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)

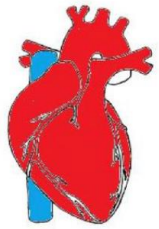
- HRS type 1 is a form of functional rapidly progressive renal failure that occurs in patients with decompensated cirrhosis with ascites[1]
- It is fatal unless timely treatment is provided
- The recommended treatment is a vasoconstrictor together with albumin
- Terlipressin is the first and only US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

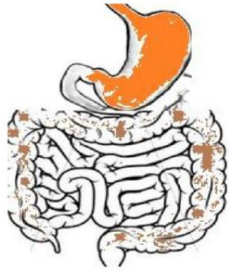
(A)



Cardiovascular circulation

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

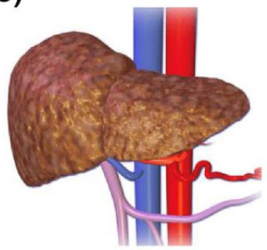
(B)



Splanchnic Circulation

- Reduction of NO levels
- Portal venous blood flow decreases

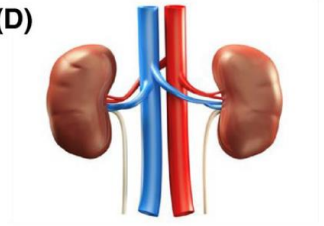
(C)



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

(Kulkarni AV, Liver International 2020)

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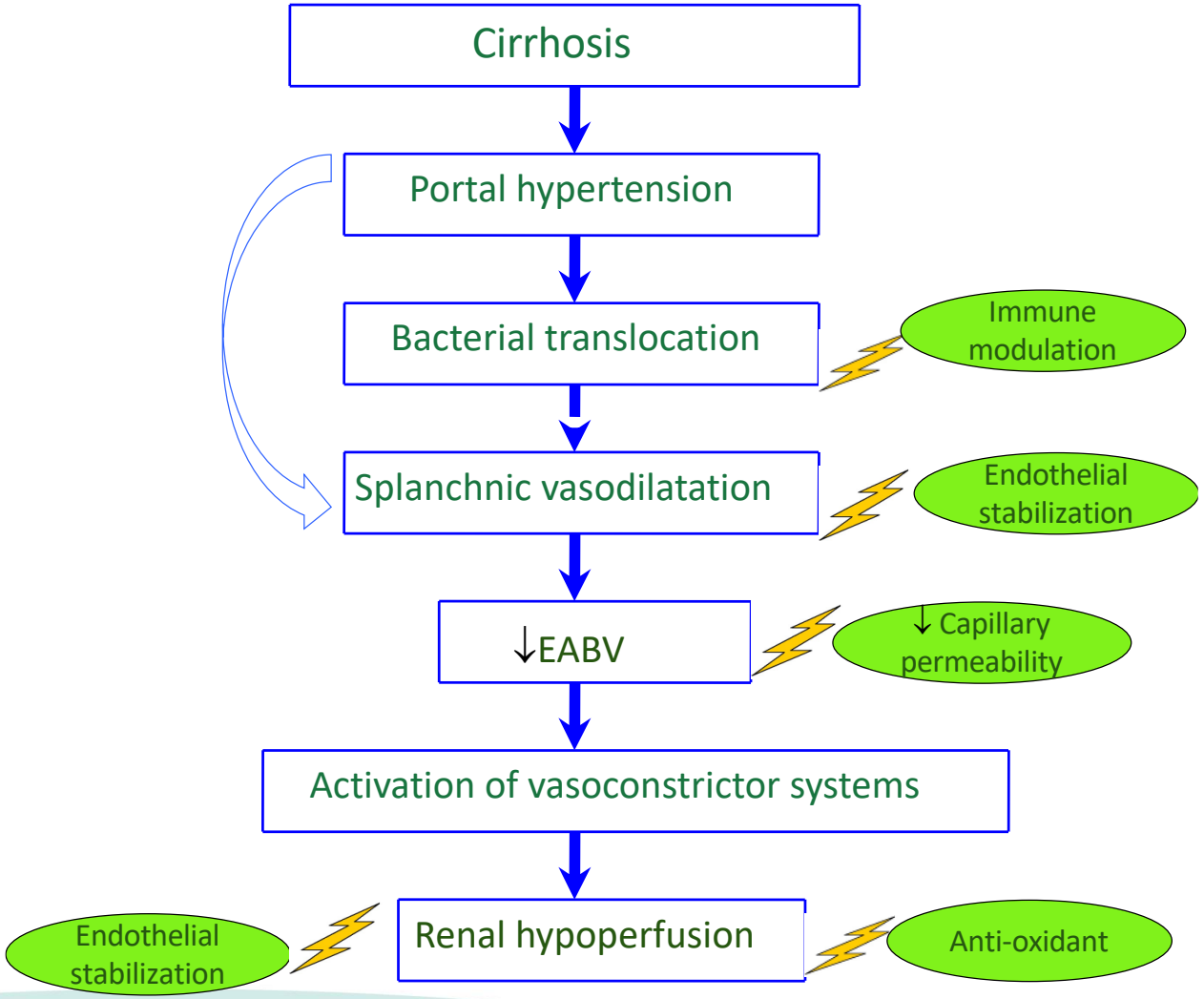
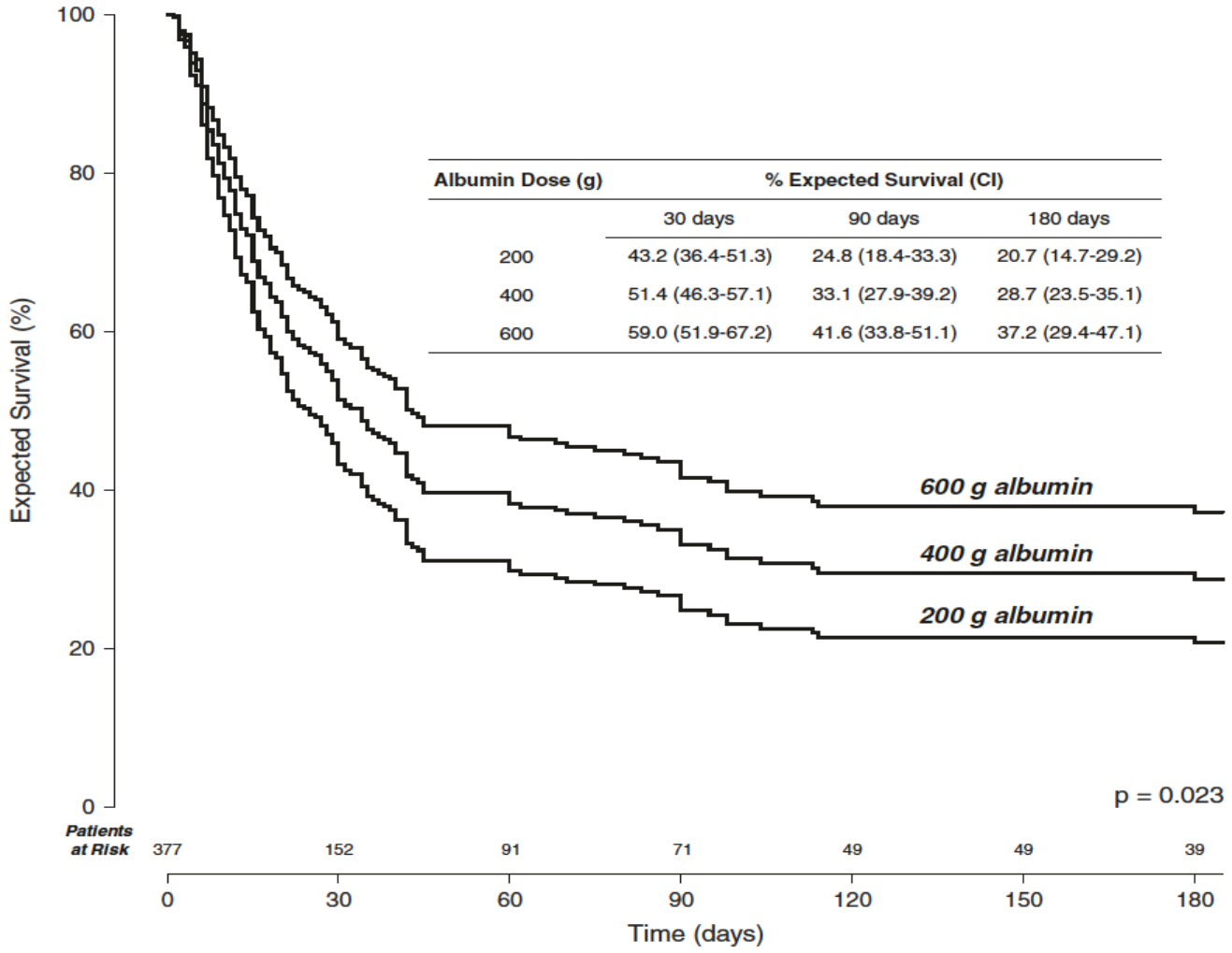
Use of Albumin in HRS



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

(Salerno F. et al, BMC Gastroenterology 2015)

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Treatment of HRS-AKI

- However, excess albumin theoretically may increase the risk for respiratory failure which was observed in 8% 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

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 efficiency and safety, based on the pooled analysis of the 2 largest randomized controlled trials of terlipressin plus albumin versus placebo in patients with HRS type 1

HRS-AKI, hepatorenal syndrome-acute kidney injury.

Methods (1)

- Data were pooled from 2 Phase III randomized, placebo-controlled studies in patients with cirrhosis, ascites & HRS1:
  - CONFIRM[1] (NCT02770716; n = 300)
  - REVERSE[2] (NCT01143246; n = 196)
- Patients were divided into albumin dose quartiles and compared

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)

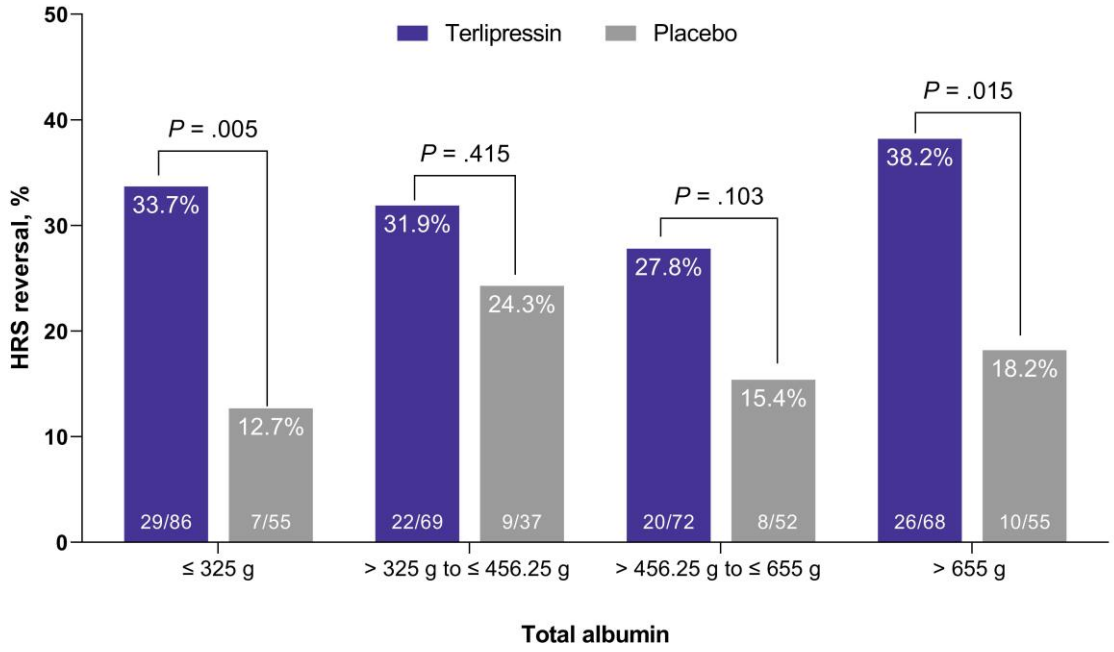
- The following clinical outcomes were assessed by total albumin quartiles:
  - Incidence of HRS reversal, defined as SCr ≤ 1.5 mg/dL by Day 14 or discharge
  - Transplant-free survival (TFS), analyzed using a Kaplan-Meier product limit method
- Total albumin included albumin administered up to 14 days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

Results

	Terlipressin					Placebo				
Albumin dose	≤325g	>325 – 456.25g	>456.25-655g	>655g	P value	≤325g	>325 – 456.25g	>456.25-655g	>655g	P value
n	86	69	72	68		55	37	52	55	
Age	55.3±10.0	55.2±11.9	53.7±10.7	53.8±9.4	0.388	54.4±10.0	56.7±10.4	51.8±11.0	54.8±9.7	0.294
M (%)	47 (57%)	34 (49%)	43 (60%)	46 (68%)	0.182	32 (58%)	21 (57%)	34 (65%)	38 (69%)	0.555
Na	132 ±5.7	132±6.8	133±5.4	134±5.9	0.596	132±5.1	132±5.8	133±6.2	134±5.7	0.402
Creatinine	3.4±0.97	3.5±1.05	3.6±1.03	3.6±1.06	0.403	3.6±1.12	3.7±1.03	3.6±1.17	3.6±1.03	0.834
INR	2.2±0.74	2.2±0.76	2.4±0.85	2.2±0.90	0.506	2.2±0.71	2.3±1.10	2.7±3.41	2.2±0.73	0.883
Bilirubin	12.3±12.2	13.6±13.3	13.2±13.1	10.4±11.7	0.285	13.6±13.1	15.7±19.3	14.1±13.9	11.3±11.9	0.917
Albumin	3.4±0.73	3.5±0.63	3.8±0.69	4.0±0.71	**<0.001**	3.3±0.63	3.6±0.61	3.7±0.78	4.4±3.4	**<0.001**
MELD-Na	32.9±6.4	33.4±5.8	33.5±6.5	31.8±7.3	0.578	32.9±5.4	32.8±6.8	33.0±6.1	32.7±5.5	0.973

HRS reversal

Figure 1. 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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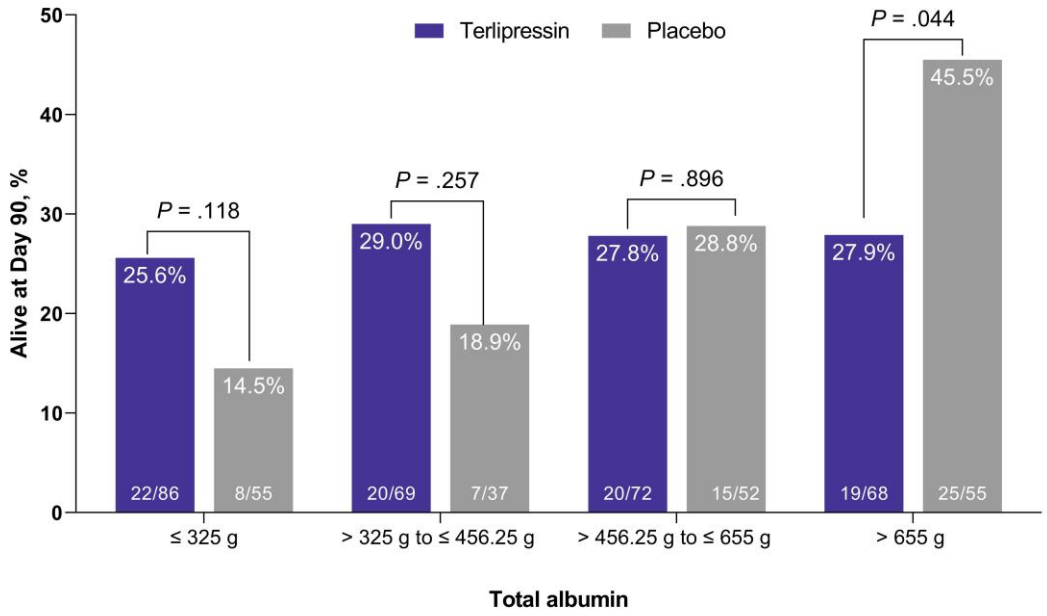
Incidence of survival without a liver transplant by Day 90

Figure 5. 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 the terlipressin patients between the albumin quartiles

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

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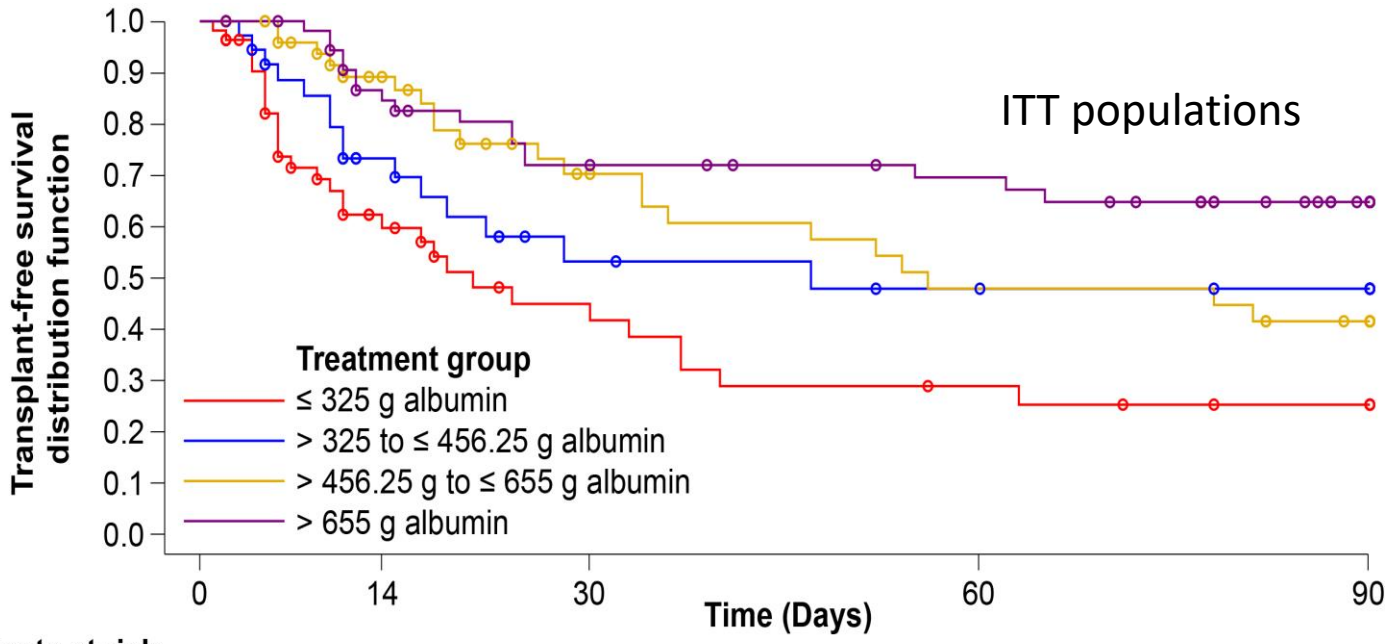
90-Day Transplant-free survival in Placebo patients



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, transplant free survival increased with increasing albumin

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

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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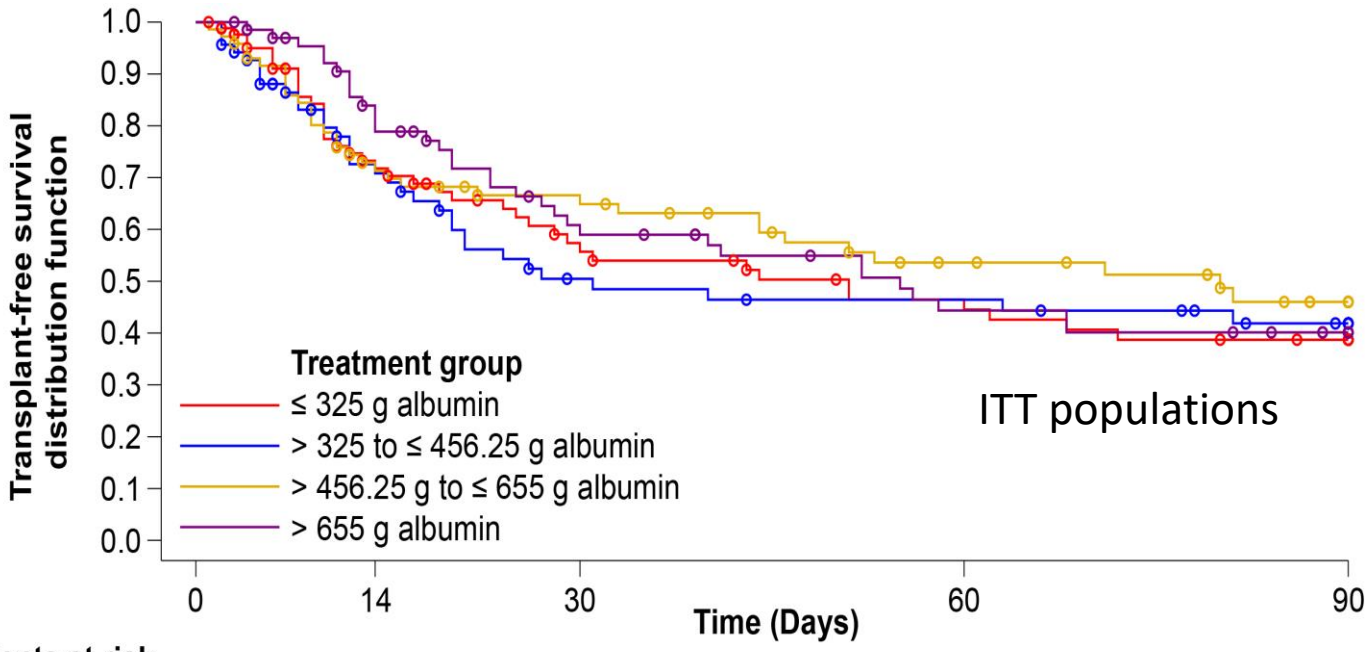
90-Day Transplant-free survival in Terlipressin patients



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

[a] Based on pooled data from CONFIRM [1] and REVERSE[2].
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 AE 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)

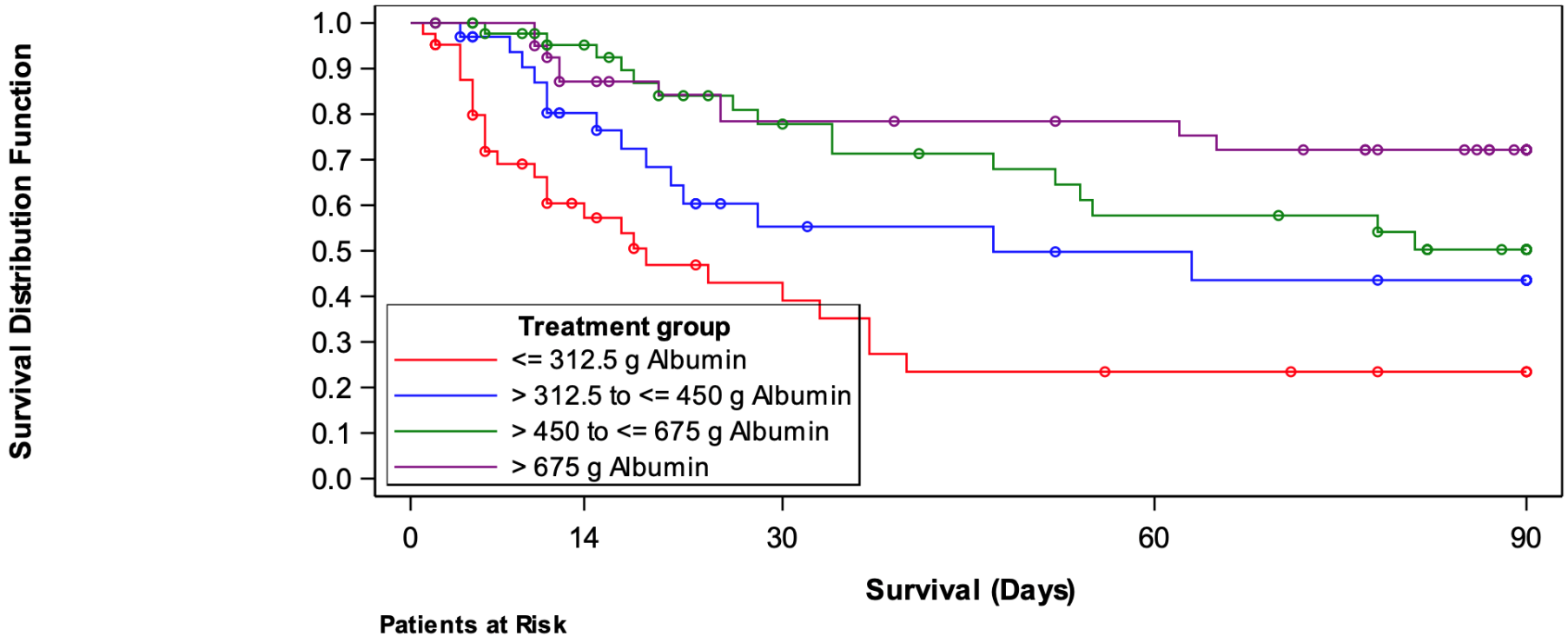
Data are presented as n (%).

AE, 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.

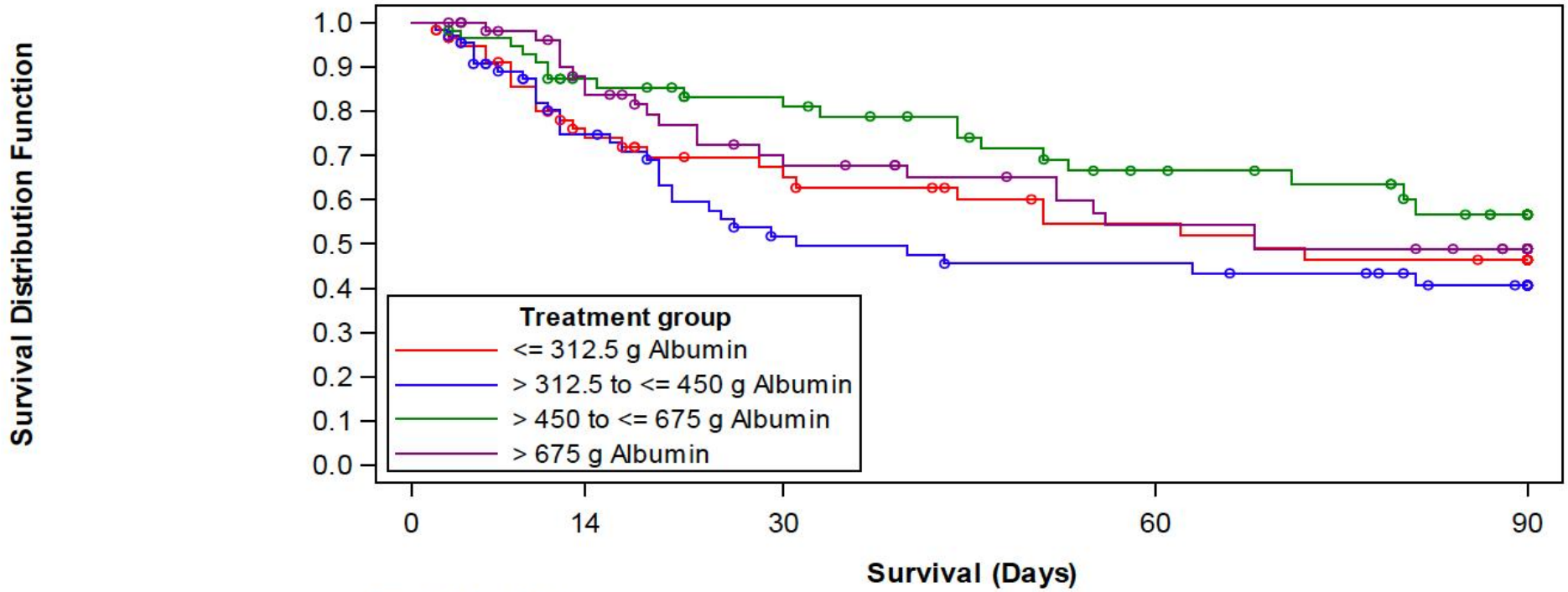
- Incidence of death from respiratory failure/sepsis/septic shock in the pooled population:
  - Terlipressin: 12.6% (37/293)
  - Placebo: 3.0% (6/194)

90-Day Transplant-free survival Without ACLF3- Placebo Patients



Patients at Risk					
<= 312.5 g Albumin	42	19	11	5	3
> 312.5 to <= 450 g Albumin	33	21	11	8	6
> 450 to <= 675 g Albumin	46	36	25	17	9
> 675 g Albumin	41	32	27	25	14

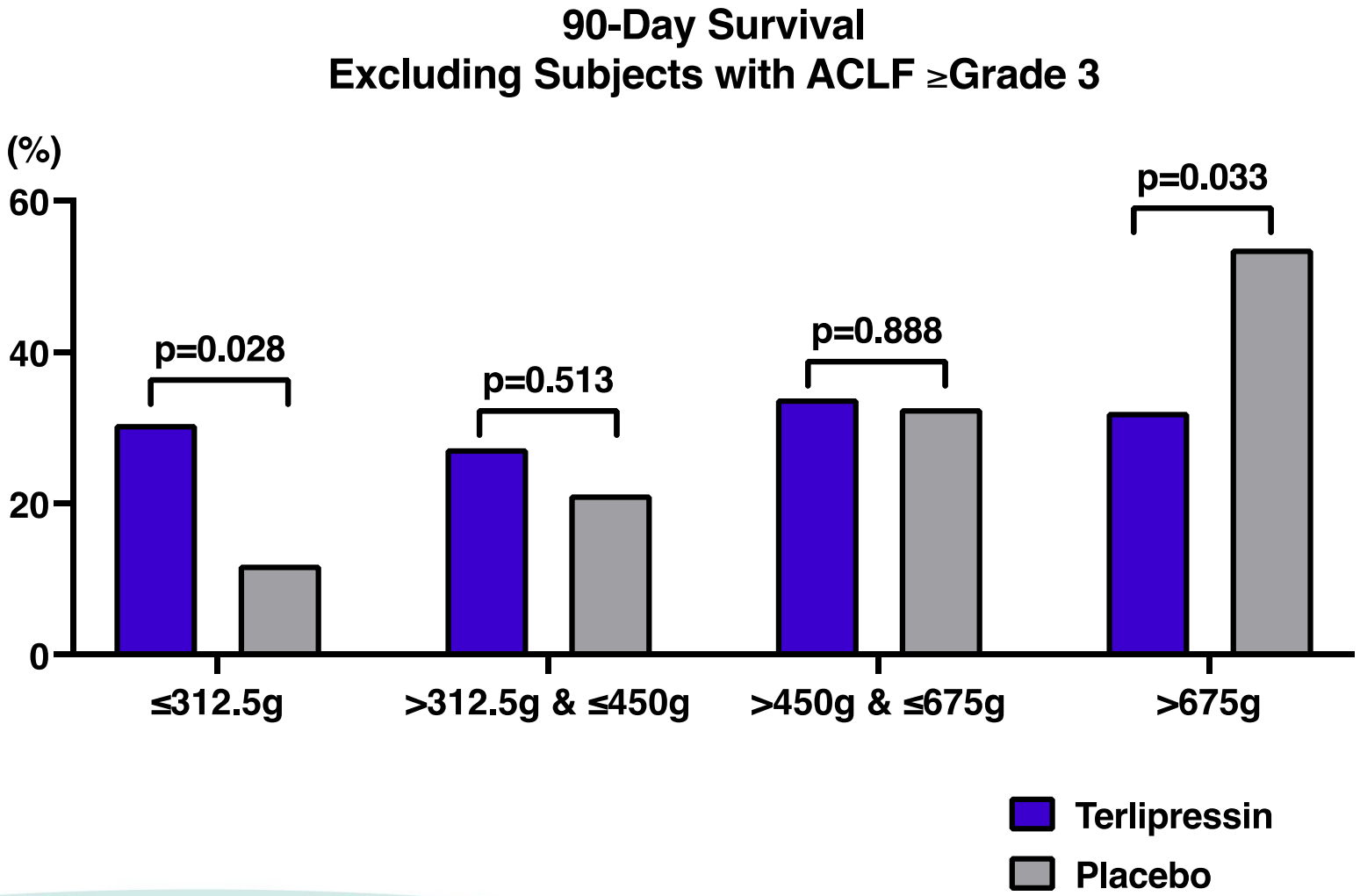
90-Day Transplant-free survival Without ACLF3- Terlipressin Patients



Patients at Risk

<= 312.5 g Albumin	59	37	29	20	16
> 312.5 to <= 450 g Albumin	66	41	25	21	13
> 450 to <= 675 g Albumin	56	44	38	24	13
> 675 g Albumin	56	42	30	20	14

90-Day Transplant-free Survival without ACLF3



Summary

- Although albumin has many beneficial effects, it is not "the more the merrier"
- When excluding patients with ACLF ≥grade 3, the use of lower doses of albumin with terlipressin provides a survival advantage over placebo
- Higher doses of albumin are not necessarily useful with terlipressin use.

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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

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Acknowledgement

- The authors would like to acknowledge the funding by Mallinckrodt Pharmaceuticals for this study

Thank you!

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