Treating HRS:
Do the Benefits Outweigh the Risks?

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Pertinent Disclosures

- Advisory Board – Mallinckrodt Pharmaceuticals

Treating HRS:
Do the Benefits Outweigh the Risks?

- Yes, they do (particularly if terlipressin is available)
- Keep in mind, although liver transplantation is the treatment of choice, the majority of patients are not liver transplantation candidates, and many others will not receive liver transplantation if they are

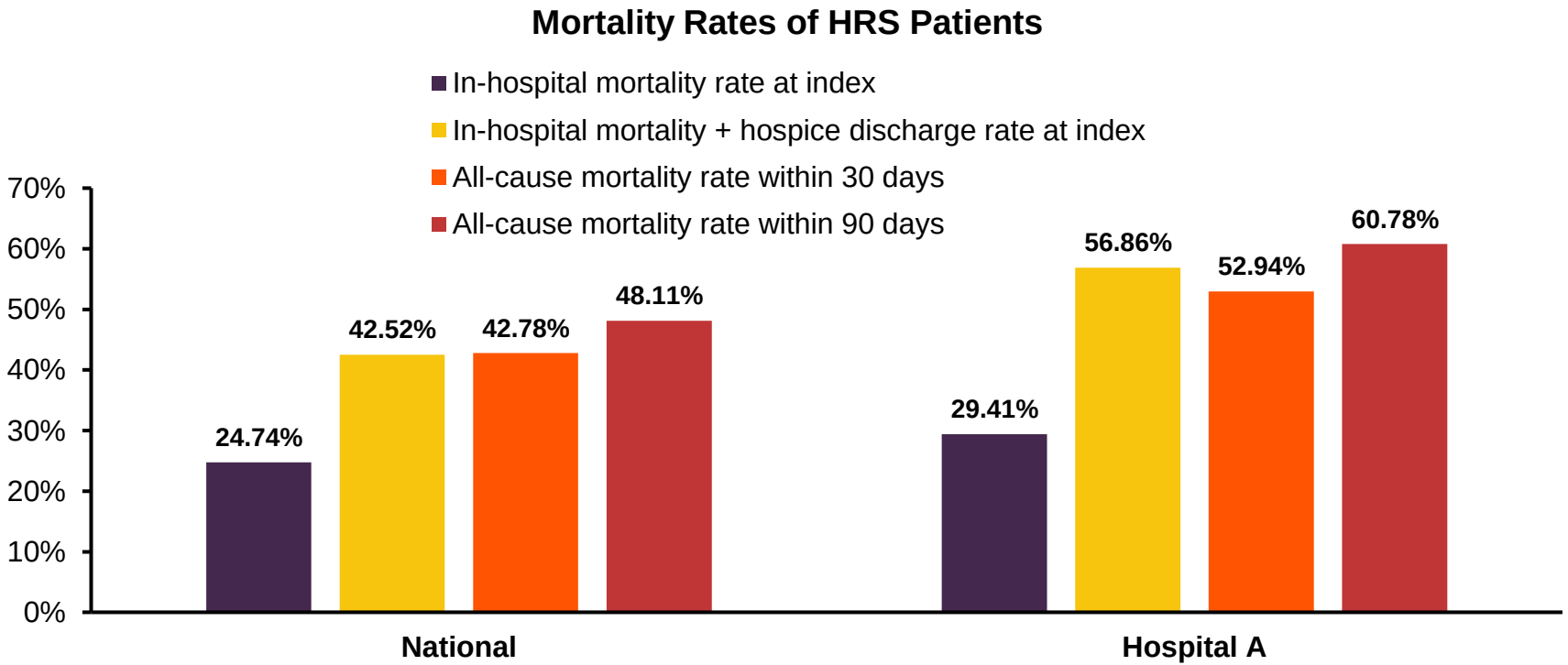
Benefits and Risks

- Depends upon which regimen is used
- Depends upon how early the regimen is used

Potential Benefits and Risks

- Benefits
  - Reversal of HRS
    - Durability of the response including lack of need of RRT
  - Improvement in renal function including at least 30% improvement
  - Transplantation-free survival at 90 days
  - Overall survival at 90 days
  - Need for RRT at 90 days
  - Post-liver transplantation outcomes
- Risks
  - Dependent upon the regimen used

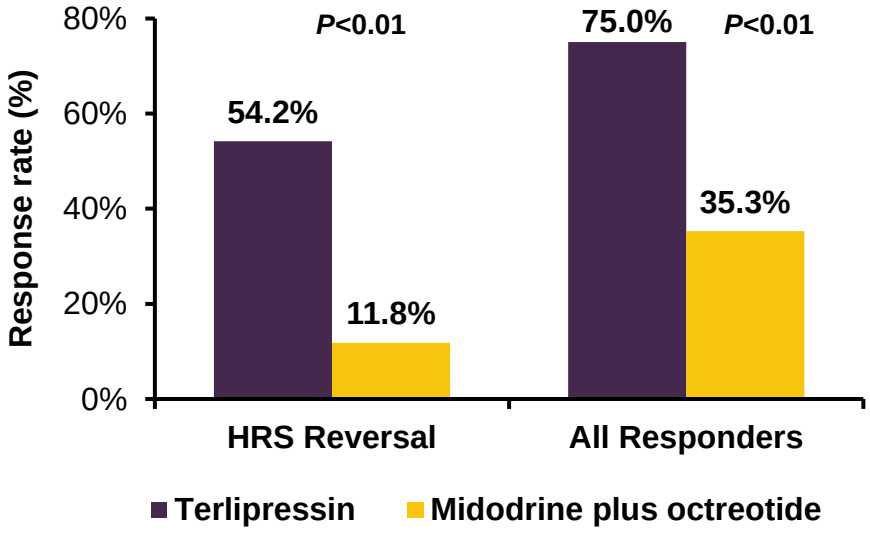
Mortality Rates for HRS Patients



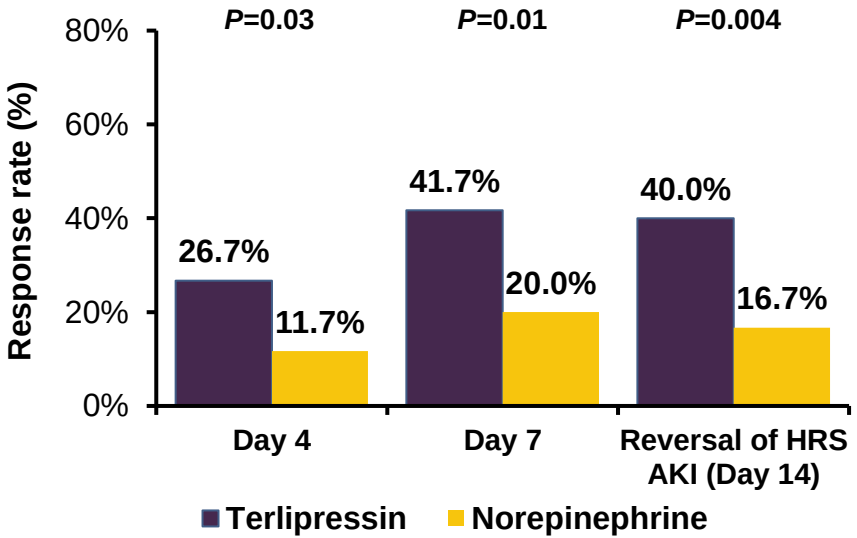
Dexur analysis of CMS Medicare claims – Jan-Dec 2017.
ICD code K767 was used to identify HRS patients for a primary or secondary cause.

Terlipressin Is a Substantial Clinical Improvement Compared to the Current Off-Label U.S. Standard of Care

Midodrine plus octreotide[1]



Norepinephrine[2]



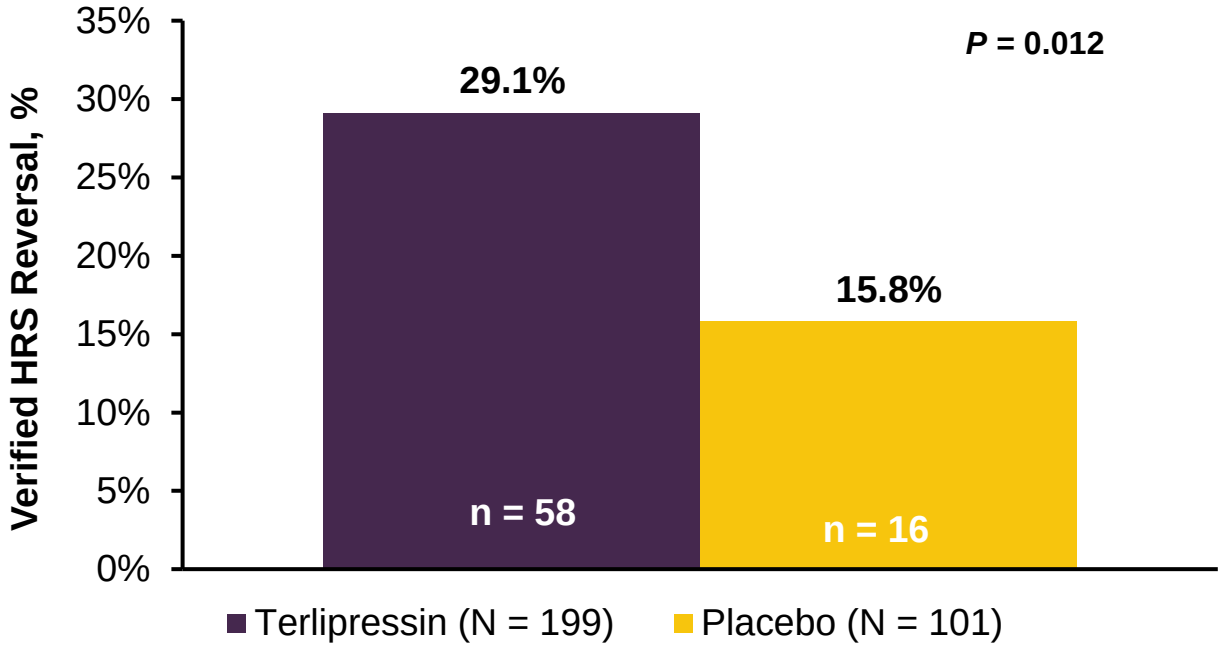
AKI – acute kidney injury.

1. Cavallin M et al. 2015; 2. Arora V et al. 2018.

Terlipressin

CONFIRM: Intent-to-Treat Population

Primary Efficacy Analysis: Verified HRS Reversal



***Z* score=2.52618**

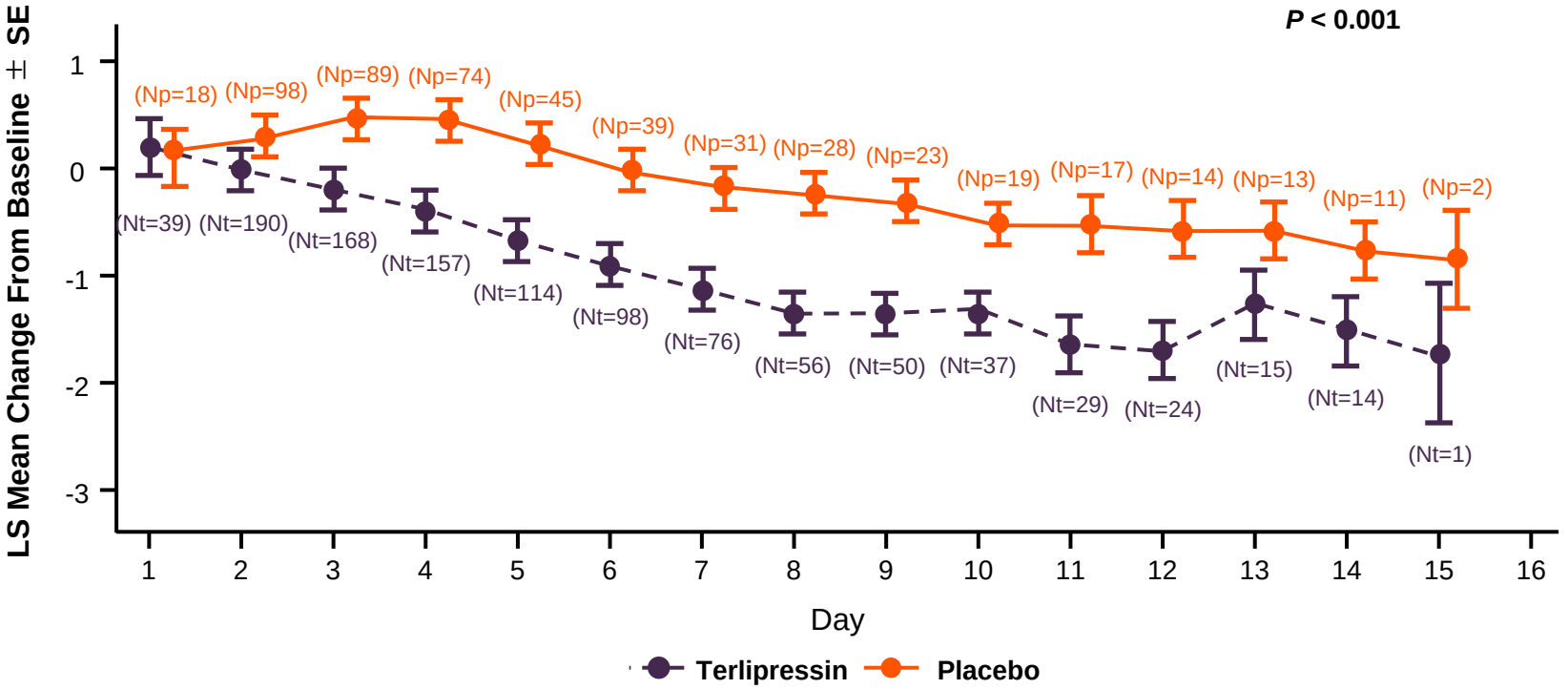
The final analysis is successful if the Z score >1.97743. Note: The incidence of verified HRS reversal is defined as the percentage of subjects with 2 consecutive SCr values ≤1.5 mg/dL at least 2 hours apart, while on treatment by day 14 or discharge. Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. Any SCr values obtained after liver transplantation, RRT, TIPS, or open-label vasopressor use are excluded. SCr values obtained after midodrine administration are included if midodrine was started on day 1 and was administered for no more than 24 hours and if the subject was enrolled on or after August 17, 2018. SCr values obtained after a single dose administration of dobutamine are included.

Source: Listings 16.2.1.3.1, 16.2.6.1.1.

CONFIRM: Intent-to-Treat Population

Improvement in Renal Function

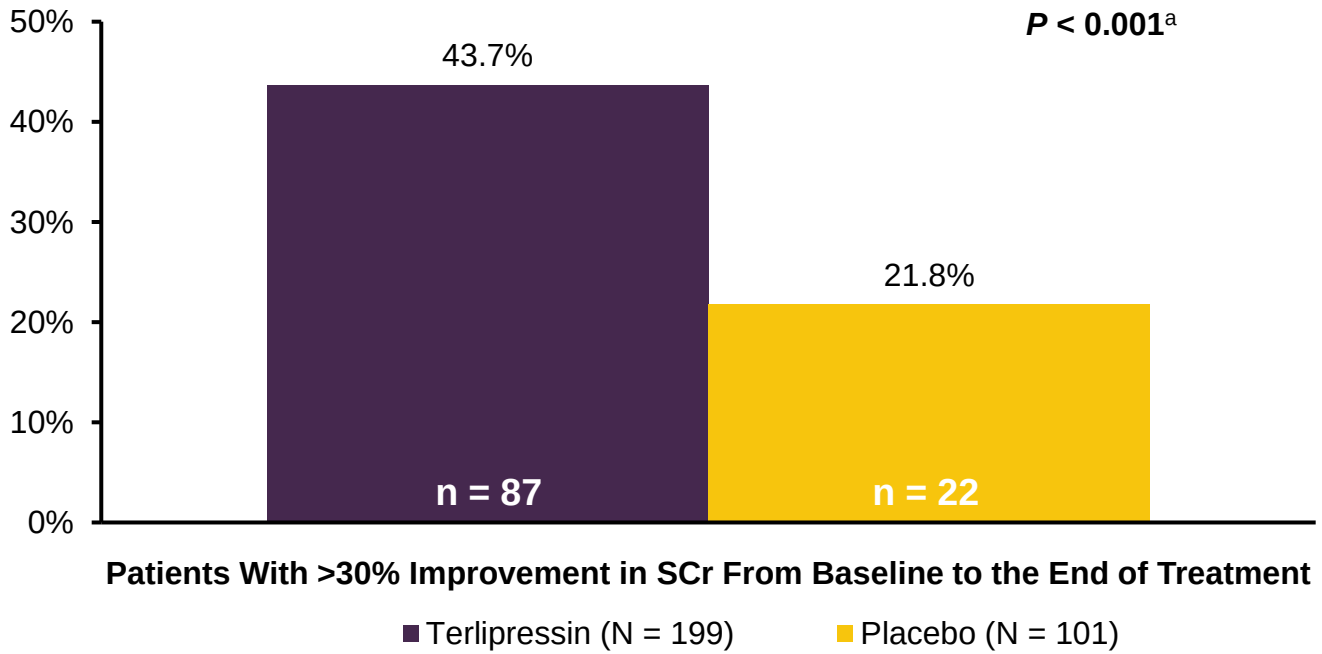
(Repeated Measures Analysis of Change From Baseline in SCr Level by Day)



LS, least square; SCr, serum creatinine.

CONFIRM: Intent-to-Treat Population

Incidence of >30% Improvement in SCr From Baseline to the End of Treatment



CMH, Cochran-Mantel-Haenszel; LVP, large volume paracentesis; N, number of subjects in the treatment group; n, number of subjects in the category of subjects in the treatment group; SCr, serum creatinine.

[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).

Source: Listings 16.2.1.3.1, 16.2.6.7.1.

The CONFIRM Study

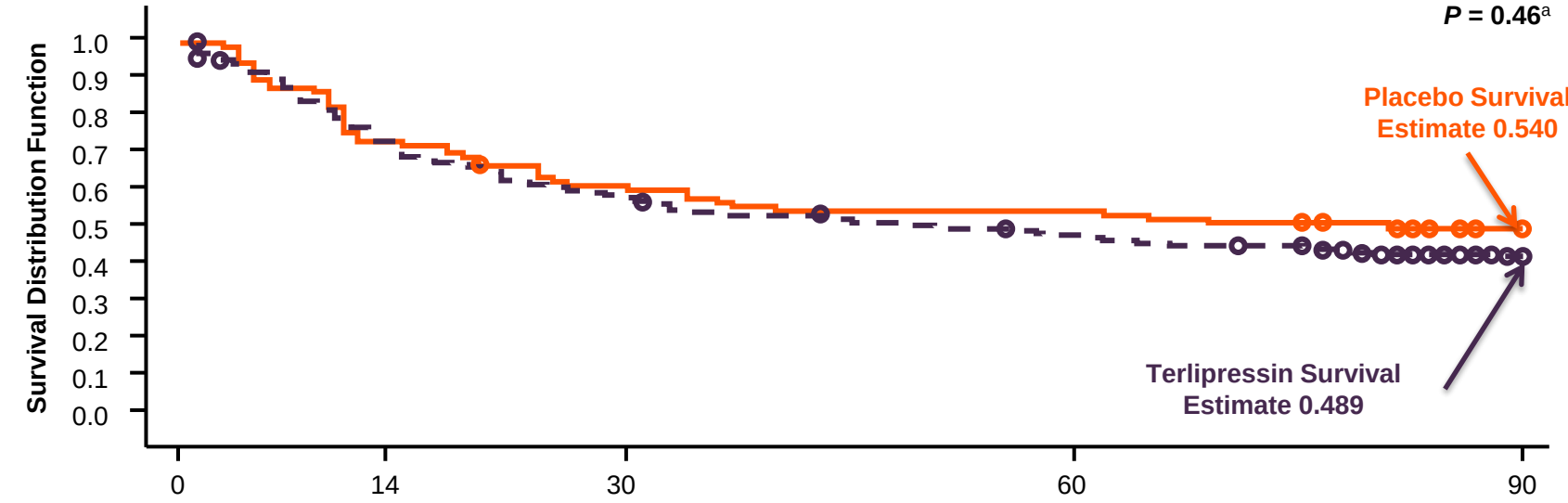
HRS Reversal by SCr Category

SCr Category	Terlipressin (N = 199)	Placebo (N = 101)
<3 mg/dL	39/79 (49.4%)	14/40 (35.0%)
≥3 to <5 mg/dL	31/97 (32.0%)	3/53 (5.7%)
≥5 mg/dL	2/23 (8.7%)	0/8 (0%)

SCr, serum creatinine.

CONFIRM: Intent-to-Treat Population

Overall Survival up to 90 Days

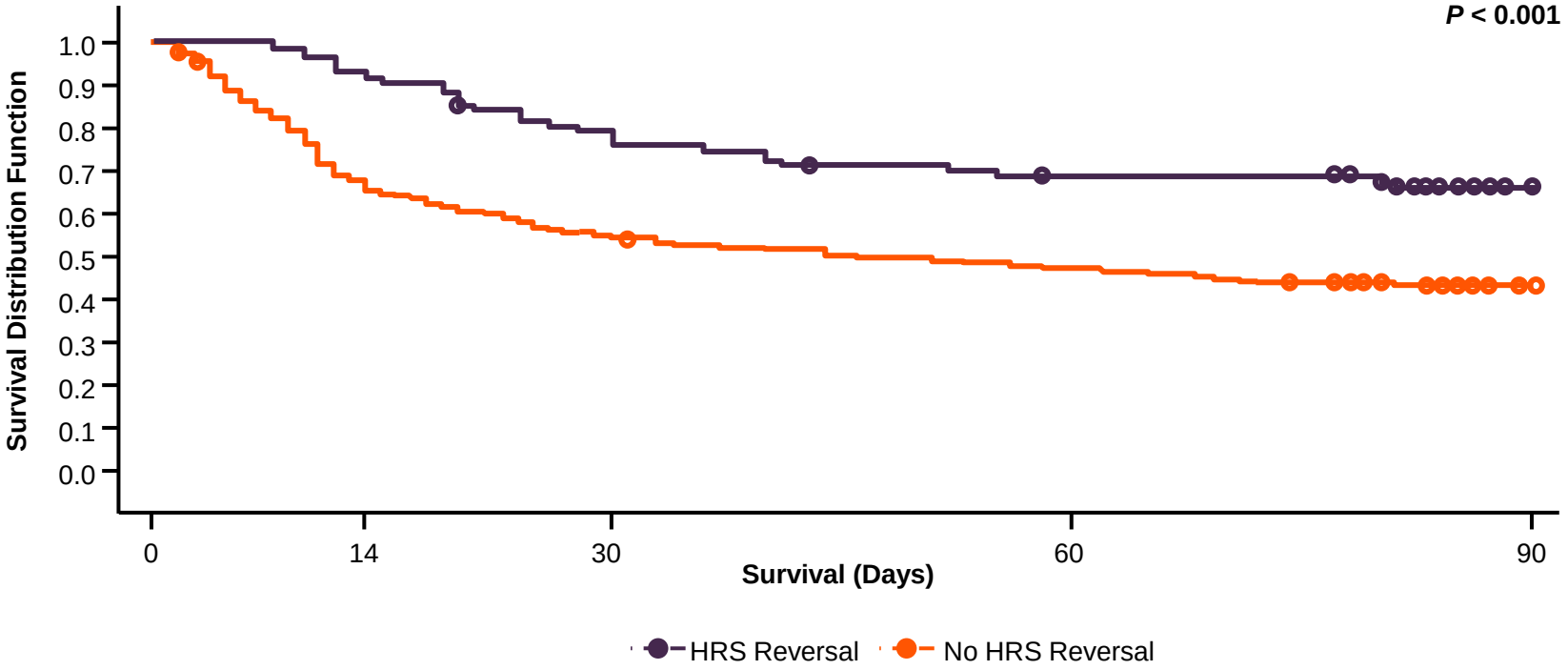


	Terlipressin	Placebo
Median Days of Survival	80.0	NA
Alive at Day 90, % (n)	49.7 (99)	55.4 (56)

LVP, large volume paracentesis; N, number of subjects in the treatment group; n, number of subjects in the category of subjects in the treatment group; NA, not available; SCr, serum creatinine.
[a]Rounded to the nearest hundredth. The *P* value comparing the survival estimates is from a 2-sample log rank test stratified by qualifying SCr (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (at least 1 single event of ≥4 vs <4 L).
Cross Reference: Table 14.2.3.4; Source: Listings 16.2.1.3.1, 16.2.6.6.1.

CONFIRM: Intent-to-Treat Population

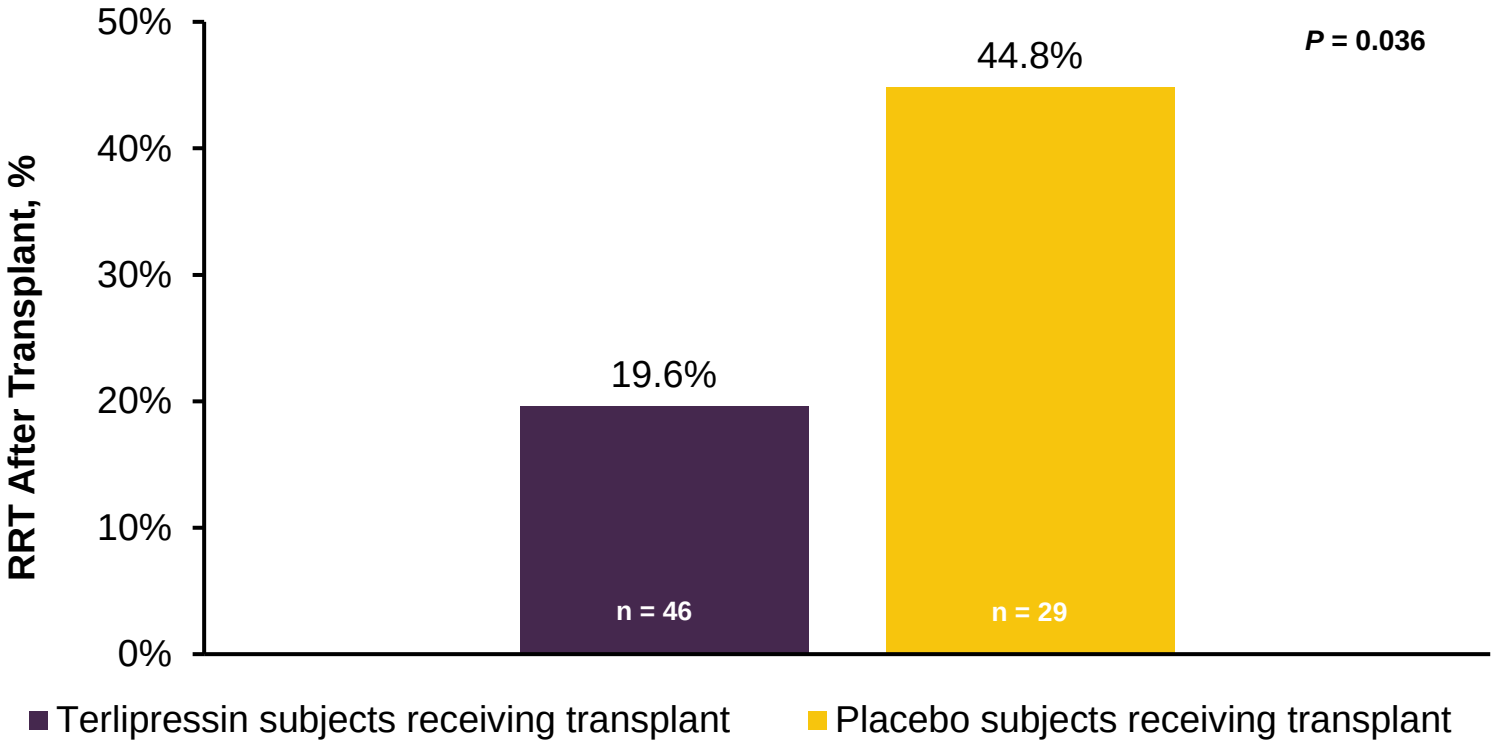
Overall Survival up to 90 Days for Subjects by HRS Reversal



Incidence of HRS reversal was significantly higher in terlipressin cohort compared to placebo, *P* < 0.001.
Cross Reference: Table 14.2.3.23.

CONFIRM: Intent-to-Treat Population

Incidence of RRT Post-Liver Transplant



n, number of subjects in the category of subjects in the treatment group.

Benefits vs Risks

- Potential benefits of therapy for HRS, in particular terlipressin, are real
  - Maximize benefits by treating patients early
- Potential risks are also real, but can be mitigated by appropriate patient selection, fluid management, recognition of infrequent ischemic side effects

Treating HRS:
Do the Benefits Outweigh the Risks?

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Disclosures

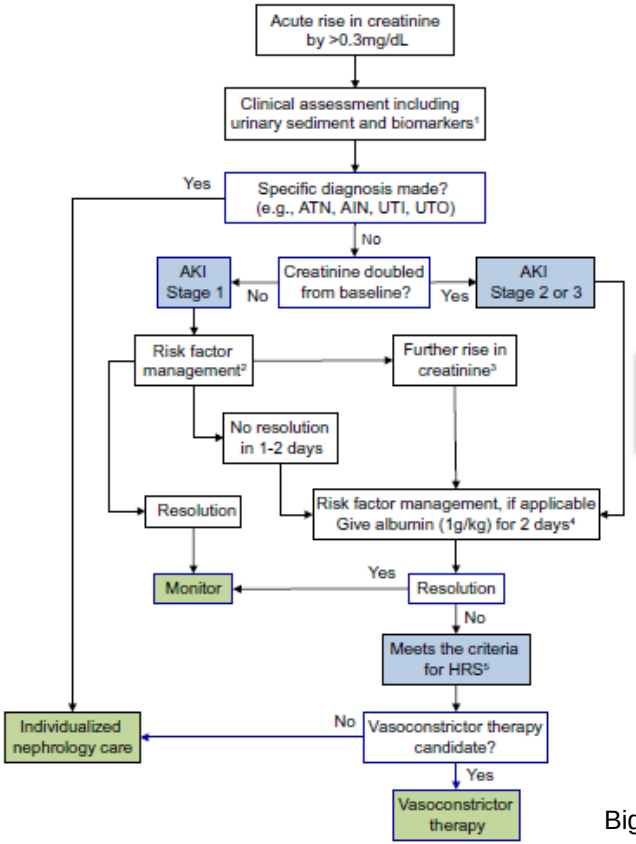
- Research grants (to my institution), consulting, advisory board – Gilead Sciences
- Consulting – Intercept

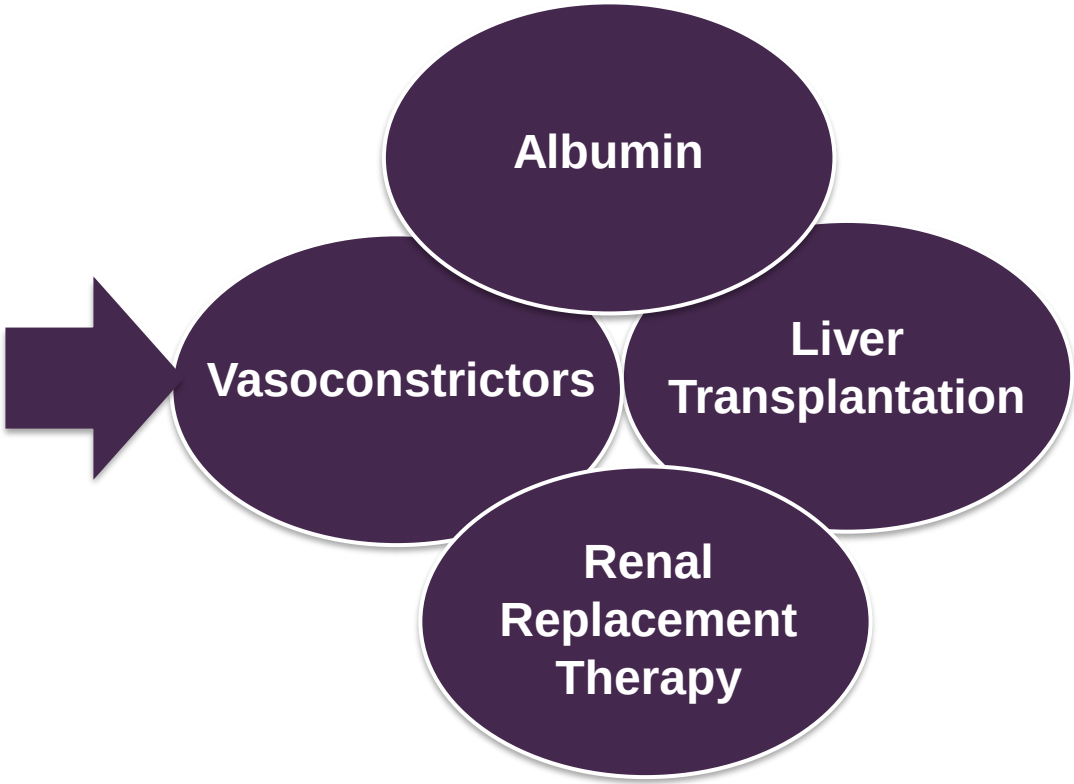
DON’T TREAT

Objectives

- Review the current medical treatment approaches for HRS
- Understand the limitations of current HRS treatments for improving patient outcomes
- Review recent data from CONFIRM Trial

2021 AASLD Practice Guidelines





Biggins, et al. Hepatology 2021

Comparative efficacy of pharmacological strategies for management of type 1 hepatorenal syndrome: a systematic review and network meta-analysis

Antonio Facciorusso, Apoorva K Chandar, M Hassan Murad, Larry J Prokop, Nicola Muscatiello, Patrick S Kamath, Siddharth Singh

- Terlipressin or Norepinephrine is superior to midodrine + octreotide for HRS reversal
- No significant differences in terlipressin vs. norepinephrine in achieving HRS reversal
- No significant improvement in short term mortality observed for vasoconstrictors
- Moderate quality data in terlipressin did not reach significance in improving short term mortality

	Short-term mortality		Reversal of hepatorenal syndrome	
	Odds ratio (95% CI)	Quality of evidence	Odds ratio (95% CI)	Quality of evidence
Efficacy vs placebo				
Midodrine plus octreotide	0·61 (0·19–1·93)	Low (network)	0·44 (0·06–3·23)	Low (network)
Noradrenaline	0·75 (0·32–1·76)	Low (network)	4·17 (1·37–12·50)	Low (network)
Terlipressin	0·65 (0·41–1·05)	Moderate (direct; imprecision, low event rate)	4·48 (1·88–10·67)	Low (network)
Dopamine plus furosemide	0·70 (0·12–4·13)	Low (network)	..	..
Efficacy vs midodrine plus octreotide				
Noradrenaline	1·50 (0·60–3·78)	Low (network)	10·00 (1·49–50·00)	Low (network)
Terlipressin	1·14 (0·39–3·33)	Very low (network)	26·25 (3·07–225·21)	Moderate (direct; imprecision, low event rate)
Dopamine plus furosemide	1·14 (0·15–8·76)	Very low (network)	..	..
Efficacy vs noradrenaline				
Terlipressin	0·93 (0·43–1·98)	Low (network)	0·99 (0·43–2·33)	Very low (network)
Dopamine plus furosemide	0·93 (0·14–6·17)	Low (network)	..	..
Efficacy vs terlipressin				
Dopamine plus furosemide	1·00 (0·18–5·67)	Low (network)	..	..

GRADE=Grading of Recommendations Assessment, Development and Evaluation. When moderate to high quality evidence were available from direct or pairwise estimates, they were used preferentially (marked as direct); when pairwise estimates provided only low or very low quality of evidence or if there were no pairwise comparisons, then estimates from network meta-analysis were used to rate quality of evidence (marked as network).

Table 2: GRADE summary of findings reporting the comparative efficacy of drugs strategies

Lancet Gastroenterol Hepatol. 2017; 2:94-102.

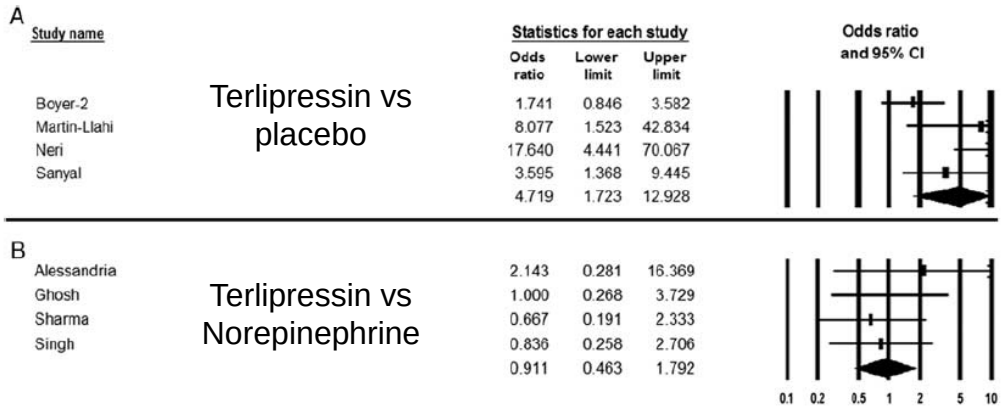
Pharmacological Therapies for Hepatorenal Syndrome

A Systematic Review and Meta-Analysis

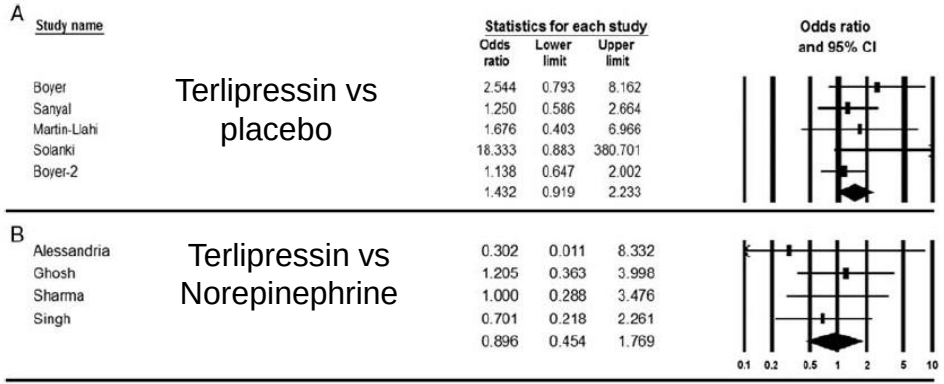
Arjun Nanda, MD, Rewanth Reddy, MBBS,* Humaira Safraz, MBBS,* Habeeb Salameh, MD,† and Ashwani K. Singal, MD, MS, FACG**

- HRS Reversal
  - Terlipressin + albumin was superior to albumin alone in achieving HRS reversal
  - No difference in odds of HRS reversal in terlipressin vs. norepinephrine
- Patient Survival
  - No significant differences in survival outcomes were observed across the different vasoconstrictors evaluated
  - No differences in survival when compared to placebo (albumin alone)

HRS REVERSAL



SURVIVAL



J Clin Gastroenterol. 2018; 52:360-367.

ORIGINAL ARTICLE

Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome

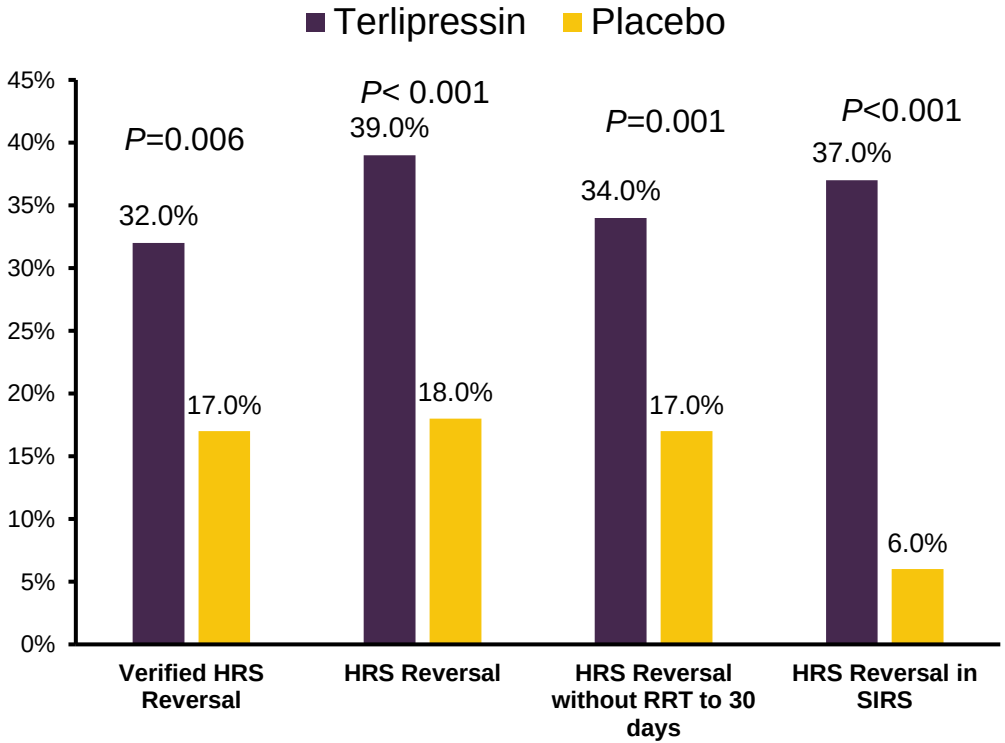
F. Wong, S.C. Pappas, M.P. Curry, K.R. Reddy, R.A. Rubin, M.K. Porayko, S.A. Gonzalez, K. Mumtaz, N. Lim, D.A. Simonetto, P. Sharma, A.J. Sanyal, M.J. Mayo, R.T. Frederick, S. Escalante, and K. Jamil, for the CONFIRM Study Investigators*

- 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

N Engl J Med. 2021;384:818-28. DOI: 10.1056/NEJMoa2008290.

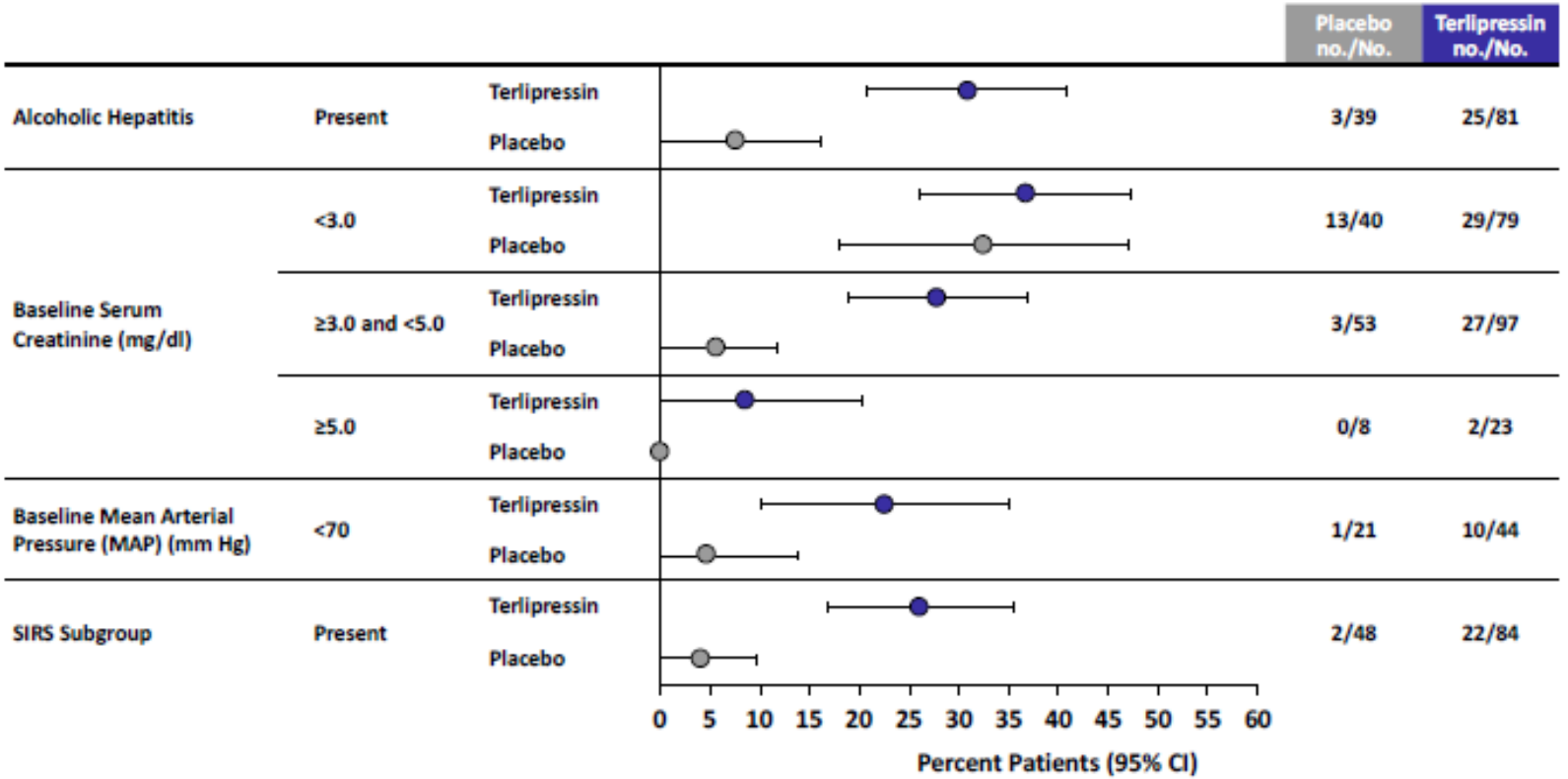
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Terlipressin (N=199)	Placebo (N=101)
Age — yr	54.0±11.3	53.6±11.8
Male sex — no. (%)	120 (60)	59 (58)
Cause of liver cirrhosis — no. (%)		
Alcohol use	134 (67)	67 (66)
Nonalcoholic steatohepatitis	42 (21)	24 (24)
Viral hepatitis	35 (18)	8 (8)
Autoimmune hepatitis	10 (5)	5 (5)
Primary biliary cirrhosis	5 (3)	3 (3)
Other cause or cryptogenic liver disease	15 (8)	8 (8)
Alcoholic hepatitis — no. (%)	81 (41)	39 (39)
Systemic inflammatory response syndrome — no. (%)†	84 (42)	48 (48)
Mean arterial pressure — mm Hg	78.7±12.1	77.5±9.4
Serum sodium level — mmol/liter	133.1±5.6	133.3±5.5
Serum creatinine level — mg/dl	3.5±1.0	3.5±1.1
Total bilirubin level — mg/dl	13.1±13.5	15.0±15.6
Albumin level — g/dl	3.7±0.7	4.0±2.6
Child–Pugh score‡	10.0±1.85	10.2±1.89
MELD score§	32.7±6.6	33.1±6.2



Wong et al. *NEJM*. 2021.

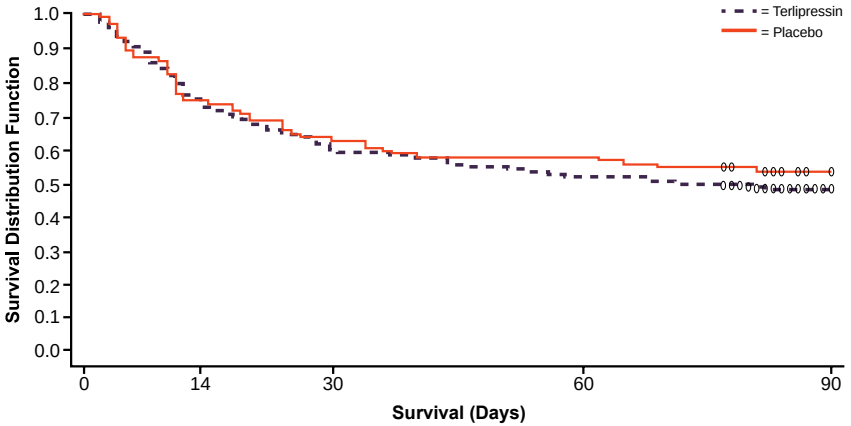
Subgroup Analyses



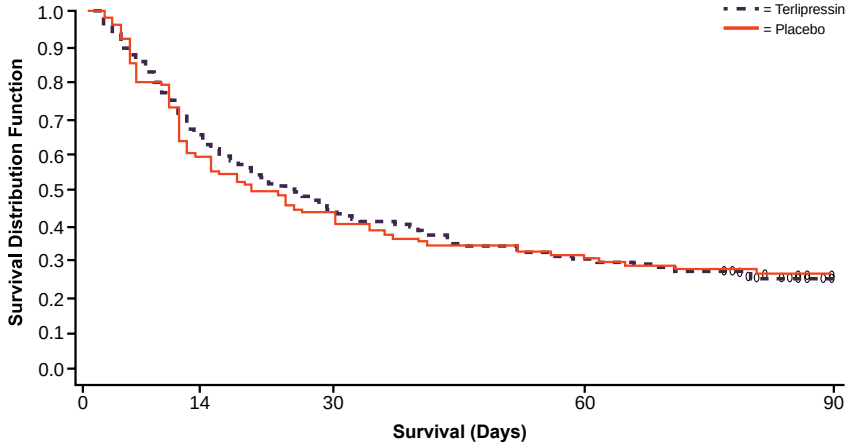
Wong et al. *NEJM*. 2021.

No Significant Differences in Survival Outcomes

Overall Survival



Transplant Free Survival



Wong et al. *NEJM*. 2021.

Table 4. Adverse Events in the Safety Population.*

Event	Terlipressin (N = 200)	Placebo (N = 99)
	number of patients (percent)	
Adverse events of any grade†	176 (88)	88 (89)
Adverse events leading to discontinuation of the trial regimen	24 (12)	5 (5)
Serious adverse events with an incidence of ≥3% in either trial group‡		
Any	130 (65)	60 (61)
Cardiac disorders	8 (4)	6 (6)
Atrial fibrillation	1 (<1)	3 (3)
Gastrointestinal disorders	30 (15)	6 (6)
Abdominal pain	10 (5)	1 (1)
Gastrointestinal hemorrhage	8 (4)	0
General disorders and administration-site conditions	11 (6)	6 (6)
Multiple organ dysfunction syndrome	9 (4)	3 (3)
Hepatobiliary disorders	37 (18)	29 (29)
Chronic hepatic failure	9 (4)	8 (8)
Alcoholic cirrhosis	4 (2)	3 (3)
Hepatic cirrhosis	6 (3)	2 (2)
Hepatic failure	9 (4)	10 (10)
Worsening of HRS	3 (2)	3 (3)
Infections and infestations	19 (10)	5 (5)
Pneumonia	4 (2)	3 (3)
Sepsis	9 (4)	0
Nervous system disorders	13 (6)	3 (3)
Hepatic encephalopathy	9 (4)	3 (3)
Respiratory, thoracic, and mediastinal disorders§	33 (16)	8 (8)
Acute respiratory failure	8 (4)	2 (2)
Respiratory failure	20 (10)	3 (3)
Vascular disorders	10 (5)	4 (4)
Shock	5 (2)	3 (3)

Death within 90 days due to respiratory disorders occurred in 22 patients (11%) in the terlipressin group and 2 patients (2%) in the placebo group.

AASLD 2021 Guidance

- The treatment of choice for HRS-AKI is vasoconstrictor drugs in combination with albumin. The preferred drug is terlipressin, administered either as IV bolus or continuous IV infusion.
- In settings where terlipressin is not available, norepinephrine should be given. If neither can be administered, a trial of oral midodrine (5 to 15 mg per every 8 hours) in combination with octreotide (100 to 200 µg every 8 hours or 50 µg/hour IV) may be considered, yet the efficacy is low.
- Given the complexity of patients with suspected HRS-AKI, decisions about management including initiation of vasoconstrictor therapy and RRT should be made, if possible, by multidisciplinary teams including specialists in hepatology, nephrology, critical care, and transplant surgery.

Biggins et al. *Hepatology*. 2021.

Take Home Points

- Development of HRS is associated with significant morbidity and mortality
- Initial evaluation and management including volume resuscitation, albumin, and discontinuation of nephrotoxic drugs
- Vasoconstrictor therapy + Albumin is associated with significant improvement in achieving HRS reversal
- However, limited benefit on short term mortality and significant adverse events emphasize importance of close monitoring