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Recognizing and Managing Acute Kidney Injury and HRS

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Speaker Bureau: Intercept, Clinical Area – PBC

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Consultant: AbbVie, Clinical Area – HCV

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Defining Acute Kidney Injury (AKI) and Hepatorenal Syndrome (HRS)

Revised HRS Definitions and Criteria: No Longer Type 1 and Type 2

Old classification	New classification	Criteria
HRS-1*	HRS-AKI (A Medical Emergency)	a) Absolute increase in sCr ≥0.3 mg/dl within 48h and/*or* b) Urinary output ≤0.5 ml/kg B.W. ≥6h* *or* c) Percent increase in sCr ≥50% using the last available value of outpatient sCr within 3 months as the baseline value
HRS-2*	HRS-NAKI: HRS-AKD, HRS-CKD	a) eGFR <60 ml/min per 1.73 m^2 for <3 months in the absence of other (structural) causes b) Percent increase in sCr <50% using the last available value of outpatient sCr within 3 months as the baseline value c) eGFR <60 ml/min per 1.73 m^2 for ≥3 months in the absence of other(structural) causes

Angeli P et al. *J Hepatol.* 2019; 71:811.

International Club of Ascites Diagnostic Criteria for HRS-AKI

- Cirrhosis; acute liver failure; acute-on-chronic liver failure
- Increase in sCr, >0.3 mg/dL within 48 hours or >50% from baseline value

  and/or
- Urinary output < 0.5 ml/kg of body weight for > 6 hours (requires use of a urinary catheter)
- No full or partial response for >2 days of diuretic withdrawal and volume expansion with albumin (dosed at 1 g/kg of body weight/day*)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- In the absence of CKD, assess for parenchymal disease, as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field), urinary injury biomarkers (if available) and/or abnormal renal ultrasonography
- Suggestion of renal vasoconstriction, with FENa <0.2% (levels <0.1% are considered highly predictive)

*Maximum 100 g/day

Angeli P et al. *J Hepatol.* 2019; 71:811.

Acute Kidney Injury (AKI) in Cirrhosis

- 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

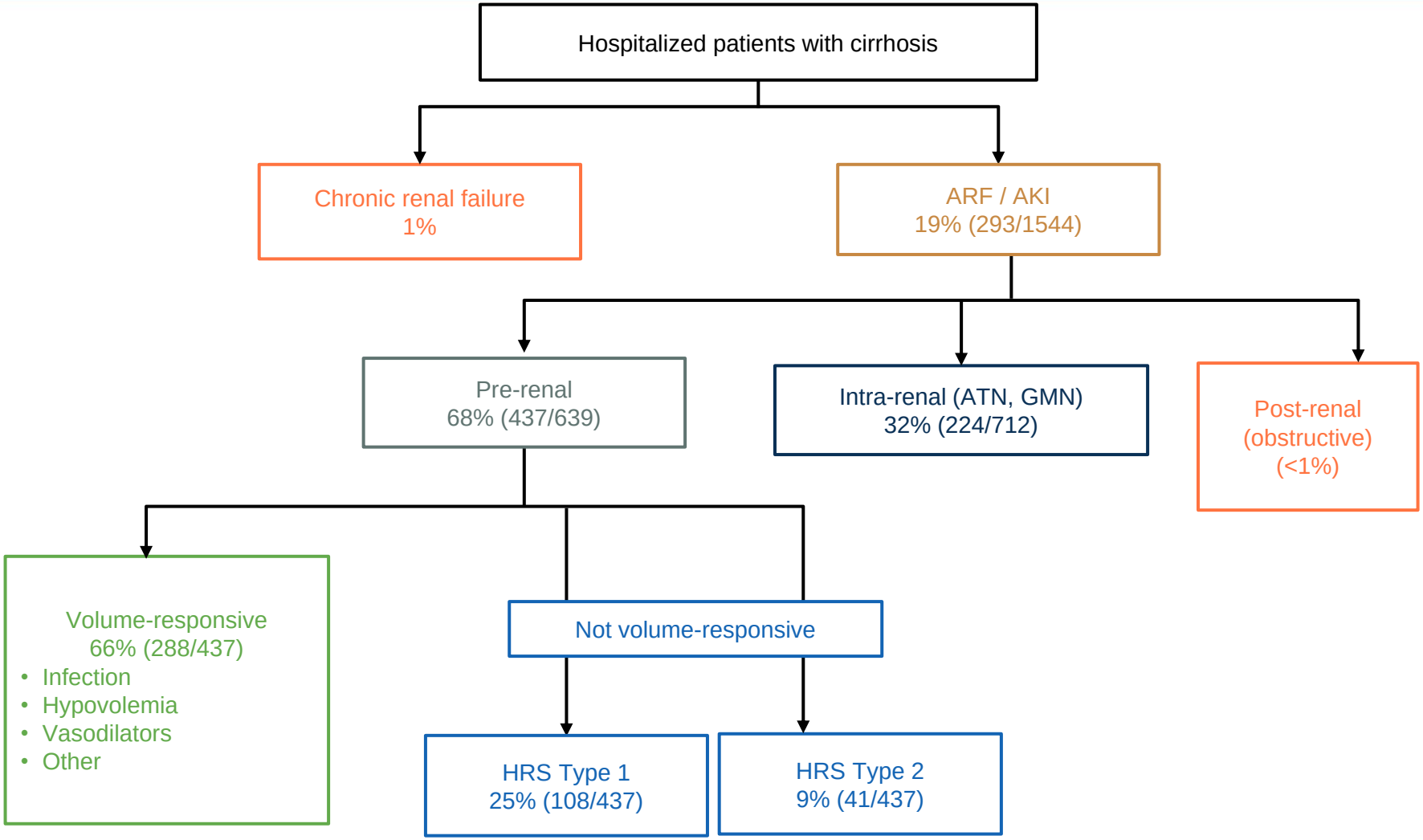
1. Arroyo V et al. *Hepatology.* 1996; 23: 164-176; 2. Angeli P et al. *J Hepatol.* 2015;62:968-974; *J Hepatol.* 2018;69:406-460.

AKI in Cirrhosis: Differential Diagnosis

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

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

Prevalence and Etiology of AKI in Cirrhosis



Garcia-Tsao et al. *Hepatology.* 2008.

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HRS-AKI Management

Pharmacologic Therapy for AKI-HRS

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.

Midodrine and Octreotide

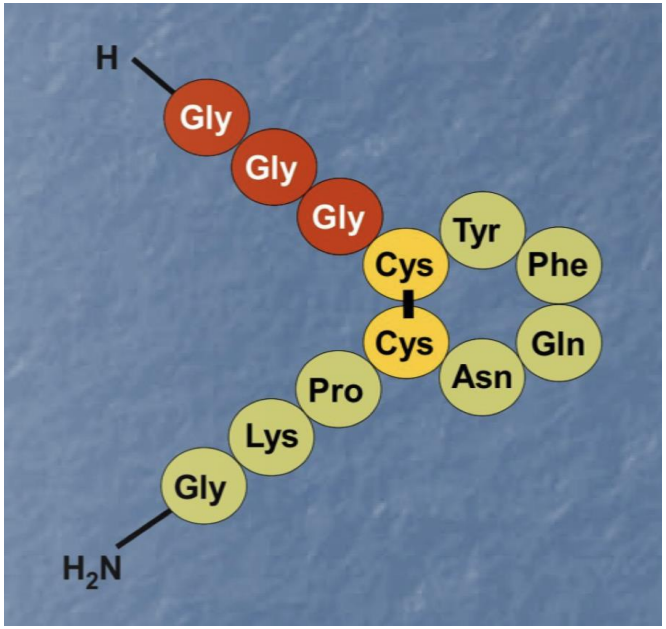
Midodrine

- Midodrine binds to alpha-1-adrenergic receptors
  - Improves systemic blood pressure and hence improves renal perfusion pressure
- Start at 7.5 mg TID
- Titrate midodrine up to 15 mg TID on consecutive doses to a mean arterial pressure of >80 mmHg

Octreotide

- Octreotide is a splanchnic vasoconstrictor that antagonizes the action of various splanchnic vasodilators
  - Not effective alone
- Start octreotide 100-200 mcg TID or IV infusion 50 mcg/hr to raise MAP by 15 mm Hg
- Maximum dose 200 mcg SC TID

Terlipressin: Under FDA Review in US*

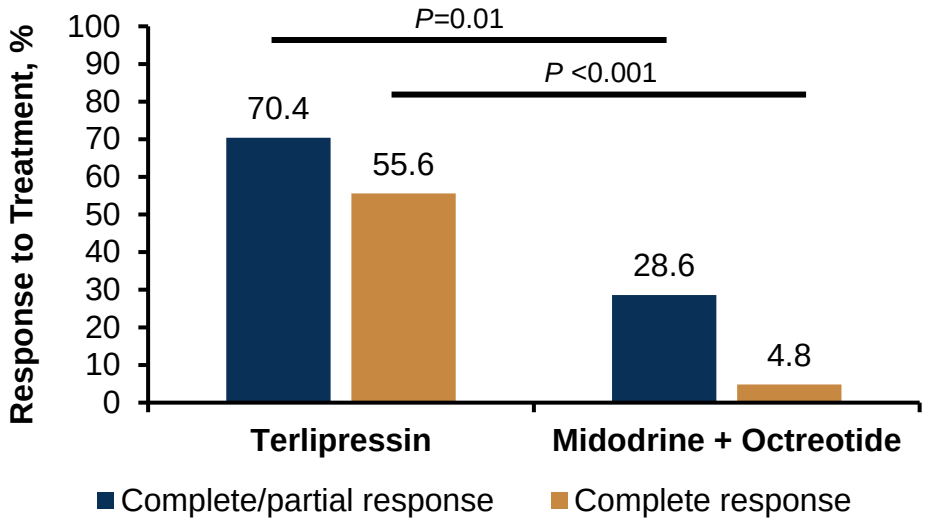


- Approved in many ex-US countries for years
- Synthetic 12 amino acid peptide
- Pro-drug
- Constrictive activity via V-1 receptors
  - Vascular and extra vascular smooth muscle cells
- Splanchnic vasoconstriction reduces portal blood flow and portal pressure
- Systemic vasoconstriction
  - Increases 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

*FDA Complete Response Letter issued September 12, 2020.

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

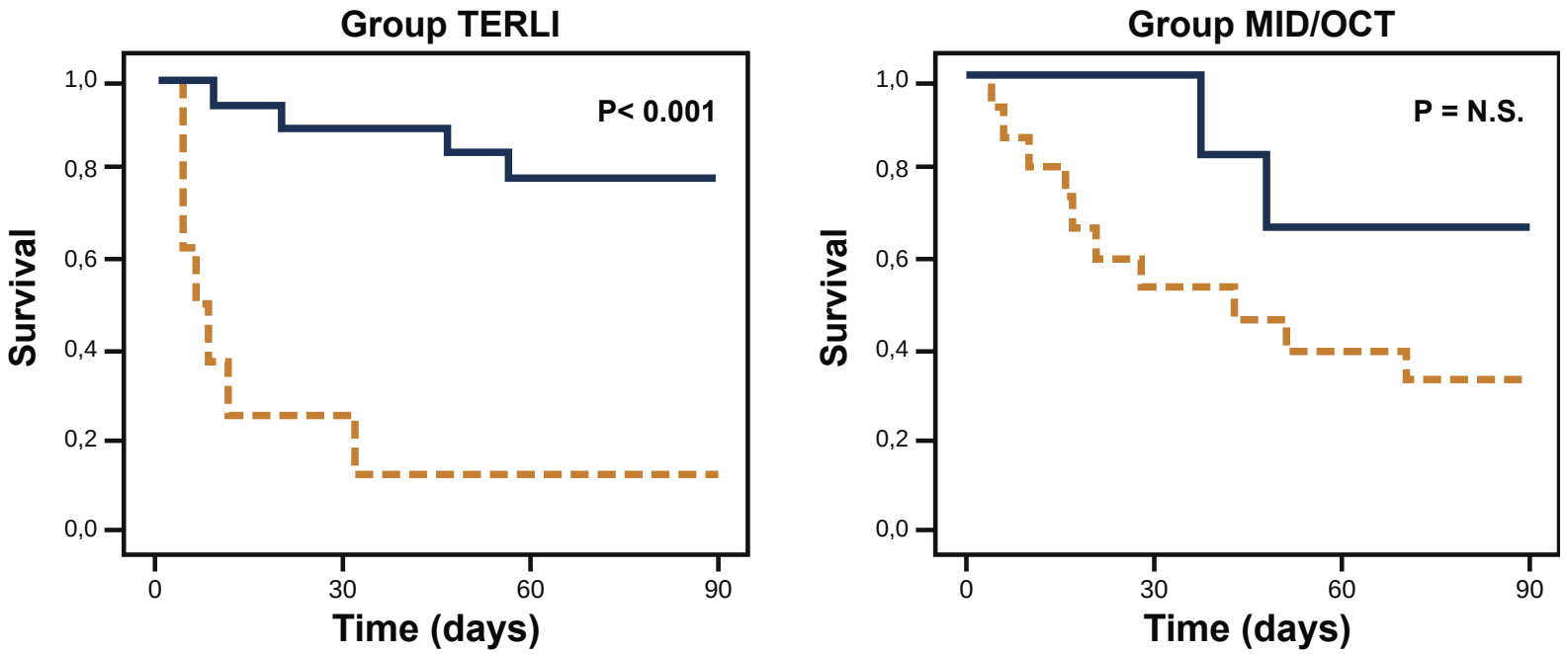
- Randomized controlled study (not blinded)
- 27 patients received terlipressin (IV 3 mg/24 hrs, progressively increased to 12 mg/24 hrs if no response)
- 22 patients received midodrine (orally at 7.5 mg TID with dose increased to max of 12.5 mg TID) and octreotide SC 100 mcg TID up to 200 mcg TID)
- 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

Probability of 90-Day, Transplant-Free Survival According to Response to Treatment



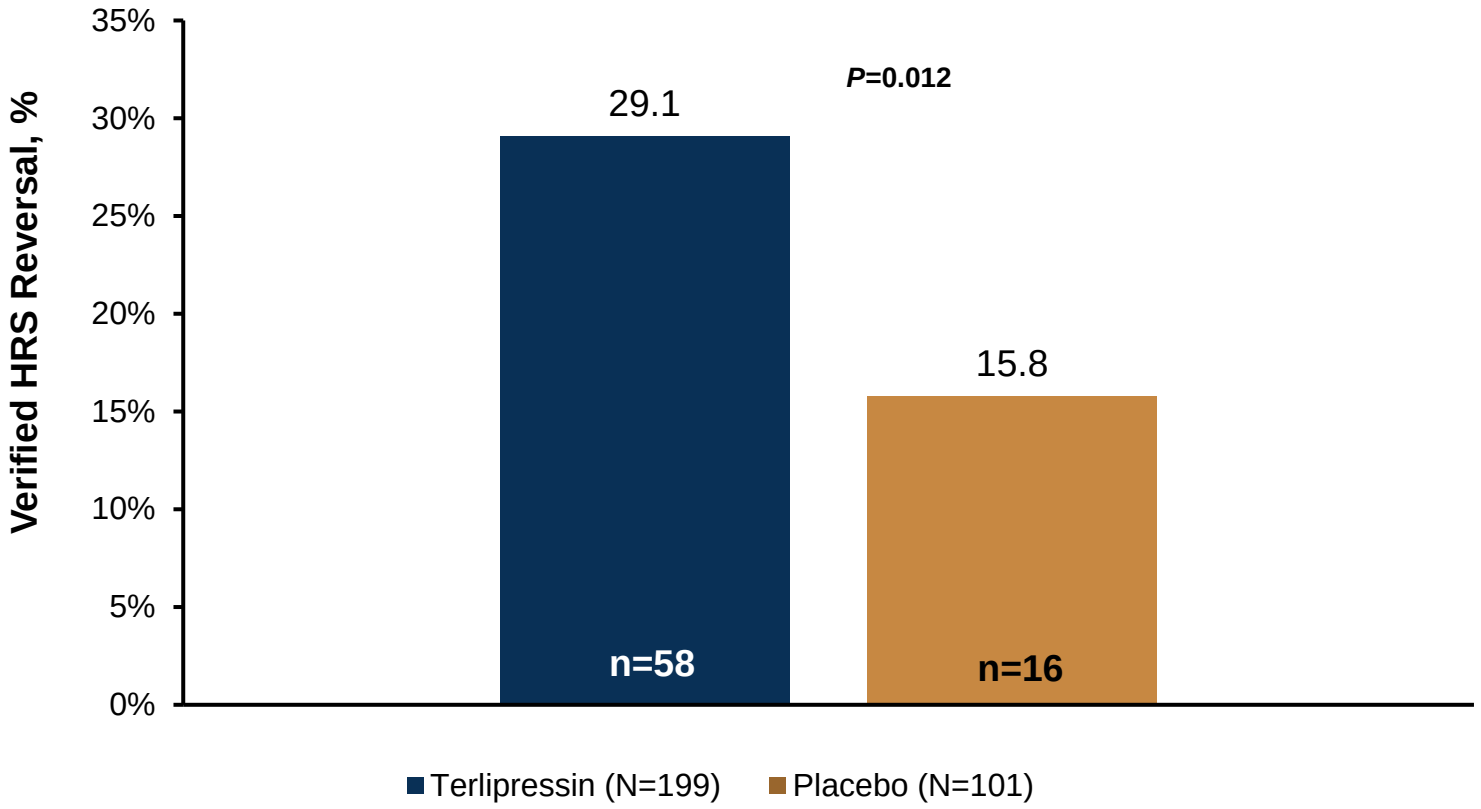
Cumulative 3-month survival in patients who were randomized to terlipressin plus albumin (**TERLI** group) or to midodrine and octreotide plus albumin (**MID/OCT** group) according to the response: solid line represents responders; dotted line represents nonresponders.
Abbreviation: N.S., nonsignificant.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

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

- 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 up to 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. *N Engl J Med*. 2021;384:818-828.

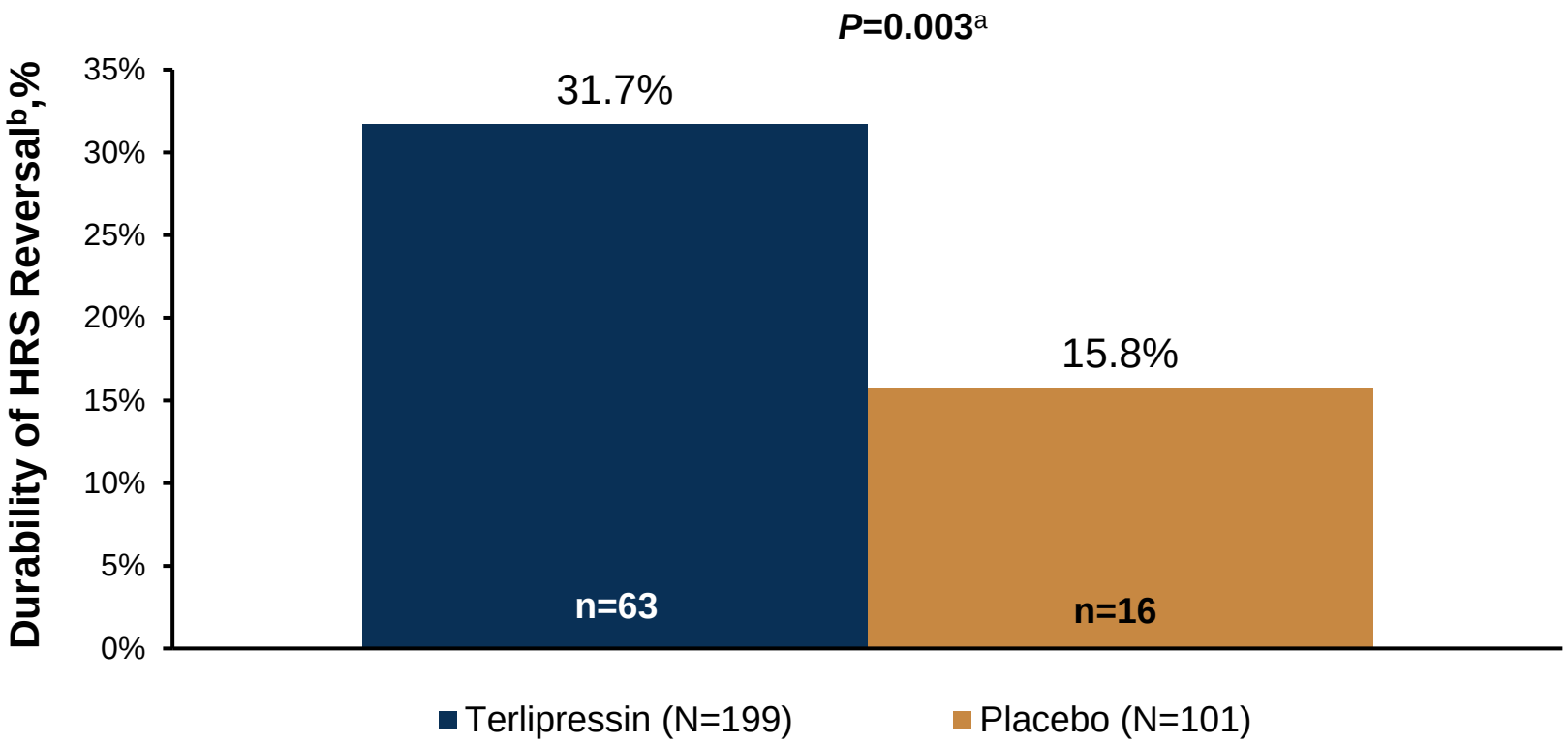
Primary Endpoint: Verified HRS Reversal (CONFIRM Study)



Z score=2.52618. The final analysis is successful if the score is >1.97743.

Wong F et al. *N Engl J Med*. 2021;384:818-828.

Secondary Endpoint: Durability of HRS Reversal (CONFIRM Study)



[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. *N Engl J Med*. 2021;384:818-828.

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

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)

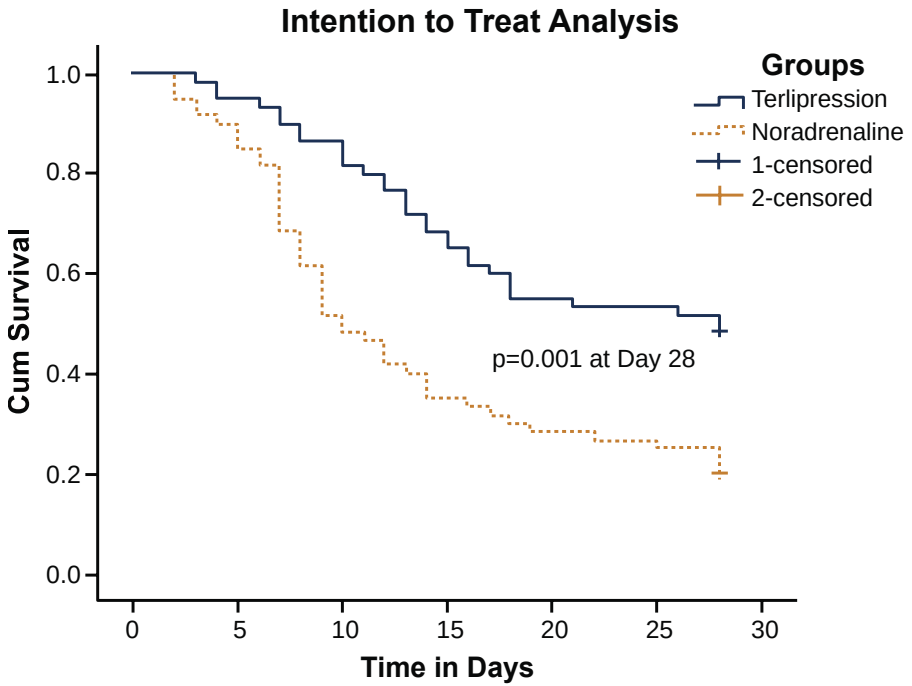
Respiratory Failure higher in both cohorts in CONFIRM than REVERSE trial;
REVERSE T 5.4% vs P 2.1%; none of the respiratory failure were reported as related to study drug.

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. *N Engl J Med*. 2021;384:818-828.

RCT (Open Label): Terlipressin vs Norepinephrine in Patients With ACLF and HRS-AKI

Continuous IV infusion of terlipressin (2 to 12 mg/day) vs. norepinephrine (0.5 to 3 mg/hour)

	Response Rate, n/N (%)		
	Norepinephrine	Terlipressin	P Value
Day 4	7/60 (11.7%)	16/60 (26.7%)	0.03
Day 7	12/60 (20%)	25/60 (41.7%)	0.01
Reversal of HRS-AKI (Day 14)	10/60 (16.7%)	24/60 (40%)	0.004



- Terlipressin reduced need for RRT
- Terlipressin improved survival

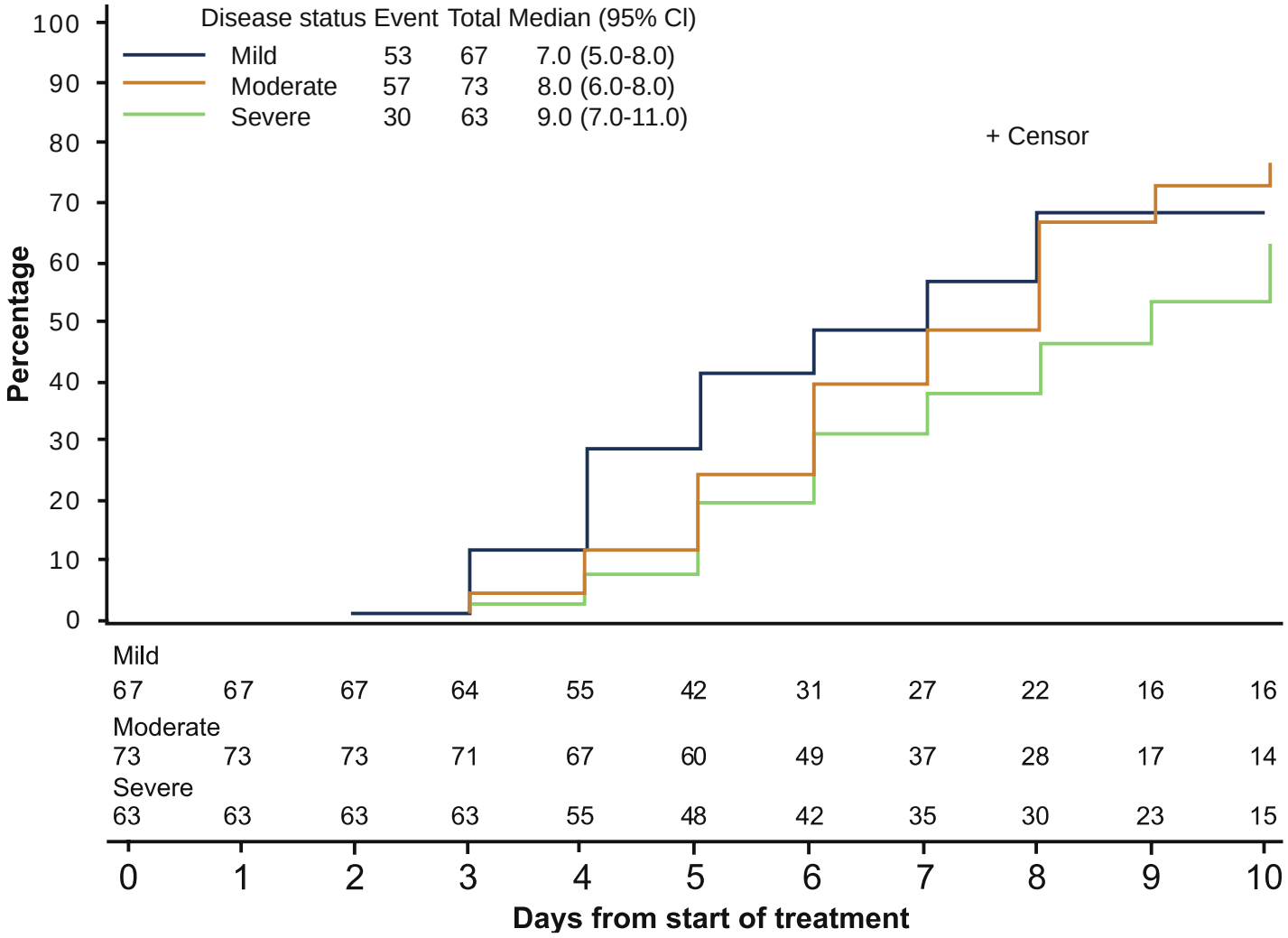
Arora V et al. *Hepatology.* 2019; 0:1-11.

Real-World Use and Outcomes With Terlipressin

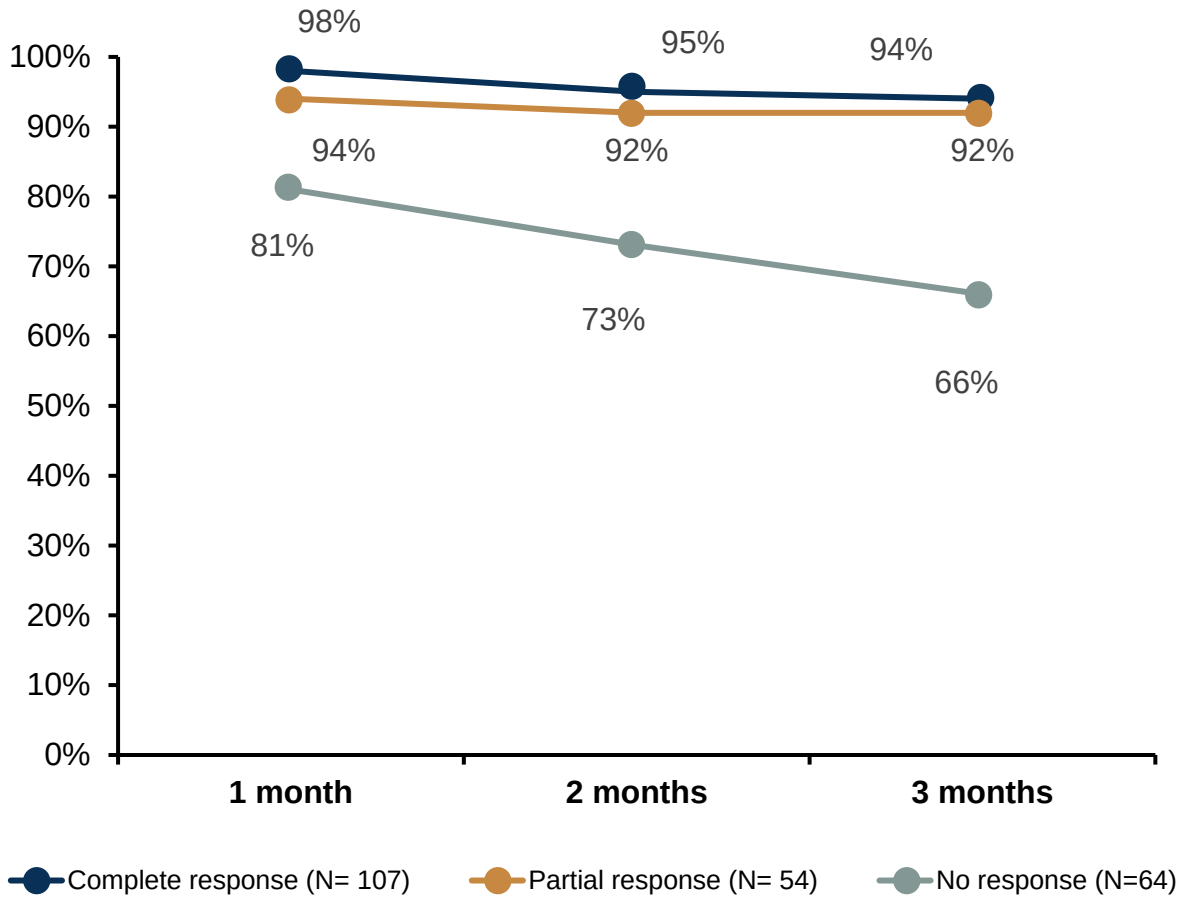
- Retrospective chart review of 225 patients diagnosed with HRS and treated with vasoconstrictors
- AKI defines by pre-treatment sCr
  - Mild: sCr <2.25 mg/dL
  - Moderate: 2.25 ≤sCr <3.5 mg/dL
  - Severe: sCr ≥ 3.5 mg/dL
- Primary outcome
  - Complete response (sCr ≤1.5 mg/dL)
  - Partial response (sCr reduction of ≥20% but sCr >1.5 mg/dL)
  - Overall response

Moore K et al. *Aliment Pharmacol Ther*. 2020 Jun 4. doi: 10.1111/apt.15836.

Timeframe to Response



Renal Response and Survival



Moore K et al. *Aliment Pharmacol Ther*. 2020 Jun 4. doi: 10.1111/apt.15836.

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]
- New AKI-HRS criteria enable earlier treatment 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.

Prevention of AKI-HRS in Patients With Cirrhosis

- Avoid NSAIDs
- Avoid ACE inhibitors
- Decrease/withdraw diuretics when decompensated
- Limiting lactulose dose to accomplish 2-3 BMs per day
- Threshold at which to discontinue beta-blockers?
- Maintain mean arterial pressure (MAP)

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

Take Home Points

- 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 earlier intervention
- Vasoactive agents (terlipressin and norepinephrine) can reverse HRS-AKI in a significant percentage of patients
- Terlipressin is superior to other agents in reversing HRS with expected survival benefits
  - Phase 3 CONFIRM US study results now available

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THANK YOU!