Current and Emerging Management Approaches for the Patient with Hepatorenal Syndrome (HRS)

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Disclosures

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Acute Kidney Injury (AKI) in Cirrhosis

- Traditional criteria (IAC 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

HRS-1 → AKI-HRS
HRS-2 → CKD-HRS

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

AKI in Cirrhosis: Differential Diagnosis

- Prerenal
  - Hypovolemia: diuretics, GI bleeding, diarrhea
  - Hepatorenal syndrome
- Acute tubular necrosis: shock, nephrotoxic drugs, other
- Nephrotoxicity: NSAIDs, Iodinated contrast, other
- Intrinsic renal disease (glomerulonephritis, interstitial nephritis)
- Obstructive
- Miscellaneous, unknown

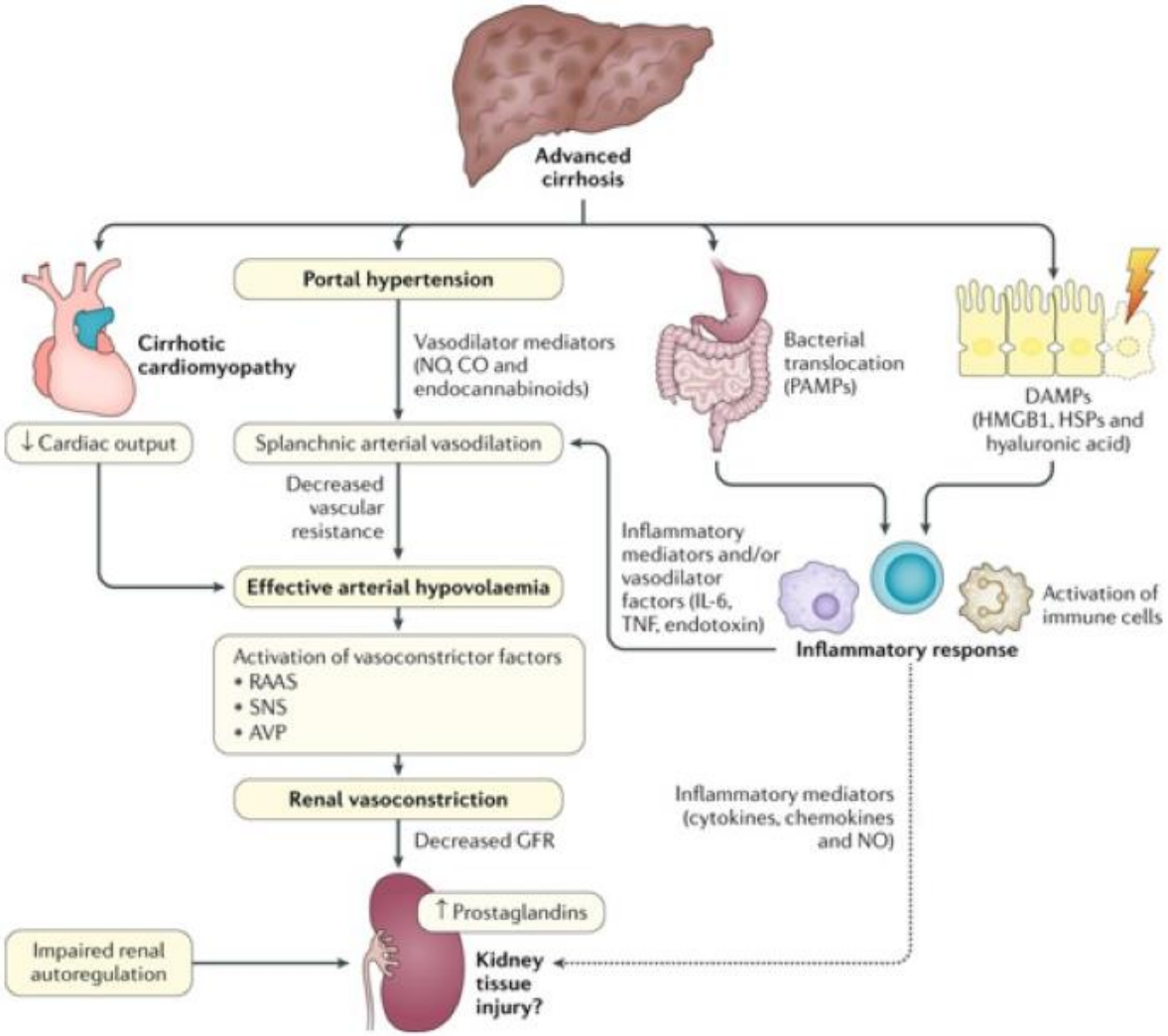
Graupera I, et al. *Clin Liver Dis.* 2013;2:128-131.

AKI in Cirrhosis: When Is It HRS?

- Diagnosis of 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 microhaematuria (> 50 RBCs /hpf)
  - Normal findings on renal ultrasonography

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

Pathophysiology AKI-HRS



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

AKI and Cirrhosis

- AKI diagnosed with AKIN criteria associated with increased mortality in patients with cirrhosis[1]
- Progression through stages strongly correlates with increased mortality[2]
- However, serum creatinine cutoff of 1.5 mg/dL is still prognostic[3]
  - Identifies patients at increased risk of mortality
- New AKI-HRS criteria enable earlier treatment (by 4 days) at lower creatinine (1 mg/dL lower)[4]
  - Baseline serum creatinine is a predictor of response to therapy

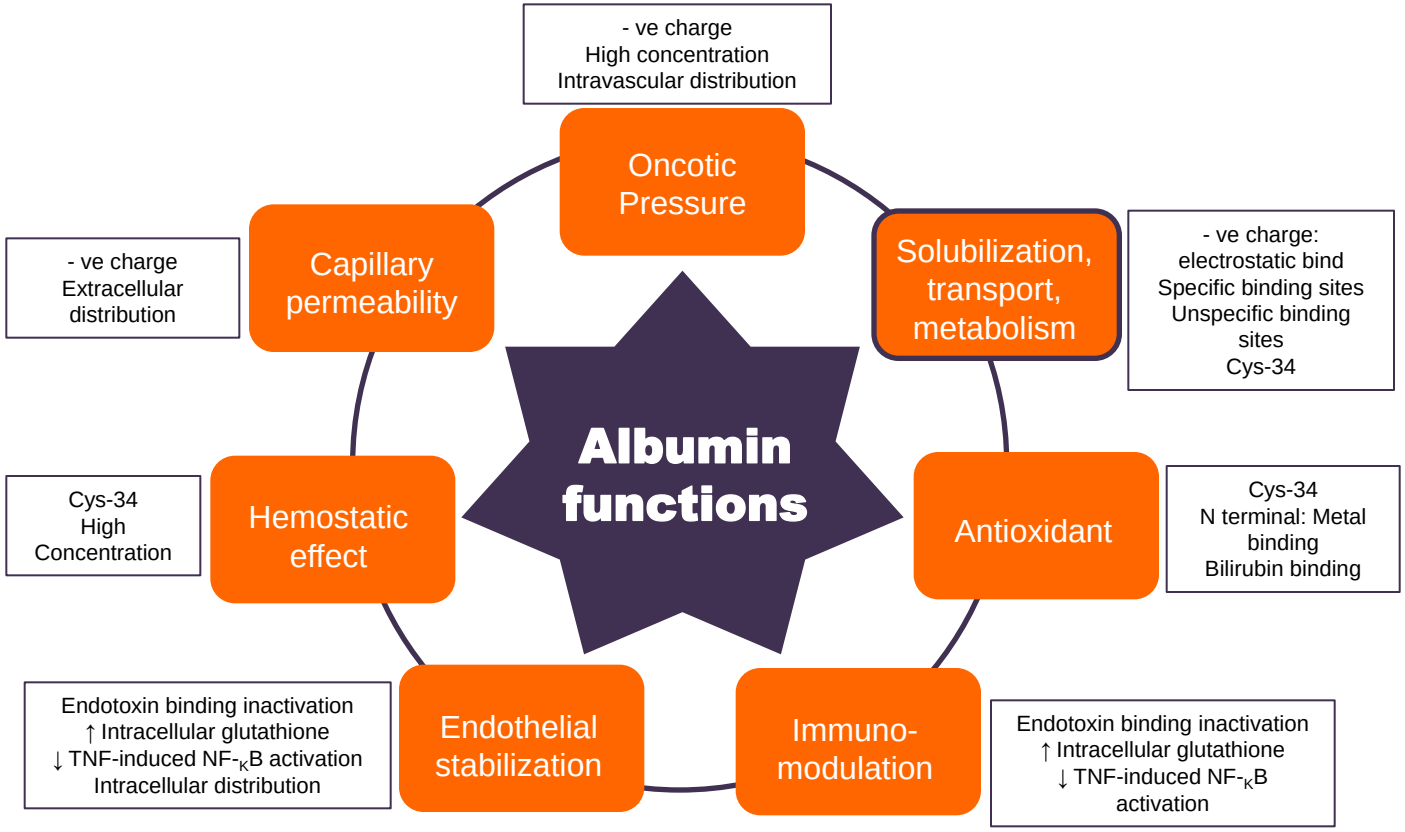
1. Piano S, et al. *Hepatology.* 2013;57:753-762; 2. Belcher JM, et al. *Hepatology.* 2013;57:753-762;
3. Fagundes C, et al. *J Hepatol.* 2013;59:474-481; 4. Wong F, et al. *Journal Hepatology.* 2019;70(1)Supp.

Initial Management

- Early identification
- Assess and treat bacterial infection
  - Blood, urine, ascitic fluid culture
- Avoid large-volume paracentesis
- Stop β-blockers
- Stop nephrotoxic medications: NSAIDs, diuretics
- Volume expansion

Tapper EB, et al. *Am J Med.* 2016;129:461-467.

Albumin: Role in the Treatment of Cirrhosis and Its Complications



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

Pharmacologic Therapy for HRS

IV Albumin

- 0.5 – 1gm/kg (max 100gm/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.

**Midodrine Plus Octreotide: Dosing

Midodrine: initially 7.5 mg oral 3 times daily

- Titrate to maximum of 12.5 mg 3 times daily

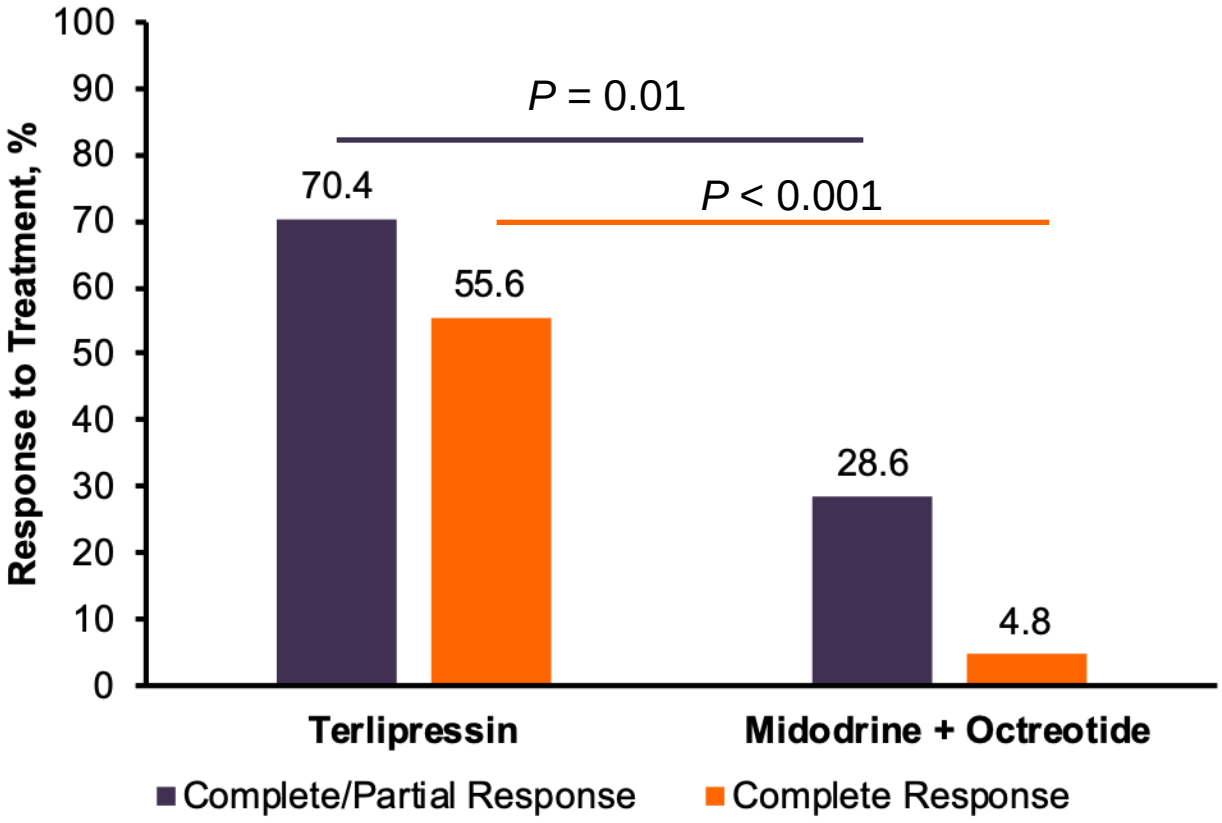
Octreotide: 100 µg SC 3 times daily

- Maximum dose 200 µg SC 3 times daily
- Titrate to achieve increase of MAP by 15 mmHg

**Note this is off-label treatment for HRS but recommended by AASLD Practice Guidelines

Runyon BA. *Hepatology.* 2013;57:1651-1653.

Improvement in Renal Function: TERLI vs MID/OCT



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

TERLI vs MID/OCT: 90-Day Survival

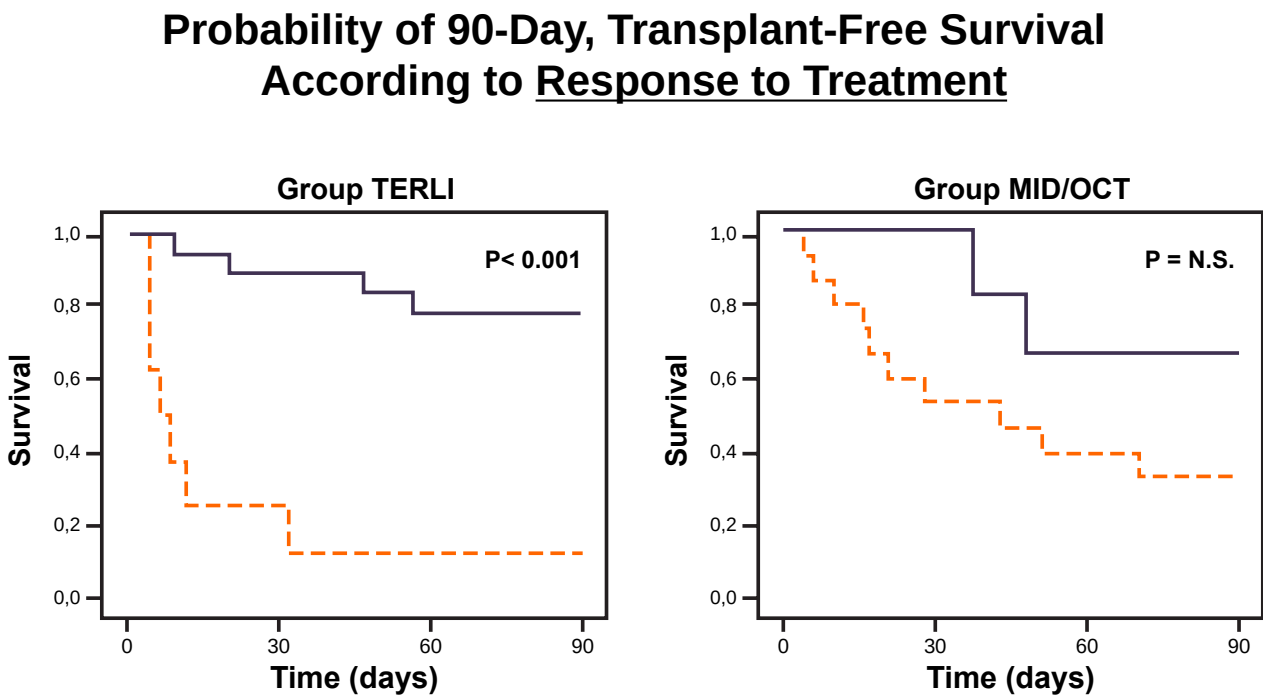


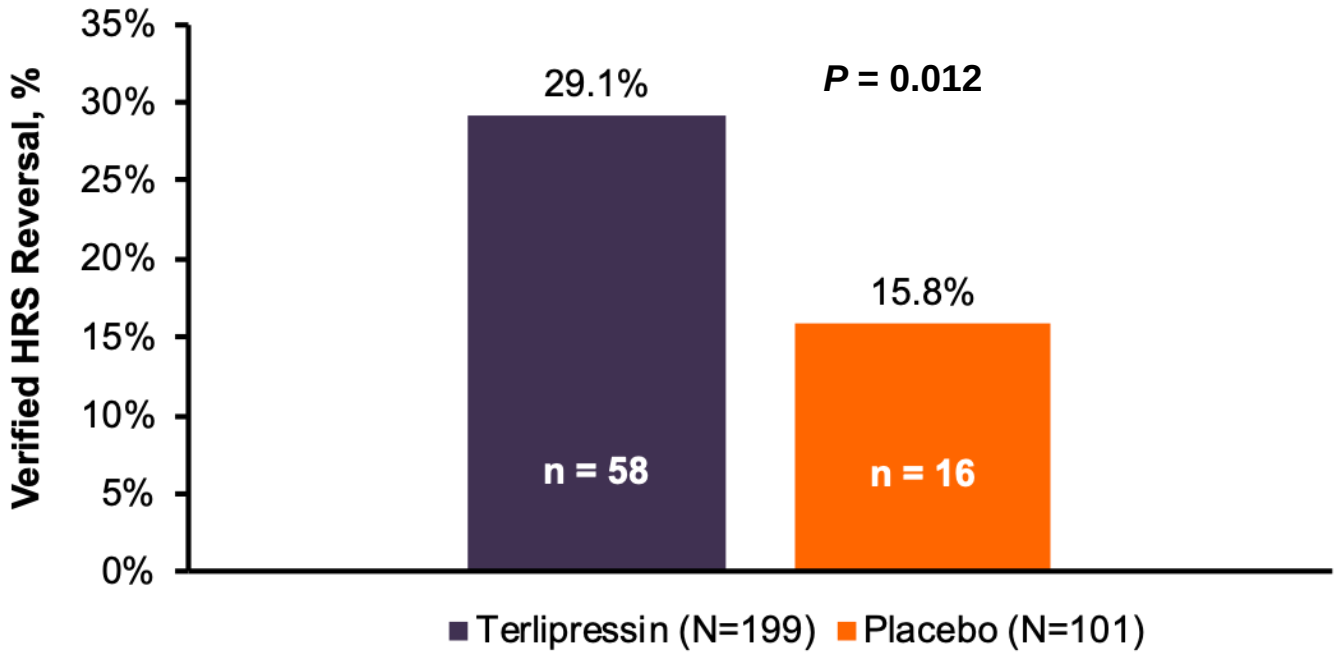
Fig. 4. Cumulative 3-month survival in patients who were randomized to terlipressin plus albumin (TERLI group) or to midodrine and octreotide plus albumin (MID/OCT group) according to the response: solid line represents responders; dotted line represents nonresponders.
Abbreviation: N.S., nonsignificant.
Cavallin M, et al. *Hepatology.* 2015;62:567-574.

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

- Randomization, 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

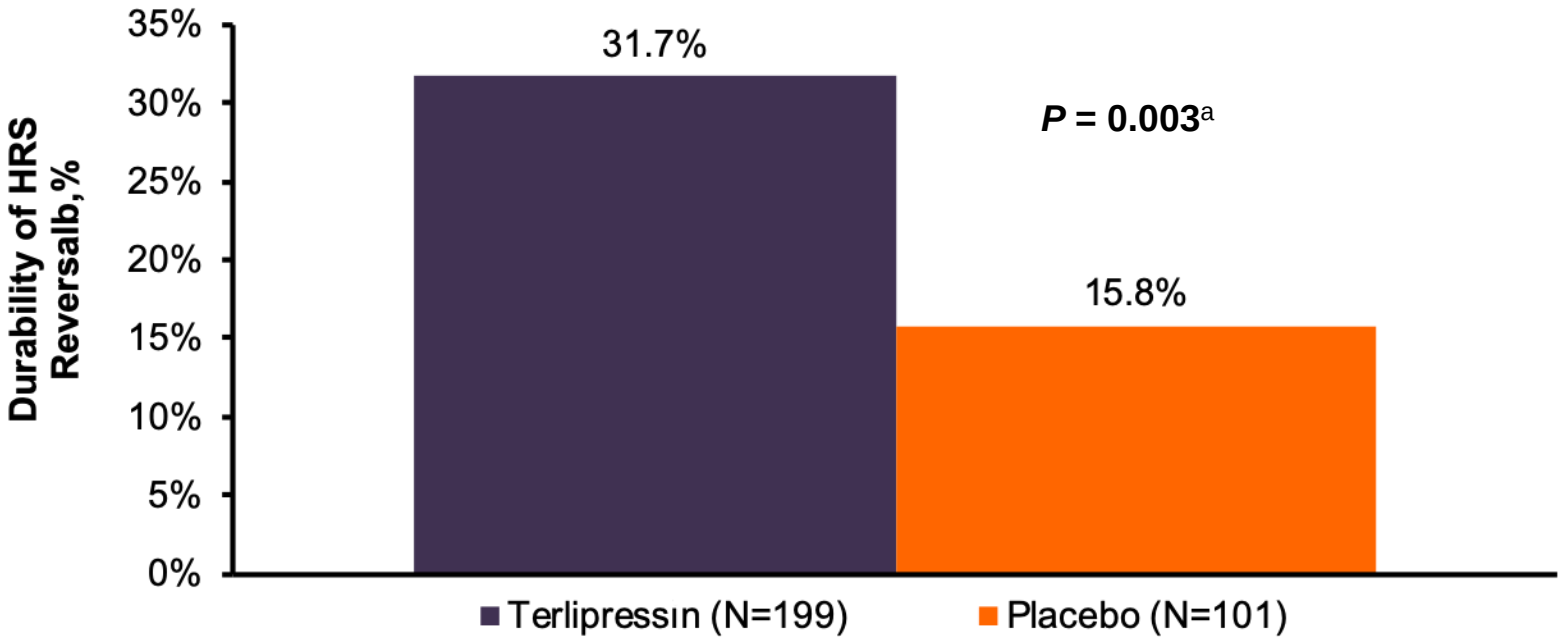
Wong F, et al. The Liver Meeting. Boston, MA. 2019. Abstract LO5.

Primary Endpoint: Verified HRS Reversal



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

Secondary Endpoint: Durability of HRS Reversal



[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 AEs (> 10% Terlipressin Patients)

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.

Prevention of HRS in Patients with Cirrhosis

- Avoid NSAIDs
- Avoid ACE inhibitors
- Decrease/withdraw diuretics when decompensated
- Consider lactulose and volume of stool output
- Threshold at which to discontinue beta-blockers?
- Maintain mean arterial pressure (MAP)
  - No good data on prevention, but an increase with successful treatment is common
  - Data suggest that those with lowest MAP may respond to medical treatment best

Take Home Points

- AKI in chronic liver disease impacts mortality
- 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
  - Phase 3 CONFIRM US study results now available

Thank you!

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