SCSG 2016 POST-AASLD SYMPOSIUM

Jointly provided by the Annenberg Center for Health Sciences at Eisenhower and the Southern California Society of Gastroenterology.

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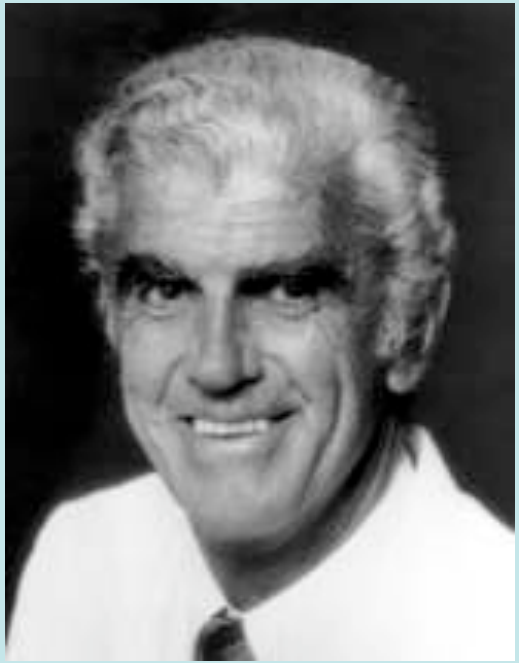
Annenberg Center For Health Sciences at Eisenhower

Imparting knowledge. Improving patient care.

Southern California Society of Gastroenterology

Telfer B. Reynolds Lecture



"Pete"

OREGON HEALTH & SCIENCE UNIVERSITY

Telfer B. Reynolds Lecture
Portal Hypertension Update 2016

Joseph Ahn, MD, MS
Associate Professor of Medicine
Director of Hepatology
Oregon Health & Science University

Update in Portal Hypertension

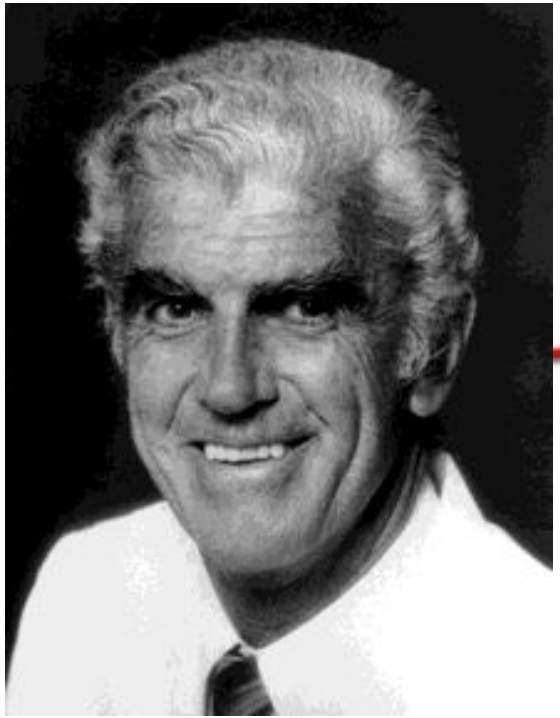
Disclosures

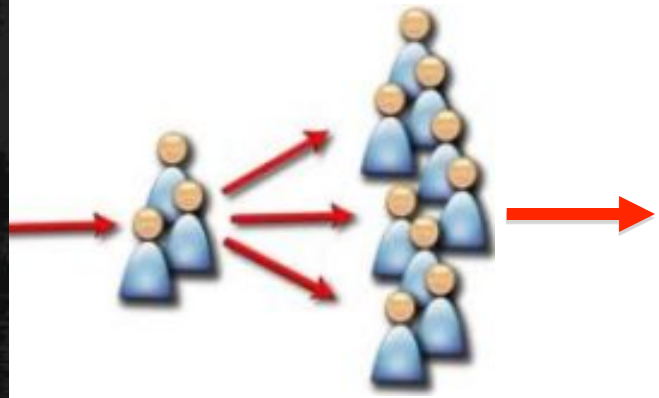
- Nothing to disclose

Update in Portal Hypertension

Dr. Telfer B. Reynolds

Trained > 100 Hepatologists





"A life is not important except in the impact it has on other lives."

Jackie Robinson

Update in Portal Hypertension

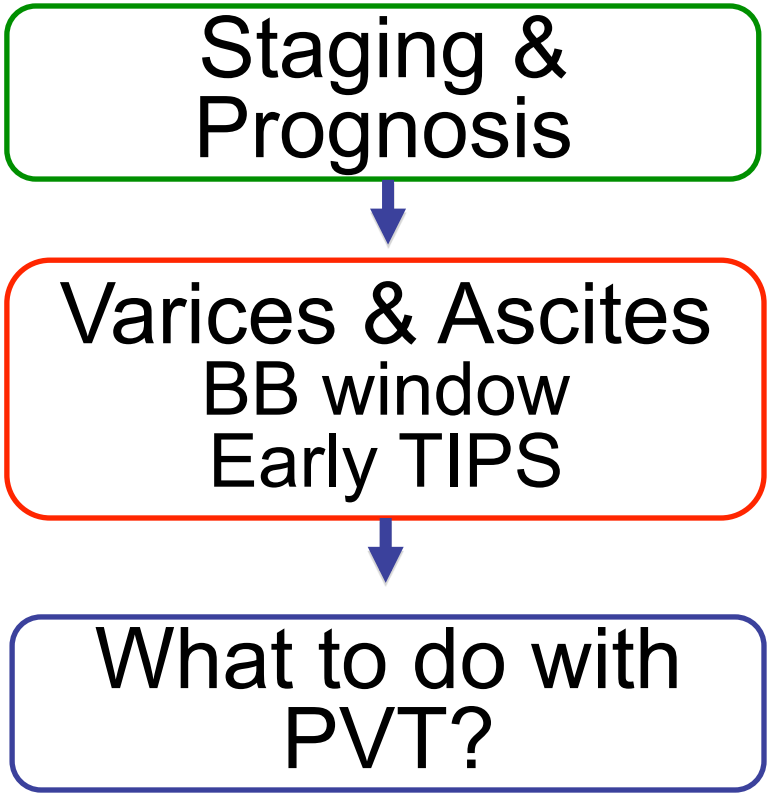
Covered in SCSG's Best of DDW 2016, Best of AASLD 2015

- Variceal bleeding
  - Restrictive blood transfusions
  - TIPS
- Hepatorenal syndrome
  - Terlipressin
- Infection- SBP
- Ascites

1. PRACTICAL
2. NOW
3. FUTURE

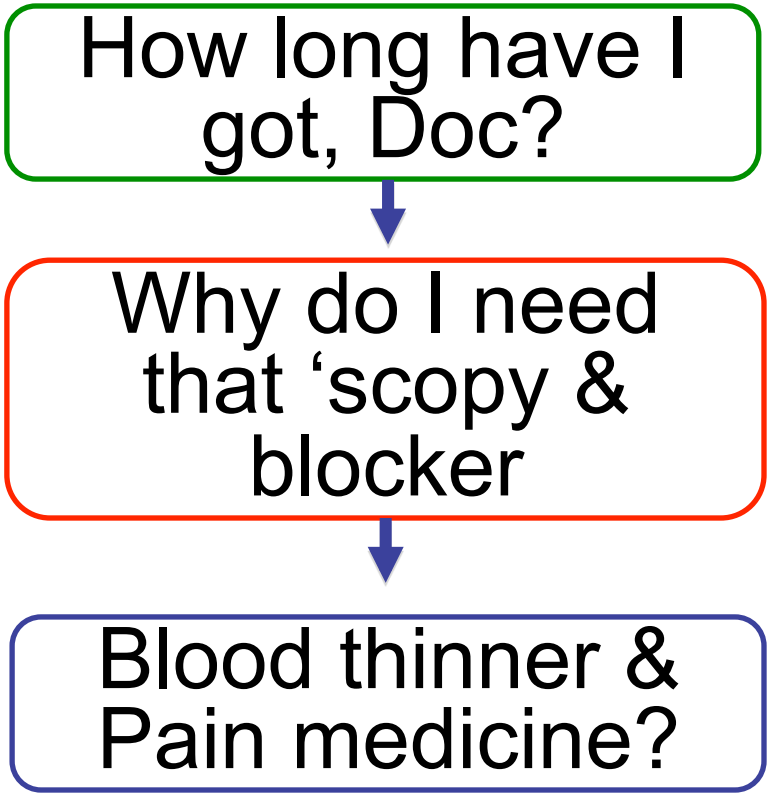
Update in Portal Hypertension

Learning Objectives



Update in Portal Hypertension

Patient Objectives



Staging & Prognosis

Era of Personalized Medicine

Recognize cirrhosis

Risk stratification by stage of cirrhosis

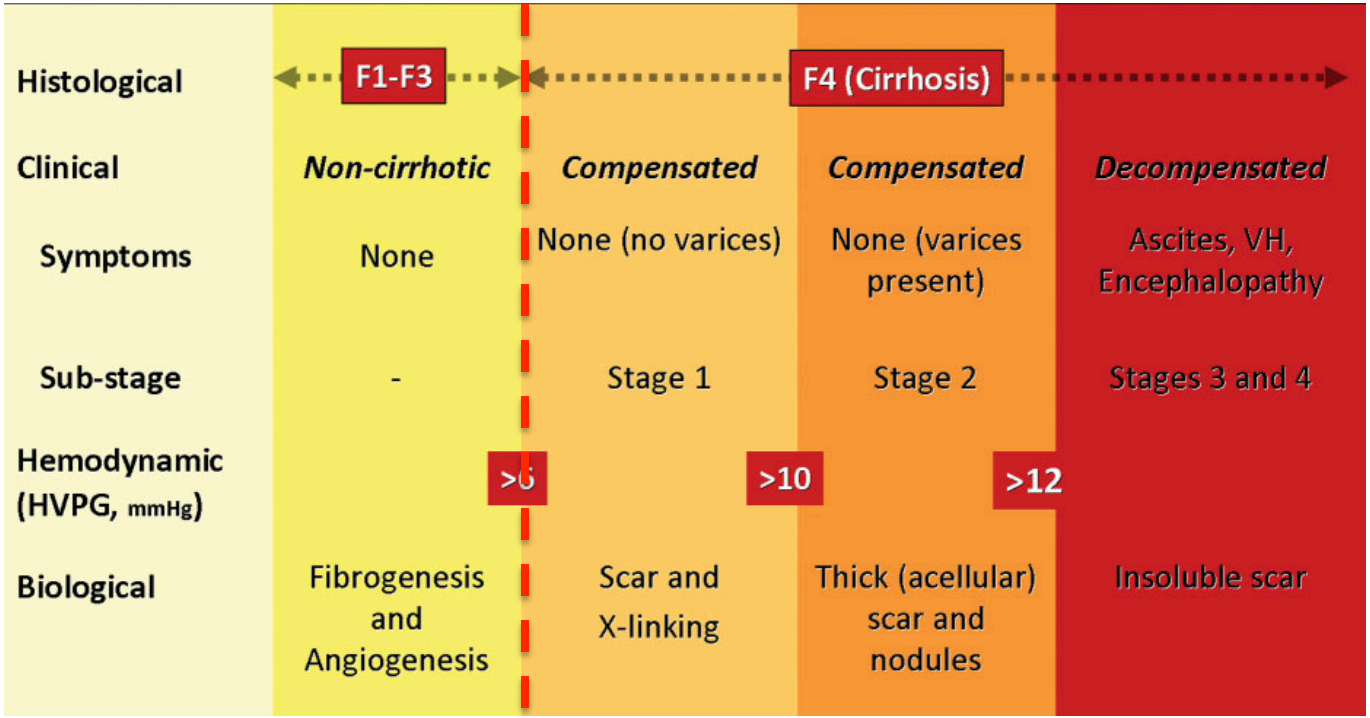
Prevent hepatic decompensation

Individualized care

Value/Outcome based care

Staging

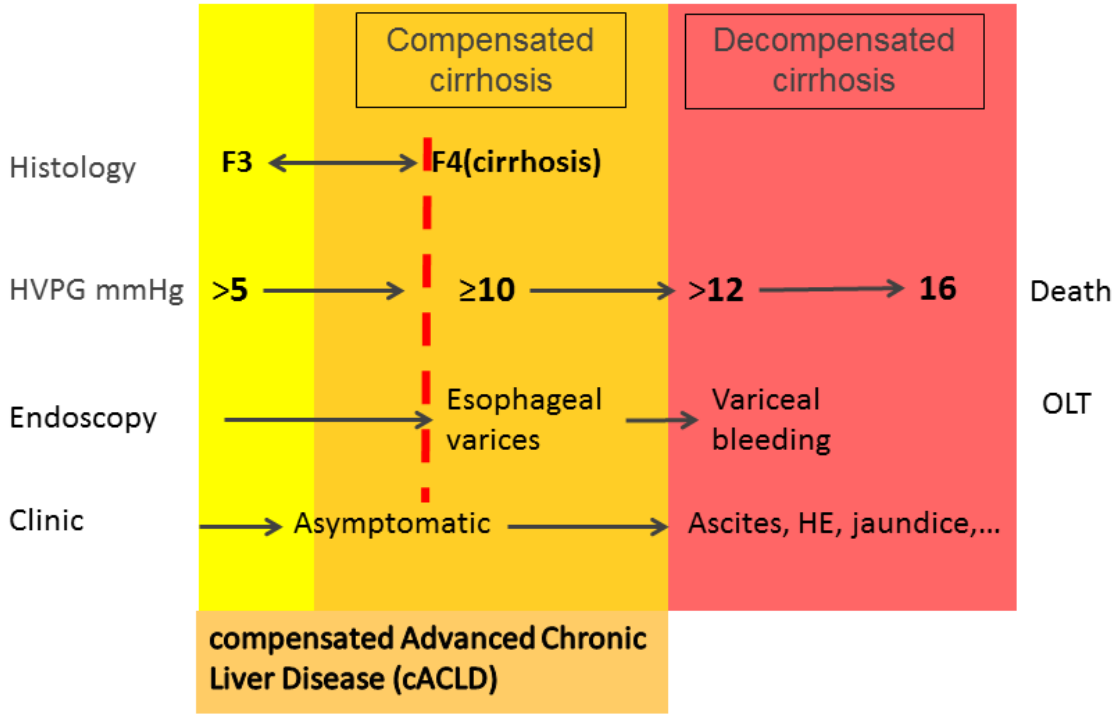
Before



Garcia-Tsao, Hepatology 2010

Staging

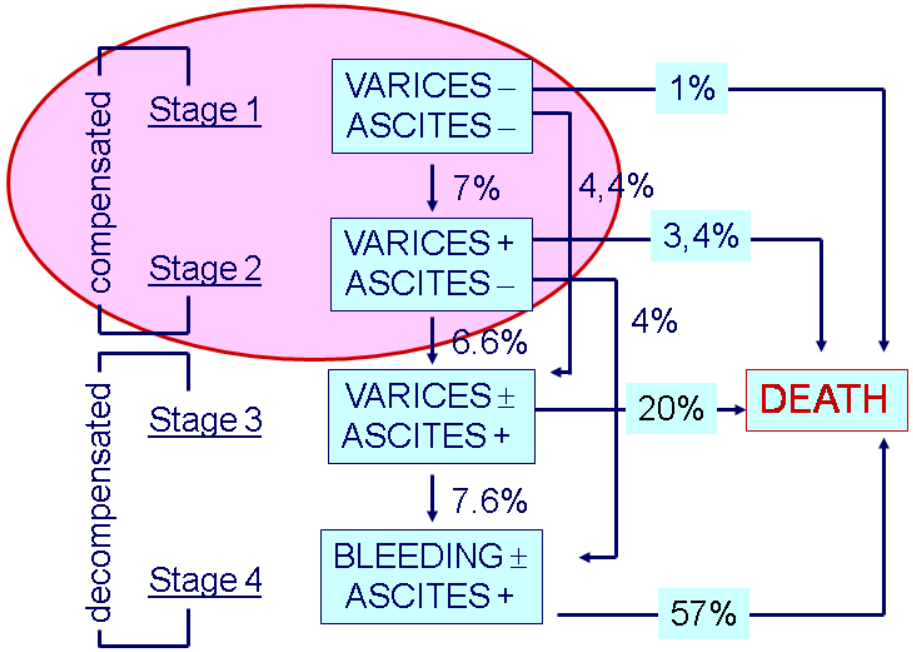
Refinement



Procopet, EASL 2016

Prognosis

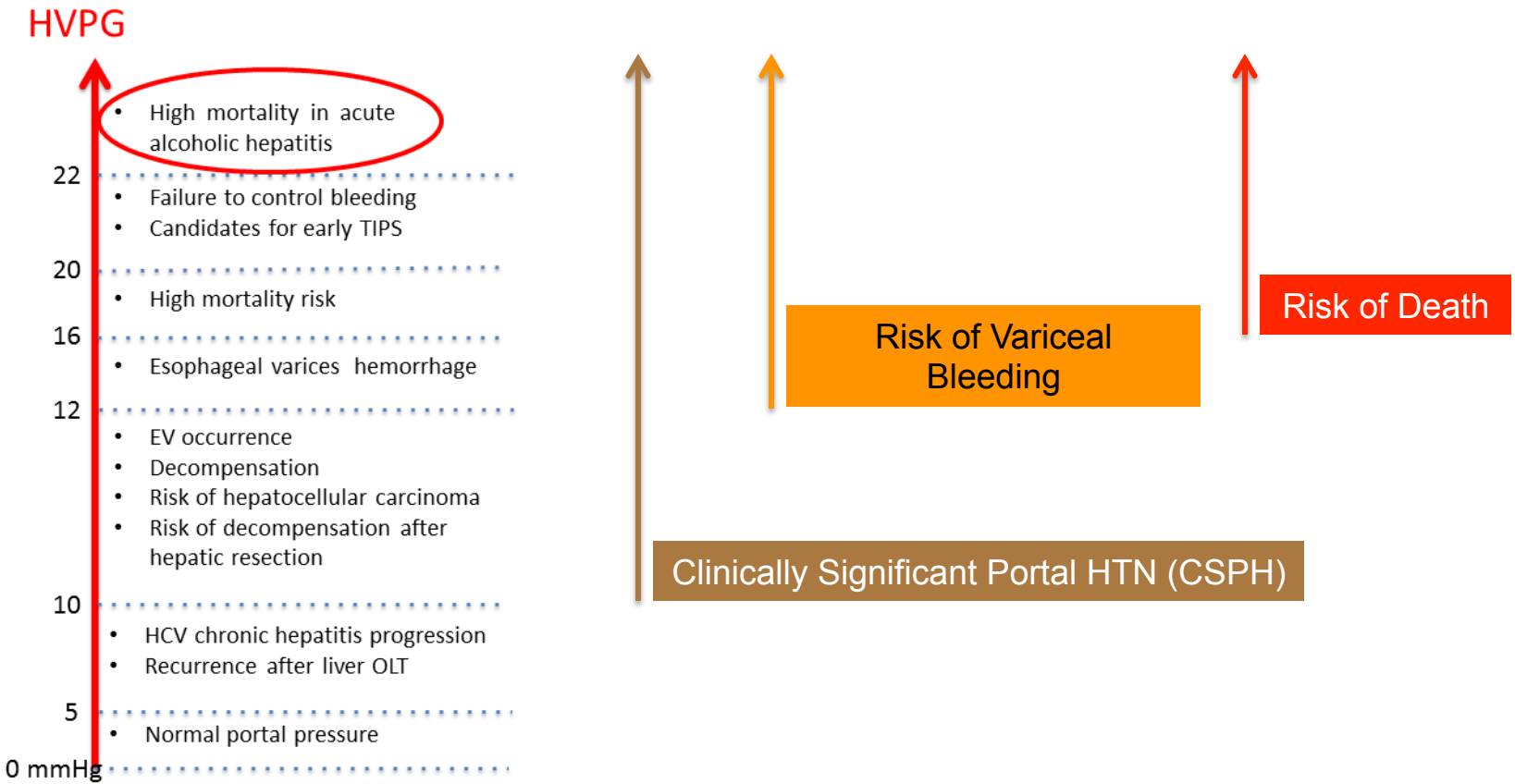
Defined by Decompensating Events



D'Amico, J Hep 2006

Prognosis

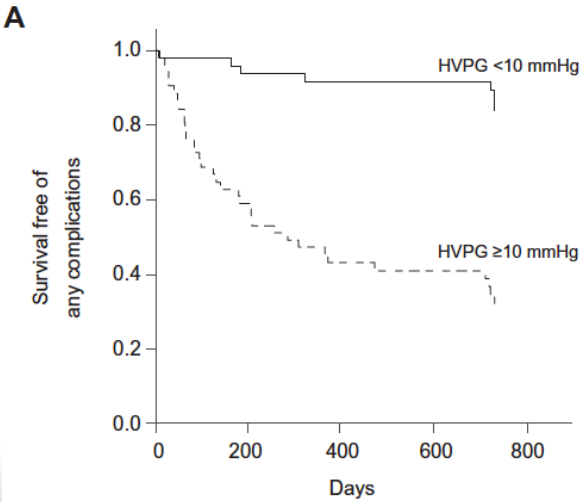
HVPG drives outcomes



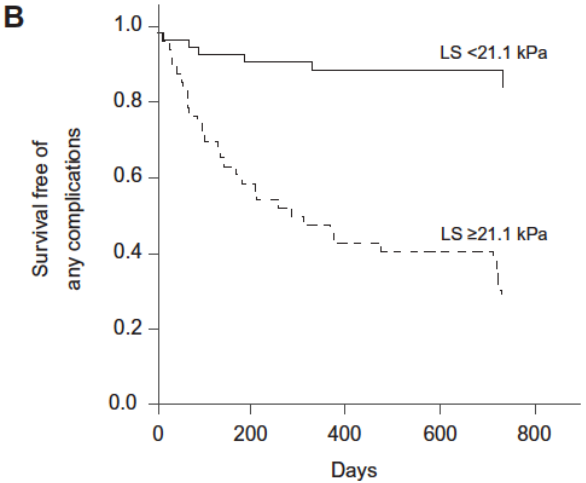
Prognosis

Transient Elastography (TE) → Liver Stiffness (LS)

- HVPG not universally available nor utilized
- However, HVPG changes not correlated to LS changes over time
- Data mainly from viral, ETOH disease



HVPG

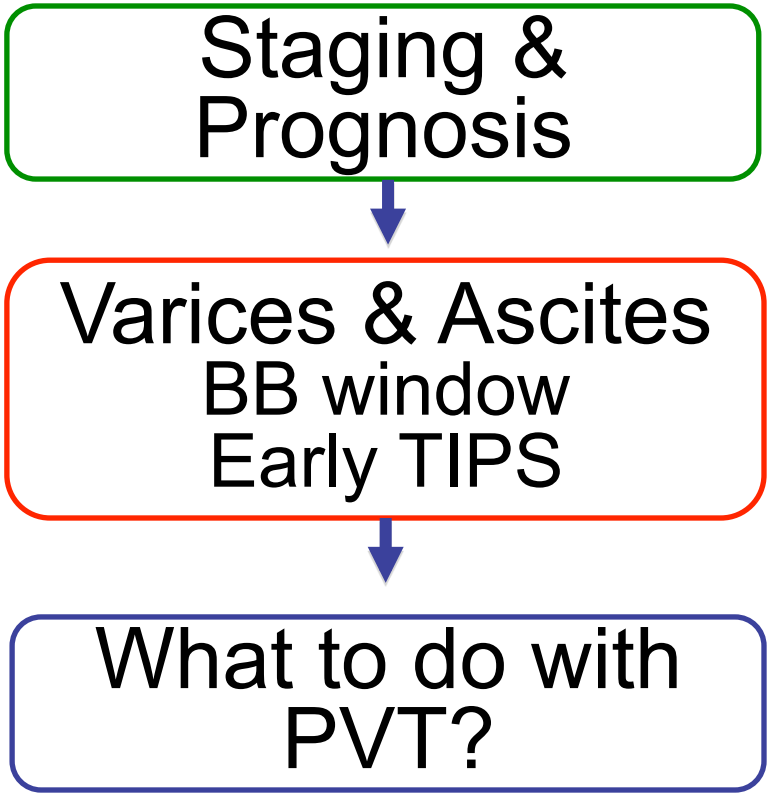


TE

Robic, J Hep 2011

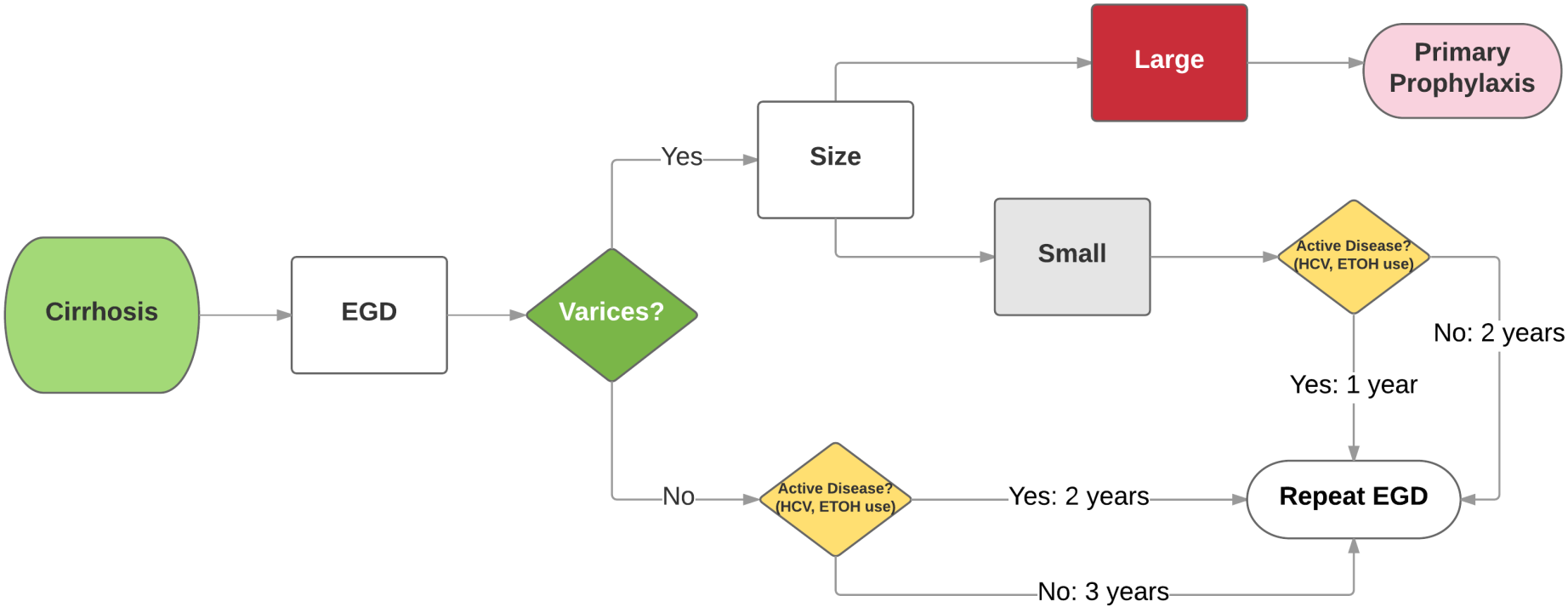
Update in Portal Hypertension

Learning Objectives



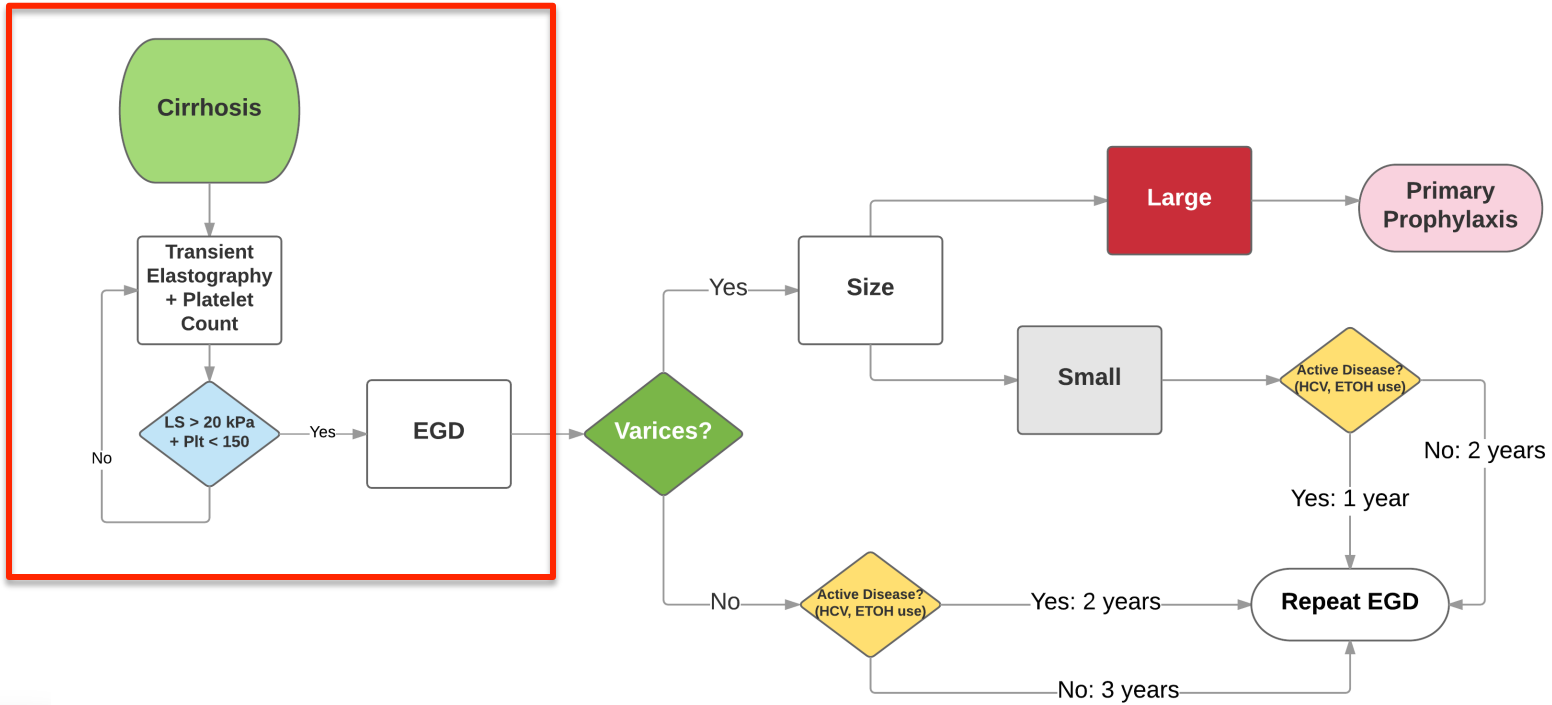
Esophageal Varices Screening

Current



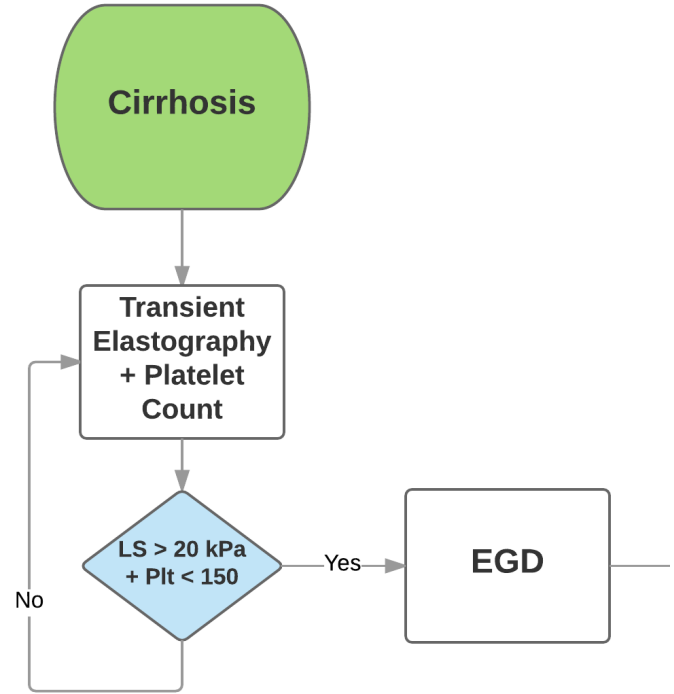
Esophageal Varices Screening

Potential Refinement- BAVENO VI



Esophageal Varices Screening

BAVENO VI



- LS < 20 kPa + Platelet > 150 may not need screening EGD
- Consensus
- Estimate ~ 20-25% screening EGDs could be circumvented

De Franchis, J Hep 2015

Esophageal Varices Screening

BAVENO criteria validation

Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices

James B Maurice[1,2], Edgar Brodkin[1], Frances Arnold[1], Annalan Navaratnam[1], Heidi Paine[2], Sabrina Khawar[1], Ameet Dhar[2], David Patch[1], James O'Beirne[1], Raj Mookerjee[1,3], Massimo Pinzani[1,3], Emmanouil Tsochatzis[1,3], Rachel H. Westbrook[1,*]

- N= 102/310 met BAVENO criteria
- 11% had EV, 2% high risk EV
- NPV 0.98 ~ BAVENO correctly identified 98% of patients who could avoid screening EGD

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Maurice, J Hep 2016, 65: 899

Esophageal Varices Screening

AASLD 2016- #1707- BAVENO criteria validation

- N= 165 HBV, HCV → screening EGD
- 25% could have avoided EGD
- Modified criteria: LS < 25 or < 30 kPa and PLT > 125,000
  - Avoid 49% EGD

1707

Screening of oesophagogastric varices in virus-related compensated advanced chronic liver disease: Baveno VI criteria and beyond

Giulia Tosetti[1], Vincenzo La Mura[2], Alessio Aghemo[1], Pietro Lampertico[1], Roberta D'Ambrosio[1], Mauro Viganò[3], Glenda Grossi[1], Mirella Fraquelli[1], Massimo Colombo[1], Massimo Primignani[1]; [1]Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; [2]2Internal Medicine, Biomedical Science for Health, IRCCS, San Donato, University of Milan, Milan, Italy; [3]Division of Hepatology, Ospedale San Giuseppe, Università di Milano, Milan, Italy

Esophageal Varices Screening

AASLD 2016- #85-BAVENO criteria refinement

- Validated Baveno- 2 cohorts in US + Italy (75/316- none had lg EV)
- Retested in US cohort of N= 205, validated in Italian cohort of 111
- Added 7 unpublished study data to guide refinements to **LS ≥ 21 + PLT < 110,000, MELD ≥ 7**

Still needs more refinement

85
Validating and refining non-invasive Baveno criteria for ruling out high-risk varices

Laura Turco[1,2], Parastoo Jangouk[1,2], de Oliveira Ana[1,2], Filippo Schepis[3], Erica Villa[3], Guadalupe Garcia-Tsao[1,2]; [1]Digestive Diseases, VA-CT Healthcare System, West Haven, CT; [2]Digestive Diseases, Yale University, New Haven, CT; [3]Gastroenterology, Policlinico di Modena - Italy, Modena, Italy

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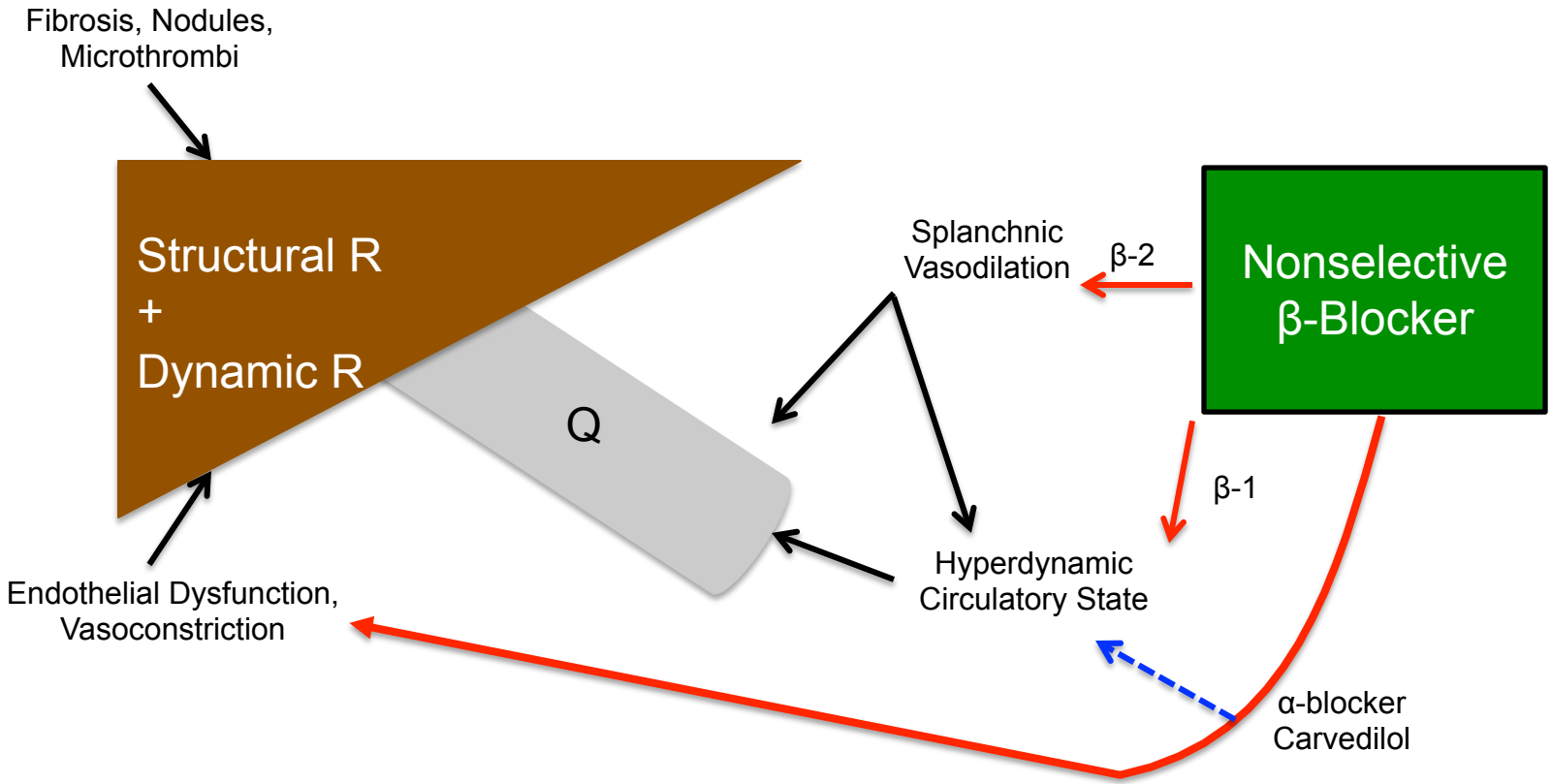
Portal Hypertension Pathophysiology

Pressure = Flow x Resistance



Beta-Blocker Prophylaxis

Evolution

AASLD PRACTICE GUIDELINES

Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis

Guadalupe Garcia-Tsao,[1] Arun J. Sanyal,[2] Norman D. Grace,[3] William Carey,[4] and the Practice Guidelines Committee of the American Association for the Study of Liver Diseases, the Practice Parameters Committee of the American College of Gastroenterology

2007

BB for ALL:
Primary Prophylaxis
Secondary Prophylaxis

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

AASLD PRACTICE GUIDELINE

Introduction to the Revised American Association for the Study of Liver Diseases Practice Guideline Management of Adult Patients With Ascites Due to Cirrhosis 2012

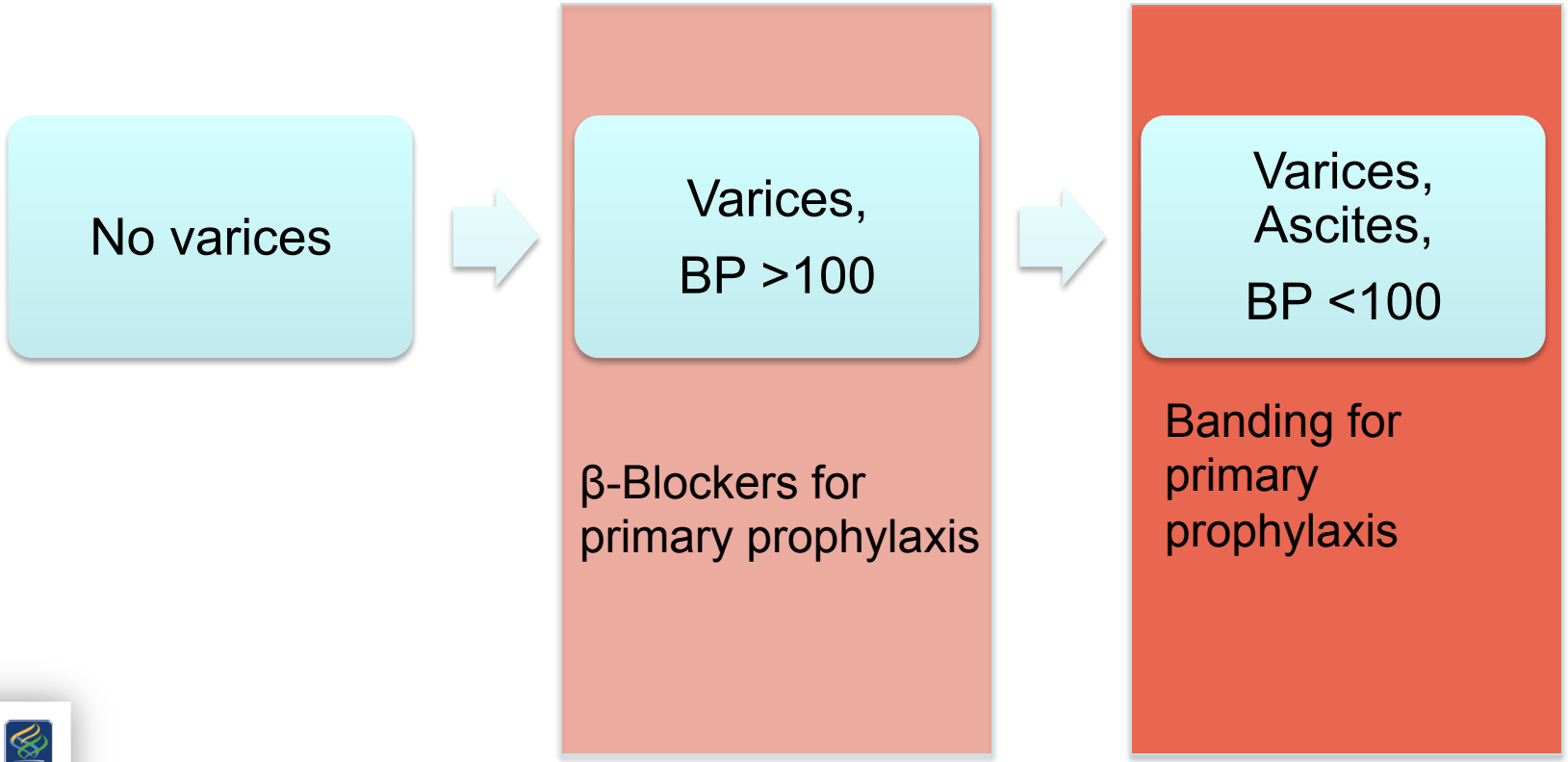
Bruce A. Runyon

2012

BB for MOST
Consider discontinue BB in refractory ascites, hypotension, azotemia

Beta-Blocker Window

Dr. Runyon's view on Beta-Blockers and ascites—"there's a window"



Courtesy of Dr. Scott Naugler

Beta-Blocker Window

Leon Schiff State-of-the-Art: Guadalupe Garcia-Tsao, AASLD 2015

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

Roberto de Franchis*, on behalf of the Baveno VI Faculty†

Department of Biomedical and Clinical Sciences, University of Milan, Gastroenterology Unit, Luigi Sacco University Hospital, Milan, Italy

"Non-selective beta-blockers should be **reduced/discontinued** in patients with refractory ascites who develop:

- Systolic blood pressure < 90 mm Hg
- Hyponatremia (<130 mEq/L)
- Acute kidney injury (Ascites Club definition)
  - Increase in creatinine ≥ 0.3 mg/dL or > 50% from baseline in 48 hours

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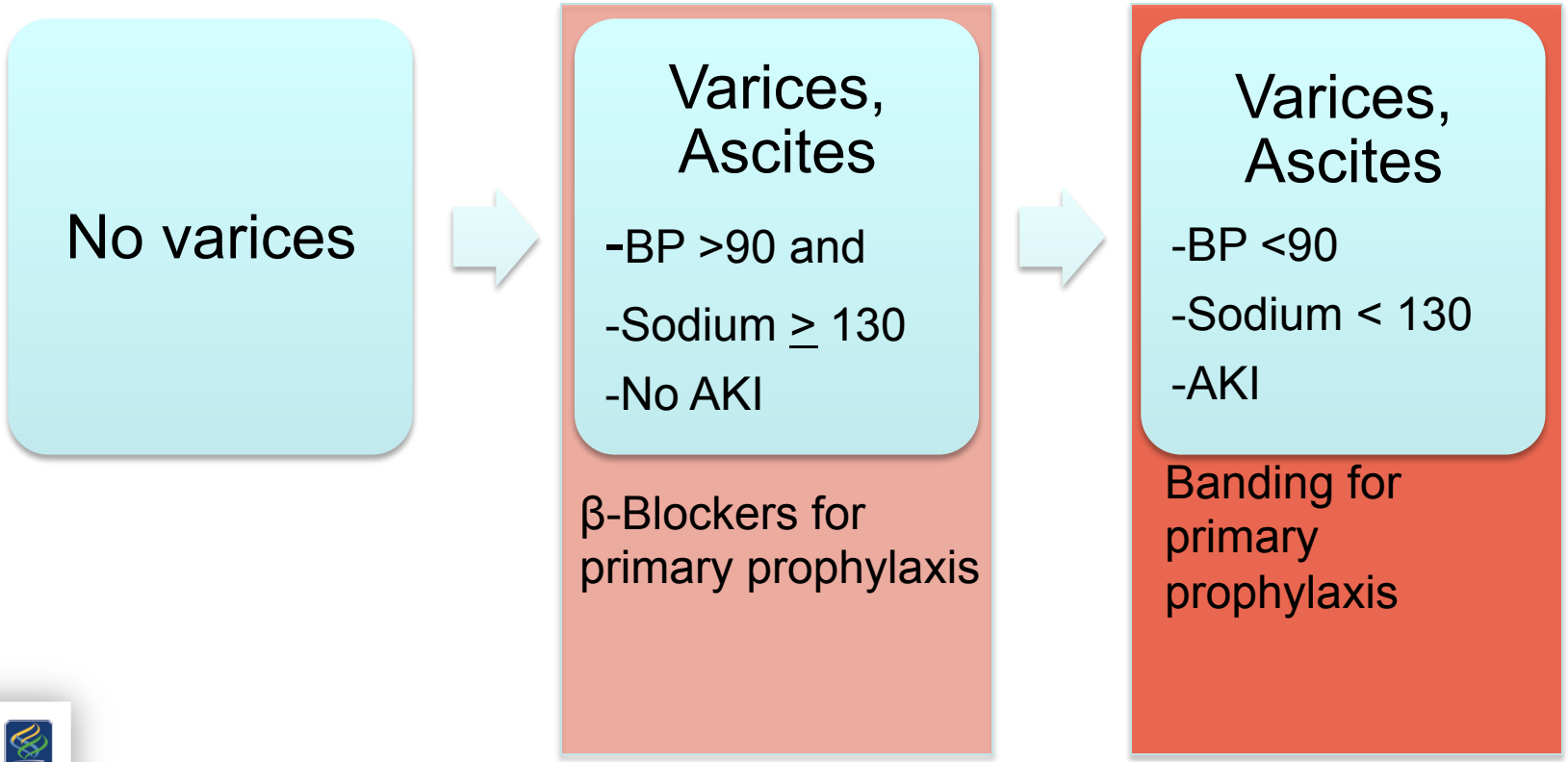
Beta-Blocker Window

Beta-Blocker window Narrows



Beta-Blocker Window

Beta blockers in cirrhosis: The window re-opens

Guadalupe Garcia-Tsao[1,2,*]

[1]Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT, USA; [2]Section of Digestive Diseases, VA-CT Healthcare System, West Haven, CT, USA

	n	Main characteristic used for grouping cirrhotic patients	% with refractory ascites	% Child-Pugh C No BB *vs.* BB	Baseline MELD No BB *vs.* BB	Baseline MAP No BB *vs.* BB	Follow-up (months)	Adjusted hazard ratio for mortality associated with BB (confidence interval)*
Sersté *et al.*	151	Refractory ascites	151	61% *vs.* 74%	18.8 *vs.* 18.9	123 *vs.* 103	8	2.61 (1.63-4.19)
Mandorfer *et al.*	182	Spontaneous bacterial peritonitis	n.s.	53% *vs.* 67%	20.0 *vs.* 21.6	83 *vs.* 77	~9.6 (147 person yr)	1.64 (1.1-2.3)
Leithead *et al.*	322 (208 matched)	Ascites on transplant list	117 (76 matched)	n.s.	16 *vs.* 17**	89 *vs.* 86‡	2.4 (72 d)	0.35 (0.14-0.86)
Bossen *et al.*	1188	Ascites in RCT of satavaptan/placebo	588	28% *vs.* 24%	11 *vs.* 12	85 *vs.* 83	12 (52 wk)	1.02 (0.74-1.40)
Mookerjee *et al.*	349	Acute-on-chronic liver failure	n.s.	n.s.	29 *vs.* 27	79 *vs.* 78	1 (28 d)	0.60 (0.36-0.98)

Key= Blood pressure

for β-Blocker patients to derive survival benefit

(Compensatory Cardiac Reserve)

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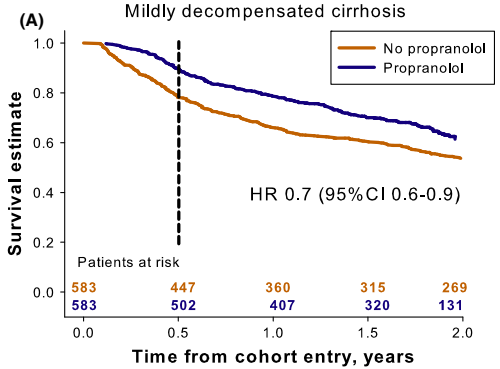
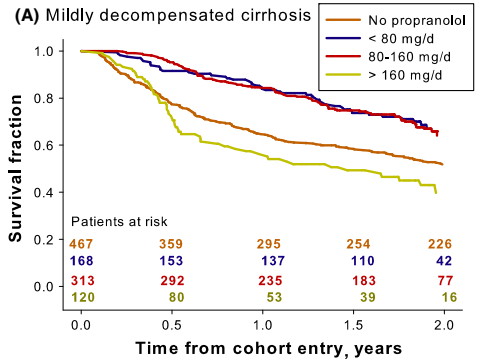
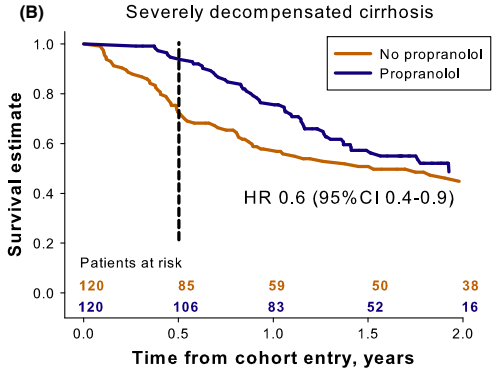
Garcia-Tsao, J Hep 2016

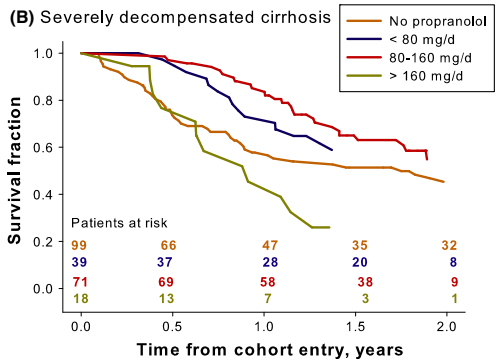
Beta-Blocker Window

Low-dose Beta-Blockers









Bang, Liv Int 2016

Beta-Blocker Window

Low-dose Beta-Blockers

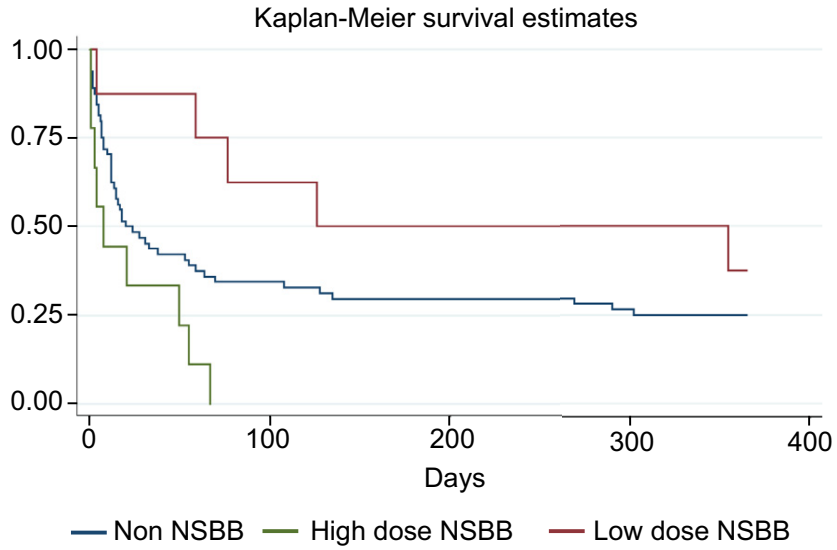


Fig. 1. Survival after first episode of spontaneous bacterial peritonitis stratified by the dose of non-selective beta blockers. (This figure appears in colour on the web.)

Madsen, J Hep 2016

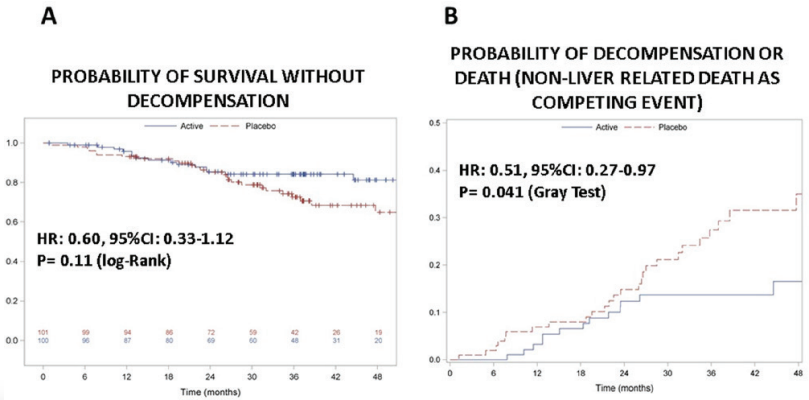
Beta-Blocker Window

Controversy Continues at AASLD 2016

LB-6

Preventing the decompensation of cirrhosis with β-blockers in patients with clinically significant portal hypertension. A multicenter double-blind placebo-controlled randomized clinical trial.

Càndid Villanueva[1,2], Agustin Albillos[2], Joan Genescà[2], Juan



1712

The comparison of long-term survival in cirrhotic patients with significant ascites and esophageal varices according to the treatment modality between endoscopic variceal ligation and non-selective beta-blockers

Jeong-Ju Yoo[1], Sang Gyune Kim[1], Young Seok Kim[1], Soung Won Jeong[1], Jae Young Jang[1], Sae Hwan Lee[1], Hong Soo Kim[1], Young Don Kim[2], Gab Jin Cheon[2], Boo Sung Kim[1]; [1]Soonchunhyang University School of Medicine, Seoul, Korea (the Republic of); [2]Gangneug Asan Hospital, Gangneug, Korea (the Republic of)

- N=269 with moderate ascites + EV
- Rx- BB vs. EBL vs. Observation
- BB- HR 1.98

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Beta-Blocker Window

2017: the Window is OPEN

No varices

Varices, Ascites

-SBP>90 and

-Sodium ≥ 130

-No AKI

β-Blockers for primary prophylaxis

Varices, Ascites

-SBP <90

-Sodium < 130

-AKI

Banding for primary prophylaxis

Beta- Blocker Prophylaxis

Right Now, Real-World

Use low doses of of β- Blockers
- Propranolol < 160 mg/d
- Nadolol < 80 mg/d
- Careful with Carvedilol impact on BP
  - Only primary prophylaxis

Hold β- Blockers
- SBP or AKI especially in refractory ascites
- Consider restart after stabilization

Acute Variceal Bleeding

Early TIPS

- High-risk patients may benefit from early TIPS (< 72 hours)
- Decreased re-bleeding
- Improved survival

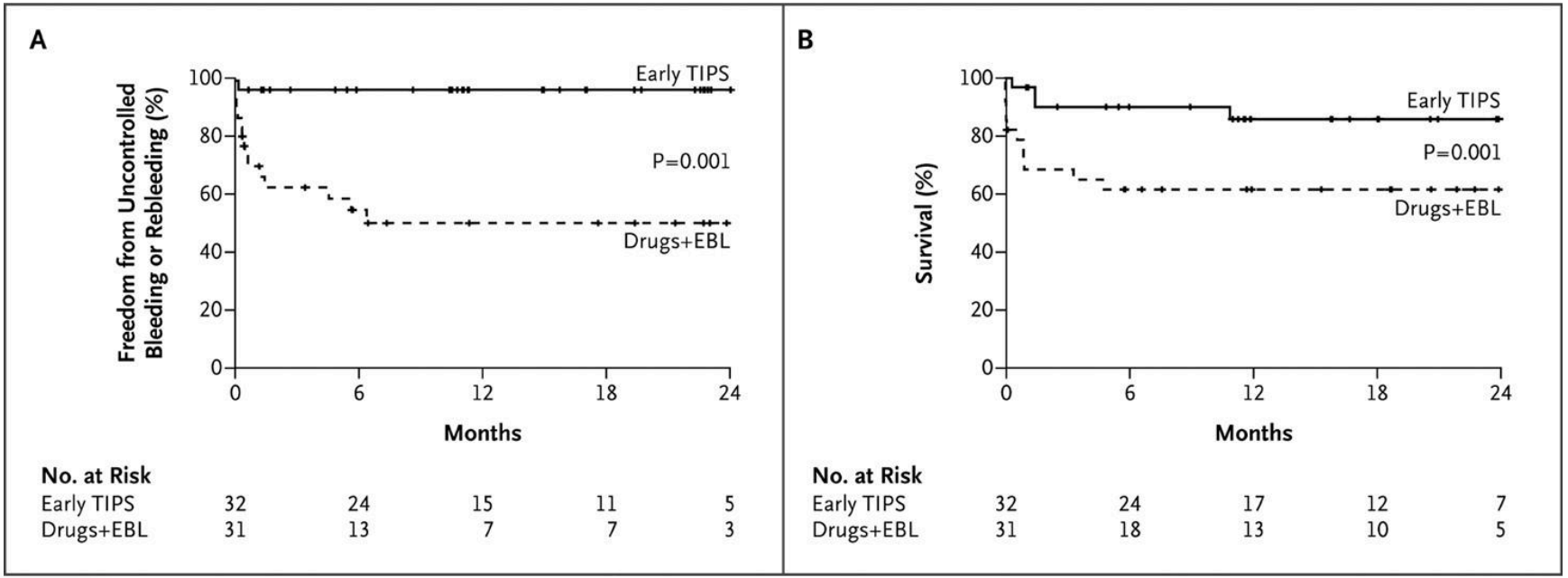
- TIPS complications
  - Hepatic failure
  - Heart failure
  - Hepatic encephalopathy
- Pulling the trigger?

Acute Variceal Bleeding

Early TIPS- Prospective RCT

Free of Bleeding

Survival



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Garcia-Pagan, NEJM 2010

Acute Variceal Bleeding

Early TIPS- Key Selection Criteria

- Inclusion
  - CTP C (10-13)
  - CTP B with active EVB @ initial EGD
- Randomized to standard care vs. TIPS

- Exclusion
  - CTP C (14,15)
  - CTP B without active EVB
- < 20% admitted for EVB included in study
  - N= 63 enrolled in 3 years
  - F/U 16 mo

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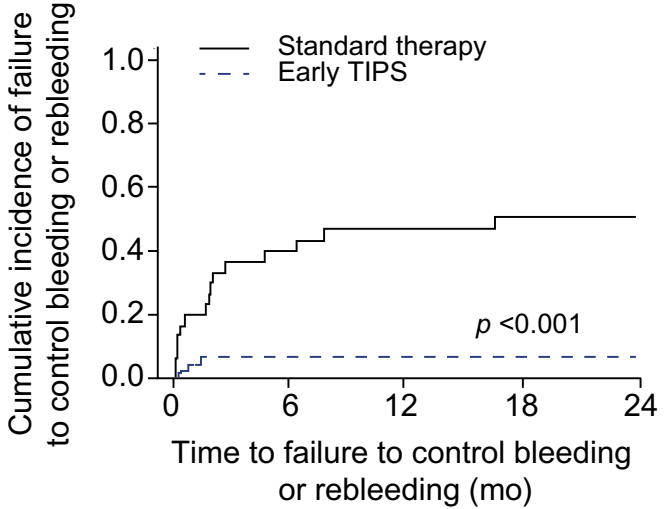
Garcia-Pagan, NEJM 2010

Acute Variceal Bleeding

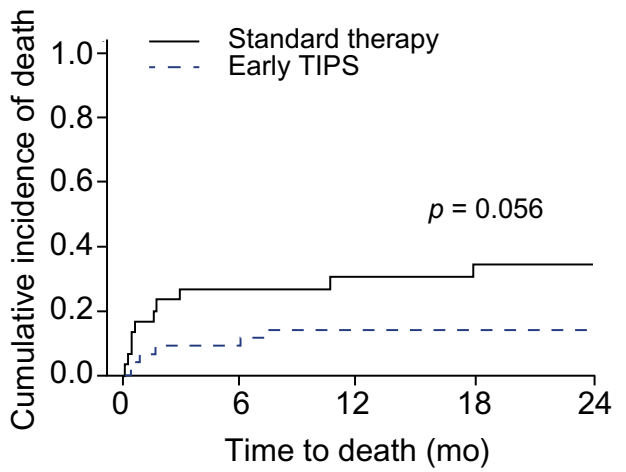
Early TIPS- Positive Retrospective Data

Rebleeding



At risk					
TIPS	45	26	16	14	12
Drugs + EBL	30	15	11	8	5

Death



At risk					
TIPS	45	30	20	16	14
Drugs + EBL	30	20	17	14	8

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Garcia-Pagan, J Hep 2013

Acute Variceal Bleeding

Early TIPS- Negative Retrospective Data

Free of Bleeding

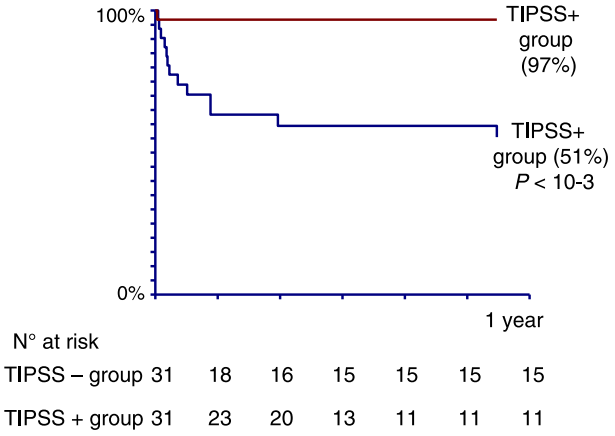

Figure 2 | One-year probability of remaining free of rebleeding in case of variceal bleeding in TIPSS+ and TIPSS− group.

Survival

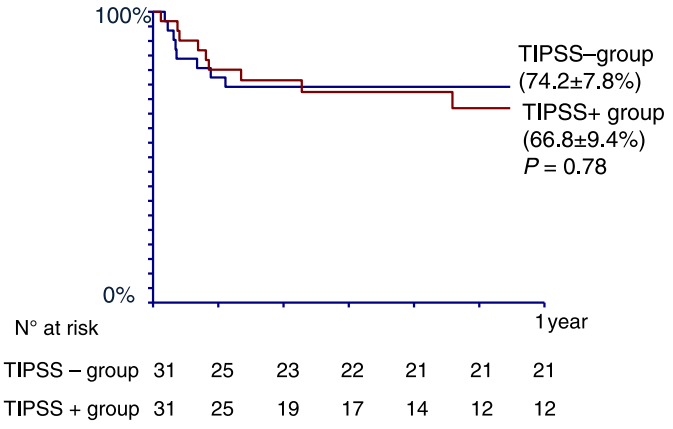

Figure 3 | One-year survival in patients with cirrhosis and variceal bleeding: comparison between TIPSS+ and TIPSS− groups.

Rudler, APT 2014

Acute Variceal Bleeding

AASLD 2016- Mixed Larger Retrospective Data

87

Early-TIPS improves survival in high-risk variceal bleeders. Results of a Multicenter Variceal Bleeding Observational Study

Virginia Hernandez-Gea[1], Bogdan Procopet[2], Álvaro Giráldez[3],

- N= 671/2168 from 34 centers
  - 434 CTP C (10-13), 237 CTP A/B
  - TIPS & management per center policy
- 82 early TIPS vs. 589 EBL

Acute Variceal Bleeding

AASLD 2016- Child C Benefit

Free of Bleeding

- 6 weeks
  - 93% TIPS vs. 81% EBL
- 1 year
  - 87% TIPS vs. 68% EBL
- P= 0.02

Survival

- Overall
  - 1 year- 70% TIPS vs. 62% EBL
  - P= 0.08
- CTP C (10-13)
  - 1 year- 66% vs. 53%
  - P= 0.034

87

Early-TIPS improves survival in high-risk variceal bleeders. Results of a Multicenter Variceal Bleeding Observational Study

Virginia Hernandez-Gea[1], Bogdan Procopet[2], Álvaro Giráldez[3],

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Acute Variceal Bleeding

Early TIPS- Who to Consider Now

CTP C (10-13)
MELD < 18

Younger patients (< 65 years old)

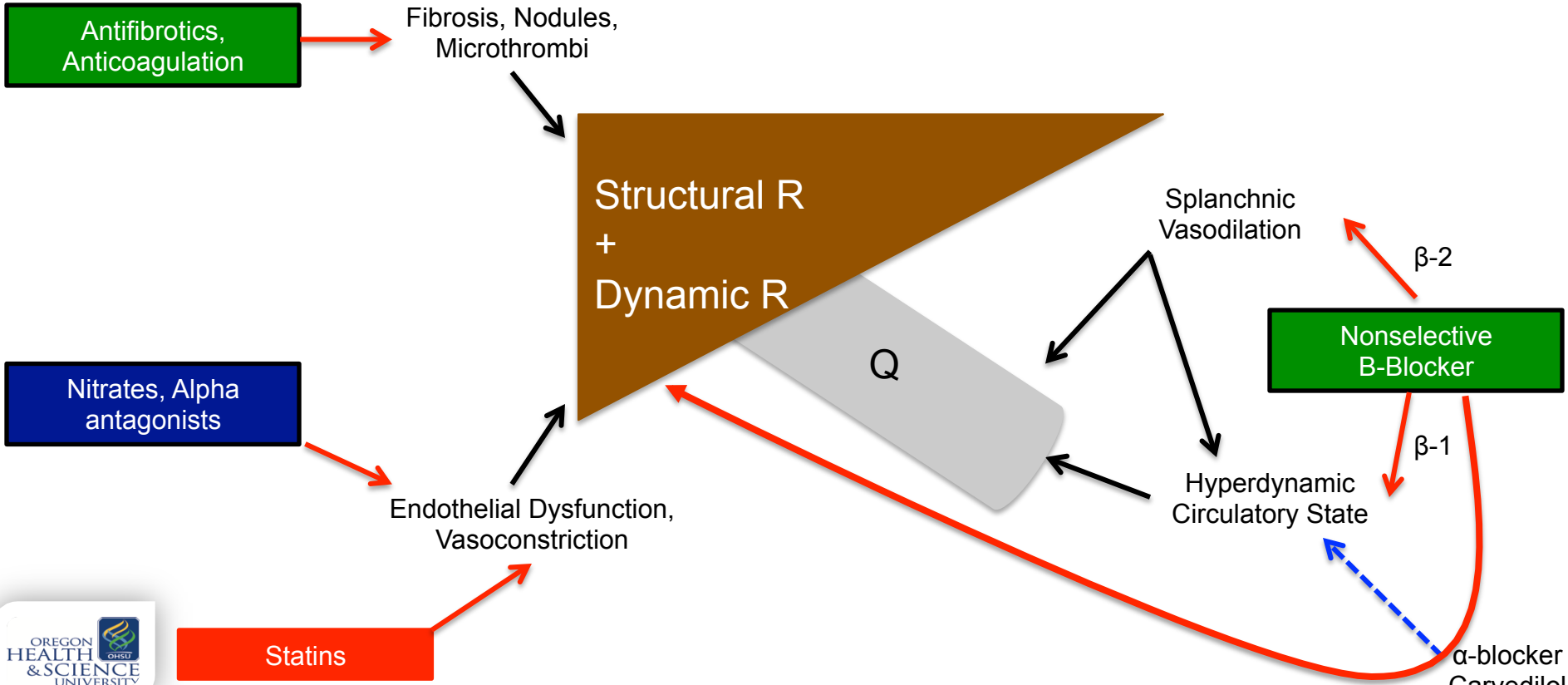
No previous hepatic encephalopathy

No TIPS contraindications:

- Cardiac disease
- Infection
- HCC

Portal Hypertension Pathophysiology

Pressure = Flow x Resistance



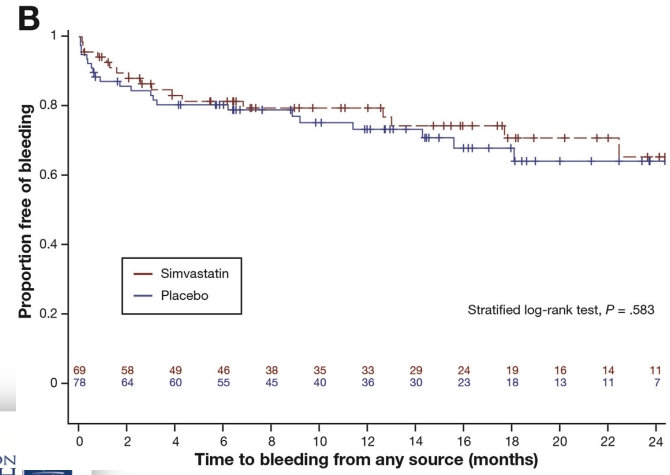
Simvastatin

Rebleeding Prevention

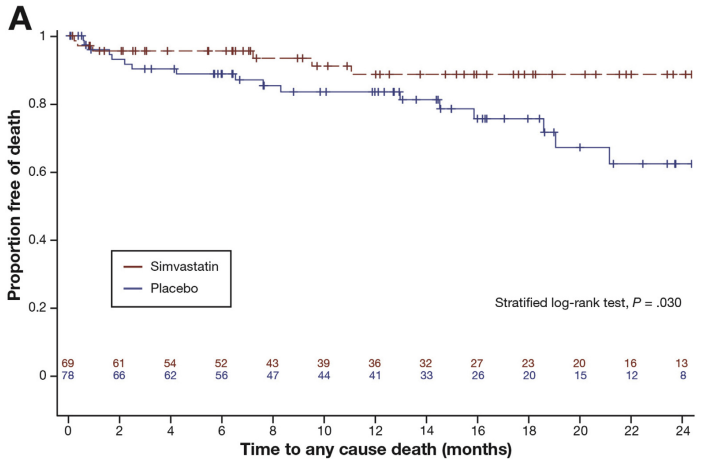
Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does Not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis

Juan G. Abraldes,[1,*] **Candid Villanueva**,[2,*] Carles Aracil,[3] Juan Turnes,[4]

Rebleeding



Survival



Abraldes, Gastro 2016

Simvastatin

Primary Prophylaxis- AASLD 2016

LB-26

Addition of simvastatin to carvedilol does not improve hemodynamic response in cirrhotics with varices without prior bleed: Preliminary results of an open label RCT

Rajan V, Ashok Choudhary, Ankur Jindal, Guresh Kumar, Shiv K. Sarin; Hepatology, Institute of liver and biliary sciences, Delhi, India

- Open-label RCT
  - N= 220 (97 data available)
  - Simvastatin + Carvedilol
- HVPG reduction nor EVB no difference
- Final results awaited

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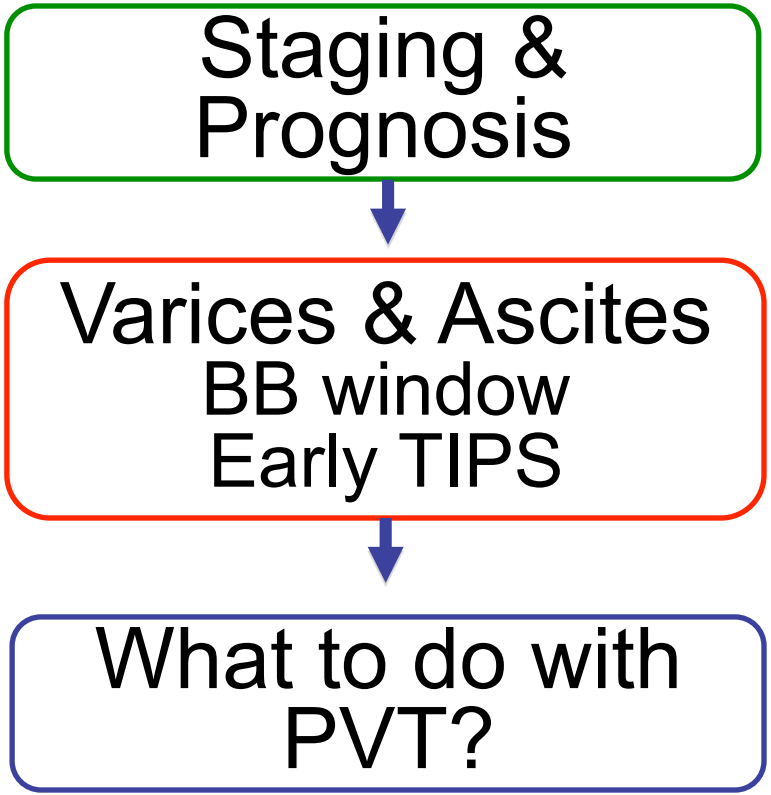
Hemodynamic Effects Of Carvedilol Plus Simvastatin In Cirrhosis With Portal Hypertension And No-Response To β-Blockers: A Double-Blind Randomized Trial

Edilmar Alvarado-Tapias[1], Alba Ardèvol[1,2], Oana Pavel[1], Rosa Montañés[1], Marianette Murzi[1], Elida Oblitas Susanibar[1], Maria Poca[1,2], Xavier Torras[1,2], Càndid Villanueva[1,2]; [1]Hospital de la santa creu i sant pau, Barcelona, Spain; [2]Centro de Investigación biomédica en red en Enfermedades Hepáticas y Digestivas, Barcelona, Spain

- RCT. N=87
- BB + Simvastatin or placebo
  - Carvedilol for IV propranolol NR
  - Nadolol for responders
- HVPG baseline & 1 mo after
- Simvastatin potentiated HVPG reduction

Update in Portal Hypertension

Learning Objectives



Portal Vein Thrombosis (PVT)

What Not to Miss

Life Threatening:
Mesenteric Vein Thrombosis ~ Dead Gut

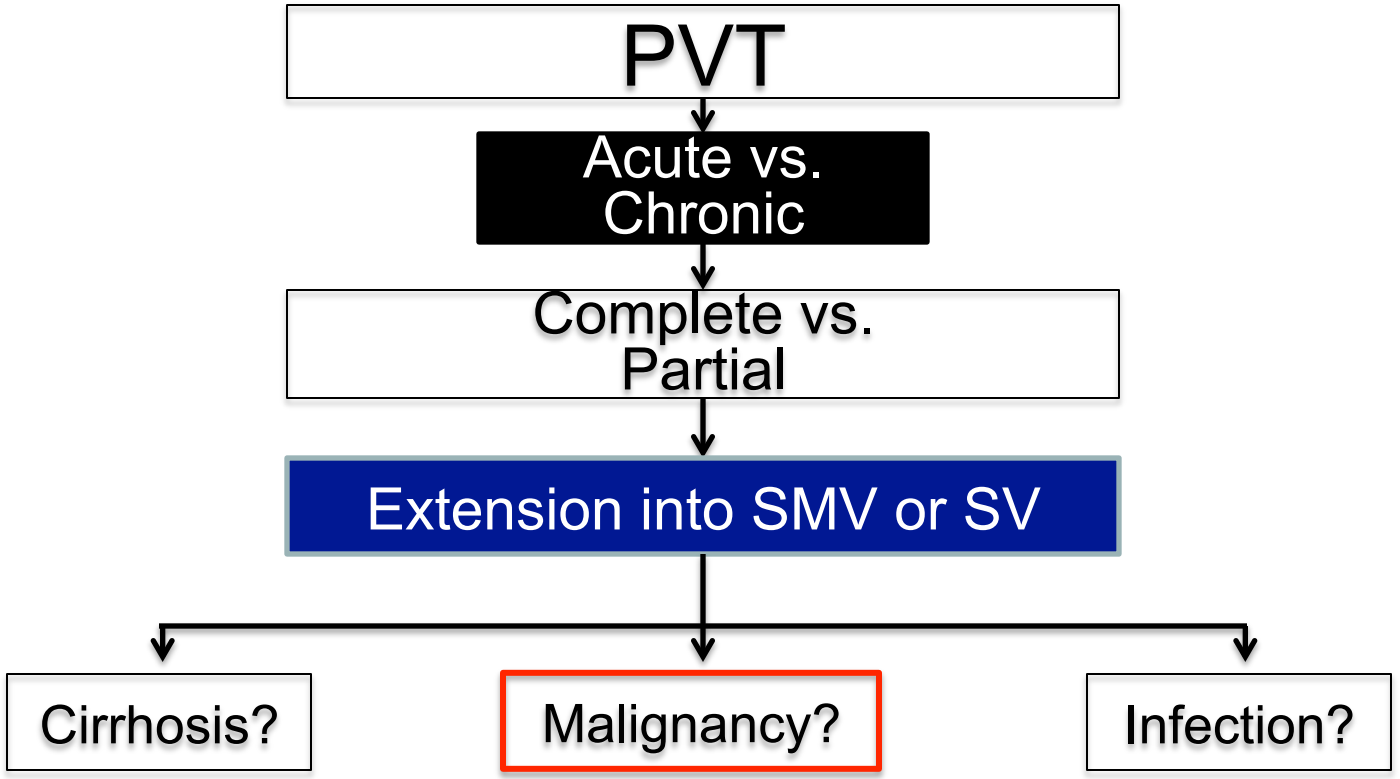
Poor prognosis:
HCC extension into PVT

Impact on Transplant Candidacy

Prothrombotic State

Portal Vein Thrombosis (PVT)

Making the Diagnosis



Portal Vein Thrombosis (PVT)

Management Goals

Recanalization

- Prevent ischemia, infarction
- Prevent progression to chronic PVT → Variceal bleeding

- Maintain liver transplant candidacy
- Prevent recurrence

Portal Vein Thrombosis (PVT)

Who to Anticoagulate?

Yes

- Acute PVT
  - No cirrhosis
  - Cirrhosis
- Prothrombotic state

No

If anticoagulation will increase complications/risk:

- High risk of bleeding

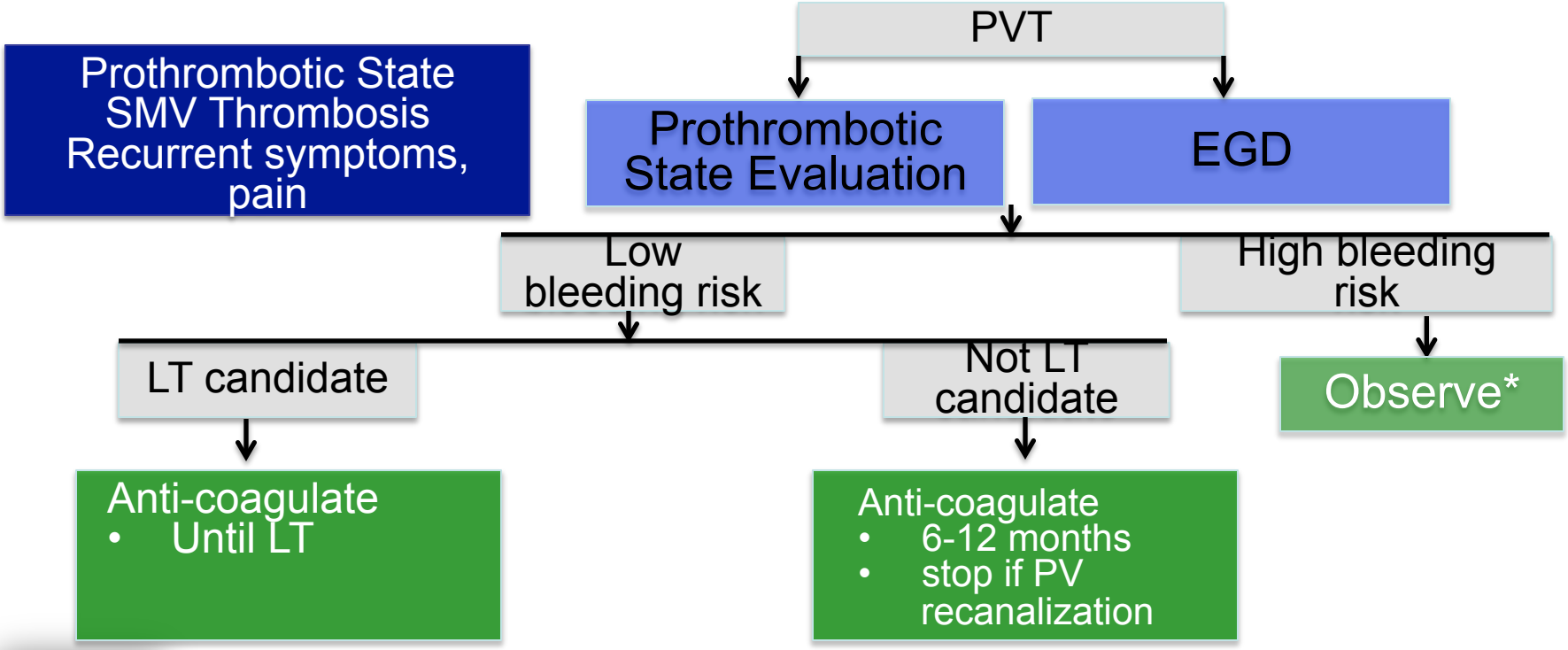
If anticoagulation won't make a difference:

- Underlying poor prognosis

? Chronic PVT with cavernous transformation

Portal Vein Thrombosis (PVT)

Portal Vein Thrombosis (PVT)—**Cirrhosis**



*Unless you consult a hematologist (Anticoagulation will be recommended)

Courtesy of Dr. Scott Naugler

Take Aways

HVPG Drives Outcomes
& LS < 20 + Plt > 150- EGD can be avoided

Beta-Blocker Window is Still Open

Early TIPS, Simvastatin need Refinement

PVT- Algorithmic Approach

OREGON HEALTH & SCIENCE UNIVERSITY OHSU

Give thanks. Give life.

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