RUTGERS
THE STATE UNIVERSITY
OF NEW JERSEY

The Kidney
(Hepatorenal - New Definition and Treatment)

Nikolaos T. Pyrsopoulos MD, PhD, MBA
Professor and Chief
Department of Medicine
Division of Gastroenterology and Hepatology
Rutgers NJMS
Medical Director Liver Transplantation
University Hospital

Introduction

- Kidney dysfunction is a common complication in cirrhosis
  - Occurs in between 20-40% of patients with cirrhosis and ascites admitted with decompensation

- Oftentimes, kidney failure is functional
  - No structural abnormalities of the kidney identified
  - Changes primarily due to hemodynamic effects associated with cirrhosis

- Traditionally, Hepatorenal Syndrome (HRS) described as the most severe form of functional kidney disease
  - Not responsive to fluid challenge

Wong, F. *Recent advances in our understanding of hepatorenal syndrome.* **Nat Rev of Gastroenterol. Hepatol.** (2012) 9*:382-391*
Adebayo, D et al. *Ascites and Hepatorenal syndrome.* **Clin Liv Dis.** (2019) 23*:659-682*

Definition

- the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure

- Definition may be changing

Gines, P. et al. *EASL clinical practice guidelines in the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis.* **Journal of Hepatology** (2010) *53:397-417*

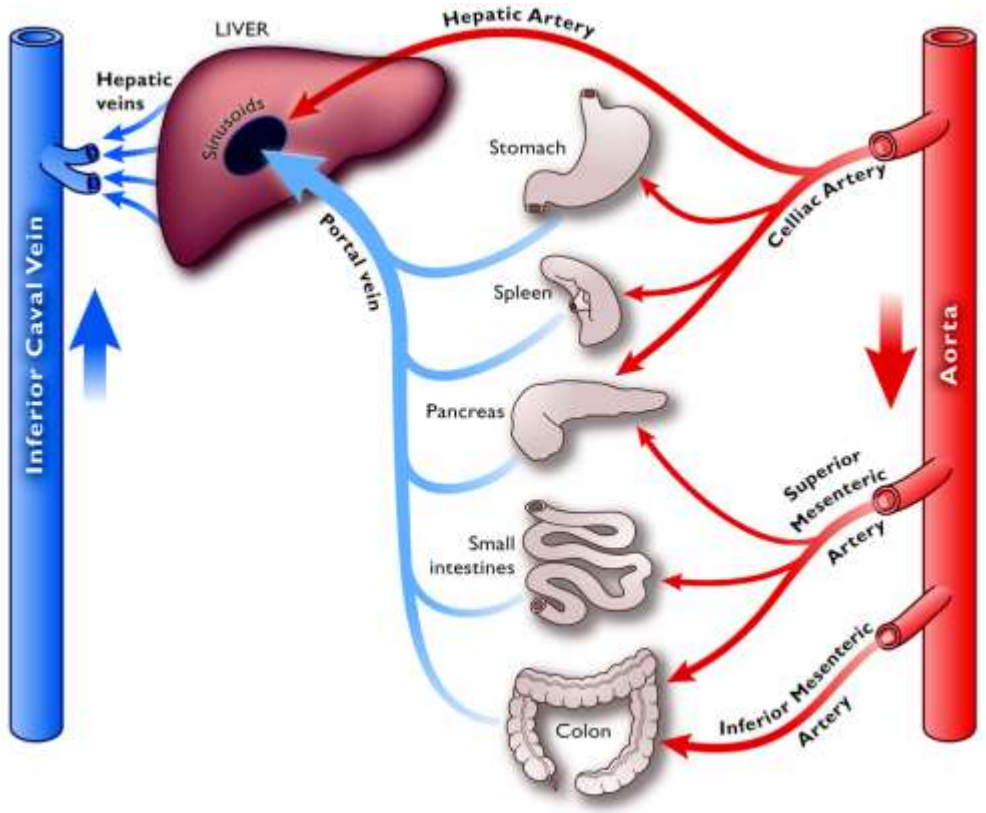
Pathophysiology

RUTGERS

- Pathophysiology of HRS is currently described via 2 main hypotheses:
  - Peripheral arterial vasodilation
  - Systemic inflammation/SIRS
    - Splanchnic vasodilatation
    - Activation of vasoconstrictor mechanisms (SNS, RAAS, ADH)
      - Ascites/edema/hyponatremia
    - Cirrhotic cardiomyopathy

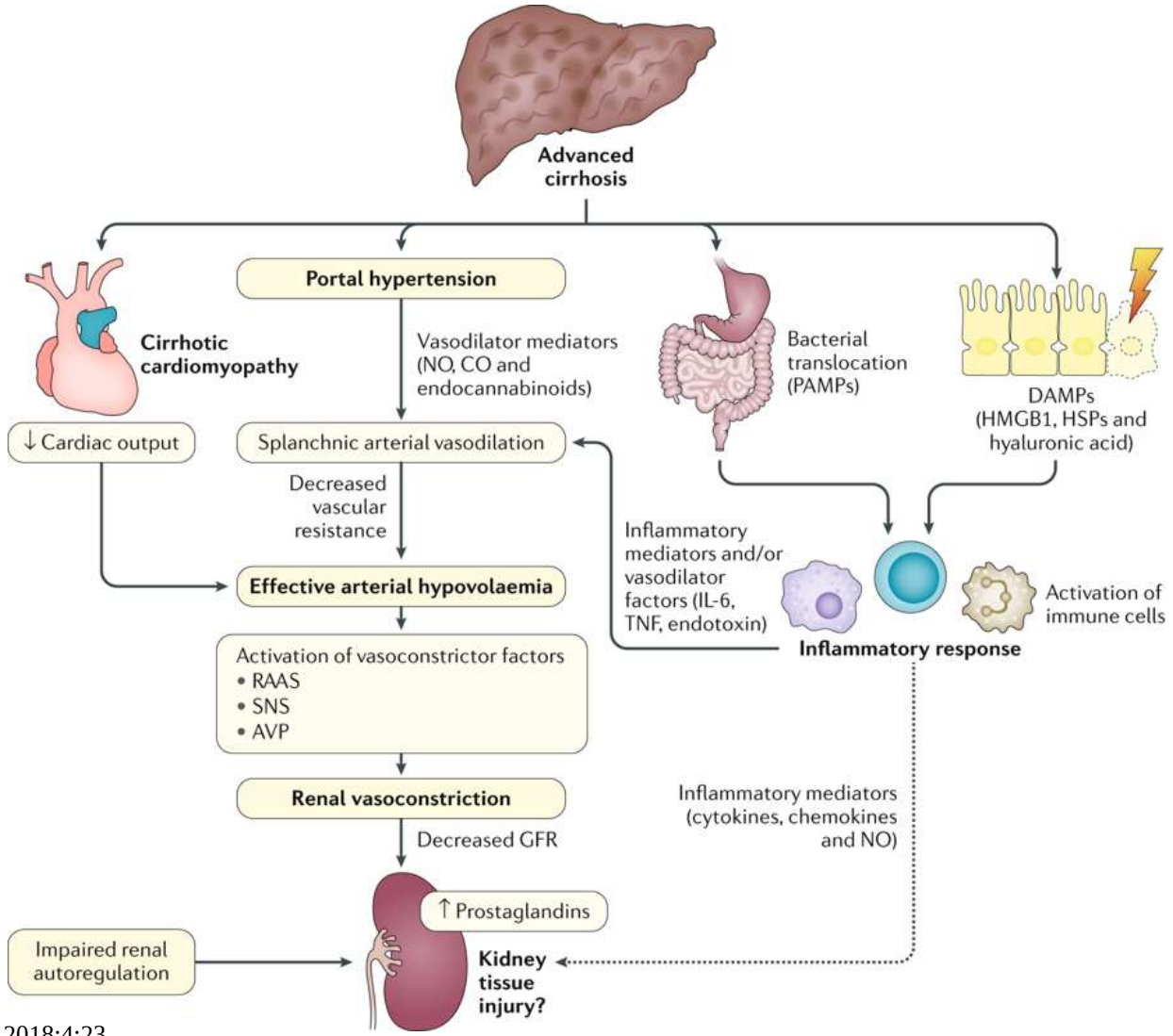
Gines, P. et al. *EASL clinical practice guidelines in the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis.* **Journal of Hepatology** (2010) *53:397-417*
Adebayo, D et al. *Ascites and Hepatorenal syndrome*. **Clin Liv Dis.** (2019) 23*:659-682*

- Splanchnic Circulation



anesthesiology.pubs.asahq.org

Pathogenesis of AKI-HRS



Ginès P, et al. *Nat Rev Dis Primers.* 2018;4:23.

Acute Kidney Injury (AKI) in Cirrhosis

RUTGERS

- Traditional criteria (International Club of Ascites criteria)[1]
  - 50% increase in SCr over baseline
  - Cut-off value of SCr: 1.5 mg/dL
- New definition of AKI[2]
  - ↑ in SCr ≥0.3 mg/dL within 48 hours *or*
  - ↑ SCr ≥50% from baseline that is known or presumed to have occurred within the prior 7 days

Stage AKI[1]	Criteria
Stage 1	Increase in SCr ≥0.3 mg/dL or an increase in SCr ≥1.5-fold to 2-fold from baseline
Stage 2	Increase in SCr >2- to 3-fold from baseline
Stage 3	Increase of SCr >3-fold from baseline or SCr ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy

1. Angeli P, et al. *J Hepatol*. 2015;62:968-974; 2. *J Hepatol*. 2018;69:406-460.

AKI in Cirrhosis: Differential Diagnosis

RUTGERS

- Prerenal
  - Hypovolemia: diuretics, GI bleeding, diarrhe
  - Hepatorenal syndrome
- Intrinsic renal disease
  - Acute tubular necrosis
  - Glomerulonephritis
  - Interstitial nephritis
- Obstructive

Graupera I, et al. *Clin Liver Dis.* 2013;2:128-131.

AKI in Cirrhosis and HRS

RUTGERS

- Diagnosis of exclusion in patients with cirrhosis and ascites
- Diagnosis of AKI according to **International Club of Ascites –** AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g per kg of body weight, 100g max)
- Absence of shock
- No current or recent use of nephrotoxic drugs
- No macroscopic signs of structural kidney injury defined as:
  - Absence of proteinuria (>500 mg/day)
  - Absence of hematuria (>50 RBCs/hpf)
  - Normal findings on renal ultrasonography

Angeli et al. *Journal of Hepatology.* 2015 vol. 62 968–974.

Albumin

RUTGERS

- 50% of plasma proteins
  - Liver produces it, 10-15 g/day
  - 30%-40% remains in the intravascular space
- Structurally:
  - 67 kDa in size, 609 amino acids
  - Charge is net negative (pH 7)
  - Circulates in net reduced form
  - Albumin has heart-shaped tertiary structure with high α-helical content

Garcia-Martinez R, et al. *Hepatology.* 2013;58:1836-1846.

Pharmacologic Therapy for AKI-HRS

RUTGERS

IV Albumin

- 0.5-1gm/kg (max 100 gm/d) for resuscitation; then
- 25 to 50 g/day

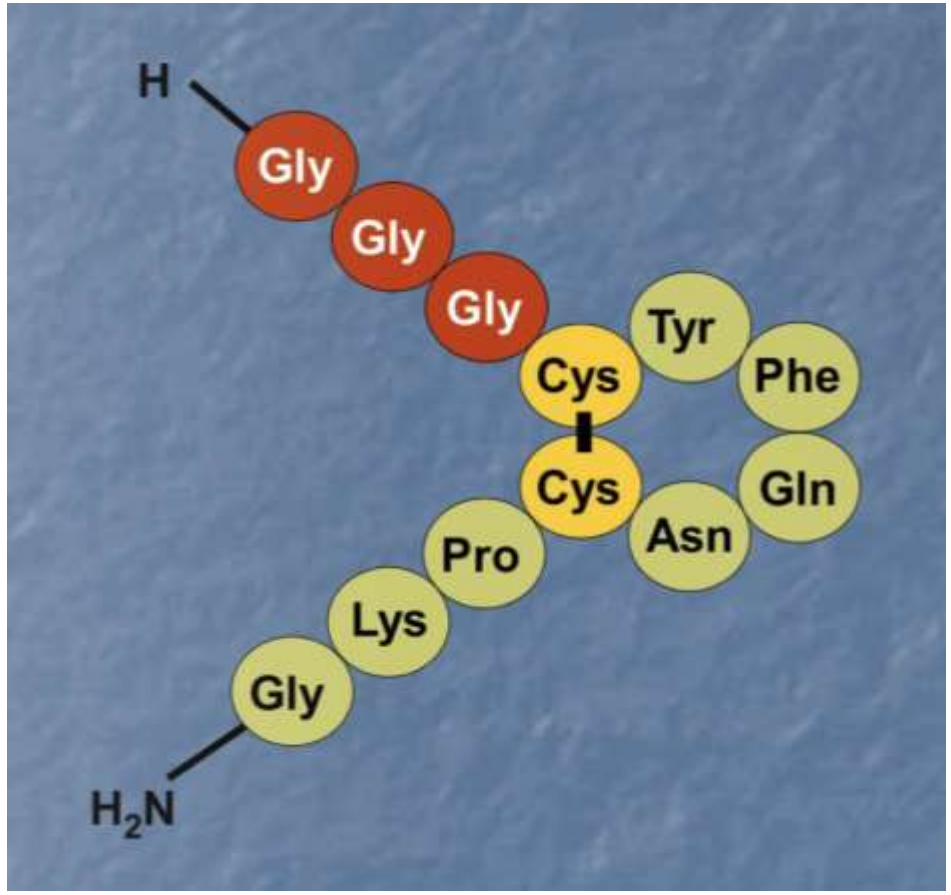
Plus

Vasoconstrictors

- Midodrine (+/- octreotide)
- Norepinephrine
- Terlipressin

Ginès P, et al. *Nat Rev Dis Primers.* 2018;4:23.

Terlipressin

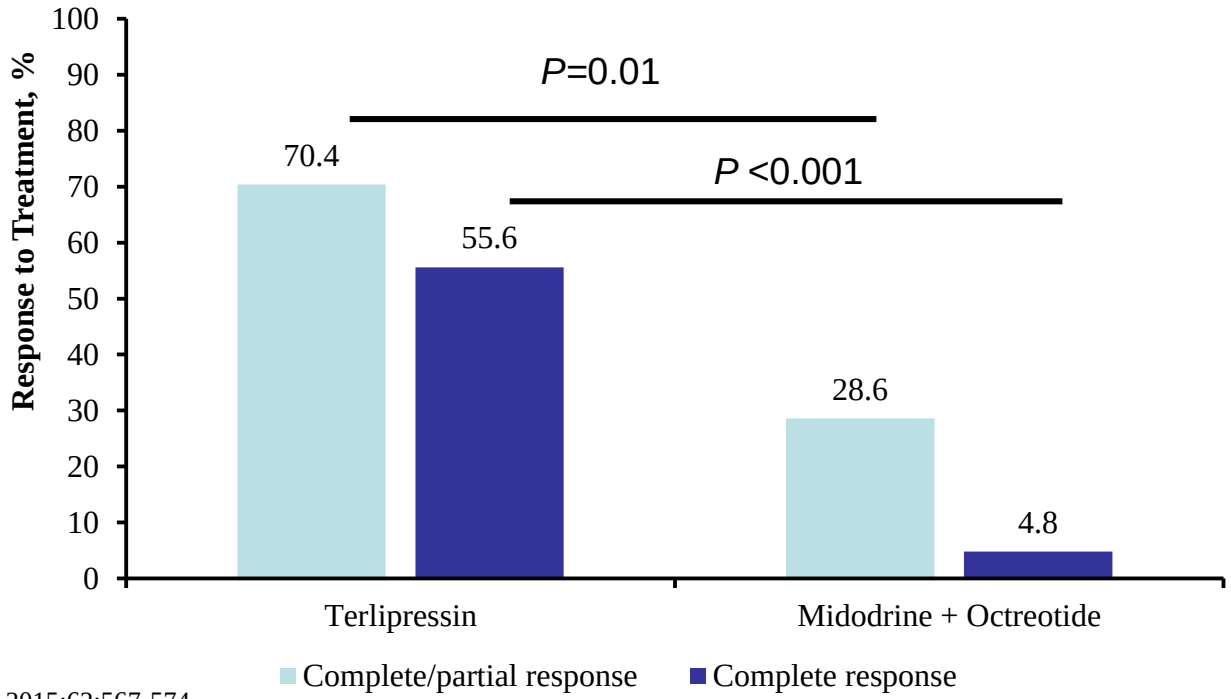


- Synthetic 12 amino acid peptide
- Pro-drug
- Constrictive activity via V-1 receptors
  - Vascular and extra vascular smooth muscle cells
- Splanchnic vasoconstriction reduces portal blood flow and portal pressure
- Systemic vasoconstriction
  - Increases effective blood volume
  - Reduces renin and angiotensin
    - Can lead to renal vasodilation
    - Can lead to improvement in serum creatinine
- V-2 agonist activity
  - Could possibly cause hyponatremia

Terlipressin + Albumin vs Midodrine/Octreotide + Albumin: Improvement in Renal Function

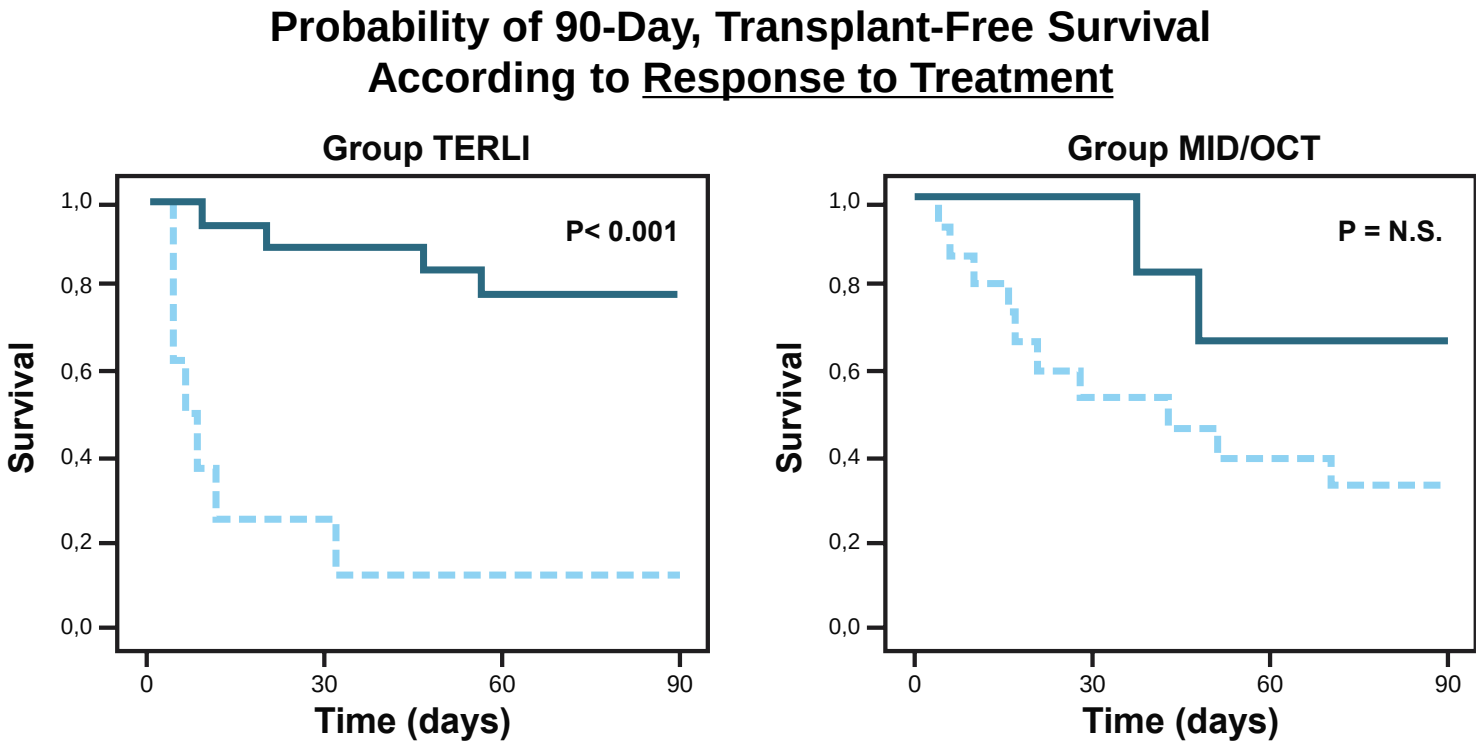
RUTGERS

- Randomized control study
- 27 patients received terlipressin (IV 3 mg/24 hrs, progressively increased to 12 mg/24 hrs if no response)
- 22 patients received midodrine (orally at 7.5 mg TID with dose increased to max of 12.5 mg TID) and octreotide SC 100 mcg TID up to 200 mcg TID).
- Both groups received albumin IV 1 g/kg of body weight on day 1 and 20-40 g/day thereafter.



Cavallin M, et al. *Hepatology*. 2015;62:567-574.

Terlipressin vs Midodrine/Octreotide: 90-Day Survival



Cumulative 3-month survival in patients who were randomized to terlipressin plus albumin (**TERLI** group) or to midodrine and octreotide plus albumin (**MID/OCT** group) according to the response: solid line represents responders; dotted line represents nonresponders.
Abbreviation: N.S., nonsignificant.
Cavallin M, et al. *Hepatology*. 2015;62:567-574.

Terlipressin + Albumin vs Albumin Alone for HRS-1 (CONFIRM Study)

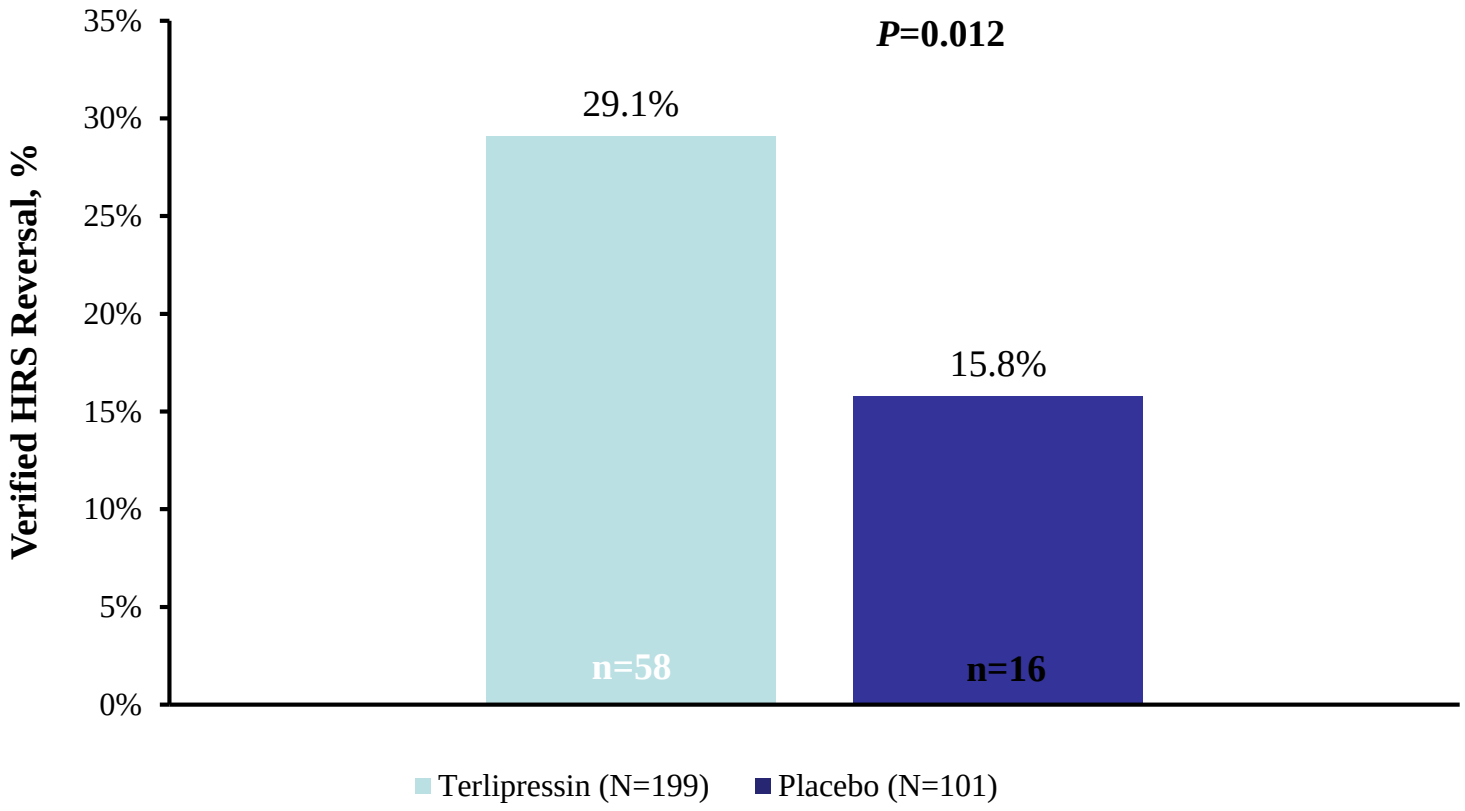
RUTGERS

- Randomized, placebo-controlled study in 300 patients
- 2:1 to terlipressin (1 mg IV every 6 hours) or placebo, plus albumin in both groups
- Treatment for 14 days unless one of the following occurred:
  - Verified HRS reversal (VHRSR) (decrease in SCr to ≤1.5 mg/dL)
  - Renal replacement therapy (RRT)
  - Liver transplantation (LT) or
  - SCr at or above baseline (BL) at Day 4
- Primary Endpoint
  - VHRSR defined as 2 consecutive SCr values ≤1.5 mg/dL, at least 2 hours apart, with patient alive without RRT for ≥10 days after the second SCr ≤1.5 mg/dL

Wong F et al. The Liver Meeting, Boston, MA 2019, Abstract LO5.

Primary Endpoint: Verified HRS Reversal (CONFIRM Study)

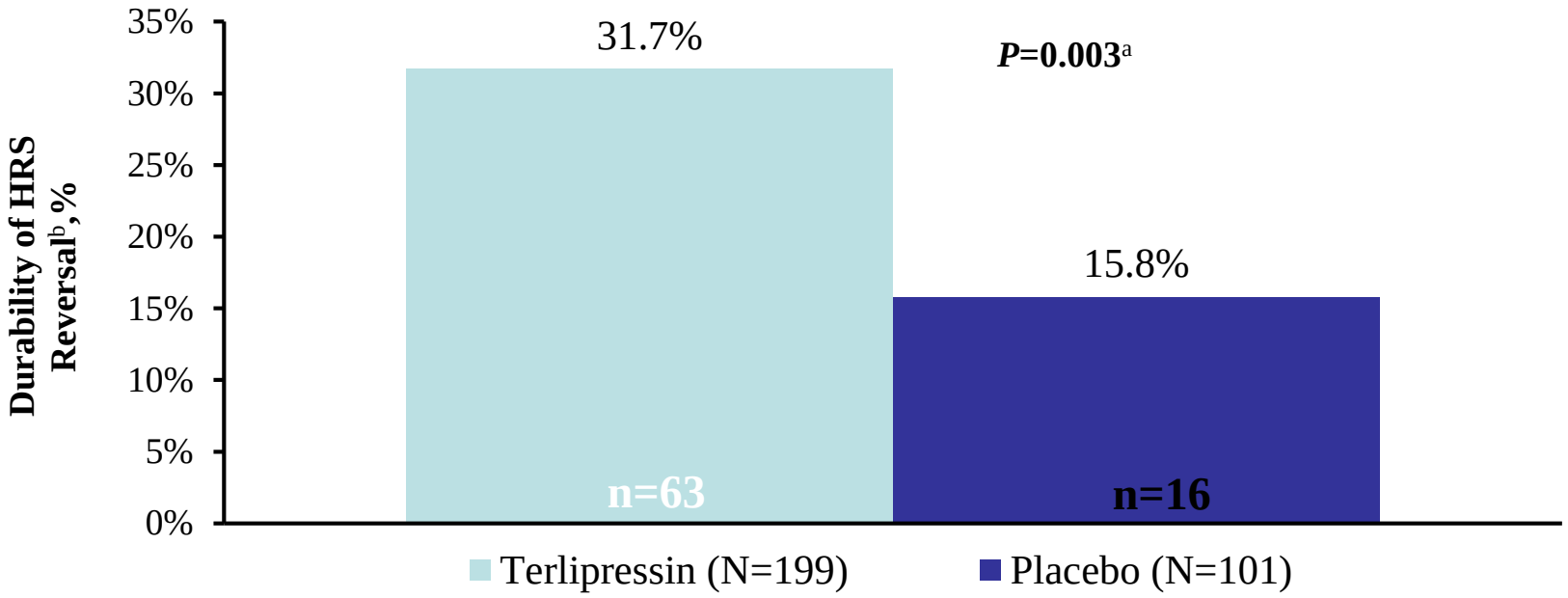
RUTGERS



Wong F et al. The Liver Meeting, Boston, MA 2019, Abstract LO5.

Secondary Endpoint: Durability of HRS Reversal (CONFIRM Study)

RUTGERS



[a]From a CMH Test stratified by qualifying serum creatinine (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (at least one single event of ≥4 vs <4 L).
[b]Percentage of subjects with HRS reversal without RRT to day 30.

Wong F et al. The Liver Meeting, Boston, MA 2019, Abstract LO5.

Incidence of Adverse Events (>10% Terlipressin Patients) (CONFIRM Study)

RUTGERS

Preferred Term[a]	Terlipressin (N=200)[b] % (n)	Placebo (N=99)[b] % (n)
Abdominal pain	19.5 (39)	6.1 (6)
Nausea	16.0 (32)	10.1 (10)
Diarrhea	13.0 (26)	7.1 (7)
Dyspnea	12.5 (25)	5.1 (5)
Respiratory failure	10.5 (21)	5.1 (5)
Hepatic encephalopathy	10.0 (20)	13.1 (13)

Respiratory Failure higher in both cohorts in CONFIRM than REVERSE trial;
REVERSE T 5.4% vs P 2.1%; none of the respiratory failure were reported as related to study drug.

AEs, adverse events; N, number of subjects in the treatment group; n, number of subjects in the category of subjects in the treatment group.
[a]Up to 7 days posttreatment. [b]Subjects experiencing multiple episodes of a given adverse event are counted once within each preferred term.
Wong F et al. The Liver Meeting, Boston, MA 2019, Abstract LO5.

Early treatment with terlipressin in patients with hepatorenal syndrome yields improved clinical outcomes in North American studies M.Curry , H.Vargas , A Befeler , N. Pyrsopoulos , V.Patwardhan , K.Jamil Hepatol Commun 2023 Jan 3;7(1):e1307.

- The incidence of HRS reversal inversely correlated with serum creatinine subgroup (<3 mg/dL, 49.2%; ≥3-<5 mg/dL, 28.0%; ≥5 mg/dL, 9.1%).
- At Day 30 follow-up, renal replacement therapy-free survival was significantly higher for patients with HRS-1 in the lower serum creatinine subgroups than in the higher subgroup (<5 vs. >5 mg/dL; p=0.01).
- Terlipressin-treated patients with HRS-1, with a lower baseline serum creatinine level, had a higher overall survival (p<0.001) and higher transplant-free survival at Day 90 (p=0.04).

- HRS is defined as AKI that does not respond to volume resuscitation upon correction of sepsis and in the absence of other renotoxic insult
- Current classification expedites the recognition of HRS-AKI and allows for potential intervention
- Vasoactive agents (terlipressin and norepinephrine) can reverse HRS-AKI in a percentage of patients
- Terlipressin is superior to other agents in reversing HRS with expected survival benefits

- Significant cause of morbidity/mortality
- Need to differentiate AKI-HRS from other causes of AKI
- AKI-HRS may co-exist with other forms of AKI
- Review of medication list critical to care
- AKI-HRS requires aggressive management strategy