

# Caso 1

**Paciente de 58 años, antecedentes de varias internaciones en el sanatorio Laprida por síndrome ascítico edematoso en el ultimo año e insuficiencia renal, que consulta por edemas en MMI, distensión abdominal y disminución del ritmo diurético. Medicado desde hacía 6 meses con furosemida 40 mg/día, espironolactona 300 mg/día, lactulosa,**

**Por no presentar mejoría clínica se realiza IC a nuestro servicio.**

**El paciente niega ingesta de alcohol.**

**Presenta serología viral negativa.**

**Paciente obeso, HTA.**

**Refiere que no realiza la dieta hiposódica adecuadamente.**

**Trae ecografía del 01/02/05 que muestra hígado compatible con hepatopatía crónica, sin MOE, abundante ascitis. Esplenomegalia.**

**Ecocardiograma normal.**

**AFP: normal**

**Se descarta PBE.**

**Se indica espironolactona 200 mg/día, lactulón, Vit B, dieta hiposódica.**

Valores	Fechas	26/11/2004	26/01/2005	14/02/2005	21/04/2005	22/04/2005	23/04/2005	24/04/2005
HEMATOCRITIO		40.0	35.0	36.0		28.0		
REC TO. DE G.BLANCOS		4000	3500	6300		4300		
REC TO. DE PLACQUETAS						81000		
ERITROSEDIMENTACION								
GLUCEMIA		85	103	105		120	301	90
UREMIA		70	71	70		79	88	59
CREATININA SANGRE		1.30		2.00		1.54	1.84	1.48
SODIO EN SANGRE		138		127		136	133	138
POTASEMIA		3.80		5.60		5.20	5.24	5.30
ASAT		24	15	11		45		
ALAI		12	9	10		19		
FOSFATASA ALCALINA			280	270				
GAMMA GLUTAMIL TRANSPEPTIDASA						166		
COLINESTERASA SERICA		1892				2030		
PROTEINAS TOTALES		6.1						
ALBUMINA SERICA		3.1		3.0				
TIEMPO DE PROTROMBINA				15.0		12.9		
TASA						90		
TIEMPO DE TROMBOPLASINA PARCIAL CO						28		
LACTICO DEHIDROGENASA -LDH-						398		
BILIRUBINEMIA TOTAL						1.79		
BILIRUBINA DIRECTA						0.43		

**ESÓFAGO: CM 39 cm de ADS. Se observan várices esofágicas pequeñas y cortas que desaparecen con insuflación- varices esofágicas grado I**

**ESTÓMAGO: cuerpo y fundus con imagen de reticulado. Hemorragias subepiteliales lineales a nivel de antro compatible con GAVE. A nivel de cardias se observan hemorragias subepiteliales, no pudiendo descartar GAVE aislado de cardias vs. gastropatía hipertensiva severa.**

**DUODENO: bulbo y segunda porción S/P**

**Conclusión:**

**Várices esofágicas Grado I**

**Gastropatía hipertensiva leve con probable GAVE aislado de cardias**

# Caso 2

Paciente que consulta por primera vez en agosto 2003, derivado de Pergamino para estudio por hipertransaminasemia asintomática.

Presenta como antecedentes de jerarquía FHA en 1982 (transfundido).

Diabético tipo 1 (Insulina NPH humana).

En pergamino se realiza elisa VHC +

En Rosario se realiza PCR VHC +

Genotipo: 1b

PBH (24 09 03):Hepatitis crónica en fase cirrótica sin componente lobular, con intensa esteatosis macro y microvacuolar, asociada a fibrosis portal y pericelular con formación de puentes y nódulos.Grado: II, Estadio: IV.

Valores	Fechas	21/08/2003	24/08/2004	03/02/2005	09/02/2007
HEMATOCRITO		43.0	47.0	43.0	42.6
REC TO. DE G BLANCOS		6900	6400	7700	8290
REC TO. DE PLAQUETAS		153000	191000	174000	
EMITROSEDIMENTACION		2			
GLUCEMIA		160	145	160	
UREMIA		42	40	35	38
CREATININA SANGRE		1.00	0.90	0.90	0.91
SODIO EN SANGRE		139	139	139	140
POIASEMIA		4.30	4.20	4.60	3.85
ASAT		170	90	140	110
ALAT		230	150	220	179
FOSFATASA ALCALINA		340	315	320	311
GAMMA GLUTAMIL TRANSPEPTIDASA		125	125	210	111
COLINESTERASA SERICA		7100	6800	7500	7890
PROTEINAS TOTALES					
ALBUMINA SERICA		4.5			4.4
TIEMPO DE PROTROMBINA		14.8		13.9	14.4
TASA		80		78	82
EDN				1	
LACTICO DEHIDROGENASA -LDE-					
BILIRUBINEMIA TOTAL		0.90			1.00
BILIRUBINA DIRECTA		0.80			0.20
COLESTEROL TOTAL		120			
TRIGLICERIDOS		216			

Eco Abdominal: H: superficie lisa, estructura homogénea. No MOE. Se visualiza vena porta de calibre conservado. Se mide diámetro en su zona próxima a la arteria hepática:12 mm. No ascitis.

V: paredes finas, alitiásica.

VB: calibre conservado

P: forma, tamaño, contornos y eco estructura conservados. No dilatación de Wirsung.

B: no se observa esplenomegalia.

AFP:(28 08 04) Cibic 6.3 ng/ml

AFP:(08 02 05) Centenario 9.2 ng/ml

# VEDA

ESÓFAGO:

CM a 40 cm de ADS. Hernia de hiatus pequeña. Mucosa normal

ESTÓMAGO: mucosa normal

DUODENO: mucosa normal

Conclusión: Hernia de hiatus

# Clinically Significant Portal Hypertensión

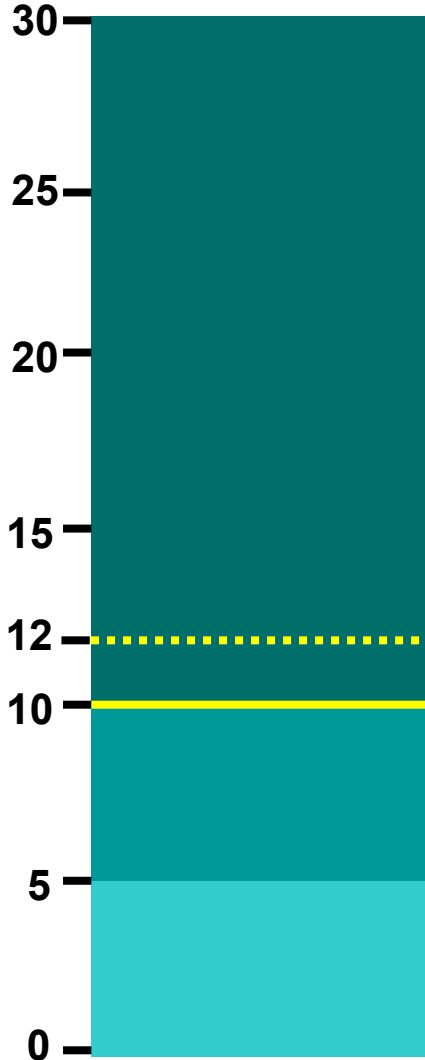
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- Clinically significant portal hypertension is defined by an increase in portal pressure gradient to a threshold above approximately 10 mmHg
- The presence of varices, variceal hemorrhage and/or ascites is indicative of the presence of CSPH

# Portal Hypertension

## Portal Pressure

(mmHg)



Portal hypertension

Normal portal pressure

Clinically significant portal hypertension

Sub-clinical portal hypertension

# Portal Hypertensión

## Pre-primary prophylaxis

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### AIMS

- To prevent variceal formation when varices are not yet present
- To decrease the growth of small varices with low bleeding risk

# LACK OF EFFECT OF PROPRANOLOL IN THE PREVENTION OF LARGE VARICES IN PATIENTS WITH CIRRHOSIS: A RANDOMIZED TRIAL

Paul Calès, Frédéric Oberti, Jean-Louis Payen, Sylvie Naveau, Dominique Guyader, Pierre Blanc, Armand Abergel, Philippe Bichard, Jean-Michel Raymond, Valérie Canva-Delcambre, Denis Vetter, Dominique Valla, Michael Beauchant, Antoine Hadengue, Bruno Champigneulle, Jean-Pierre Pascal, Thierry Poynard, Didier Lebrec and the French-Speaking Club for the Study of Portal Hypertension

**Study design:** Multicenter, RCT, double blind

**Population:** 206 cirrhotic patients ( $\cong$  82% alcoholics)

  
No varices (n:79)      Small varices (n:127)

**Aim:** Prevention of the formation of large varices

**Drug:** Long-acting propranolol  
Fixed daily dose: 160 mg

**Follow-up:** 2 years

# RESULTS

- Large varices { Propranolol (31%) p<0.05 at 2 years  
Placebo (14%) NS at 3 years

Ocurrence of large varices according to the presence of small varices or the absence of varices at inclusion

Varices at inclusion	Propranolol	Placebo	p
Absent	17	4	0.29
Small	52	30	0.11

- Bleeding: Propranolol (n:3) vs. Placebo (n:4) NS
- Death: Propranolol (n:9) vs. Placebo (n:10) NS

One third of the patients were lost to follow-up

# A Placebo-Controlled Clinical Trial of Nadolol in the Prophylaxis of Growth of Small Esophageal Varices in Cirrhosis

CARLO MERKEL,\* RENATO MARIN,<sup>†</sup> PAOLO ANGELI,\* PIERLUIGI ZANELLA,<sup>§</sup> MARTINA FELDER,<sup>||</sup> ELISABETTA BERNARDINELLO,\* GIORGIO CAVALLARIN,<sup>¶</sup> MASSIMO BOLOGNESI,\* CARLO DONADA,<sup>#</sup> BARBARA BELLINI,\* PIERLUIGI TORBOLI,\*\* ANGELO GATTA,\* and the GRUPPO TRIVENETO PER L'IPERTENSIONE PORTALE

\*Department of Clinical and Experimental Medicine, University of Padua, Padua; <sup>†</sup>General Hospital of Dolo, Dolo; <sup>§</sup>General Hospital of Thiene, Thiene; <sup>||</sup>General Hospital of Bolzano, Bolzano; <sup>¶</sup>General Hospital of Chioggia, Chioggia; <sup>#</sup>General Hospital of Pordenone, Pordenone; and \*\*General Hospital of Trento, Trento, Italy

**Study design:** Multicenter, RCT, single blind

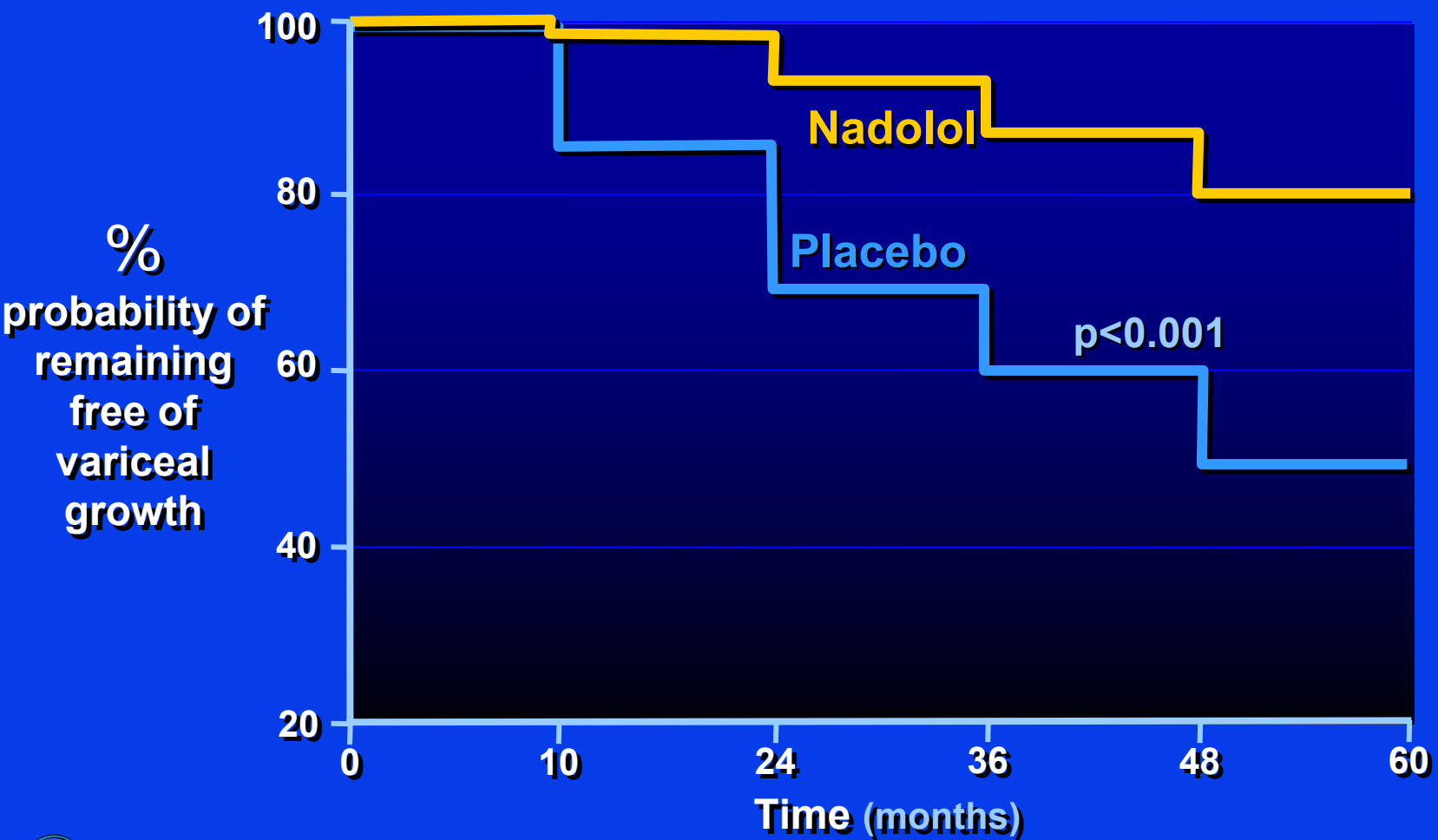
**Population:** 161 cirrhotic patients with small varices  
(57% alcoholics)

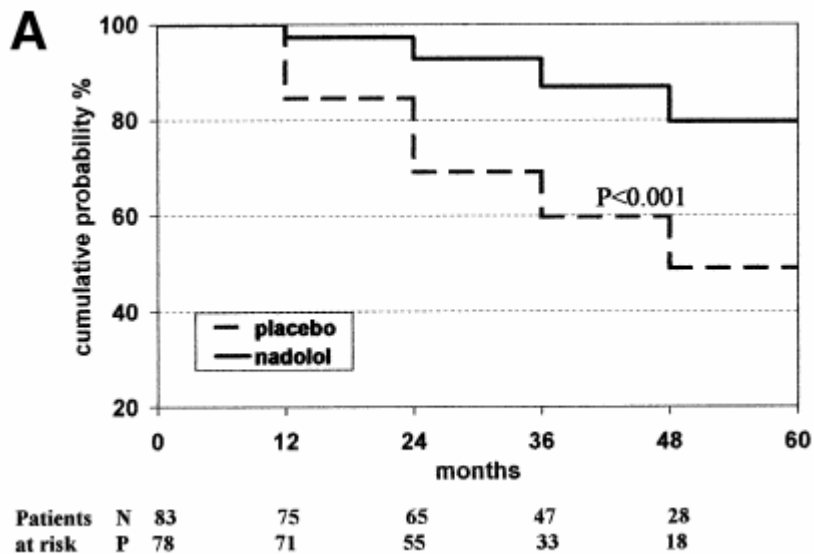
**Aims:** a) Prophylaxis of growth of small varices  
b) Variceal bleeding / death / drug-related adverse effects / regression of varices

**Drug:** Nadolol  
Mean daily dose:  $62 \pm 25$  mg

**Mean follow-up:** 36 months

# Nadolol May Prevent the Growth of Small Varices





Variceal growth

Nadolol (n:9)

Placebo (n:29)

p < 0.001

Probability of remaining free of bleeding after a diagnosis of variceal aggravation

Nadolol

Placebo

NS

Regression of varices

Nadolol (n:15)

Placebo (n:5)

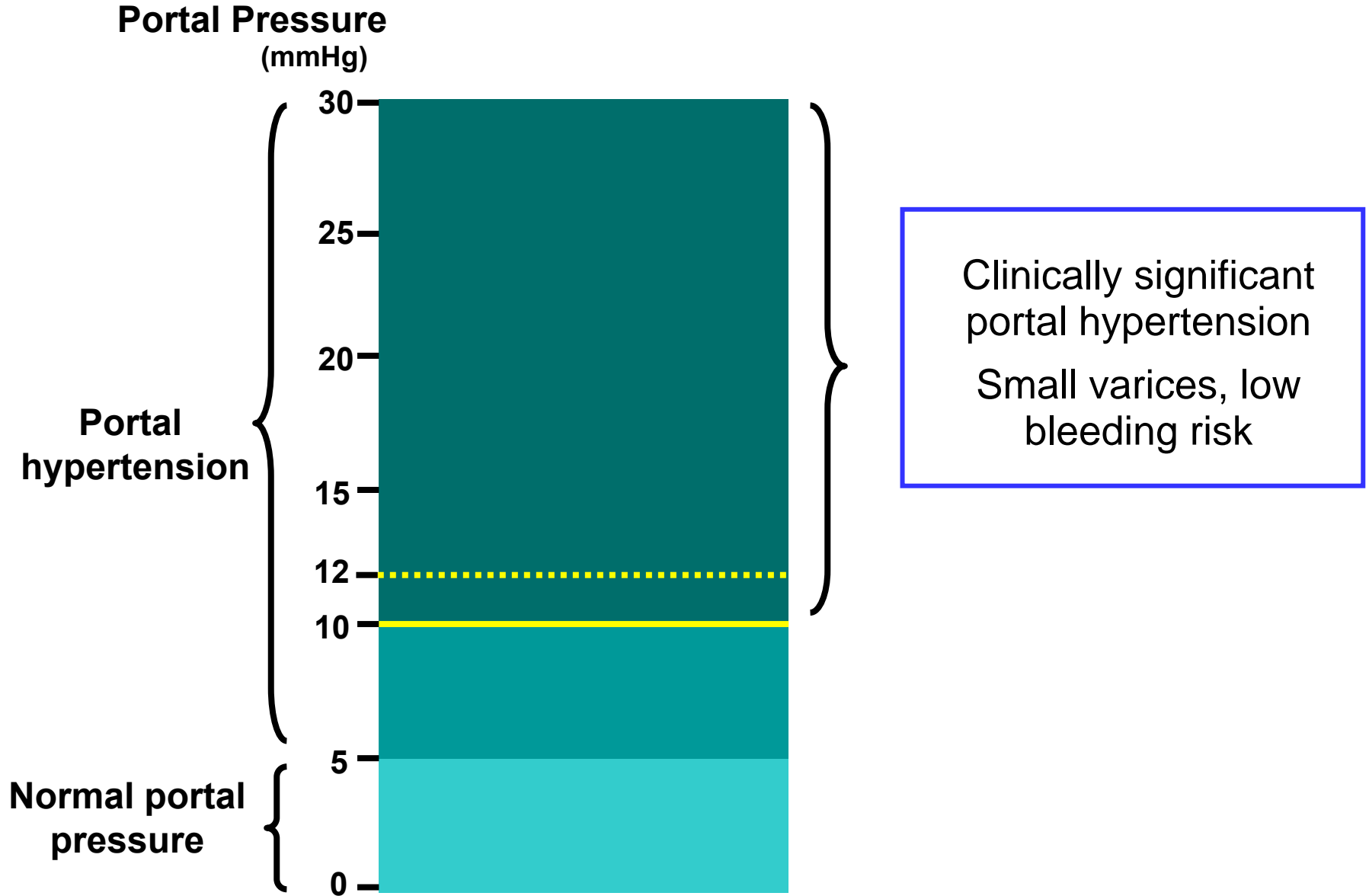
Cumulative probability of regression

Nadolol (24%)

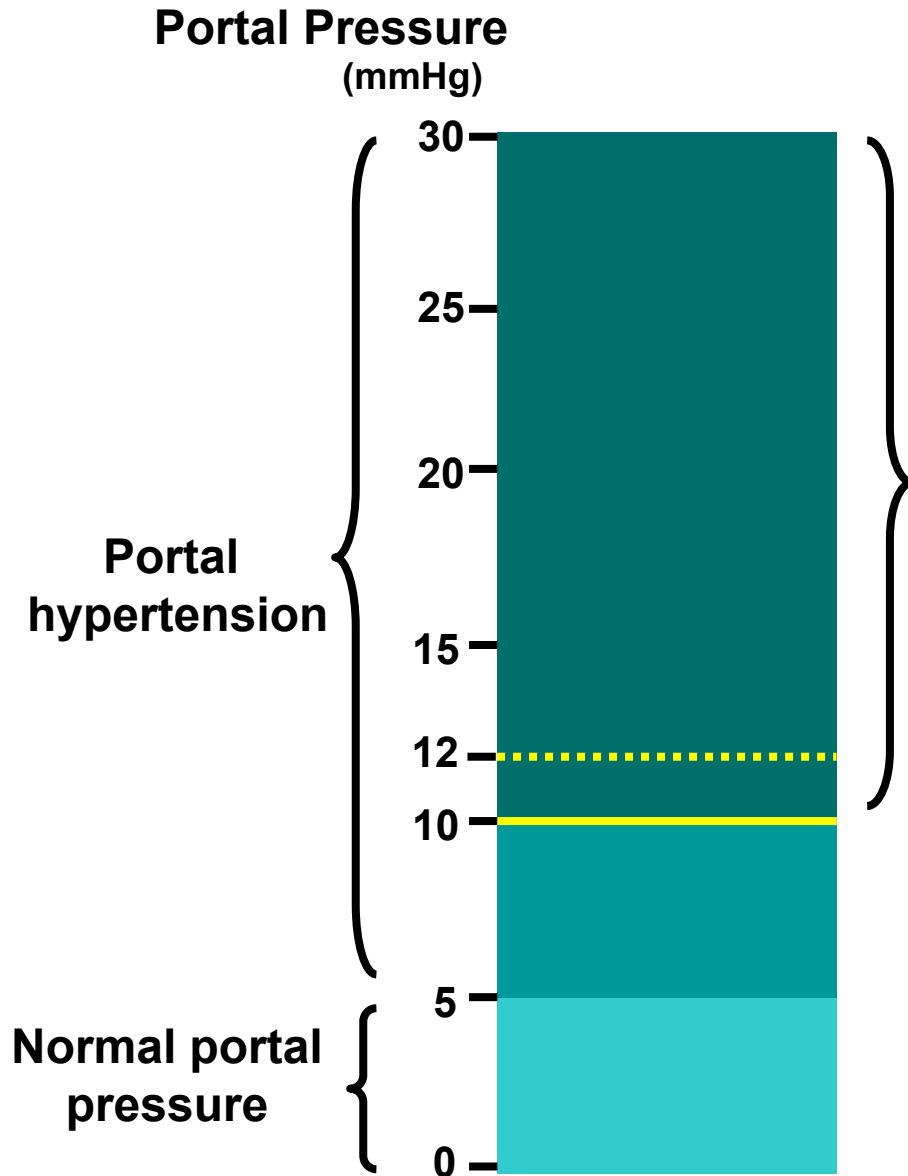
Placebo (11%)

p = 0.003

# Pre-primary prophylaxis: the field



# Pre-primary prophylaxis: the field



Clinically significant portal hypertension  
Small varices, low bleeding risk

## Re-definitions

Variceal regression as a main aim ?

An earlier switching point in therapy once preventing growth fails ?

Small varices with high risk bleeding endoscopic signs. What to do ?

# Patients with small varices

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- Patients with small varices could be treated with non-selective  $\beta$ -blockers to prevent progression of varices and bleeding, but further studies, especially as relates to prevention of bleeding, are required before a formal recommendation on their use can be made (5;D)
- Patients with small varices with red weal signs or of Child C class have an increased risk of bleeding and may benefit from treatment (5;D)

ORIGINAL ARTICLE

# Beta-Blockers to Prevent Gastroesophageal Varices in Patients with Cirrhosis

Roberto J. Groszmann, M.D., Guadalupe Garcia-Tsao, M.D., Jaime Bosch, M.D., Norman D. Grace, M.D., Andrew K. Burroughs, M.B., Ch.B., Ramon Planas, M.D., Angels Escorsell, M.D., Juan Carlos Garcia-Pagan, M.D., David Patch, M.B., B.S., Daniel S. Matloff, M.D., Hong Gao, M.D., Ph.D., and Robert Makuch, Ph.D.,  
for the Portal Hypertension Collaborative Group

**Study design:** Multicenter, RCT, double blind

**Population:** 213 cirrhotic patients without varices (HVPG >6 mmHg)  
(53% HCV related)

**Aims:** a) Prevention of the formation of varices and variceal hemorrhage

b) To evaluate the predictive value of sequential measurements of HVPG in the development of



**Primary events**

Varices  
Variceal hemorrhage

**Secondary events**

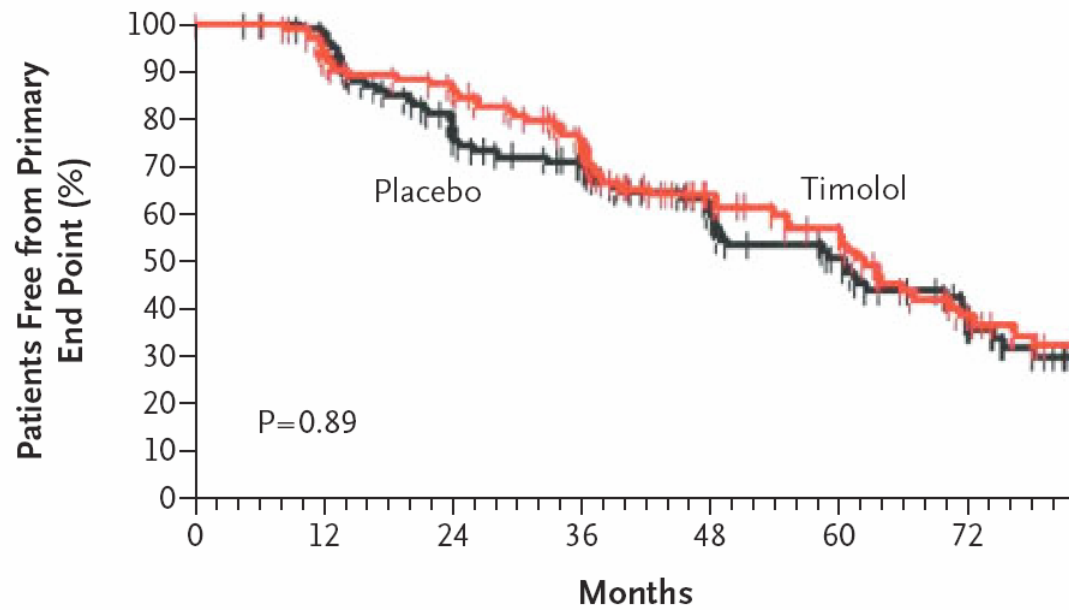
Ascites  
Encephalopathy

**Terminating events**

Transplant  
Death

**Drug:** Timolol - Mean daily dose: 10.8 mg

**Median follow-up:** 4.2 years

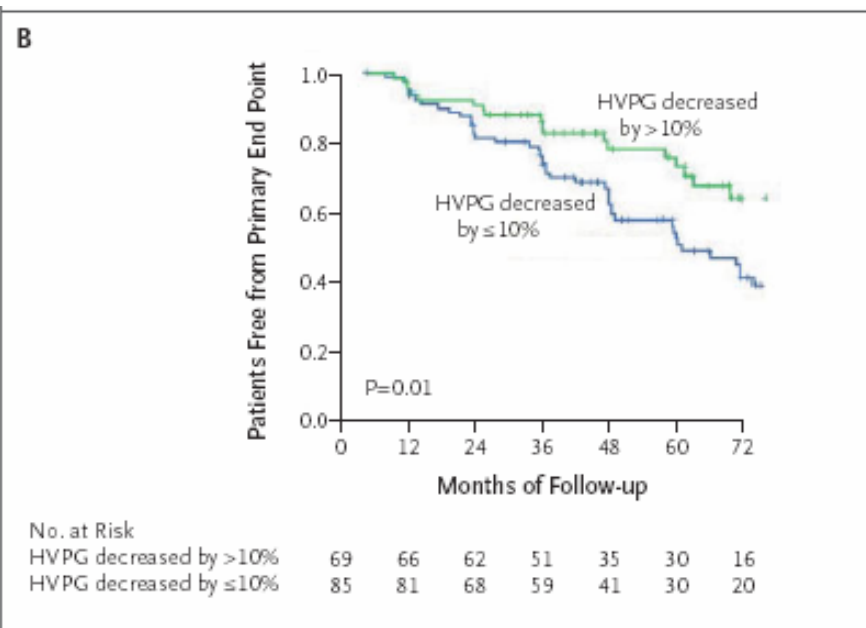
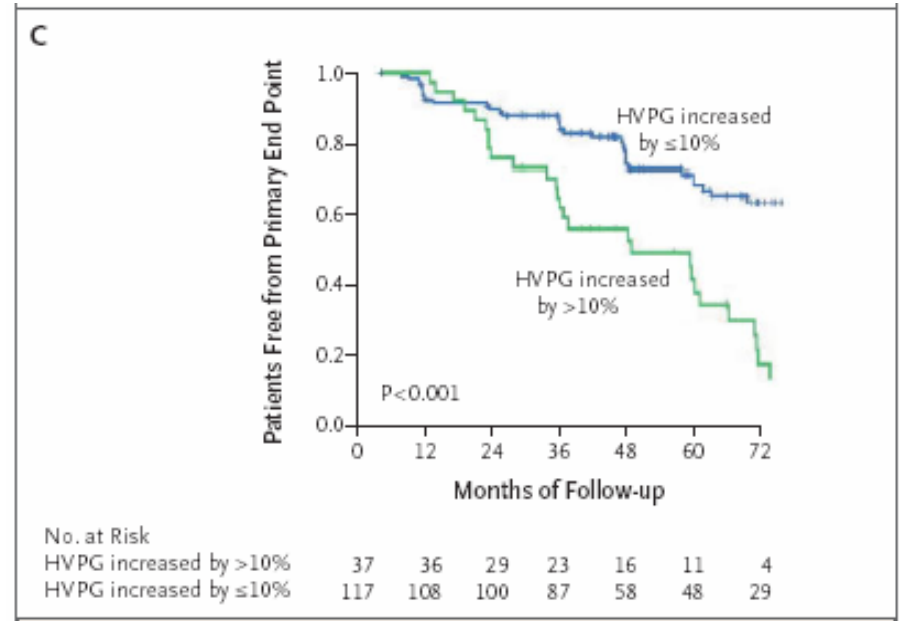
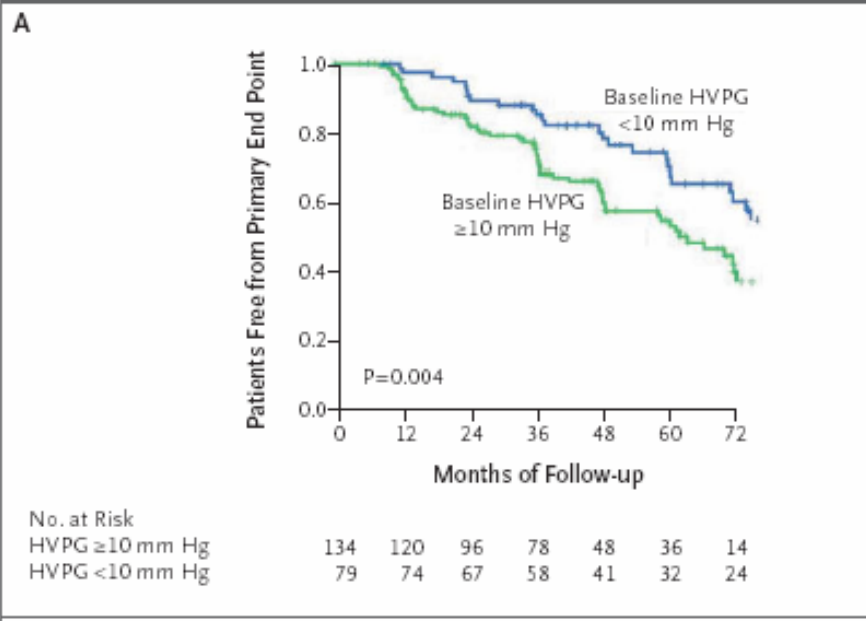


**No. at Risk**

Placebo	105	99	75	65	46	37	20
Timolol	108	97	89	72	46	34	20

**Figure 1. Kaplan–Meier Estimates of the Percentages of Patients Who Did Not Reach the Primary End Point of Varices or Variceal Bleeding.**

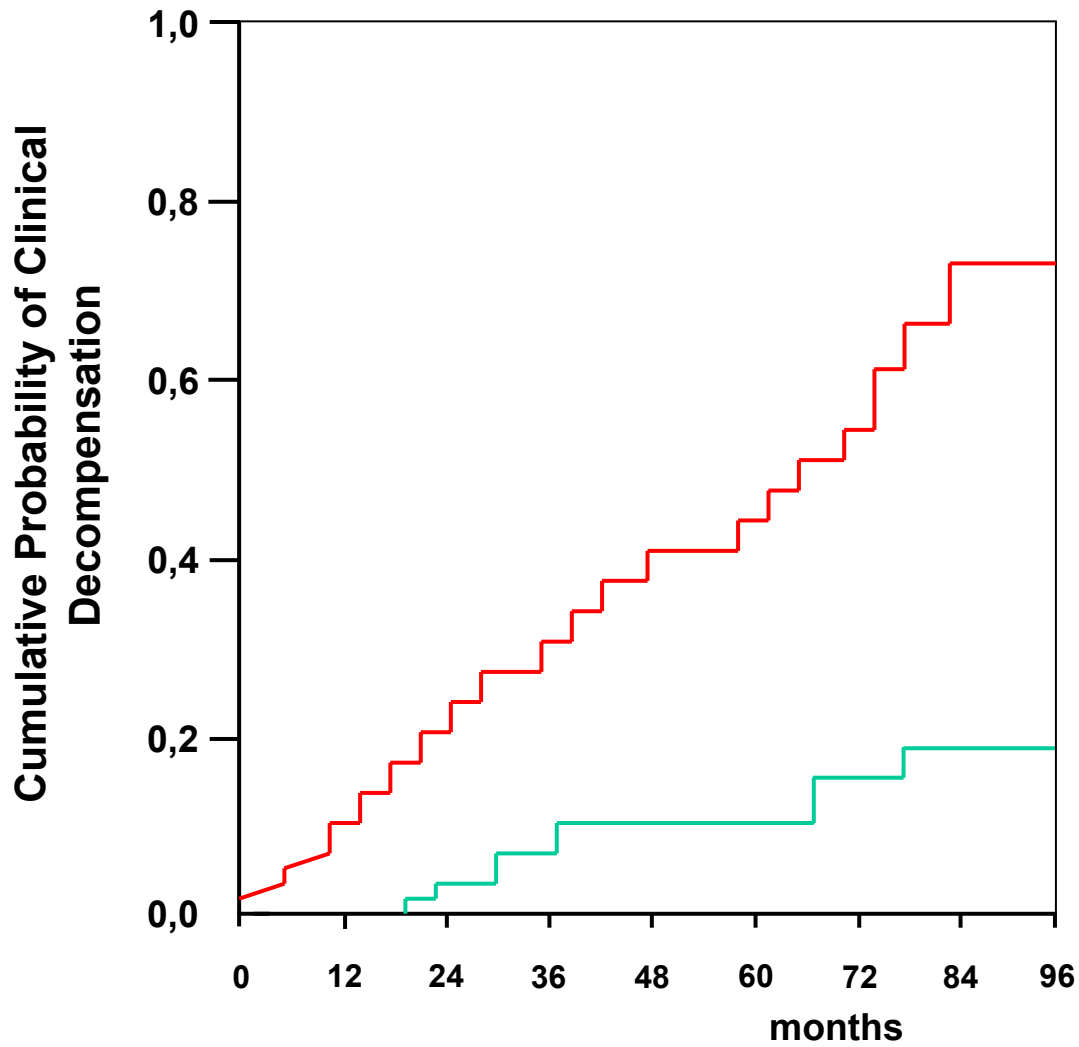
Cumulative percentages of patients who did not reach the primary end point at 12, 24, 36, and 60 months were 91 percent, 86 percent, 79 percent, and 60 percent, respectively, in the timolol group and 97 percent, 82 percent, 78 percent, and 57 percent, respectively, in the placebo group.



**Figure 3.** Probability of Remaining Free of the Primary End Point of Varices or Variceal Bleeding, According to the HVPG at Baseline (Panel A) and the Presence or Absence of Either a Decrease in HVPG by More Than 10 Percent (Panel B) or an Increase in HVPG by More Than 10 Percent (Panel C) at One Year.

# HEPATIC VENOUS PRESSURE GRADIENT PREDICTS CLINICAL DECOMPENSATION IN PATIENTS WITH COMPENSATED CIRRHOSIS

Cristina Ripoll, Roberto J Groszman, Guadalupe García-Tsao, Norman Grace,  
Andrew Burroughs, Ramón Planas, Angels Escorsell, Juan Carlos García-Pagán,  
Robert Makuch, David Patch, Daniel S Matloff, Jaime Bosch and the Portal  
Hypertension Collaborative Group



**HVPG <10 mmHg**

At risk 79 72 66 55 44 32 14

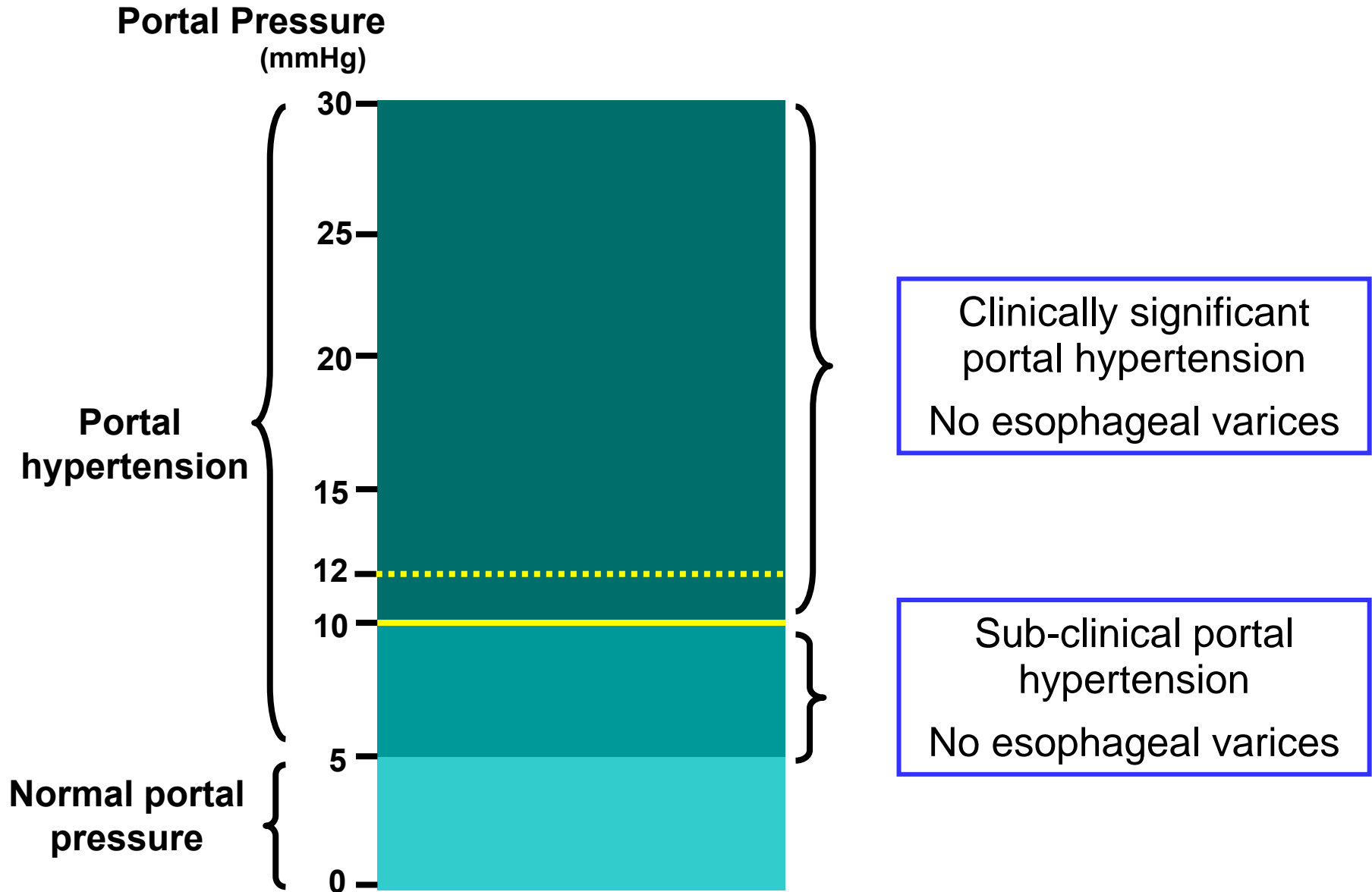
Events 0 0 2 4 6 6 8

**HVPG ≥10 mmHg**

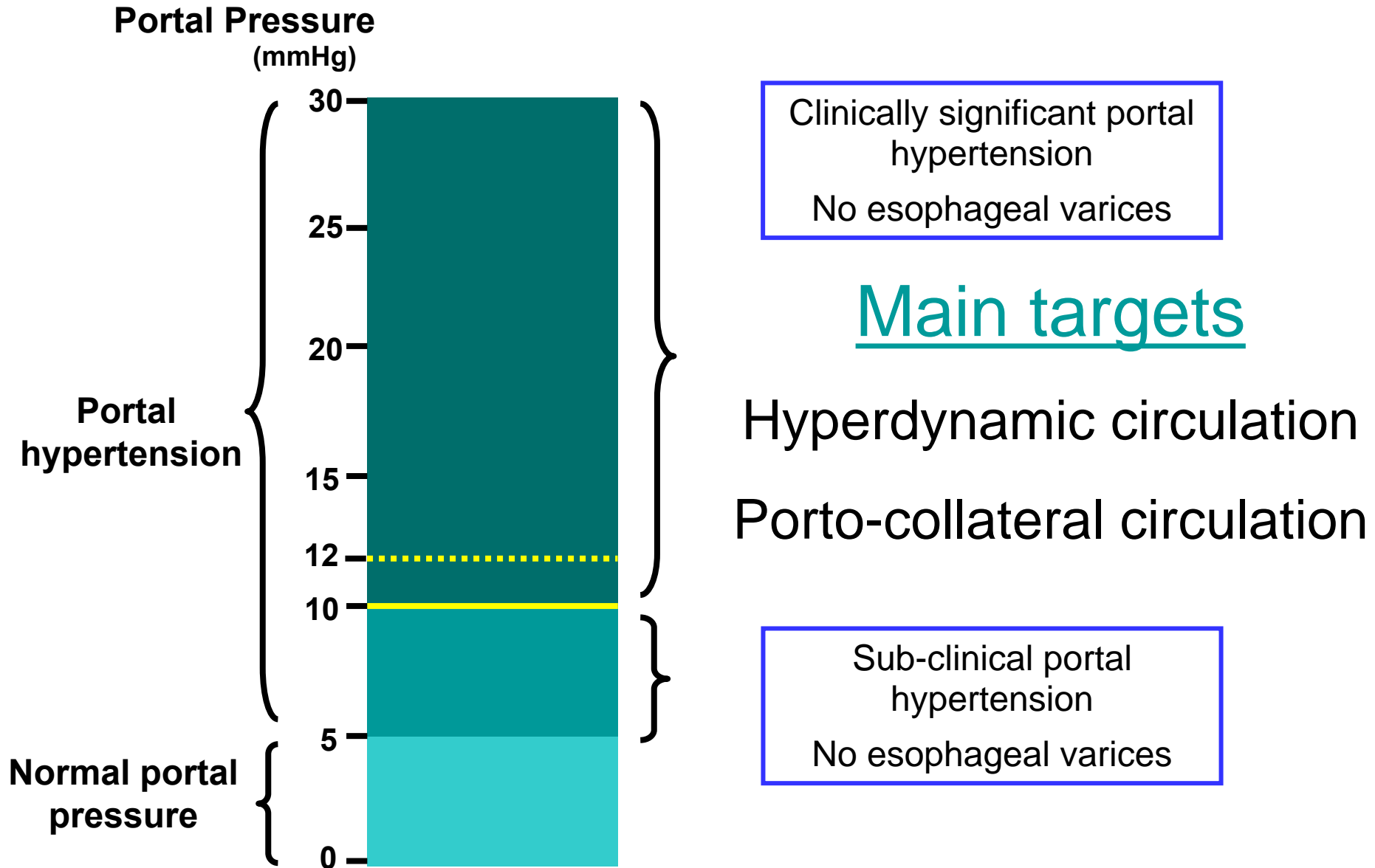
At risk 134 112 86 73 49 34 3

Events 0 15 29 33 44 47 54

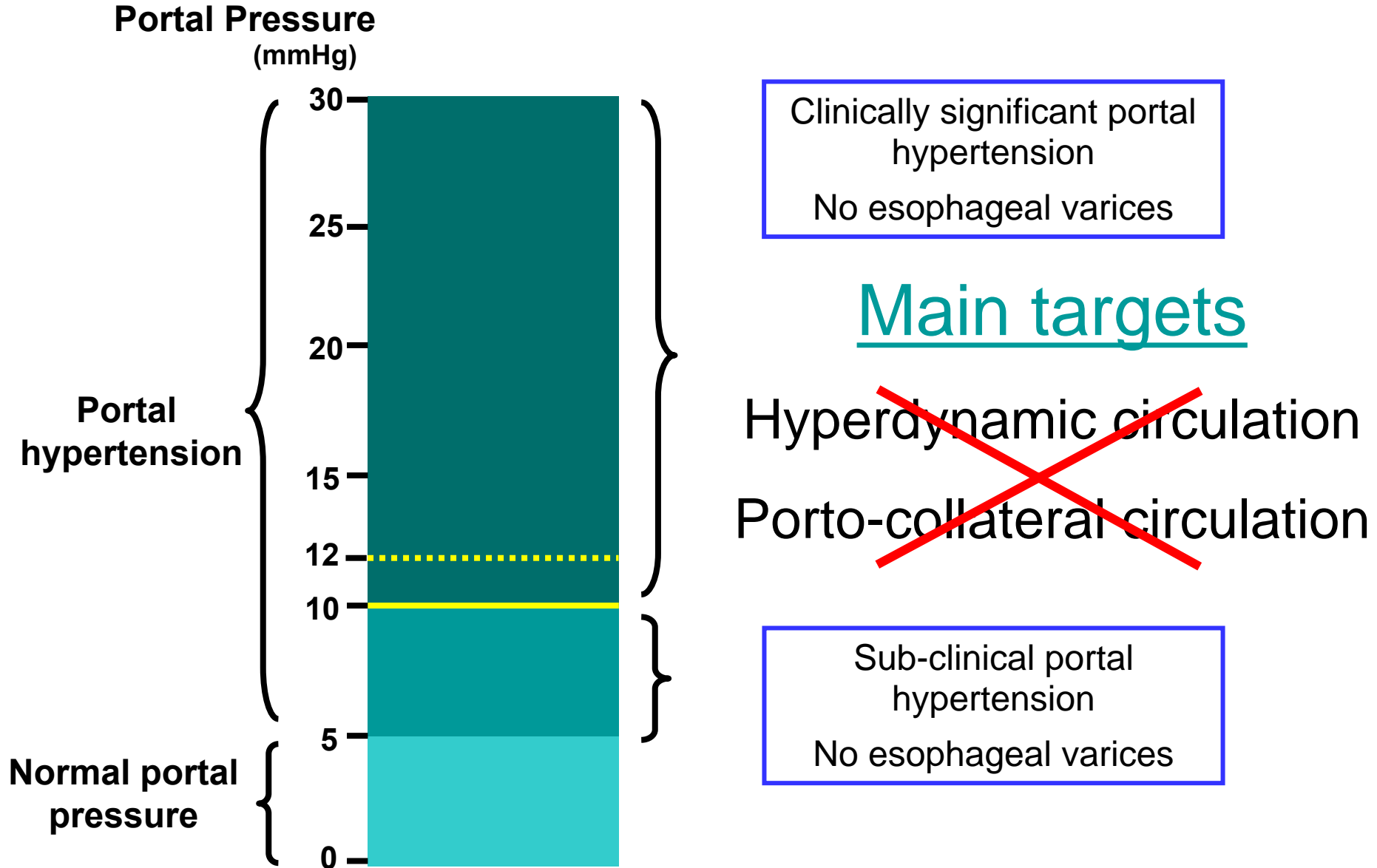
# Pre-primary prophylaxis: the field



# Pre-primary prophylaxis: the field



# Pre-primary prophylaxis: the field



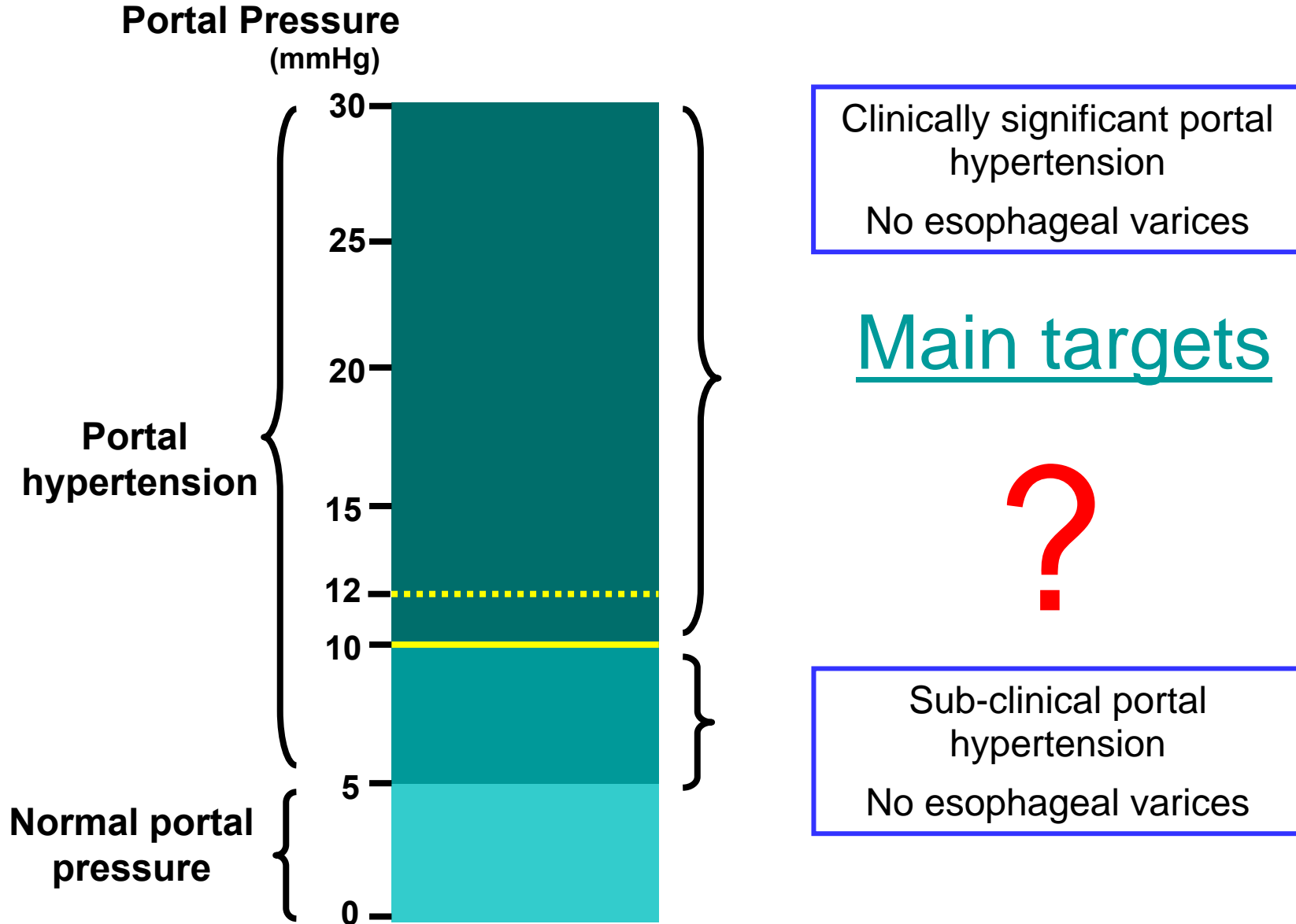
# Portal Hypertensión

## Pre-primary prophylaxis

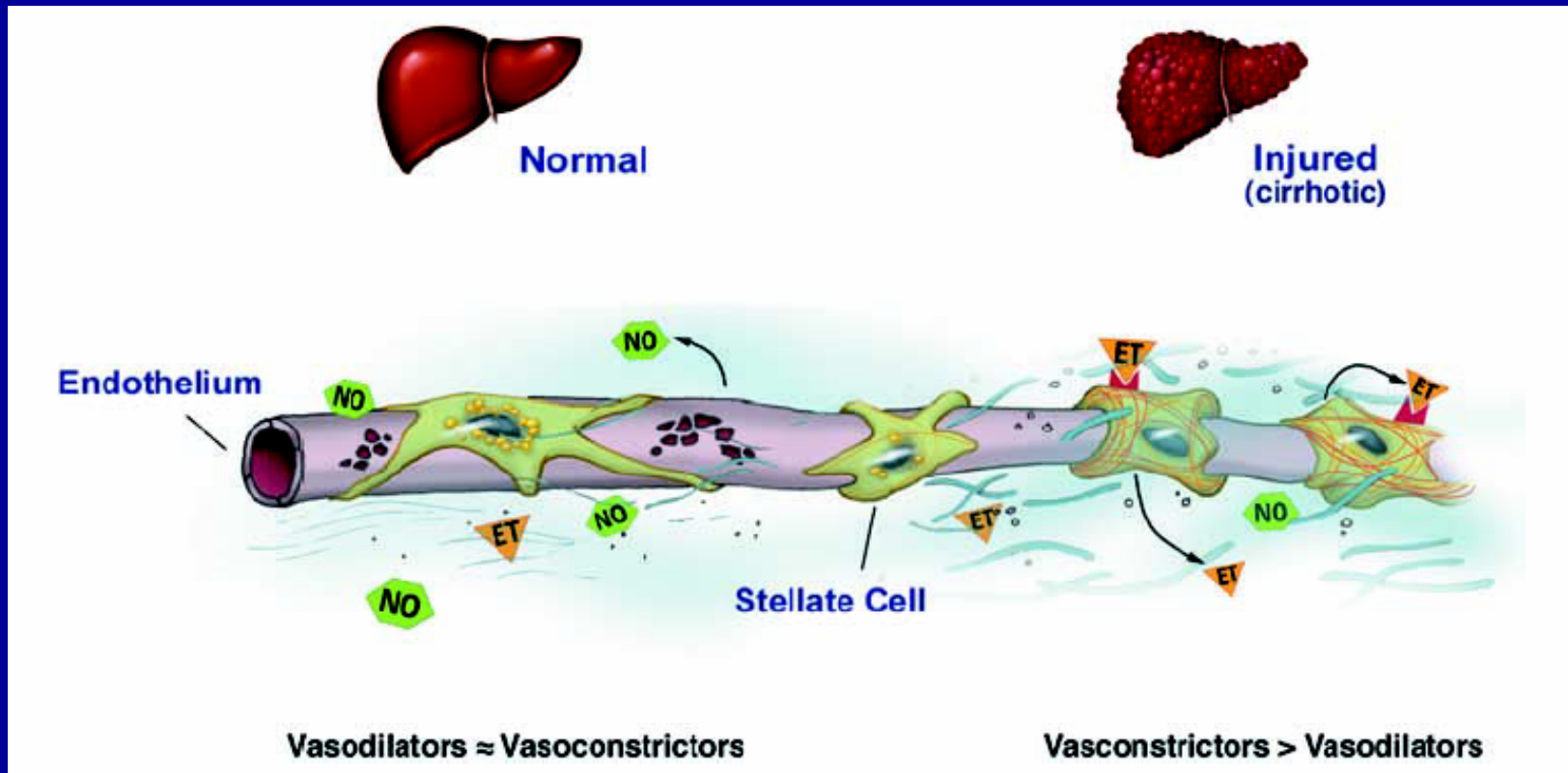
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- Hepatic Venous Pressure Gradient (HVPG) is predictive of varices formation (1b;A)
- All cirrhotic patients should be screened for varices at diagnosis (1b;A)
- There is no indication, at this time, to treat patients to prevent the formation of varices (1b;A)

# Pre-primary prophylaxis: the field

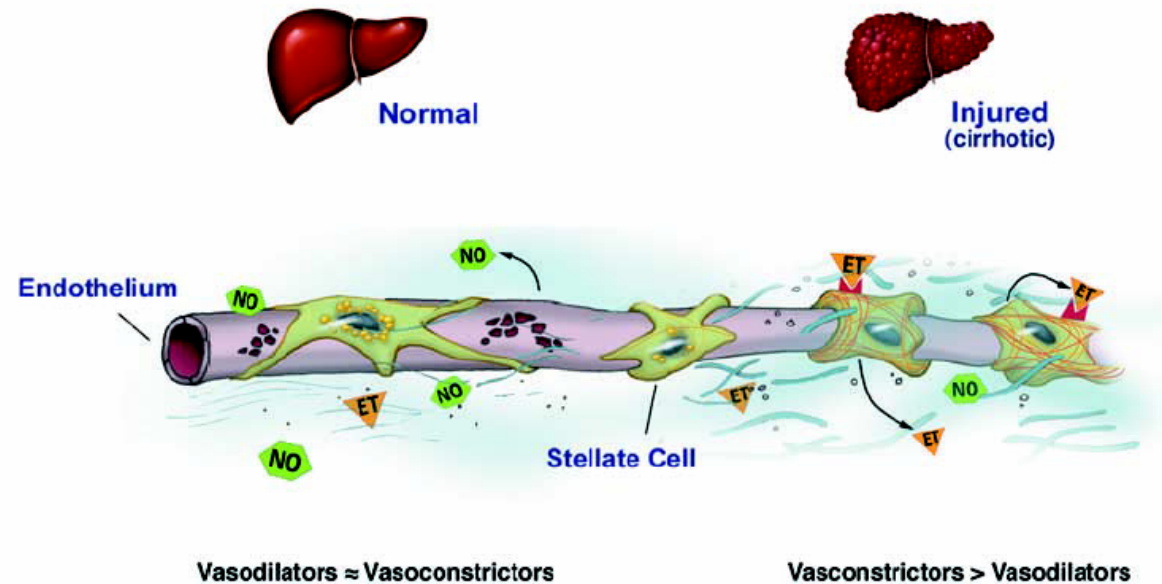


# The Endothelial Dysfunction



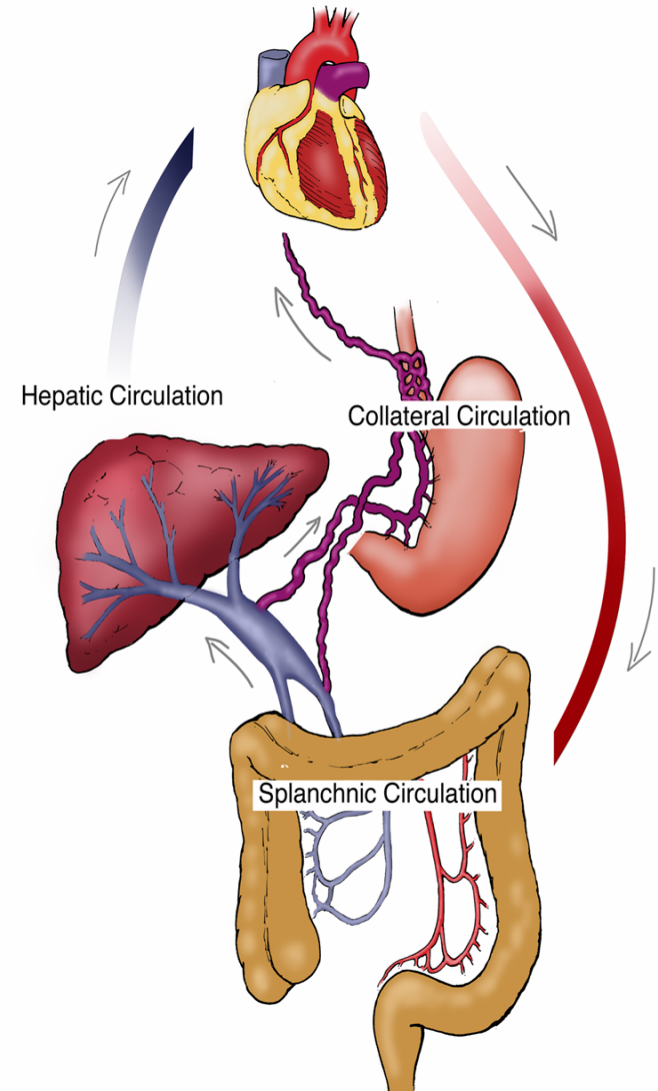
# The Endothelial Dysfunction

- Liver “selective” NO donors  
Proc Natl Acad Sci USA 2001
- eNOS gene transfer  
Gut 2002
- Low doses ISMN  
Hepatology 2003
- Statins  
Gastroenterology 2004  
J Hepatol 2007
- PDE-5 inhibitors  
J Hepatol 2006
- Ascorbic acid  
Hepatology 2006
- BH<sub>4</sub> supplementation  
Hepatology 2006
- Liver “selective” H<sub>2</sub>S donors  
AASLD Basic Research Conference 2007



# The Collateral Circulation

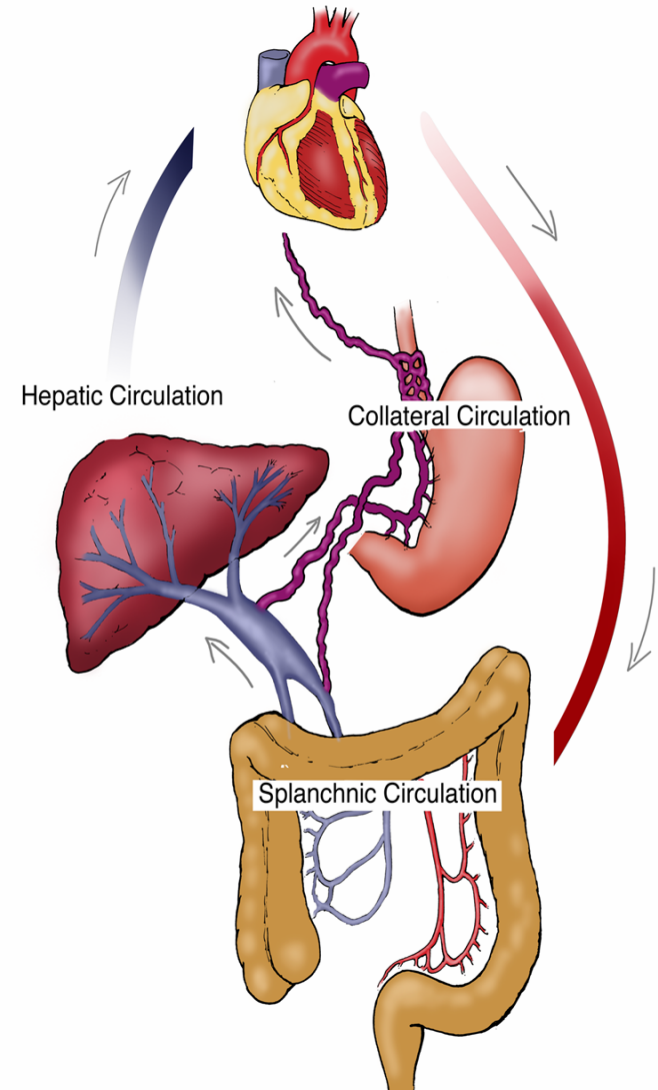
- A major cause of complications of portal hypertension is the development of collateral circulation that connects the portal hypertensive vasculature with the lower pressure systemic venous system
- The collateral circulation develops through distinct physiologic processes including **vasodilation**, **vascular remodeling**, and **angiogenesis**



# The Collateral Circulation

## Anti-angiogenic strategies

- VEGF receptor-2 monoclonal antibody  
Gastroenterology 2004
- VEGF receptor-2 autophosphorylation inhibition  
J Hepatol 2006
- HO-1 blockade  
J Hepatol 2006
- NAD(P)H oxidase inhibition  
Gut 2007
- Combined VEGF and PDGF blockade  
AASLD Basic Research Conference 2007



# Ethiological Treatment

Alcoholic liver disease  
Abstinence

Autoimmune liver disease  
Immunosuppression

Wilson's disease  
Copper chelation

Morbid obesity  
Weight reduction

Hemochromatosis  
Phlebotomy

Chronic viral hepatitis  
Antivirals

Early PBC  
URSO

