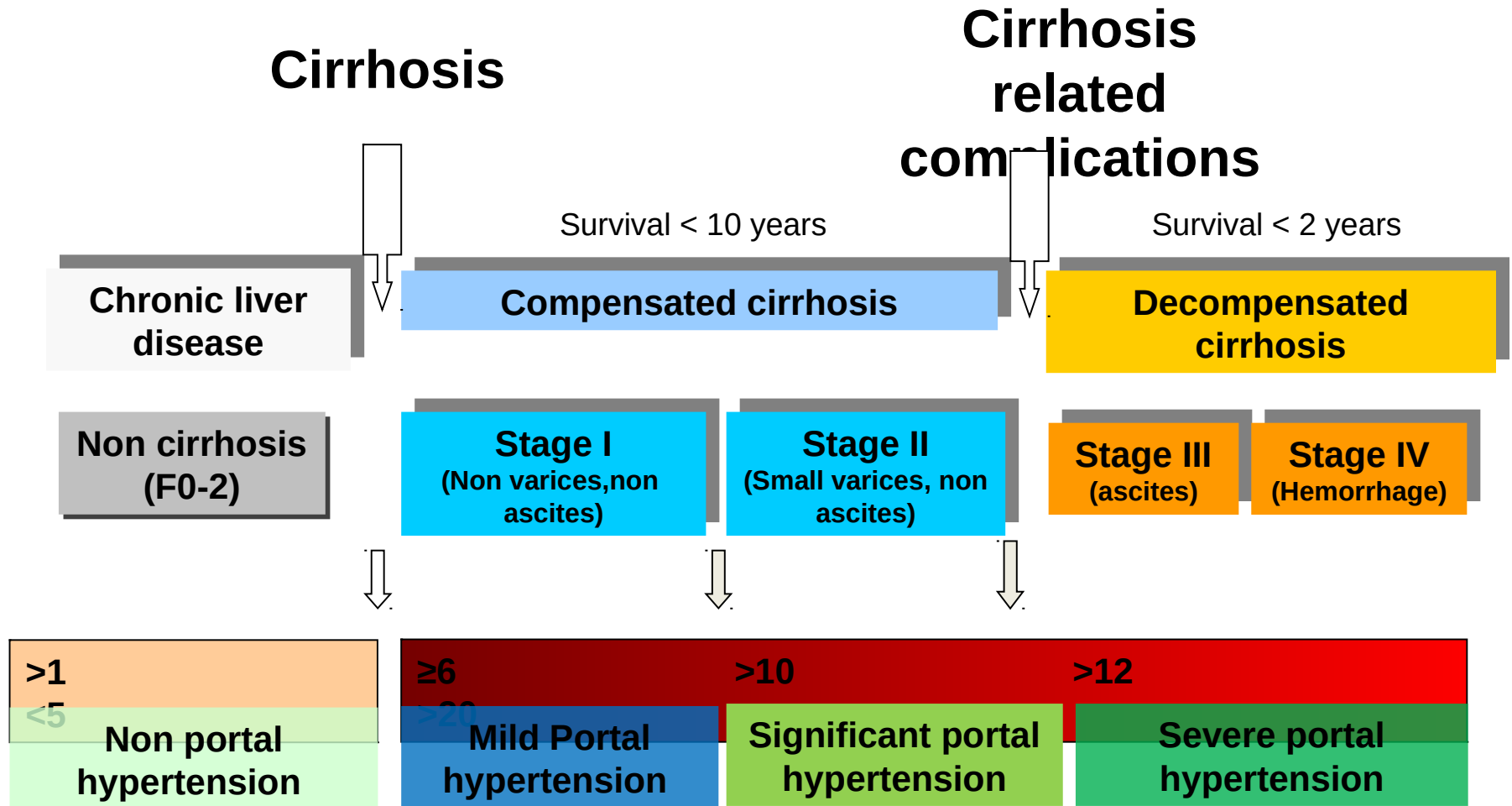
# BETA-BLOCKERS IN CIRRHOSIS.PRO.

Angela Puente Sánchez. MD PhD

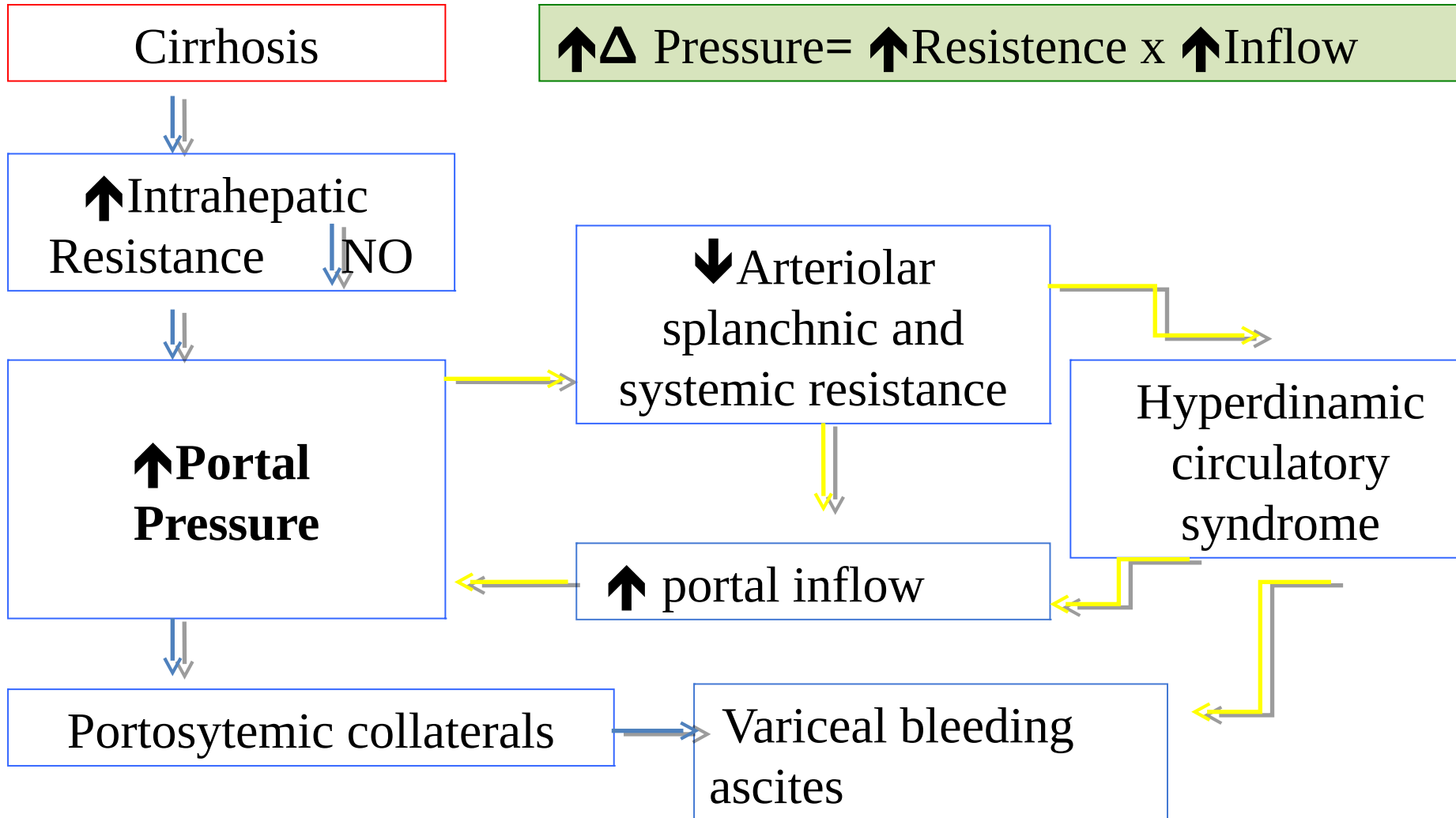
Hepatology Unit. Gastroenterology department

Marques de Valdecilla University Hospital. Santander

# INTRODUCTION. Natural history of cirrhosis



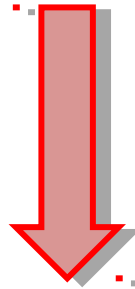
# Pathophysiology of portal hypertension



# Beta blocker therapy in cirrhosis.

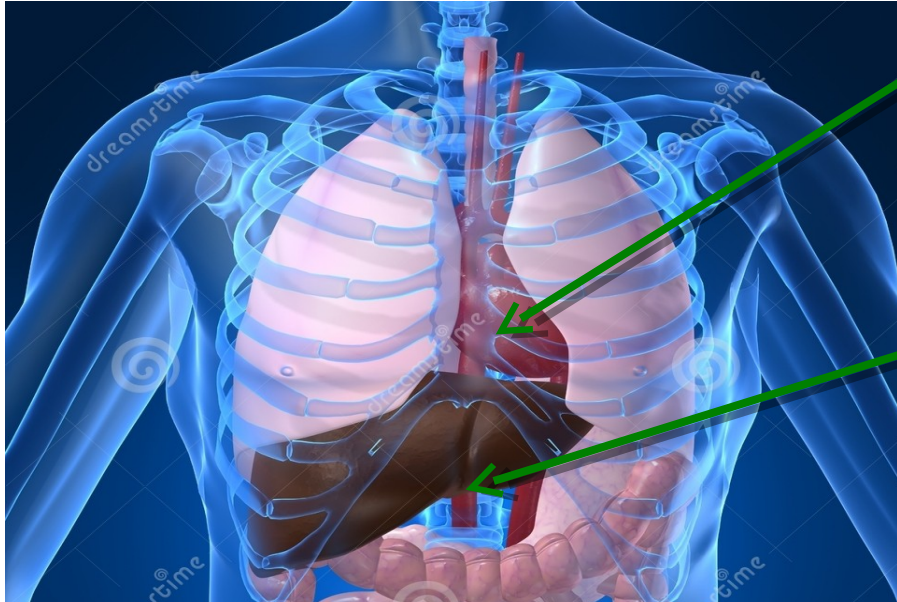
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INDICATION



PREVENTION OF VARICEAL BLEEDING

# Action mechanism Non cardioselective Beta-blockers (NSBB): **Nadolol and propranolol**



$B_1$  adrenergic blockade

↓ cardiac output

$B_2$  adrenergic blockade

splanchnic vasoconstriction

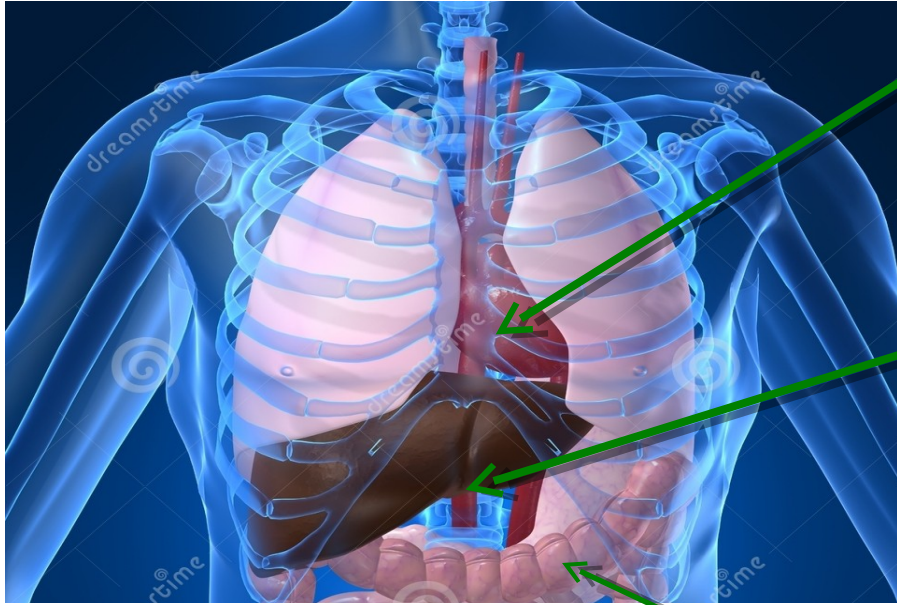
↓ Portal blood flow

## Adverse effects ( $B_2$ )

- abrupt cessation: angina, myocardial infarction, increased airways resistance
- exacerbations of peripheral artery disease
- impaired glucose recovery from insulin-induced hypoglycemia
- depression, fatigue, and sexual dysfunction

# Action mechanism Non cardioselective Beta-blockers:

## Carvedilol



$B_1$  adrenergic blockade

↓ cardiac output

$B_2$  adrenergic blockade  
(partial agonist)

splanchnic vasoconstriction  
↓ Portal blood flow

### Adverse effects

Less  $B_2$  effects

Hypotension

Fatigue

$\alpha_1$  adrenergic blockade

↓ Arterial pressure

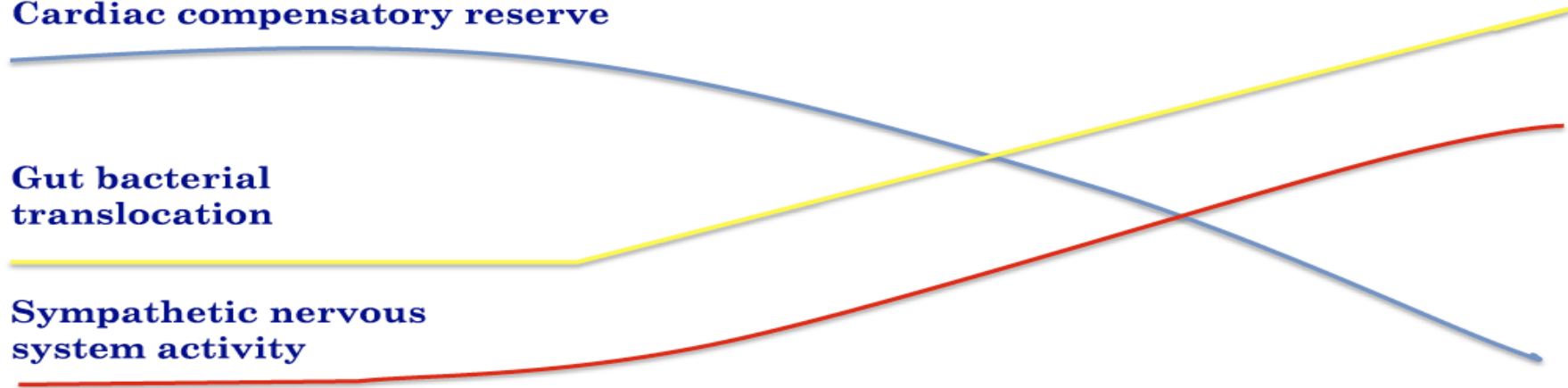
↑ Hepatic blood flow

# THE THERAPEUTIC WINDOW OF NSBB:

Cardiac compensatory reserve

Gut bacterial translocation

Sympathetic nervous system activity



BB have **no effect on survival**

BB **improve survival** by reducing the risk of variceal bleeding and bacterial translocation

BB **reduce survival** due to a negative impact on the cardiac compensatory reserve. The inability to increase the cardiac output during stress compromises organ perfusion.

Window opens

Window closes

**Early cirrhosis**

- I. No risk of bacterial translocation
- II. No increase in sympathetic nervous system activity
- III. Cardiac compensatory reserve intact

**Compensated and decompensated cirrhosis**

(Medium-large varices)

- I. Increased risk of bacterial translocation
- II. Increased sympathetic nervous system activity
- III. Cardiac compensatory reserve intact and blood pressure and organ perfusion protected

**End-stage cirrhosis**

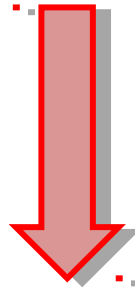
(Refractory ascites)

- I. Increased risk of bacterial translocation
- II. Maximum sympathetic nervous system stimulation
- III. Cardiac compensatory reserve impaired

# Beta blocker therapy in cirrhosis.

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INDICATION



PREVENTION OF VARICEAL BLEEDING



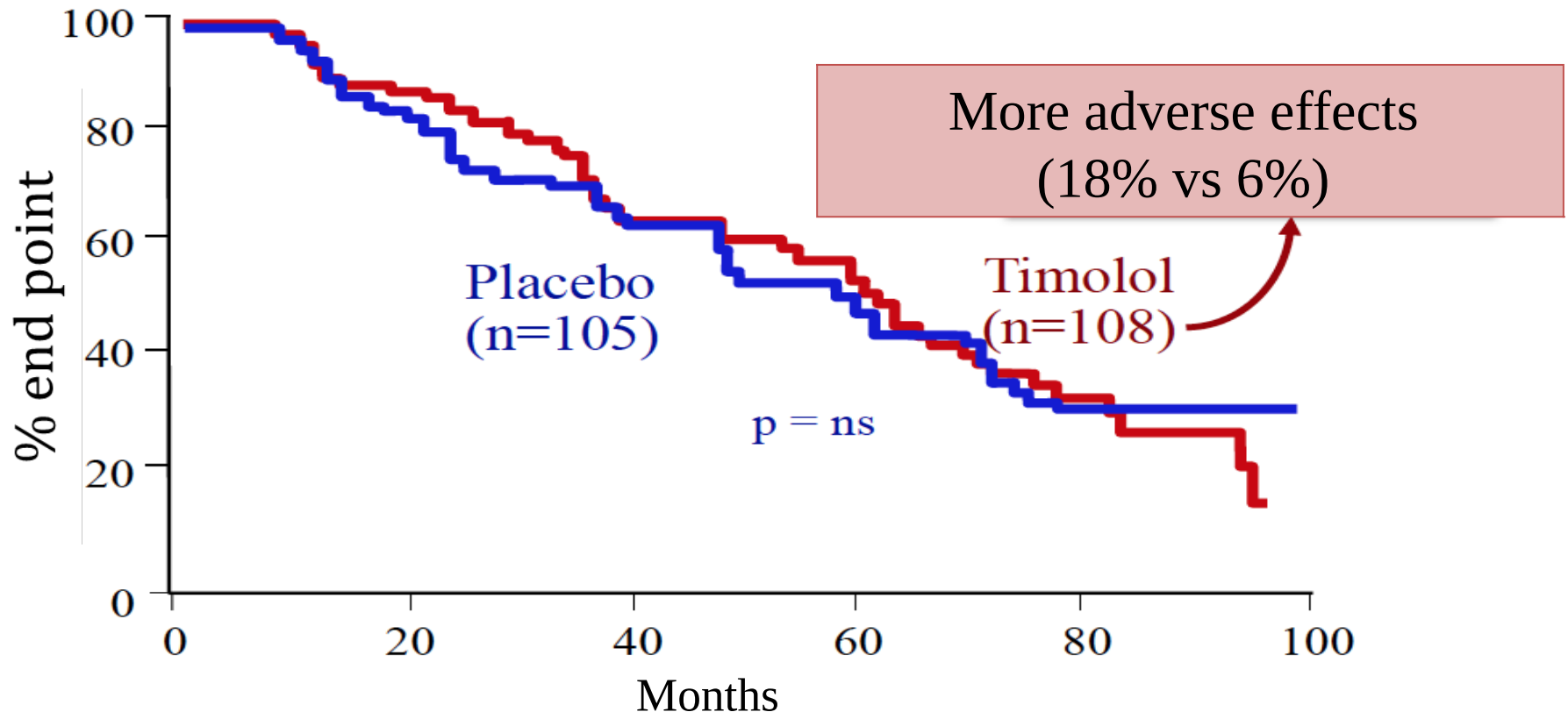
1. Preprimary prophylaxis
2. Primary prophylaxis
3. Secondary prophylaxis



# Variceal bleeding. Preprimary prophylaxis.

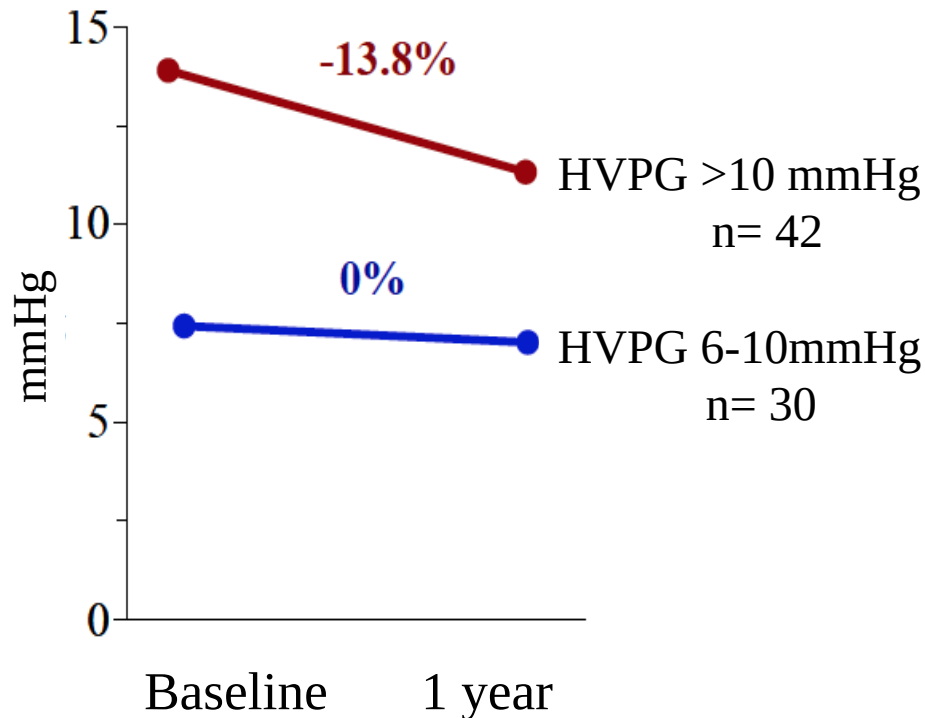
## Timolol vs placebo

End-point: development of varices or variceal hemorrhage



# Variceal bleeding. Preprimary prophylaxis.

## Timolol treatment



BB don't prevent variceal development and don't improve mild portal hypertension

Multicentric spanish study: PREDESCI (NCT01059396)

To assess whether BB decrease the risk of decompensation in compensated cirrhosis with HVPG >10mm Hg.

# Variceal bleeding. Preprimary prophylaxis.

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Position Paper

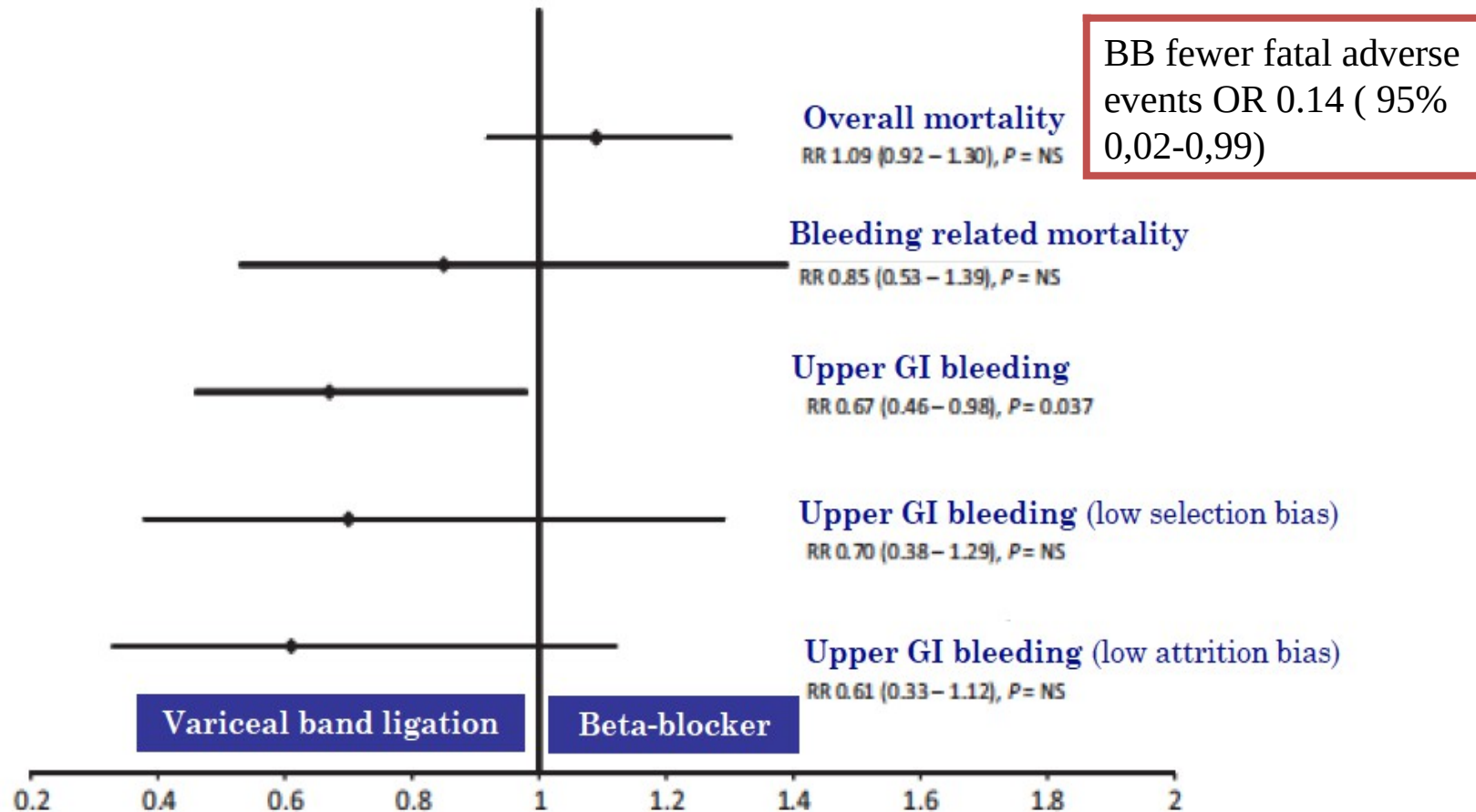


## **Expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension**

- There is no indication, at this time, to use beta blockers to prevent the formation of varices (1b;A)
- Aetiological treatment ( including obesity) may reduce portal hypertension and prevents complications in patients with established cirrhosis (1b;A)
- The clinical use of statins is promising and should be evaluated in further phase III studies (1b;A).

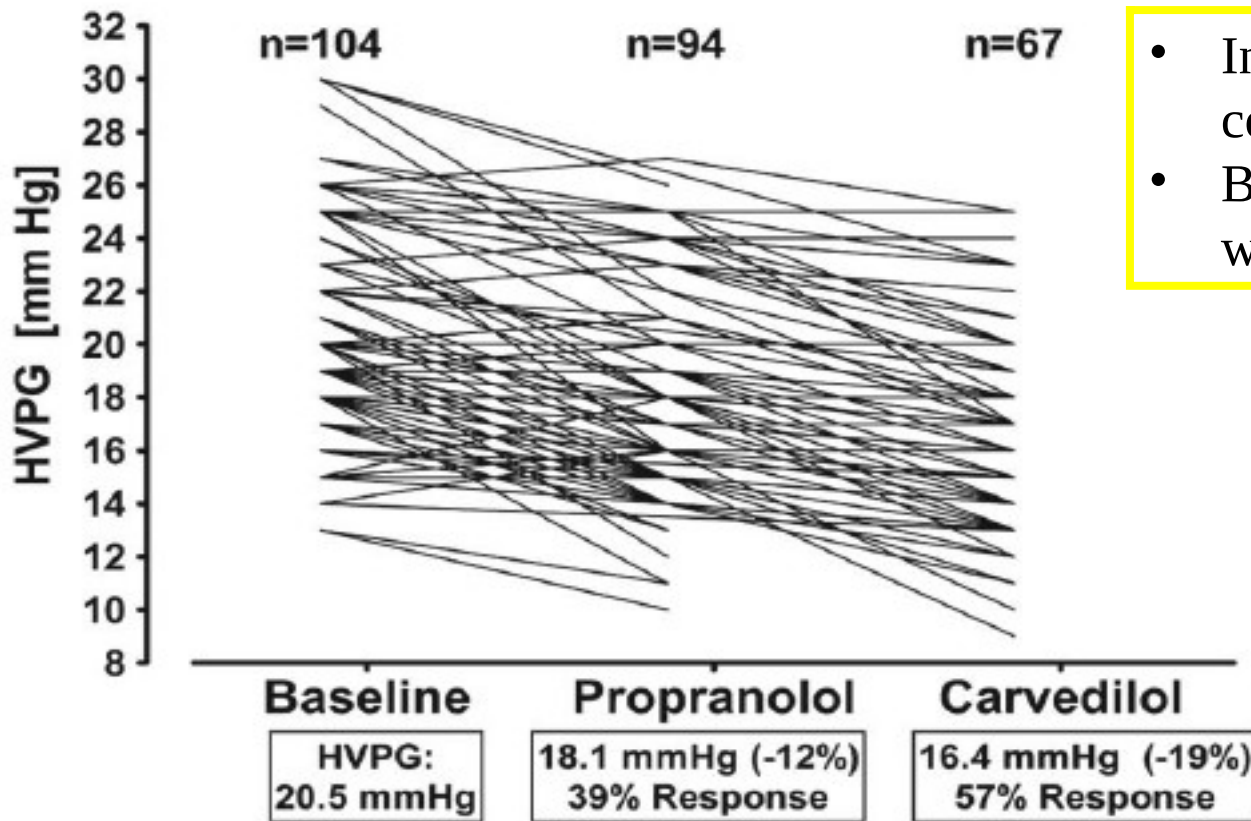
# Variceal bleeding. Primary prophylaxis

## Meta-analysis of 19 trials ( 1504 patients)



# Variceal bleeding. Primary prophylaxis

## Hemodynamic response to propranolol and carvedilol



- Indication in compensated cirrhosis
- Be careful in patients with ascites

# Variceal bleeding. Primary prophylaxis

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Position Paper



## **Expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension**

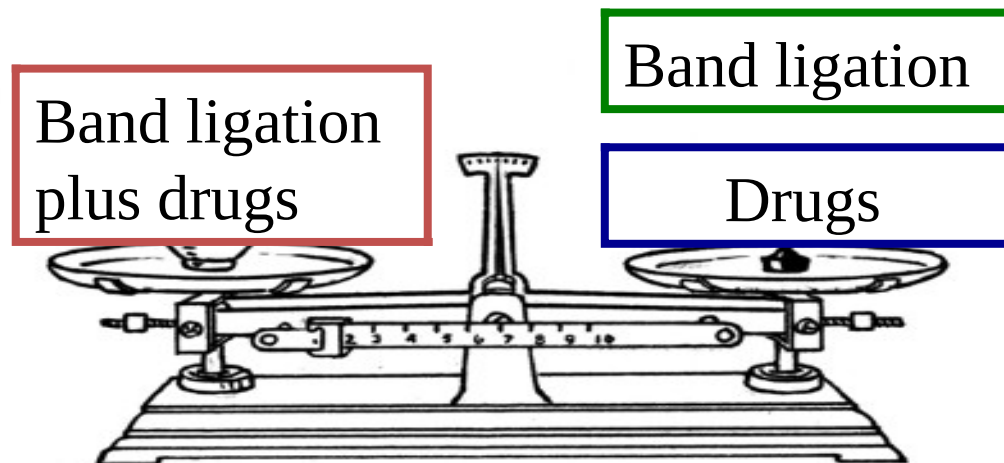
### **Patients with medium-large varices**

- 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).

### **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.

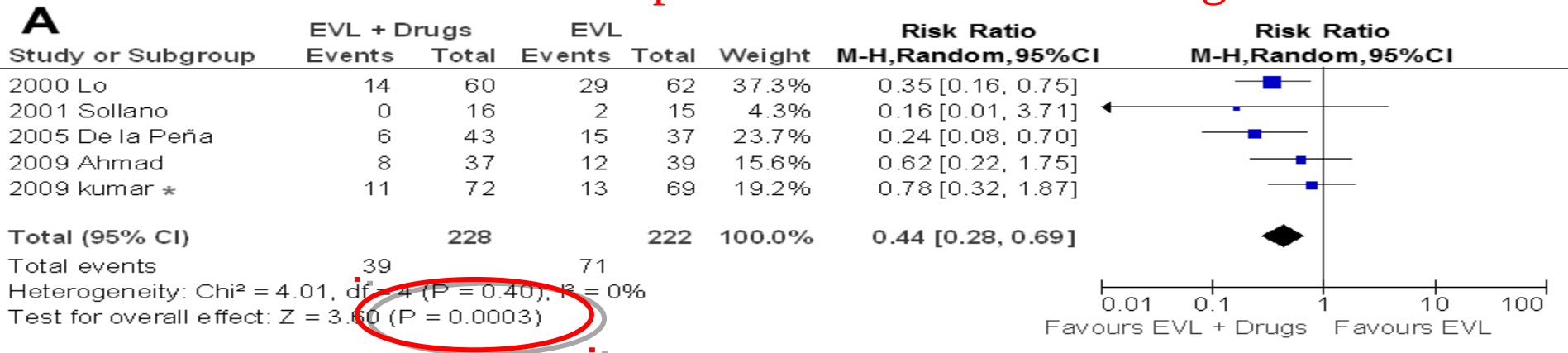
## Is the combination of medical therapy and EBL still the recommended approach for all patients?



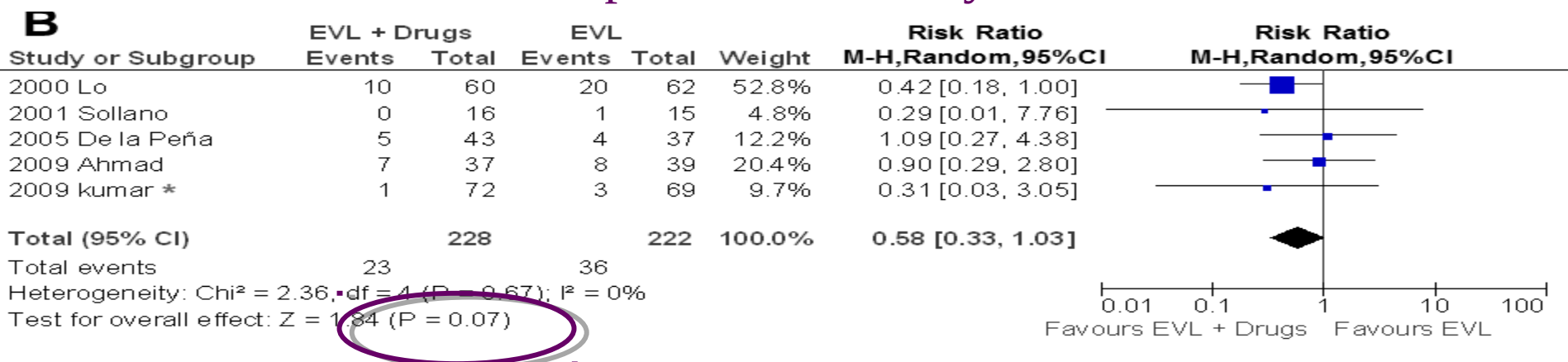
# Variceal bleeding. Secondary prophylaxis

Pooled meta-analysis of trials comparing EVL vs EVL plus drugs (476 patients)

## Forest plots for overall rebleeding



## Forest plots for mortality

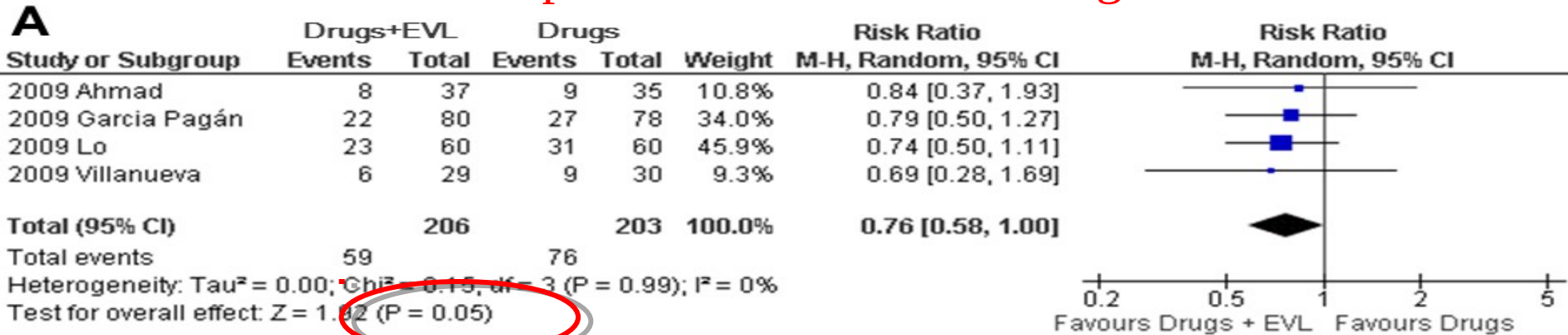




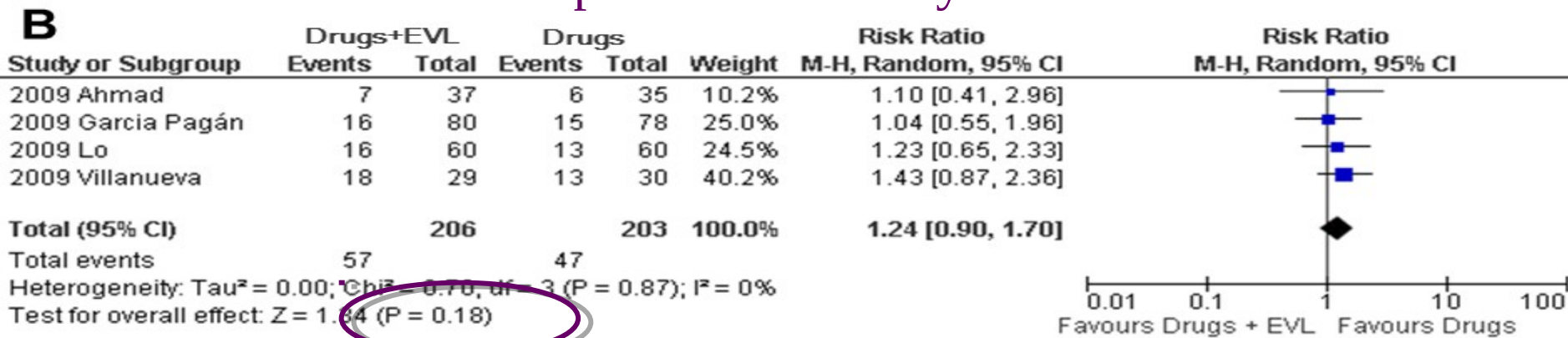
# Variceal bleeding. Secondary prophylaxis

Pooled meta-analysis of trials comparing EVL plus drugs vs **drugs** (476 patients)

## Forest plots for overall rebleeding



## Forest plots for mortality



# Variceal bleeding. Secondary prophylaxis

Position Paper



## **Expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension**

- First line therapy for all patients is the combination of NSBB (propranolol or nadolol) + EVL (1a;A).
- EVL should not be used as monotherapy unless there is intolerance/contraindications to NSBB (1a;A).
- NSBB should be used as monotherapy in patients with cirrhosis who are unable or unwilling to be treated with EVL (1a;A).
- Covered TIPS is the treatment of choice in patients that fail first line therapy (NSBB + EVL) (2b;B).
- Because carvedilol has not been compared to current standard of care, its use cannot be recommended in the prevention of rebleeding (5;D).

# Use of NSBB in frequent situations

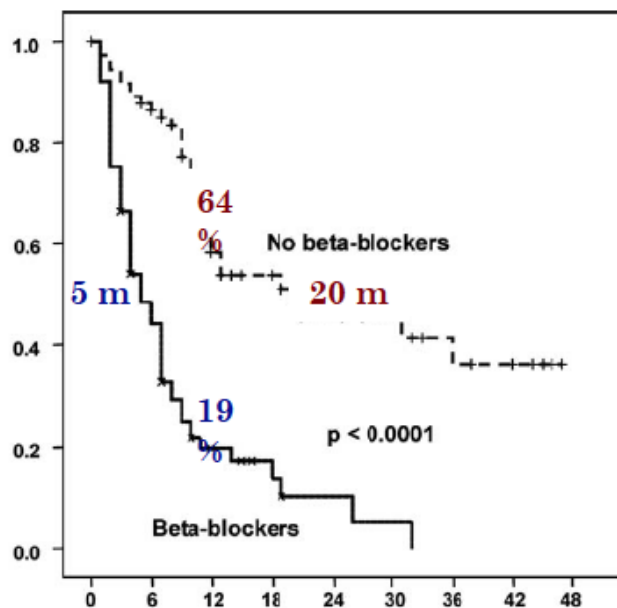
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1. Refractory ascites, hepatorenal syndrome and SBP
2. Portal thrombosis

# 1.Refractory ascites, SBP and hepatorenal syndrome

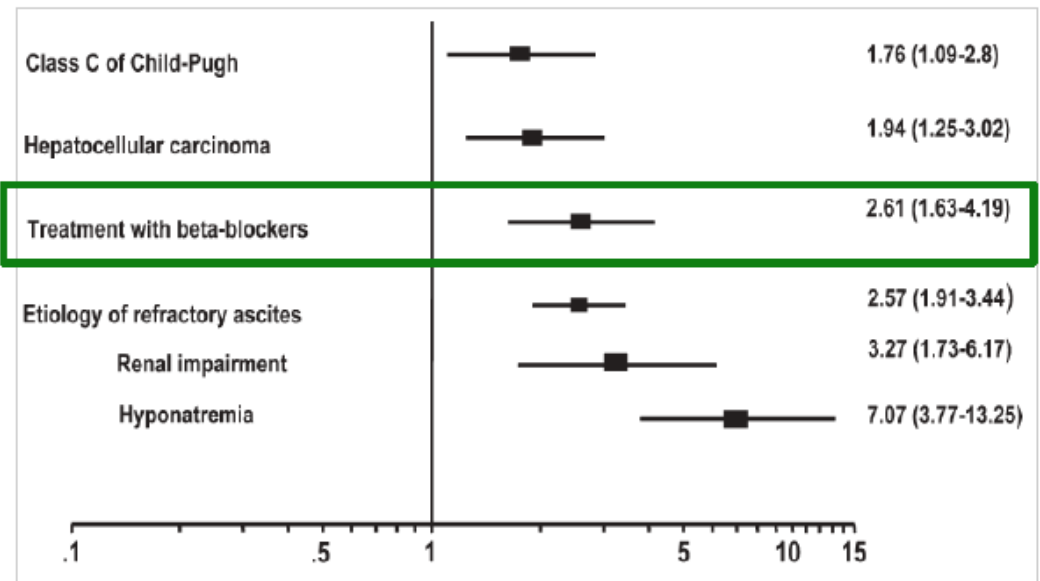
151 cirrhotic patients with refractory ascites  
Retrospective study

## Survival



Months

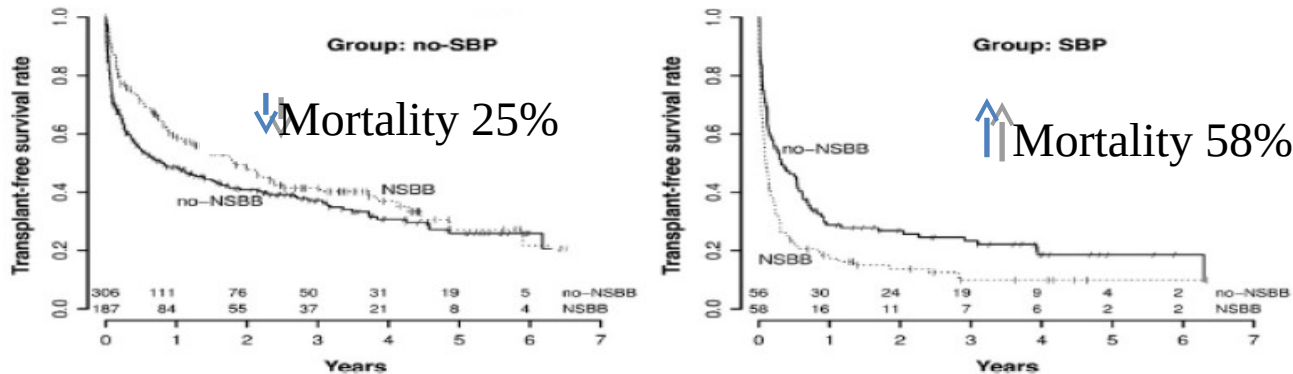
## Independent predictors of mortality



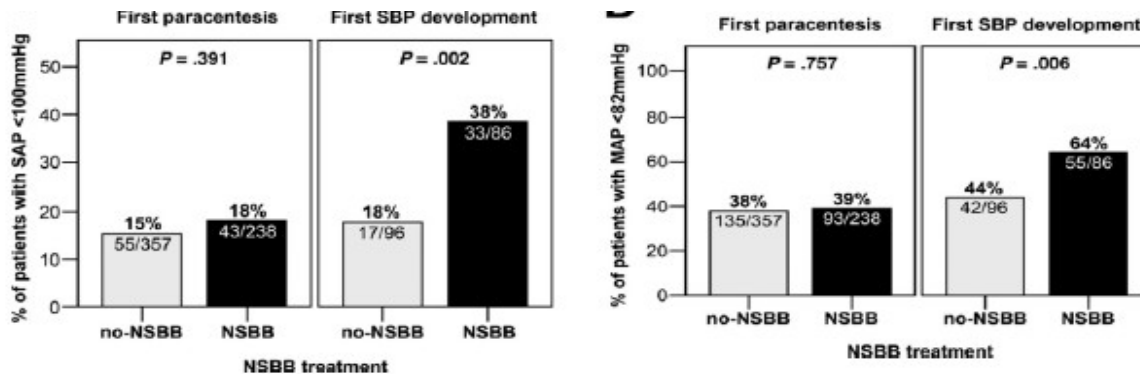
Hazard ratio

# 1.Refractory ascites, SBP and hepatorenal syndrome

## NSBB influence in survival in order to SBP



## NSBB influence in arterial pressure after first paracentesis or SBP



NSBB increase the risk of death and SBP

# 1.Refractory ascites, SBP and hepatorenal syndrome

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Position Paper



## **Expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension**

### **Primary prophylaxis and use of NSBB in patients with end-stage liver disease**

- The safety of NSBB in subgroups with end-stage disease (refractory ascites and/or spontaneous bacterial peritonitis) has been questioned (2b;B).
- NSBB contraindications may be absent when the therapy is firstly prescribed but need to be monitored during the evolution of the disease (5;D).
- Close monitoring is necessary in patients with refractory ascites, and reduction of dose or discontinuation can be considered in those who develop low blood pressure and impairment in renal function (4;C).
- If NSBB are stopped endoscopic band ligation should be performed (5;D).

# 1.Refractory ascites, SBP and hepatorenal syndrome

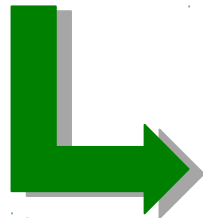
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## Secondary prophylaxis and use of NSBB in patients with end-stage liver disease

- In patients with cirrhosis and refractory ascites NSBB should be used cautiously with close monitoring of blood pressure, serum sodium and serum creatinine (4;C).
- Until randomized trials are available NSBB should be reduced/discontinued if a patient with refractory ascites develops any of the following events (5;D):
  - Systolic blood pressure <90 mmHg
  - Hyponatremia (<130 mEq/L)
  - Acute kidney injury
- The consequences of discontinuing NSBB in the setting of secondary prophylaxis are unknown.

## 2. Portal thrombosis

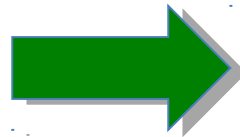
NSBB decrease  
portal vein flow



	Portal vein flow velocity		OR ( 95%CI)
	<15 cm/s	>15 cm/s	
Portal venous thrombosis incidence	47,8%	2%	44,9 (5,3- 282)



Only one study has  
demonstrated it in  
cirrhotic patients



No evidence for NSBB  
discontinuation



# CONCLUSIONS:

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- **Primary prophylaxis**
  - Nadolol/ propranolol in high risk varices or Child C patients with small varices
  - Carvedilol in compensated cirrhosis.
- **Secondary prophylaxis**
  - NSBB are the key treatment, but EVL must be done
  - Covered TIPS is the treatment of choice in patients that fail first line therapy (NSBB + EVL)
- **Window hypothesis**
  - Non efficacy in early stages of cirrhosis (HVPG <10 mmHg)
  - Hemodynamic and non hemodynamic effects



**Thank you for your attention**