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Hepatorenal Syndrome

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Outline

- **Definitions (hepatorenal syndromes, HRSs)**
- **HRS type 1**
  - **Pathophysiology**
  - **Diagnosis**
  - **Prevalence, prognosis**
  - **Treatment**
  - **Prevention**

Clinical Presentation of HRSs

- Prerenal failure
- Type 1: acute & severe
- Type 2: chronic & moderate

*Arroyo et al., on behalf of the IAC. Hepatology 1996;23:164-76.

Characteristics of Patients with Cirrhosis and Type 1 HRS

Age (yr)	56±1
Male sex (%)	72
Alcohol (%)	90
Child-Pugh (score)	11.8±0.2
Arterial pressure (mm Hg)	65±2
Serum Na+ (mmol/L)	127±1
Serum creatinine (µmol/L)	2.8±1.1

Moreau et al. Gastroenterology 2002;122:923-30.

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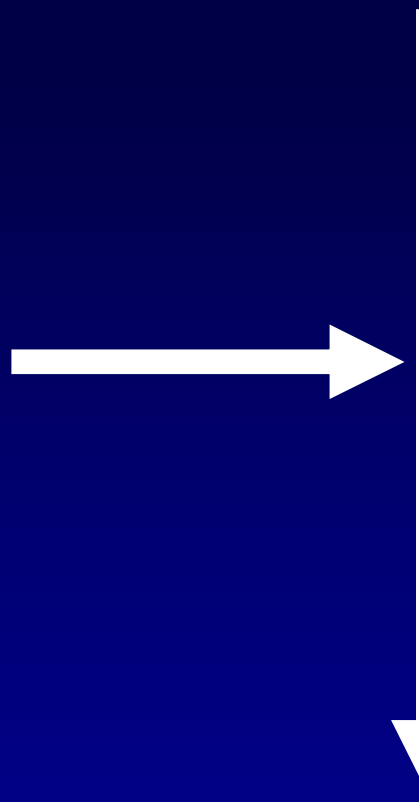
Precipitating factors 60%

<u>Inflammation without shock</u>

SBP, other infections,
GI bleeding,
Acute alcoholic hepatitis

<u>Other</u>

LV paracentesis without iv albumin

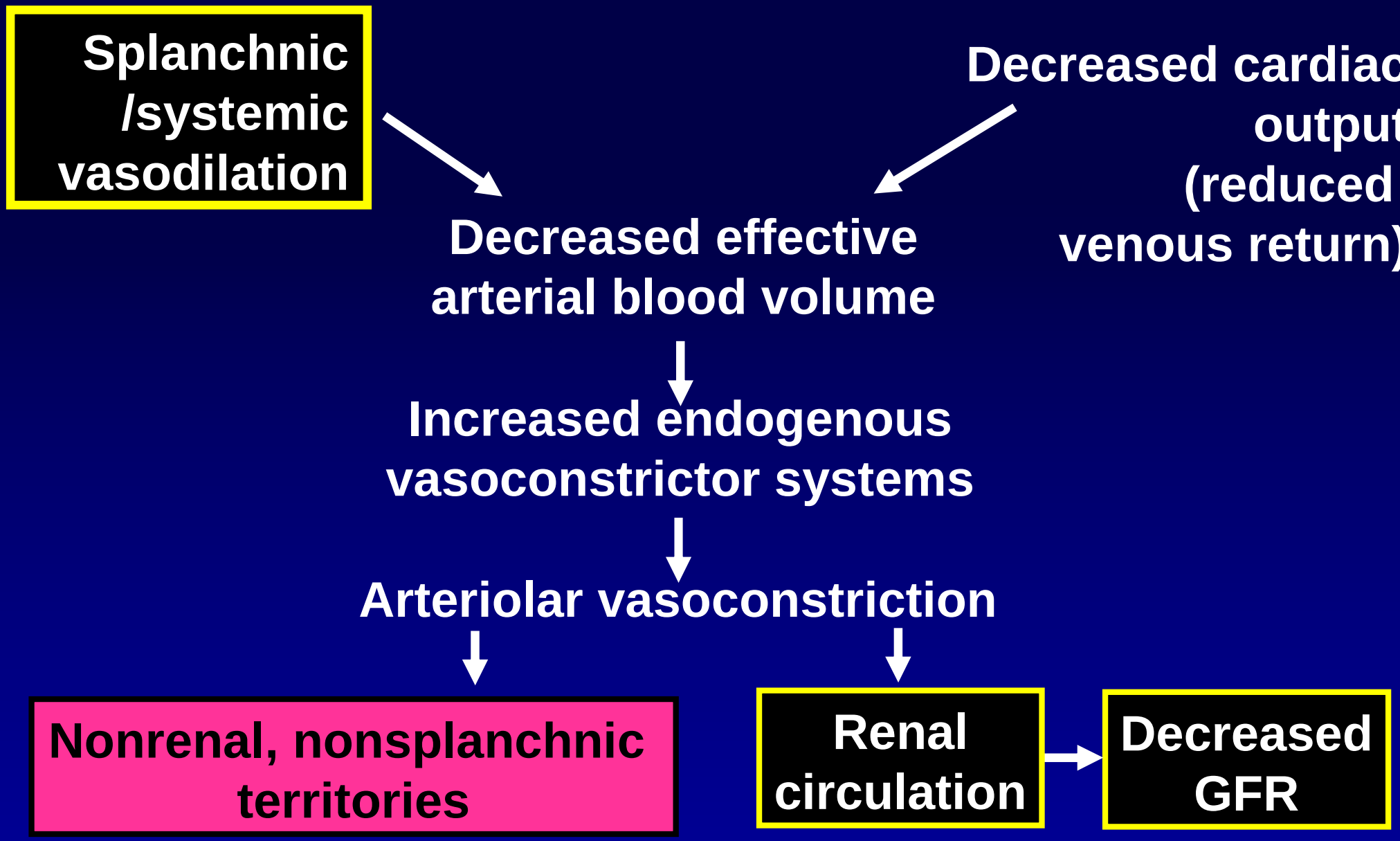


Pre-HRS state

Type 1 HRS

Moreau and Lebrec. Hepatology 2003;37:233-43.
Terra et al. Gastroenterology 2005;129:1944-53.

HRS Pathophysiology



Moreau and Lebrec. Hepatology 2006;43:385-94.

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Expected Causes of AKI in Patients with Cirrhosis

Underlying Problem	Possible Causes
Prerenal (renal hypoperfusion)	
Intravascular volume depletion	Hemorrhage, vomiting, diarrhea, bacterial sepsis, diuretic therapy
Decreased effective perfusion volume to kidneys	Type 1 HRS, nephrotic syndrome
Impaired renal blood flow from exogenous agents	Angiotensin-converting-enzyme inhibitors, NSAIDs, COX-2 inhibitors, contrast media
Intrarenal	
Acute tubular necrosis (ATN)	Ischemia; toxins (including drugs such as aminoglycosides, NSAIDs, COX-2 inhibitors, & contrast media); sepsis
Glomerular disease	Acute proliferative glomerulonephritis: bacterial endocarditis, post-infectious glomerulonephritis
Interstitial disease	Allergic reaction to drugs, pyelonephritis
Postrenal	Benign prostatic hypertrophy

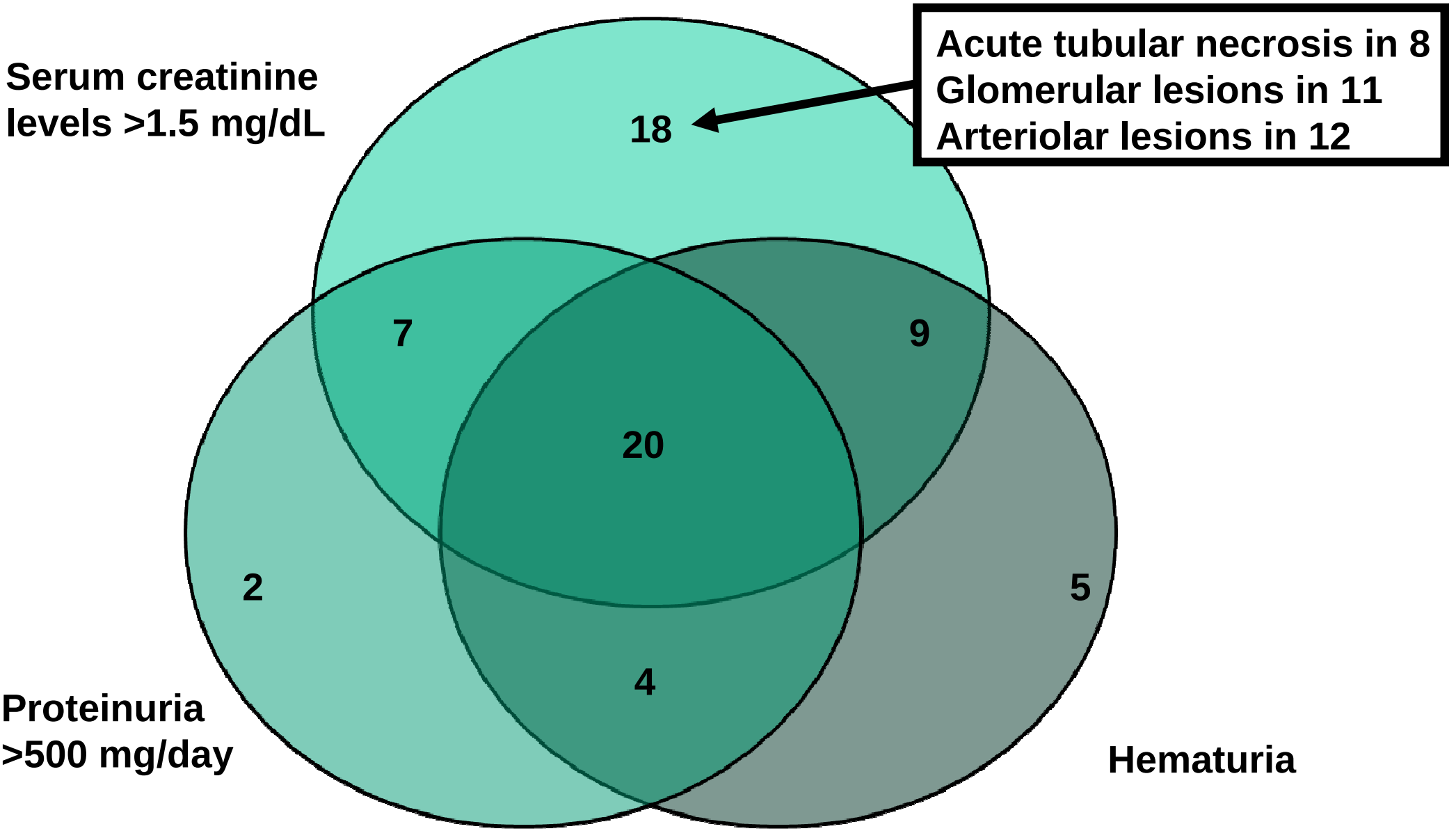
Moreau and Lebrec. Hepatology 2003;37:233-43. Garcia-Tsao et al. Hepatology 2008;48:2064-77.
Ginès and Schrier. N Engl J Med 2009;361:1279-90.

IAC Major Diagnostic Criteria for HRS

- Cirrhosis with ascites
- Serum creatinine >1.5 mg/dL
  - HRS-1: doubling of the initial serum creatinine to a level >2.5 mg/dL in less than 2 weeks
- No improvement of serum creatinine with diuretic withdrawal and volume expansion with albumin
- Absence of shock
- No current or recent nephrotoxic agent
- Absence of parenchymal kidney disease:
  - Proteinuria <500 mg/day, red cells <50 HPF, normal renal ultrasonography.

Salerno et al. on behalf of the IAC. Gut 2007;56:1310-8.

Indications of Renal Biopsy in 65 Patients With Cirrhosis Without Shock



Trawalé et al. Liver Int 2010;30:725-30.

Unmet Medical need:
Biomarkers for Ischemic ATN in Patients with Cirrhosis

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Acute Organ Failures at Admission of Patients with Cirrhosis and Acute Decompensation

	Patients (N=1,343)	Prevalence (%)
No organ failure	901	67.1
1 organ failure or more	442	32.9
Liver	207	15.4
Kidney (Screat ≥2 mg/dL)	169	12.6
Coagulation	105	7.8
Cerebral	99	7.4
Cardiovascular	64	4.8
Lungs	32	2.4

*Modified SOFA score. Moreau et al. Gastroenterology 2013, in press.

Prognostic of HRS in Patients with Cirrhosis and Acute Decompensation

	Mortality (%)*
• Screat 1.5–≤1.9 mg/dL without any organ failure (OF)	5
• Screat 1.5–≤1.9 mg/dL + single OF (liver, coagulation, circulation, lungs)	22
• Single kidney failure	22
• Kidney failure + another organ failure	30
• Kidney failure + ≥ 2 other organ failures	79

*At 28 days. Moreau et al. Gastroenterology 2013, in press.

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Treatment of HRS: Principles

- Liver transplantation (LTx)
  - Ideal treatment
  - High mortality post-LTx
  - Organ shortage
- Bridge to LTx is needed.

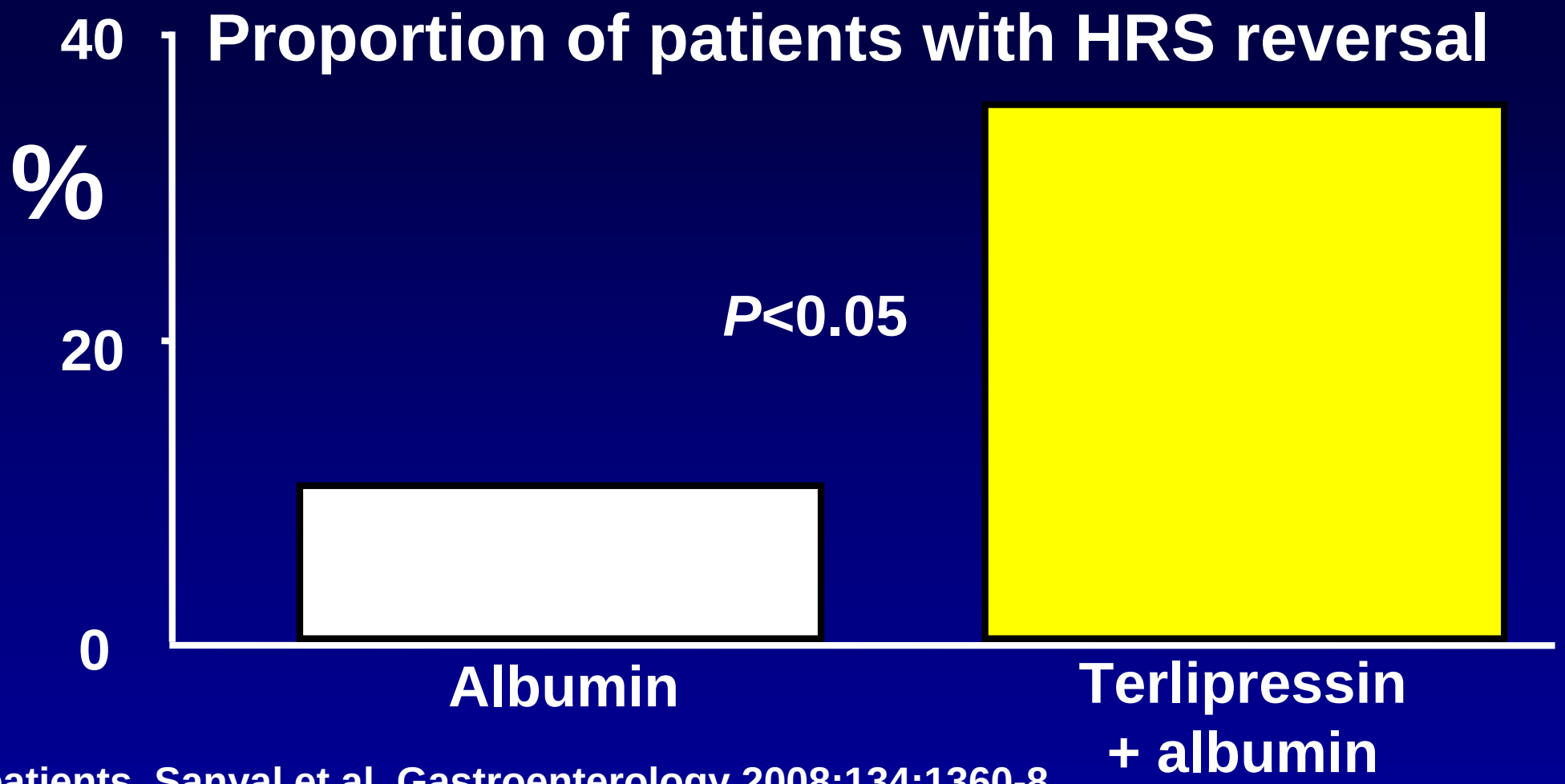
Moreau and Lebrec. Hepatology 2006;43:385-94.

Vasoconstrictor Therapy is the Paradigm for the Treatment of Type 1 HRS

- **Vasopressin analog:**
  - **Terlipressin**

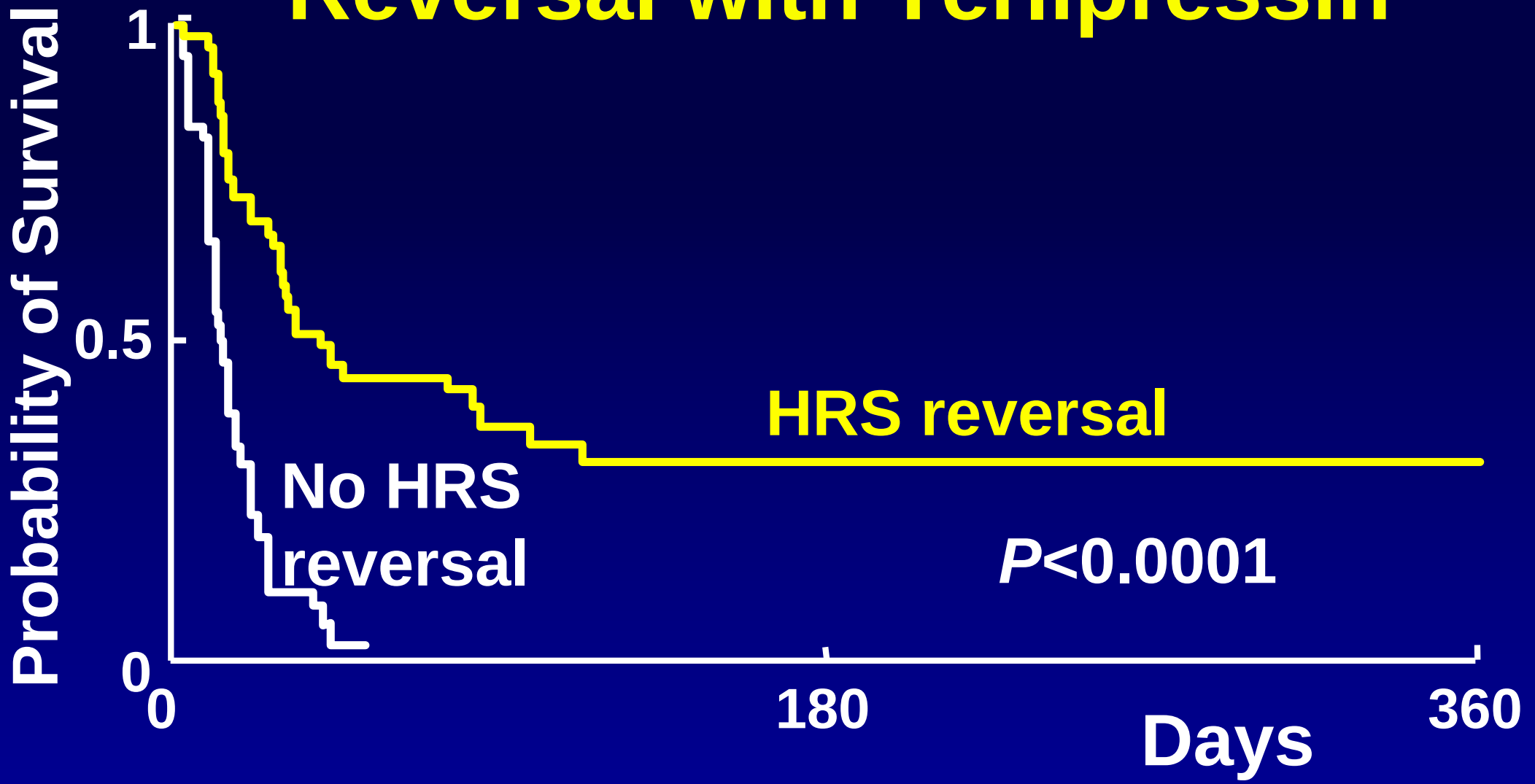
- **α-adrenoceptor agonists:**
  - **Noradrenaline**
  - **Midodrine**

RCTs of Terlipressin Plus Albumin in Patients with Type 1 HRS



153 patients. Sanyal et al. Gastroenterology 2008;134:1360-8.
Martin-Llahi et al. Gastroenterology 2008;134:1352-9.

Survival According to HRS Reversal with Terlipressin



Moreau et al. Gastroenterology 2002;122:923-30.

Predictors of HRS Reversal with Terlipressin

- Lower creatinine levels at the time of HRS diagnosis
- Lower MELD scores at the time of HRS diagnosis
- Significant pressor response to terlipressin
- At least 3 days of terlipressin therapy

Colle et al. J Gastroenterol Hepatol 2002;17:882-8.
Sanyal et al. J Hepatol 2011;55:315-21.

Terlipressin Plus Albumin for HRS: Safety

1st Author	No. Patients	Ischemic Events (%)
Uriz	9	0
Moreau	99	15
Ortega	13	<10
Solanki	12	25
Sanyal	56	10
Martin-Llahi	23	26

Vasoconstrictor Therapy is the Paradigm for the Treatment of Type 1 HRS

- Vasopressin analog:
  - Terlipressin
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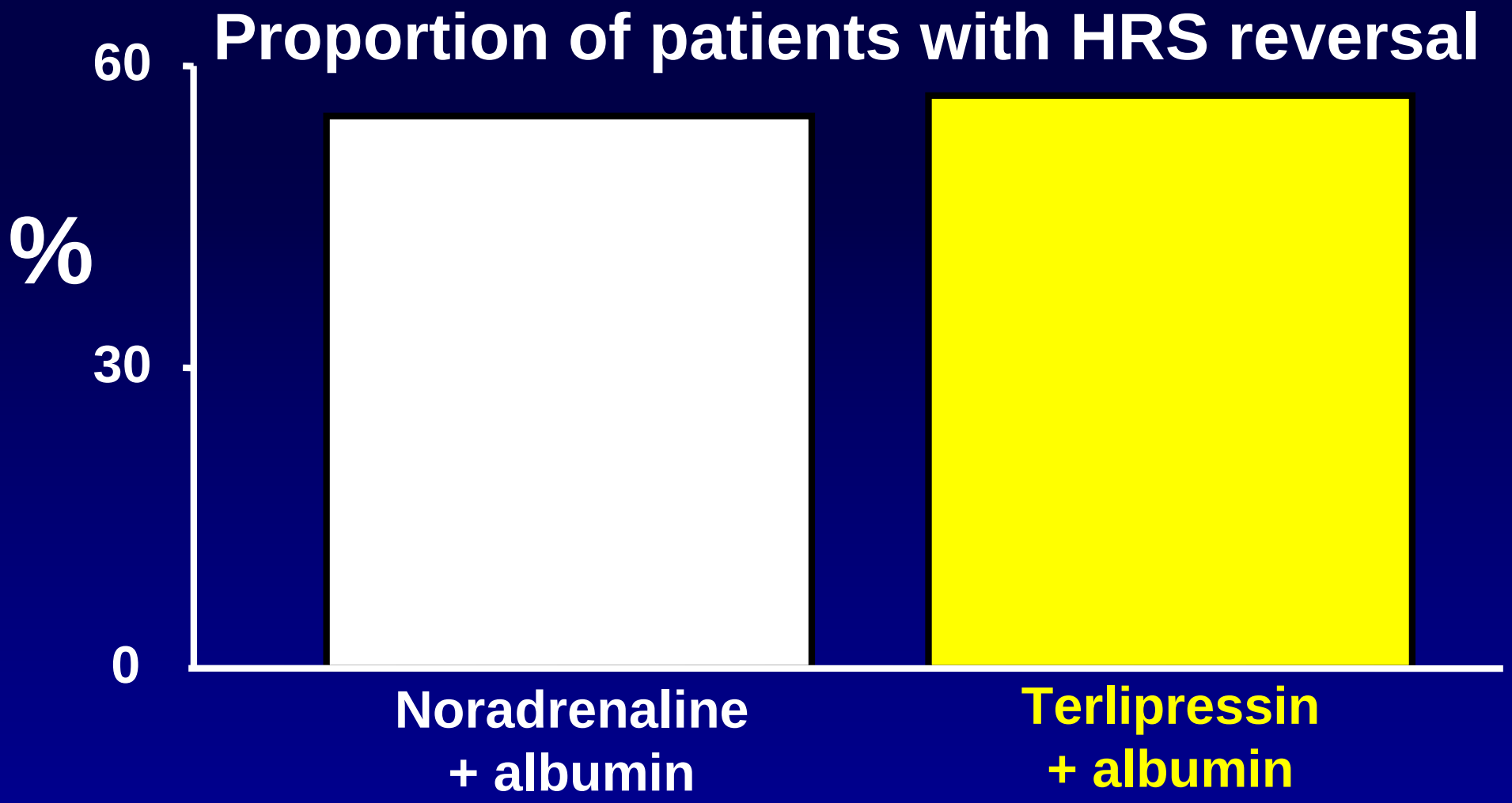
Noradrenaline *vs.* Terlipressin for HRS



41 patients. Alessandria et al. J Hepatol 2007, 2007;47:499-505.
Sharma et al. Am J Gastroenterol 2008;103:1689-97.

Vasoconstrictor Therapy is the Paradigm for the Treatment of Type 1 HRS

- Vasopressin analog:
  - Terlipressin

- α-adrenoceptor agonists:
  - Noradrenaline
  - Midodrine: no RCT.

RCTs with Extracorporeal Liver Support Systems

Target population	RCT	Evidence
Encephalopathy (Grade III-IV)	MARS	Improves encephalopathy
Multiple organ failure	Prometheus	Does not reduce overall mortality; Reduces mortality if MELD score >30 or type 1 HRS
Multiple organ failure	MARS	Does not reduce mortality; Improves hepatic encephalopathy

Hassanein et al. Hepatology 2007;46:1853-62.
Rifai et al. Gastroenterology 2012 ;142:782-9.
Bañares et al. Hepatology 2013;57:1153-62.

Criteria for CLKT

- **For AKI**
  - — **Dialysis >8 weeks.**
- **For CKD**
  - — **GFR <30 mL/min**
  - — **Renal biopsy:**
    - → **Glomerulosclerosis >30% and/or interstitial fibrosis >30%**
    - → **Prominent vascular changes (Clichy)**

Eason et al. Am J Transplant 2008;8:2243-51. Francoz et al. J Hepatol 2010;52:605-13. Trawalé et al. Liver Int 2010;30:725-30.

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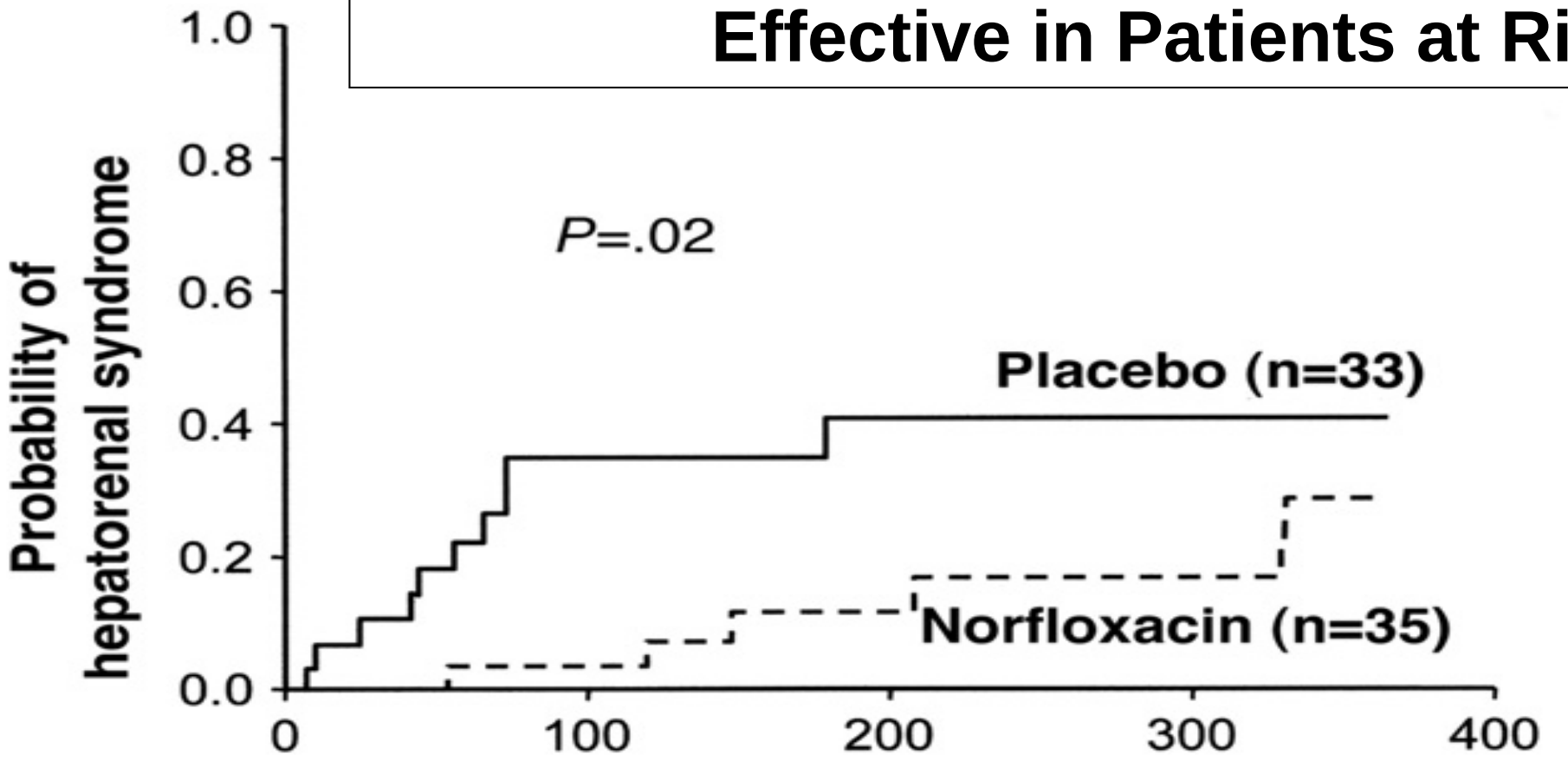
Prevention of HRS in Patients with SBP without Shock

End Points	Cefotaxime alone (N=63)	Cefotaxime + albumin (N=63)
Resolution infection (%)	94	98
HRS (%)		
Overall	33	10*
Low-risk group**	7	0
Death (%)		
In hospital	29	10*
At 3 months	41	22*

*P<0.05. **Baseline serum bilirubin <4 mg/dL and creatinine <1 mg/dL.

Sort et al. N Engl J Med 1999;341:403-9.

Primary Prophylaxis of SBP is Effective in Patients at Risk



Patients at risk

Norfloxacin	35	26 (1)	17 (3)	14 (4)	10 (6)
Placebo	33	13 (9)	7 (10)	2 (10)	1 (10)

Fernandez et al. Gastroenterology 2007;133:818-24.

Conclusions

- Type 1 HRS is a prerenal failure which complicates cirrhosis. It is relatively common.
- Its prognosis is severe: it is related to serum creatinine levels and the existence and number of ‘non-kidney’ organ failures.
- Terlipressin plus iv albumin is the first-line treatment for HRS type 1. The room for α-adrenergic agents is not established.
- Type 1 HRS may be preventable.

Modified Sequential Organ Failure Assessment (SOFA) Score For Patients with Cirrhosis (CLIF-SOFA Score)

Organ/system	0	1	2	3	4
Liver: Bilirubin, mg/dL	<1.2	≥1.2-<1.9	≥2-< 5.9	≥6-<12	≥12
Kidney: Creatinine, mg/dL	<1.2	≥1.2-<1.9	≥2-<3.5	≥3.5-<5	≥5
Cerebral (HE grade)	No HE	1	2	3	4
Coagulation: INR	<1.1	1.1-1.25	1.26-1.5	1.51-2.5	>2.5 or platelets ≤20 x 10^3 /µL
Circulation: MAP (mm Hg)	≥70	<70	Dopamine ≤5 or dobutamine* or terlipressin*	>5-≤15 or E ≤0.1 or- NE ≤0.1	>15 >0.1 >0.1
Lungs: PaO_2/FiO_2 or SpO_2/FiO_2	>400 >512	≤400 >357-≤512	≤300 >214- ≤357	≤200 >89- ≤214	≤100 ≤89

*any dose. E: epinephrine; NE: norepinephrine; doses for vasoconstrictors are µg/kg.min .

Moreau et al. Gastroenterology 2013, in press.

Definition of ACLF and Grades

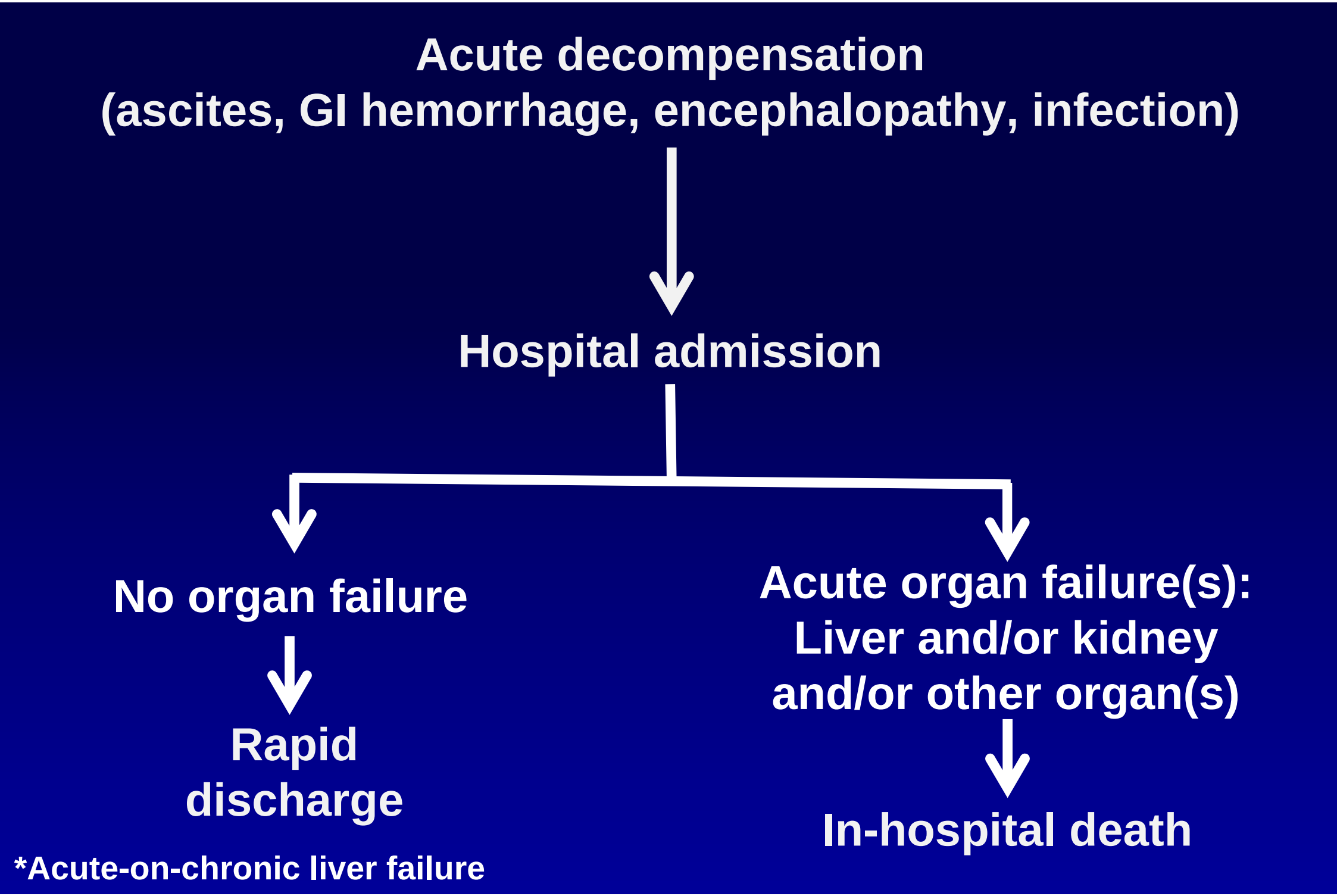
ACLF Grade	Definition	Mortality (%)*
No ACLF	• No organ failure (OF) • Single OF (liver, coagulation, circulation, lungs) + Screat <1.5 mg/dL + no HE • Single cerebral failure + Screat <1.5 mg/dL	4.7
ACLF-1	• Single kidney failure • Single OF (liver, coagulation, circulation, lungs) + Screat 1.5–≤1.9 mg/dL and/or grade 1-2 HE • Single cerebral failure + Screat 1.5–≤1.9 mg/dL	22.1
ACLF-2	2 OF	32.0
ACLF-3	≥ 3 OF	78.6

*At 28 days. Moreau et al. Gastroenterology 2013, in press.

Patients of the CANONIC Study

- 2,100 consecutive patients prospectively evaluated in 29 European hospitals in 12 countries.
- From Feb 1 to Aug 15, 2011.
- Inclusion criteria:
  - Patients with cirrhosis admitted to hospital for an acute decompensation of cirrhosis (ascites, GI hemorrhage, encephalopathy, bacterial infection)
- Main exclusion criteria:
  - Patients admitted for scheduled procedures.
  - Decompensation following partial hepatectomy.
  - HCC outside Milan criteria.
  - Severe chronic extrahepatic disease.

Moreau et al. Gastroenterology 2013, in press.


Acute decompensation
(ascites, GI hemorrhage, encephalopathy, infection)
Hospital admission
No organ failure
Rapid
discharge
Acute organ failure(s):
Liver and/or kidney
and/or other organ(s)
In-hospital death
*Acute-on-chronic liver failure