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Post-AASLD Update

End-Stage Liver Disease

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Hepatic/Splenic Shear Wave Velocity

- 143 cirrhotic patients undergoing EGD for assessment of varices
  - Male (n=84), Age (64.8±12.5)
  - 19 HBV, 86 HCV, 38 Other

Esophageal varices	None (n=58)	Small (n=60)	Medium (n=25)
Liver Vs	1.46	2.27	2.47
Spleen Vs	2.58	3.06	3.71

Red sign	None (n=122)	Present (n=21)
Liver Vs	1.90	2.36
Spleen Vs	2.88	3.59

Detection of Moderate Eso. Varices	Cut-off	AUROC
Liver Vs	2.09	0.71
Spleen Vs	3.45	0.90

Iijima. AASLD 2014 Abstract 162

Physical Exercise and Portal Hypertension

- Randomized controlled trial (n=23)
  - CTP A/B (15/8), MELD 10±2.9, 30% HCV
  - Exercise: 40 supervised sessions of stationary bike and kinesiology (14 weeks) with target HR of 60-80% of maximum
  - >80% adherent

	PE+Nutrition (n=11)	Nutrition (n=12)
Baseline HVPG	14.5 (11.0-18.5)	11.5 (3.5-17.3)
Post Intervention HVPG	11.5 (8.5-16.8)	14.0 (9.0-22.2)
Mean change	-2.5	+4.0
	Decreased leg cramps No HE No variceal bleeding	

Macias-Rodriquez. AASLD 2014 Abstract 96

Statins and Portal Hypertension

- Statins:
  - HMG-CoA reductase inhibition
  - Up-regulation of eNOS
    - Increased Nitric oxide (NO) production
    - Vasodilation: potential reduction in pHTN
- Prospective randomized trial
  - Cirrhosis (by US w/ Doppler or EGD)
  - Interim report with n=22
  - Randomization
    - Simvastatin (40mg qd)
    - Placebo
  - Primary end point: reduction of HVPG
    - By 20% or to <12 mmHg

Flores. AASLD 2014 Abstract 2037

Statins and Portal Hypertension

	Simvastatin	Placebo
HVPG reduction		
- All	36%	0%
- Baseline HVPG>12 mmHg	50%	0%
Decrease in Azygous vein blood flow	38%	19%
Mod-severe AE	N/A	N/A

2/3 also taking NSBB: No interference

Flores. AASLD 2014 Abstract 2037

Statins and Portal Hypertension

- NCX-6560
  - NO-releasing derivative of atorvastatin
  - Greater lipid-lowering, anti-thrombotic and anti-inflammatory property
  - Lower risk of myopathy
- Animal data (3 week bile duct ligated rat model)

Simvastatin	Atorvastatin	NCX-6560	Vehicle
Muscle toxicity Liver toxicity Increased mortality	Reduced Portal Pressure (11-15%)		
		Lower incidence of muscle toxicity Better diuresis Decreased creatinine Increased NO production	

Rodriguez. AASLD 2014 Abstract 2005

Relative Adrenal Insufficiency

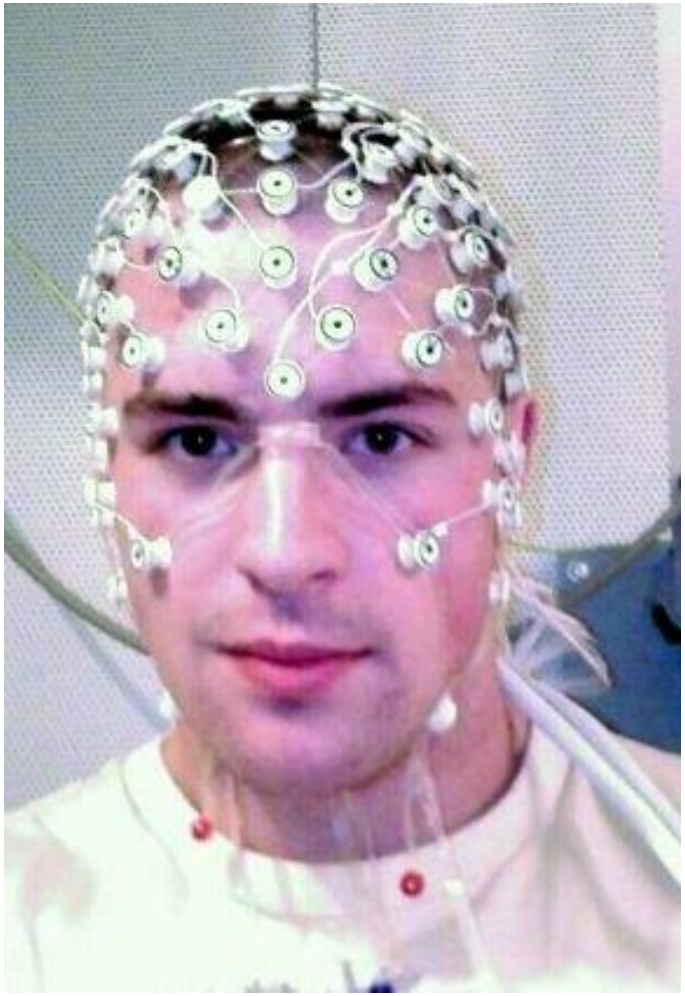
- Italian single center study (n=94, decompensated cirrhosis)
- Adrenal function test (short synacthen test)
  - Baseline total cortisol < 35mcg/dl
  - <9 mcg/dl increase after stimulation
- Prevalence of relative adrenal insufficiency = 43%

	No RAI	RAI
Age	62 yrs	57 yrs
MELDNa	18	22
CRP	11.5 mg/dl	15.0 mg/dl
Total-C/HDL-C	2.1/0.6 mmol/L	1.5/0.4 mmol/L
Bacterial infection	14%	46%
90 day LT-free survival	91%	71%

- Independent predictors of survival: MELDNa, Age and RAI

Piano. AASLD 2014 Abstract 92

EEG-Light for HE Diagnosis



Schiff. AASLD 2014 Abstract 208

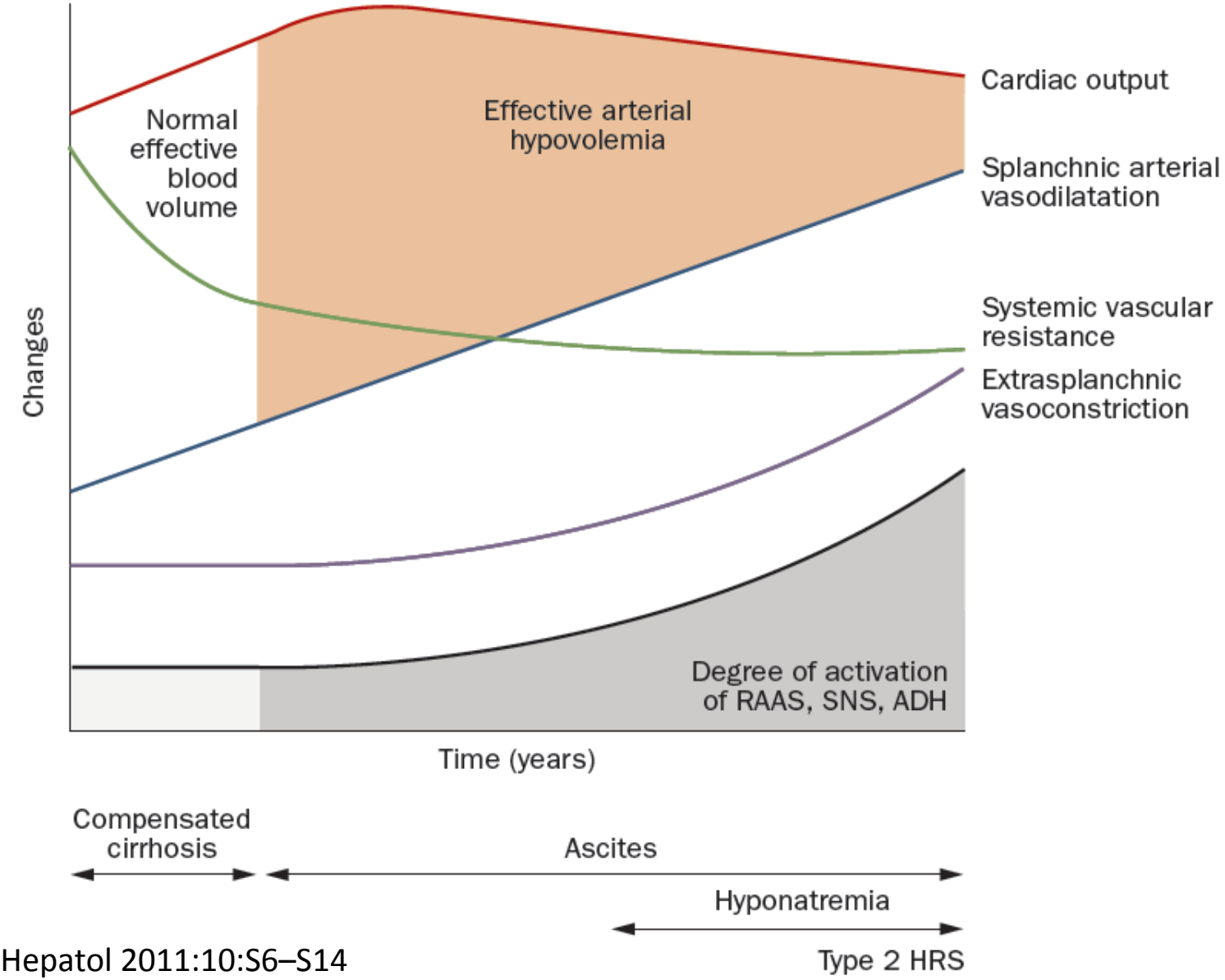
EEG-Light for HE Diagnosis

- Two representative EEG measures
  - Mean dominant frequency (MDF)
  - Relative power of theta band (Theta%)

	MDF	Theta%
Standard versus Light EEG	r=0.52 (p<0.01)	r=0.52 (p<0.01)
Light EEG versus MELD	r=-0.49 (p=0.04)	r=-0.61 (p<0.01)
Light EEG versus Ammonia (venous, fasting)	r=-0.47 (p=0.02)	r=-0.47 (p=0.02)

Schiff. AASLD 2014 Abstract 208

Circulatory and Renal Changes in Cirrhosis



Arroyo. Ann Hepatol 2011:10:S6–S14

Use of Non-selective β-Blockade (NSBB) in ESLD

- Effect of NSBB on portal hypertension (pHTN)
  - Single center study, 294 patients with cirrhosis
  - Propranolol i.v. 0.15 mg/Kg

	Mild pHTN (n=81)	Significant pHTN (n=194)
Baseline	HVPG 6-10 mmHg	HVPG >10 mmHg Small varices (n=114) No varices (n=80)
Liver stiffness	19 kPa	30kPa
MELD	5.6	6.5
Splenomegaly	40%	63%
Systemic vascular resistance	1469 dyne.s.cm	1336 dyne.s.cm
Cardiac index	2.8	3.3
HVPG response to propranolol		
Pre-Post change	7.3 – 6.6 mmHg (-8%)	14.7 - 12.2 mmHg (-16%)
>20% reduction	12%	40%

Villanueva. AASLD 2014 Abstract 2036

Benefits of β-blockade in Cirrhosis

Non-selective β-blocker (NSBB) is beneficial in patients with cirrhosis and esophageal varices.

- Reduced incidence of variceal hemorrhage
- Reduced incidence of ascites
- Improved survival

Current AASLD Guideline (2007) recommends NSBB for:

- Primary prophylaxis in patients with low risk bleeding (Child A, no red signs) and medium/large varices
- Primary prophylaxis in patients at high risk of bleeding (e.g., Child B/C) regardless of the variceal size
- Secondary prophylaxis (in conjunction with variceal ligation)

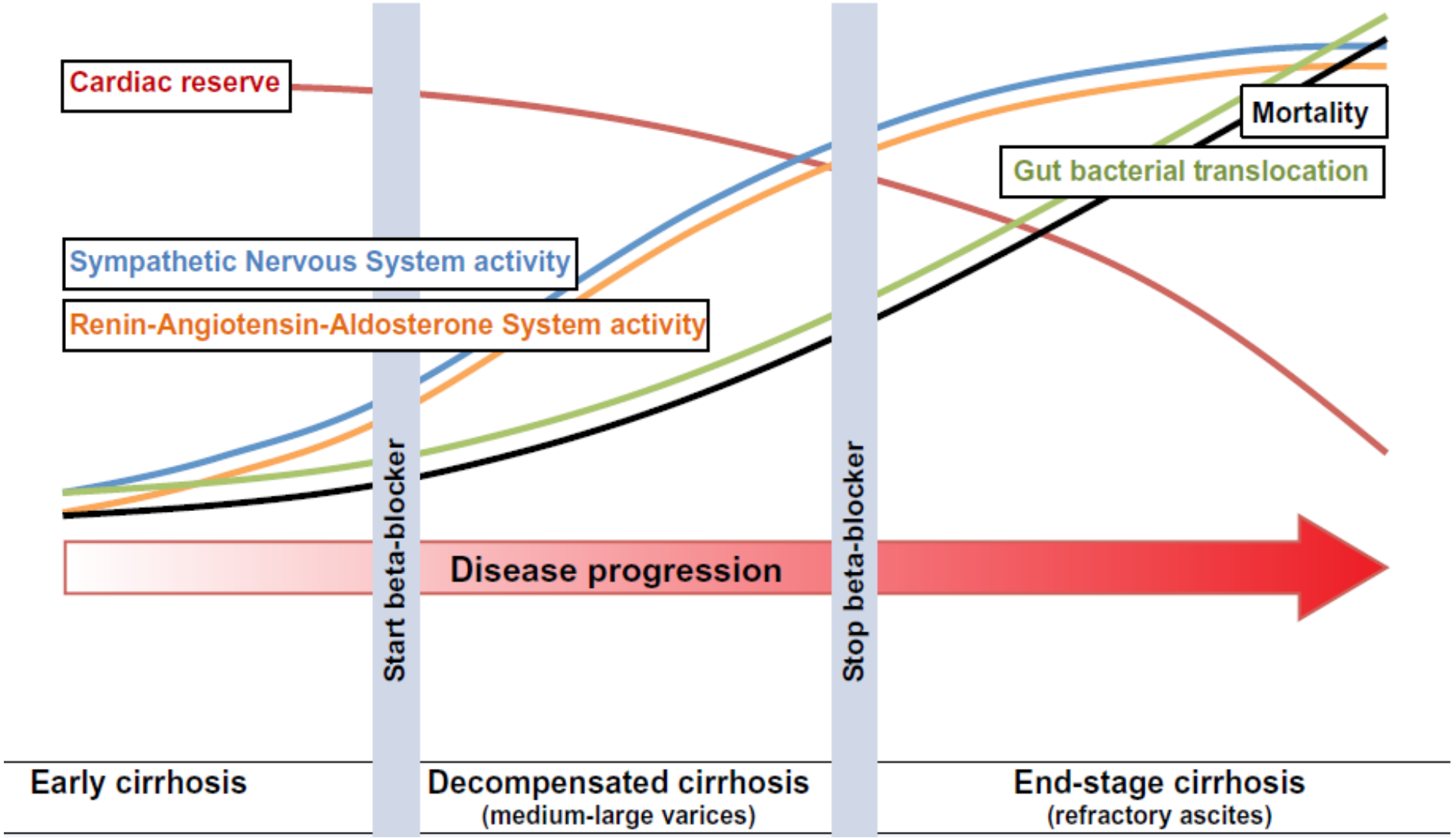
Am J Gastroenterol 2012; 107:418–427

Potential Harm of NSBB

- NSBBs are associated with paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites.
- NSBBs are associated with poor survival in patients with refractory ascites.
- Among patients with cirrhosis and SBP, NSBBs increase risk for hepatorenal syndrome and acute kidney injury and reduce transplant-free survival.

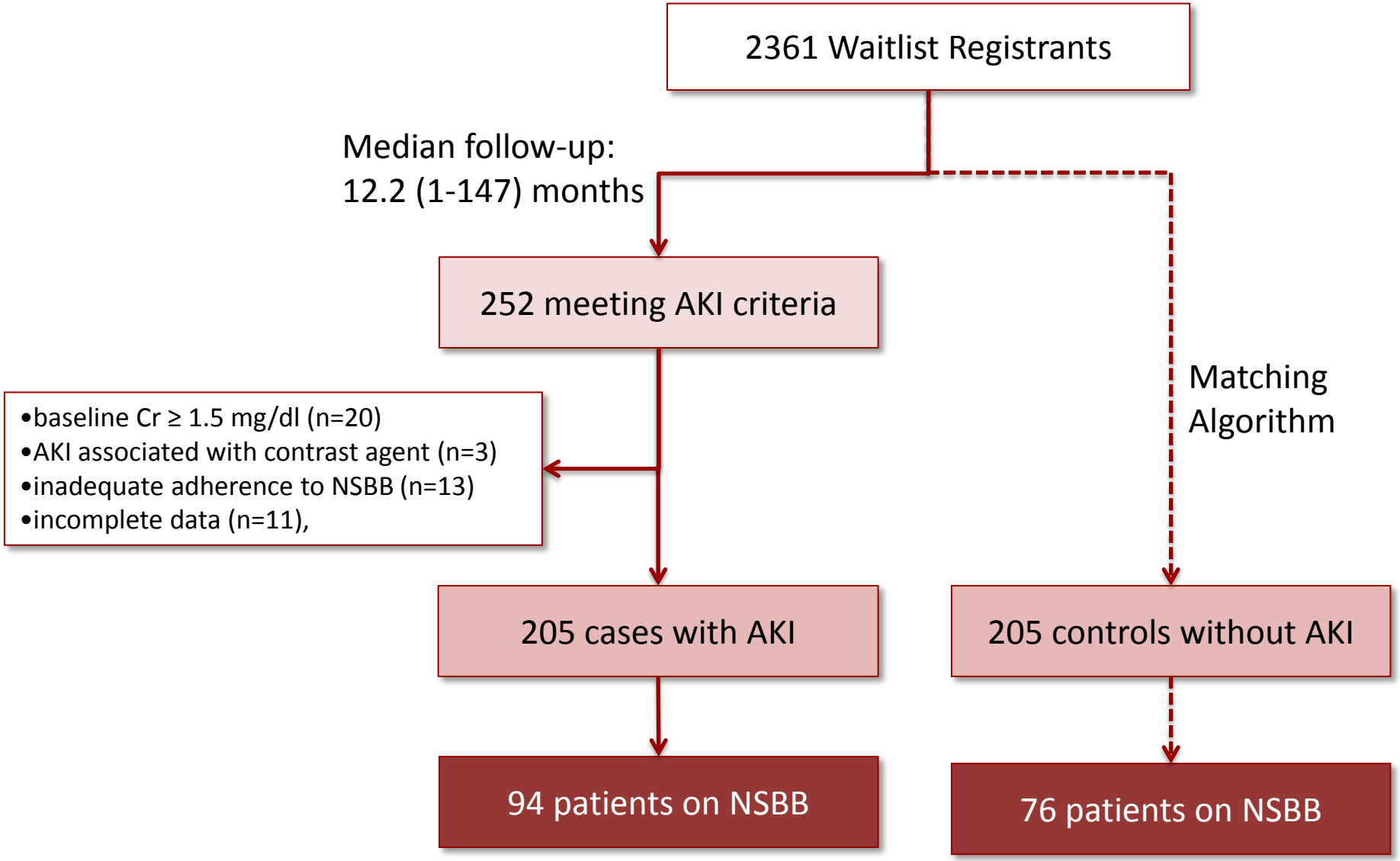
J Hepatol 2011;55:794-9; HEPATOLOGY 2010;52:1017-1022; Gastroenterology 2014;146:1680–1690

Window Theory



Am J Gastroenterol 2012; 107:418–427

NSBB and Acute Kidney Injury



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Predictors of AKI – Multivariable Analysis*

	HR	95% CI		p	Interaction
MELD-Na at Baseline	1.66	(1.36	- 2.02)	<0.001	
NSBB and ascites (-)	0.16	(0.06	- 0.48)	0.001	<.001
NSBB and ascites (+)	3.78	(1.93	- 7.39)	<0.001	

* Cox proportional hazards model stratifying on matched pairs and adjusting for age, sex, race, etiology of cirrhosis, presence of HCC

Kim AASLD 2014

Terlipressin for Hepatorenal Syndrome Type 1

- Terlipressin:
  - Vasopressin analogue (vasoconstrictor)
  - Used for HRS and acute variceal hemorrhage
  - Not available in US or Canada

- US Pivotal trial (#2)
  - HRS type 1
    - Cr > 2.5 mg/dl
    - Doubling of creatinine within 2 weeks
    - No improvement in renal function after
      - Diuretic withdrawal
      - Albumin challenge

Boyer. AASLD 2014 Abstract 114

Terlipressin for Hepatorenal Syndrome Type 1

	Terlipressin + Albumin	Placebo + Albumin	p
n	97	99	
Confirmed reversal of HRS (primary endpoint) Cr<1.5mg/dl x2 over 48 hours	20%	13%	0.22
Reversal of HRS (Cr<1.5mg/dl)	24%	15%	0.13
Delta creatinine	-1.2 mg/dl	-0.6 mg/dl	<0.01
SAE	63%	56%	0.56

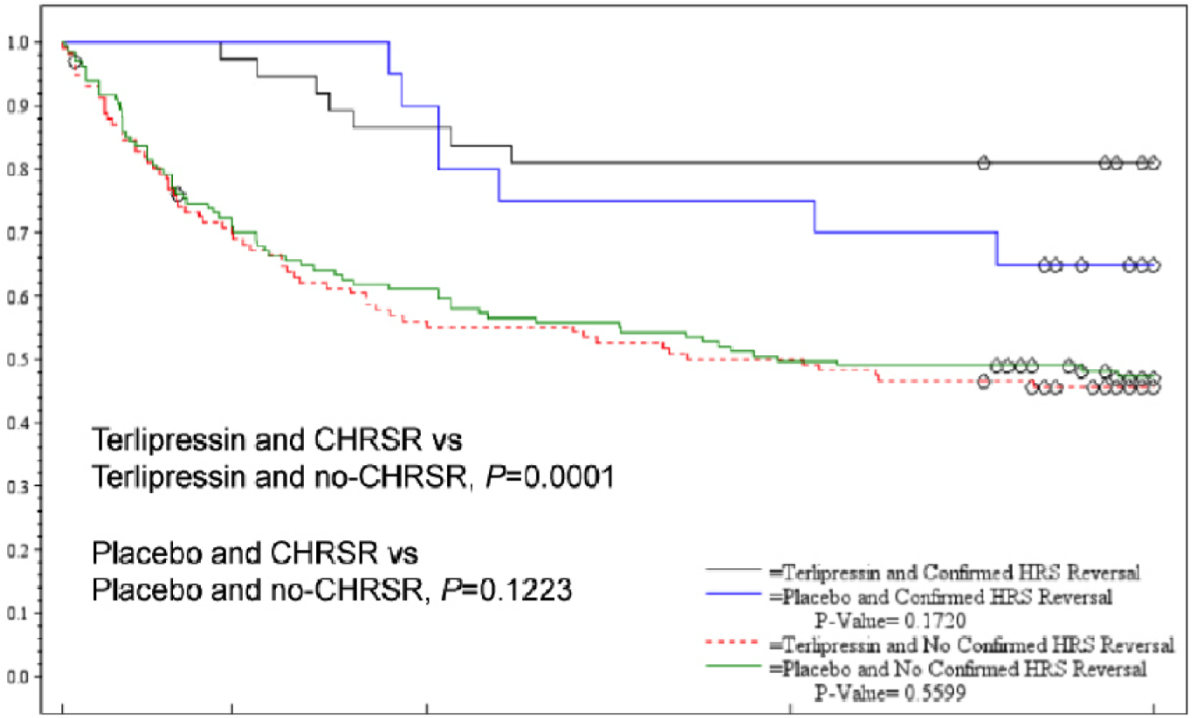
Boyer. AASLD 2014 Abstract 114

Terlipressin for HRS-1: Combined Analysis

- Two registration trials: OT-0401 (n=112) and REVERSE (n=196)

Confirmed reversal of HRS (CHRSR)	Terlipressin + Albumin (n=153)	Placebo + Albumin (n=155)	p
	24.2%	12.9%	0.01

- CHRSR vs. No CHRSR
  - Less RRT
  (7% vs. 43%)
  - Better survival

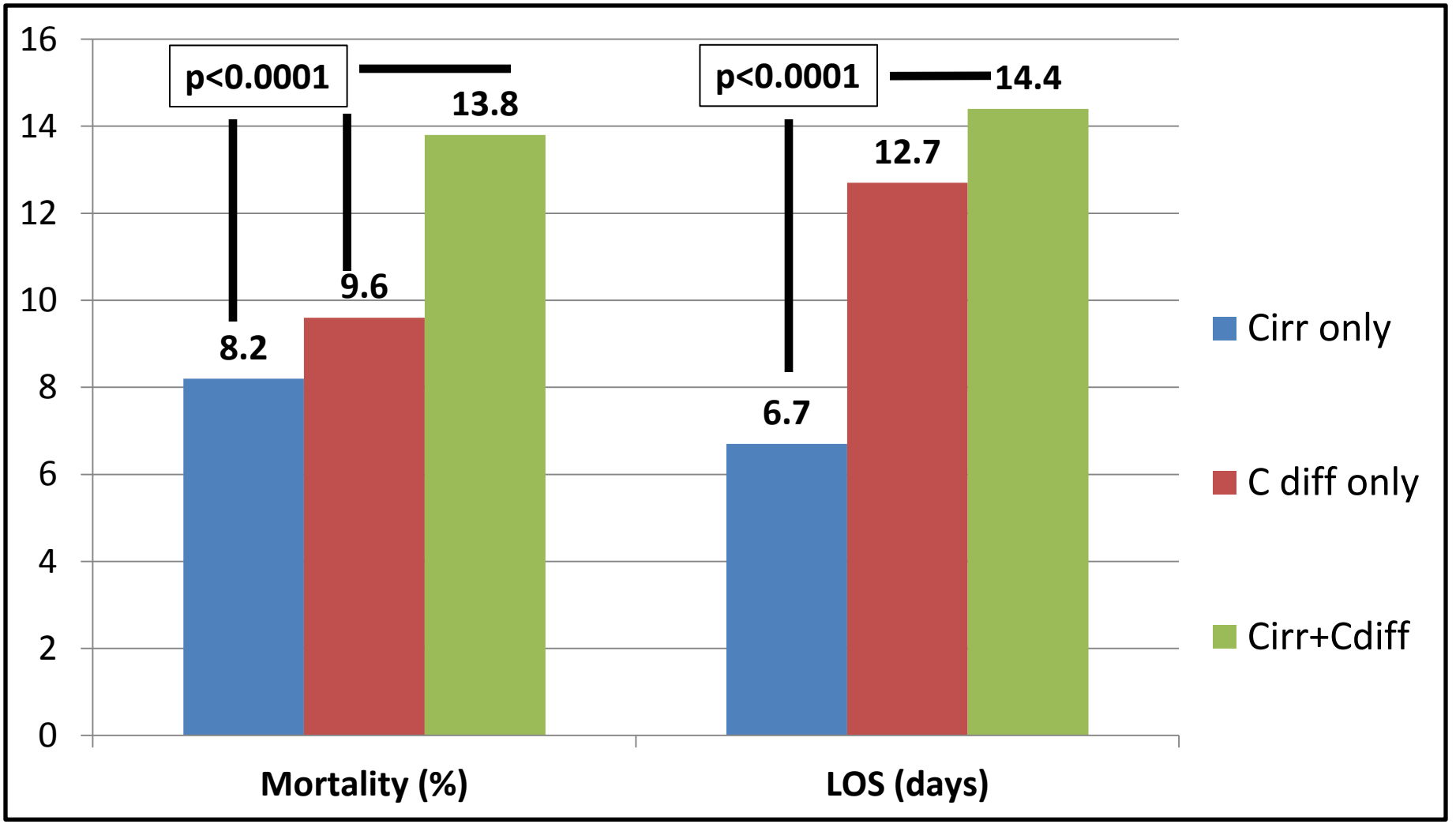


Sanyal. Gastro 2008:1360, Sanyal. AASLD 2014 Abstract 114

PPIs and Infections in Cirrhosis

- All patients with cirrhosis should undergo an extensive evaluation to see if they need the PPI that they are currently on
- Consider discontinuing PPIs if they are not required or question the need to continue this therapy

C. difficile worsens outcomes in cirrhosis



Bajaj JS et al Am J Gastroenterol 2010

Summary: Infections in Cirrhosis

- Infections profoundly affect the natural history of cirrhosis and are a major cause of ACLF
- The epidemiology and bacteriology of infections is changing radically, in part due to medications and prophylaxis
- A high index of suspicion, flexible, rapid and appropriate antibiotics and prevention of acute kidney injury is required to improve survival
- Prevention of further infections remains a challenge

Treatment of SBP

- Randomized open label trial
- Difficult-to-treat SBP
  - Hospital acquired (>48h after admission)
  - Microbial resistance
  - Inadequate response (<25% decrease in ascitic ANC @48h)
  - Recurrent SBP
- Randomized to:
  - Cefipime (1g tid)
  - Imipenem (1g tid)
- Patients:
  - 253 with SBP (out of 957 undergoing diagnostic paracentesis)
  - Difficult-to-treat SBP (n=175)

Jindahl. AASLD 2014 Abstract 162

Difficult-to-treat SBP

	Cefipime	Imipenem
n	88	87
Resistance to first abx	39%	48%
Early response - >25% reduction in ANC - Negative culture	59%	52%
SBP resolution	66%	61%
Mortality	39%	38%

Jindahl. AASLD 2014 Abstract 162

Terlipressin in Cirrhosis and Septic Shock

- Terlipressin versus norepinephrine as vasopressor in patients with decompensated cirrhosis and septic shock
- Open-label, randomized controlled trial
- Randomization <30 minutes of ICU admission
  - Terlipressin 1.3-5.2 mcg/min
  - Norepinephrine 7.5-60 mcg/min
  - Target MAP > 65 mmHg

Choudhury. AASLD 2014 Abstract 113

Terlipressin in Cirrhosis and Septic Shock

	Terlipressin (n=38)	Norepinephrine (n=40)	p
MELD	34	34	NS
CTP	12.5	13	NS
MAP@6hr	91%	80%	0.18
Failure	25%	63%	<0.05
MAP maintenance	94%	73%	0.02
Tx withdrawal @48hr	50%	25%	0.03
Increased urine output	59%	36%	0.05
Variceal bleeding	0%	15%	0.03
AE	41%	23%	0.12

Choudhury. AASLD 2014 Abstract 113