Albumin Dosing With Terlipressin for the Treatment of HRS-AKI: A Double-Edged Sword

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Disclosures

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- River 2 Renal – Consultancy

Hepatorenal Syndrome (HRS)

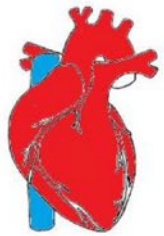
- HRS type 1 is a form of functional rapidly progressive renal failure that occurs in patients with decompensated cirrhosis with ascites[1]
- It is frequently fatal unless timely treatment is provided
- The recommended treatment is a vasoconstrictor together with albumin
- Terlipressin is the first and only US FDA-approved vasoconstrictor recommended to treat patients with cirrhosis and ascites with a rapid reduction in kidney function[2]

1. Biggins S et al. *Hepatology*. 2021; 74(2):1014−1048; **2.** TERLIVAZ® (Terlipressin). Full Prescribing Information. Mallinckrodt Pharmaceuticals; 2022.

Use of Terlipressin in HRS

Terlipressin

(A)



Cardiovascular circulation

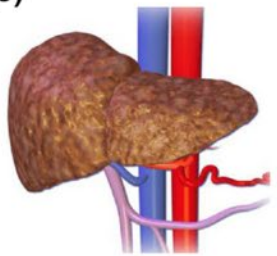
- Increase in systemic vascular resistance
- Increase in mean arterial pressure.
- Reduced heart rate and cardiac output
- Unaltered myocardial perfusion and stroke volume.

(B)

Splanchnic Circulation

- Reduction of NO levels
- Portal venous blood flow decreases

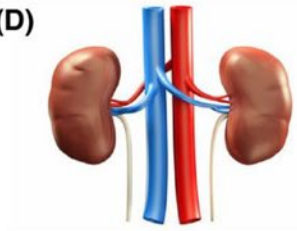
(C)



Hepatic Circulation

- Decrease in hepatic arterial resistance.
- Decrease in HVPG

(D)



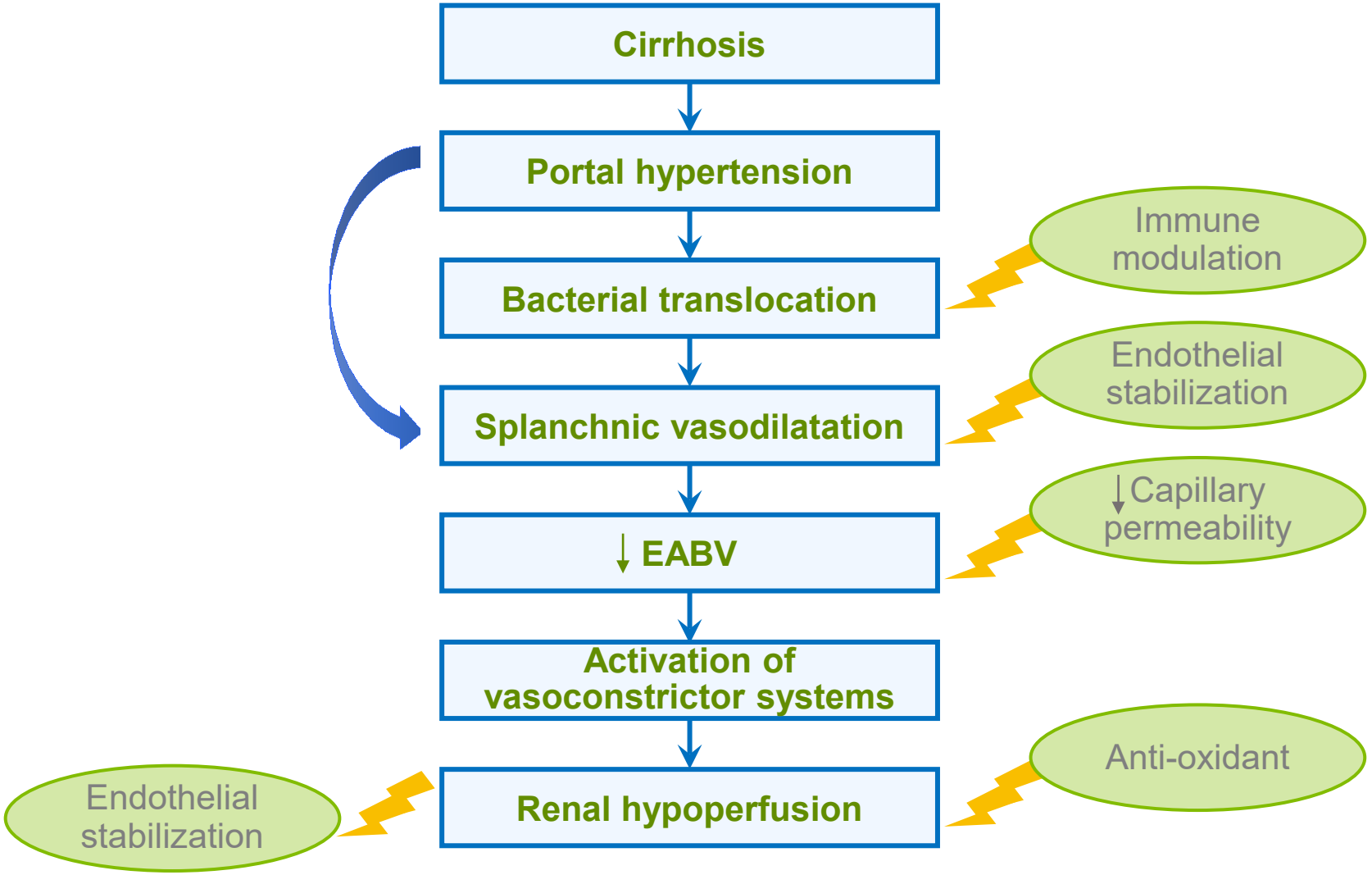
Renal circulation

- Increase in renal perfusion pressure.
- Decrease in renal arterial resistance indices.
- Reduction in free water clearance

HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; NO, nitric oxide.

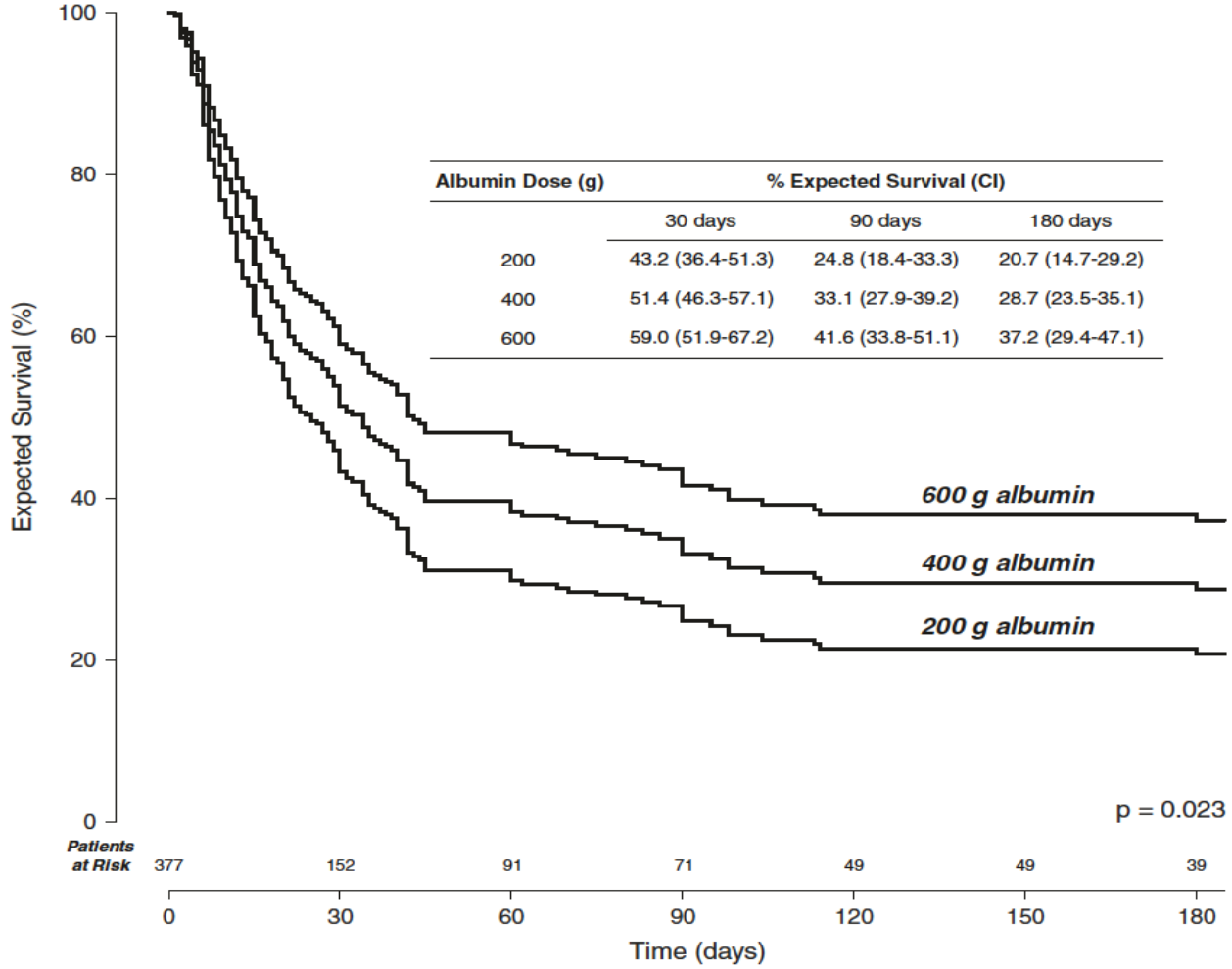
Reproduced from Kulkarni AV et al. *Liver Int.* 2020; 40: 2888–2905.

Use of Albumin in HRS



EABV, effective arterial blood volume; HRS, hepatorenal syndrome.

Use of Albumin in HRS



Albumin Dose (g)	% Expected Survival (CI)		
	30 days	90 days	180 days
200	43.2 (36.4-51.3)	24.8 (18.4-33.3)	20.7 (14.7-29.2)
400	51.4 (46.3-57.1)	33.1 (27.9-39.2)	28.7 (23.5-35.1)
600	59.0 (51.9-67.2)	41.6 (33.8-51.1)	37.2 (29.4-47.1)

19 studies, 574 patients
Various vasoconstrictors

HRS, hepatorenal syndrome.
Reproduced from Salerno et al. *BMC Gastroenterology*. 2015; 15:167.

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Treatment of HRS

- However, excess albumin theoretically may increase the risk for respiratory failure which was observed in 10% of patients who received terlipressin in the recent CONFIRM trial[1]
- The optimal dose of albumin to be given pre- and during HRS treatment remains unclear

HRS, hepatorenal syndrome.

1. Wong F et al. *N Engl J Med*. 2021;384(9):818−828.

Aim

- To evaluate the optimal dose of albumin with respect to efficacy and safety, based on the pooled analysis of the 2 largest placebo-controlled, randomized trials of terlipressin plus albumin versus placebo in patients with HRS type 1

HRS, hepatorenal syndrome.

Methods (1)

- Data were pooled from 2 Phase III randomized, placebo-controlled studies in patients with cirrhosis, ascites, and HRS type 1:
  - CONFIRM[1] (NCT02770716; n = 300)
  - REVERSE[2] (NCT01143246; n = 196)
- Patients were divided into albumin dose quartiles and compared

HRS, hepatorenal syndrome.

1. Wong F et al. *N Engl J Med*. 2021;384(9):818−828; **2.** Boyer TD et al. *Gastroenterology*. 2016;150(7):1579−1589.

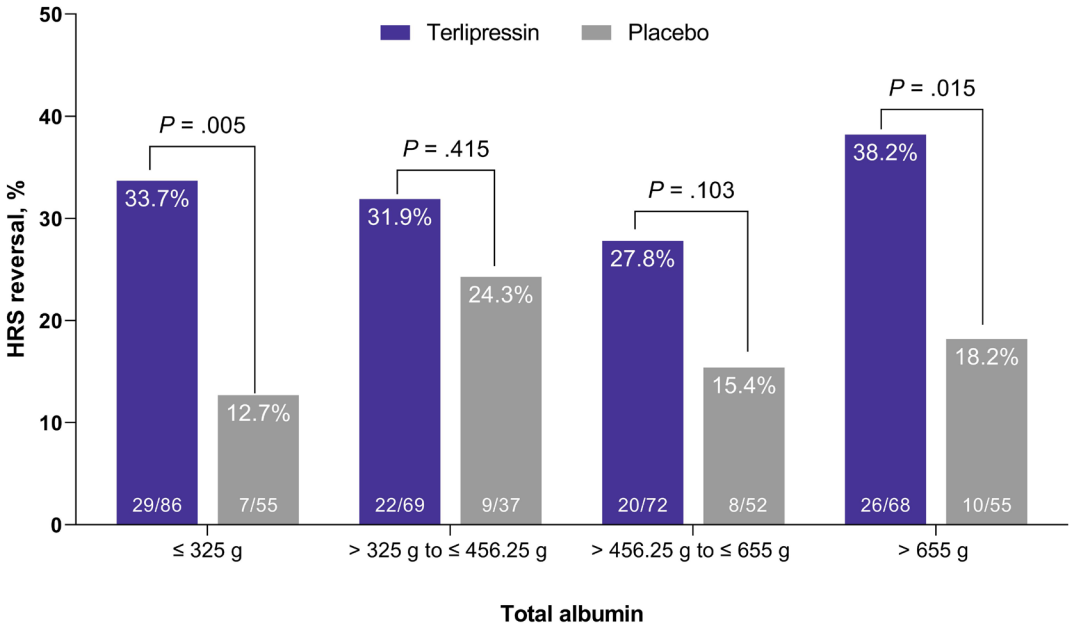
Methods (2)

- The following clinical outcomes were assessed by total albumin quartiles:
  - Incidence of HRS reversal, defined as SCr ≤ 1.5 mg/dL by Day 14 or discharge
  - TFS, analyzed using a Kaplan-Meier product limit method
- Total albumin included albumin administered up to 14 days prior to randomization, and concomitant albumin administered during study treatment

HRS, hepatorenal syndrome; SCr, serum creatinine; TFS, transplant-free survival.

HRS Reversal

Incidence of HRS reversal by Day 90 by quartiles of total albumin and treatment group; ITT population[a]



- The incidence of HRS reversal was numerically higher among patients in the terlipressin group (vs placebo) across all albumin subgroup levels
- There was no dose-response relationship between total albumin use and HRS reversal for either treatment group

[a] Based on pooled data from CONFIRM[1] and REVERSE[2].
HRS, hepatorenal syndrome; ITT, intent-to-treat.

1. Wong F et al. *N Engl J Med*. 2021;384(9):818−828; **2.** Boyer TD et al. *Gastroenterology*. 2016;150(7):1579−1589.

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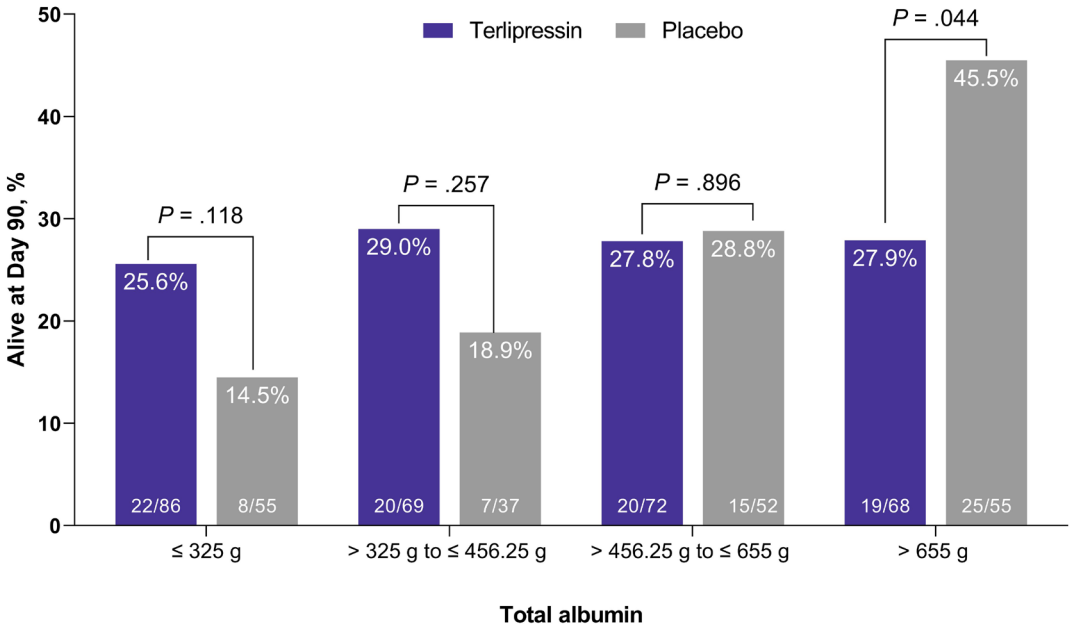
Incidence of Survival Without a Liver Transplant by Day 90

Incidence of survival by Day 90 without a liver transplant by quartiles of total albumin; ITT population[a]



- In the highest albumin quartile (ie, > 655 g), significantly more patients were alive without a transplant in the placebo group (vs terlipressin group) by Day 90
- No such differences were observed among patients in the ≤ 655 g total albumin quartiles

[a] Based on pooled data from CONFIRM[1] and REVERSE[2].
ITT, intent-to-treat.

1. Wong F et al. *N Engl J Med*. 2021;384(9):818−828; **2.** Boyer TD et al. *Gastroenterology*. 2016;150(7):1579−1589.

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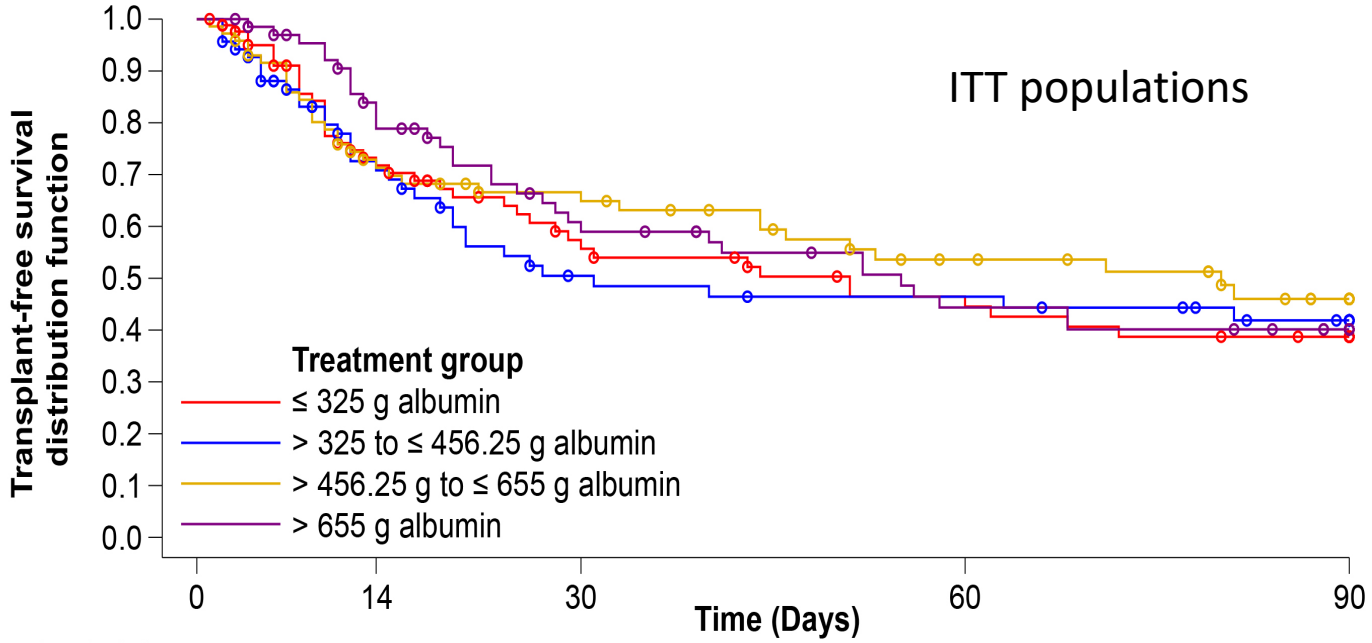
90-Day Transplant-Free Survival in Terlipressin Patients



Patients at risk					
≤ 325 g albumin	86	50	34	24	18
> 325 to ≤ 456.25 g albumin	69	41	25	22	15
> 456.25 g to ≤ 655 g albumin	72	47	39	25	14
> 655 g albumin	68	50	33	21	15

There was no clear relationship between total albumin use and TFS in the terlipressin group

ITT, intent-to-treat; TFS, transplant-free survival.

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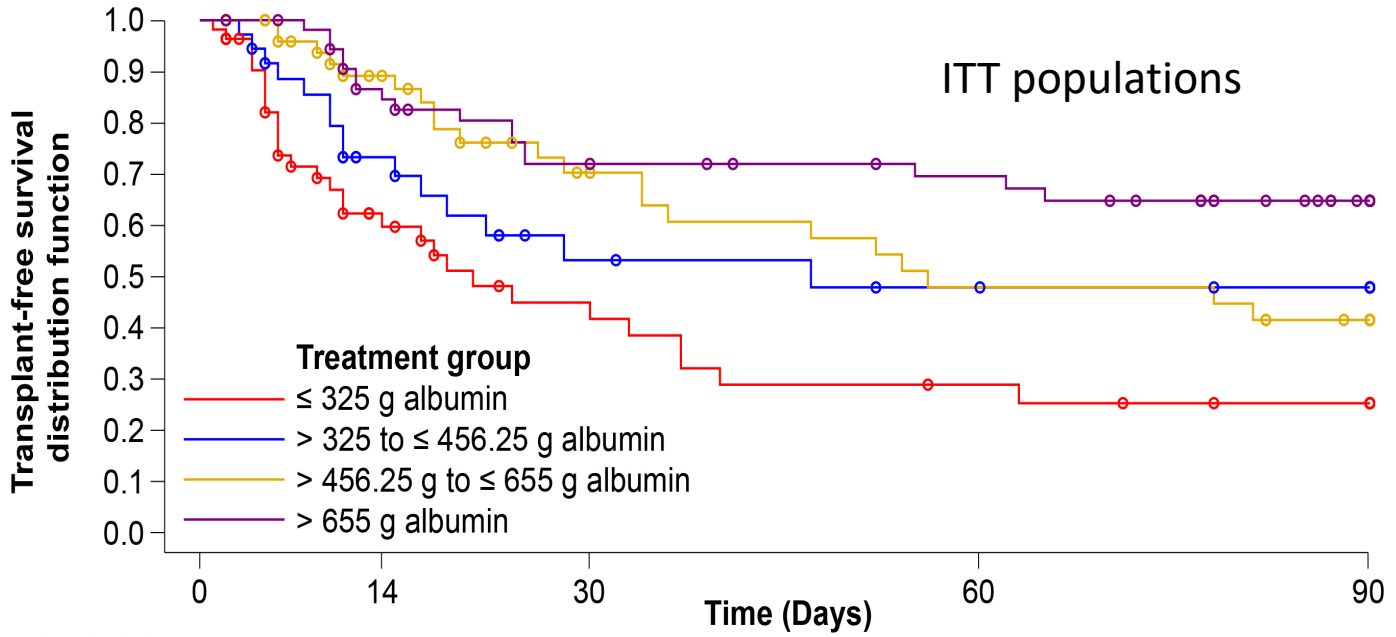
90-Day Transplant-Free Survival in Placebo Patients



Patients at risk					
≤ 325 g albumin	55	24	14	8	5
> 325 to ≤ 456.25 g albumin	37	20	11	8	6
> 456.25 g to ≤ 655 g albumin	52	36	23	15	10
> 655 g albumin	55	43	34	29	14

In the placebo group, TFS increased with increasing albumin

ITT, intent-to-treat; TFS, transplant-free survival.

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Adverse Events Leading to Death up to 30 Days

Table 1. AEs leading to death reported up to 30 days posttreatment (≥ 3%); Safety population

	CONFIRM[1]		REVERSE[2]	
	Terlipressin (n = 200)	Placebo (n = 99)	Terlipressin (n = 93)	Placebo (n = 95)
Total AEs leading to death	83 (41.5)	40 (40.4)	35 (37.6)	34 (35.8)
MODS	9 (4.5)	3 (3.0)	8 (8.6)	5 (5.3)
Chronic hepatic failure	9 (4.5)	8 (8.1)	9 (9.7)	5 (5.3)
Hepatic failure	9 (4.5)	9 (9.1)	1 (1.1)	5 (5.3)
Respiratory failure	**11 (5.5)**	**0 (0.0)**	**4 (4.3)**	**1 (1.1)**
Sepsis	**4 (2.0)**	**0 (0.0)**	**3 (3.2)**	**2 (2.1)**
Acute respiratory failure	**6 (3.0)**	**1 (1.0)**	**2 (2.2)**	**1 (1.1)**
Septic shock	**4 (2.0)**	**0 (0.0)**	**3 (3.2)**	**1 (1.1)**
Hepatorenal syndrome	2 (1.0)	3 (3.0)	4 (4.3)	2 (2.1)
Hepatic cirrhosis	6 (3.0)	1 (1.0)	0 (0.0)	1 (1.1)
Renal failure	3 (1.5)	0 (0.0)	2 (2.2)	1 (1.1)
Alcoholic cirrhosis	4 (2.0)	3 (3.0)	1 (1.1)	1 (1.1)

Data are presented as n (%).

AEs, adverse events; MODS, multiple organ dysfunction syndrome.

1. Wong F et al. *N Engl J Med*. 2021;384(9):818−828; **2.** Boyer TD et al. *Gastroenterology*. 2016;150(7):1579−1589.

- Incidence of death from respiratory failure/sepsis/septic shock in the pooled population:
  - Terlipressin: 12.6% (37/293)
  - Placebo: 3.1% (6/194)

Summary

- A lower incidence of survival in the patients who received terlipressin could be related, in part, to more frequent deaths from respiratory failure, sepsis, or septic shock
- No apparent optimal dose of albumin during terlipressin therapy could be identified

Conclusions

- The relationship between albumin use and the balance between efficacy and safety is complex
- This *"double-edged sword"* underscores the need for careful patient selection and monitoring of albumin use to avoid volume overload

Acknowledgments

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GPP 2022, Good Publication Practice 2022 Update; ICMJE, International Committee of Medical Journal Editors.

Thank you!

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