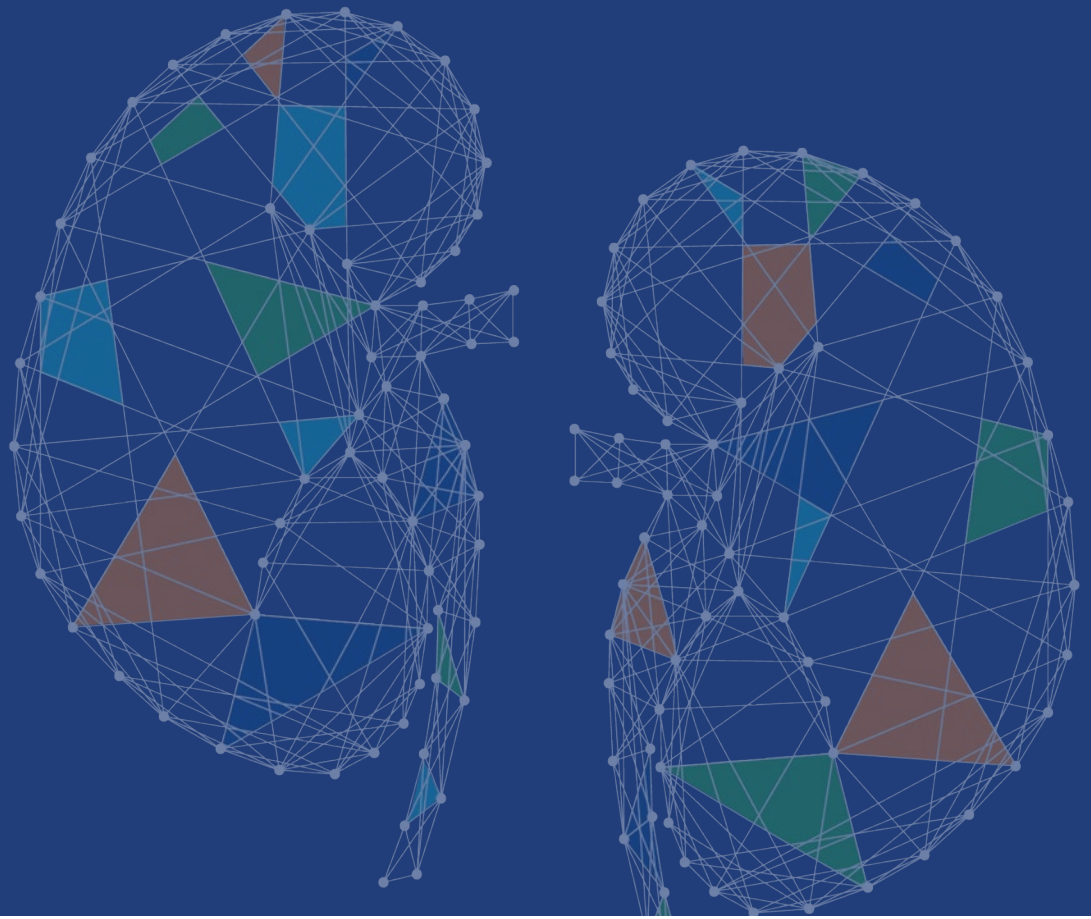
Terlipressin Improves Renal Replacement Therapy–Free Survival in Hepatorenal Syndrome Type 1



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Disclosure

- **Presenter: Juan Carlos Q. Velez**
- Juan Carlos Q. Velez: Consulting (Retrophin), Scientific Advisor or Membership (Mallinckrodt Pharmaceuticals), Speakers Bureau (Otsuka Pharmaceuticals)
- This study was funded by Mallinckrodt Pharmaceuticals. Medical writing and editorial support was provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Mallinckrodt Pharmaceuticals
- We thank the research staff, patients, and families who participated in the phase 3 studies of terlipressin

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Hepatorenal Syndrome Type 1

- Hepatorenal syndrome type 1 (HRS-1) is a severe, potentially reversible form of acute kidney injury in patients with advanced cirrhosis[1,2]
- Preexisting renal dysfunction and the need for renal replacement therapy (RRT), before and after liver transplantation, is associated with negative outcomes, including increased healthcare costs and decreased survival[3-6]
- Left untreated, HRS-1 has an 80% mortality rate within 3 months and a median survival time of 2–4 weeks[7]
- Currently, there are no approved pharmacologic treatments available in North America for treatment of HRS-1

1. Velez JCQ, et al. *Nat Rev Nephrol*. 2020;16:137-155. 2. Salerno F, et al. *Gut*. 207;56:1310-1318. 3. Weber ML, et al. *Liver Transpl*. 2012;18:1290-1301. 4. Zand MS, et al. *Clin Transpl*. 2011;25:213-221. 5. Nair S, et al. *Hepatology*. 2002;35:1179-1185. 6. Weismuller TJ, et al. *Scand J Gastroenterol*. 2008;43:736-746. 7. Boyer TD, et al. *Gastroenterology*. 2016;150:1579-1589.

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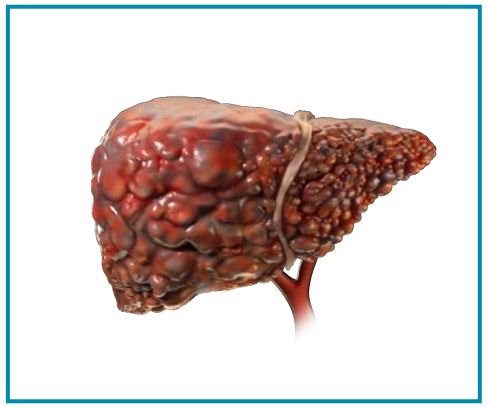
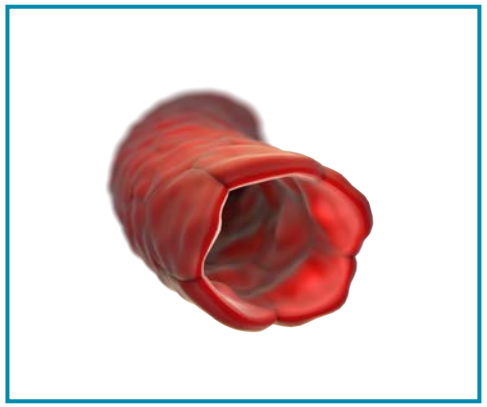
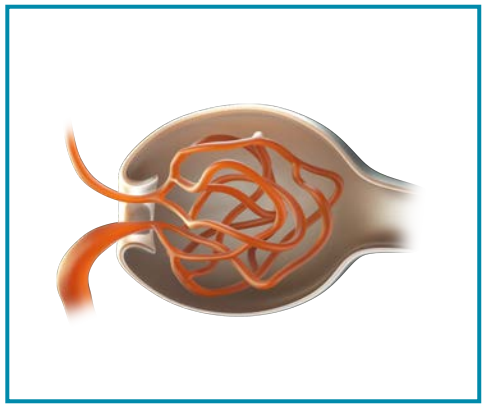
Pathogenesis of HRS-1



Advanced cirrhosis[1]



Arterial hypotension and very low systemic vascular resistance[1]



Renal vasoconstriction[2,3]

Decline in GFR[1,3]

Progression to HRS-1[1]

GFR, glomerular filtration rate; HRS-1, hepatorenal syndrome type 1.

1. Wong F. *Nat Rev Gastroenterol Hepatol.* 2012;9:382-391. 2. Sanyal AJ, et al. *Gastroenterology.* 2008;134:1360-1368. 3. Velez JCQ, et al. *Nat Rev Nephrol.* 2020;16:137–155.

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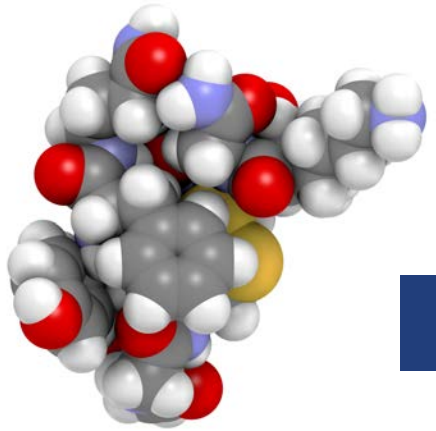
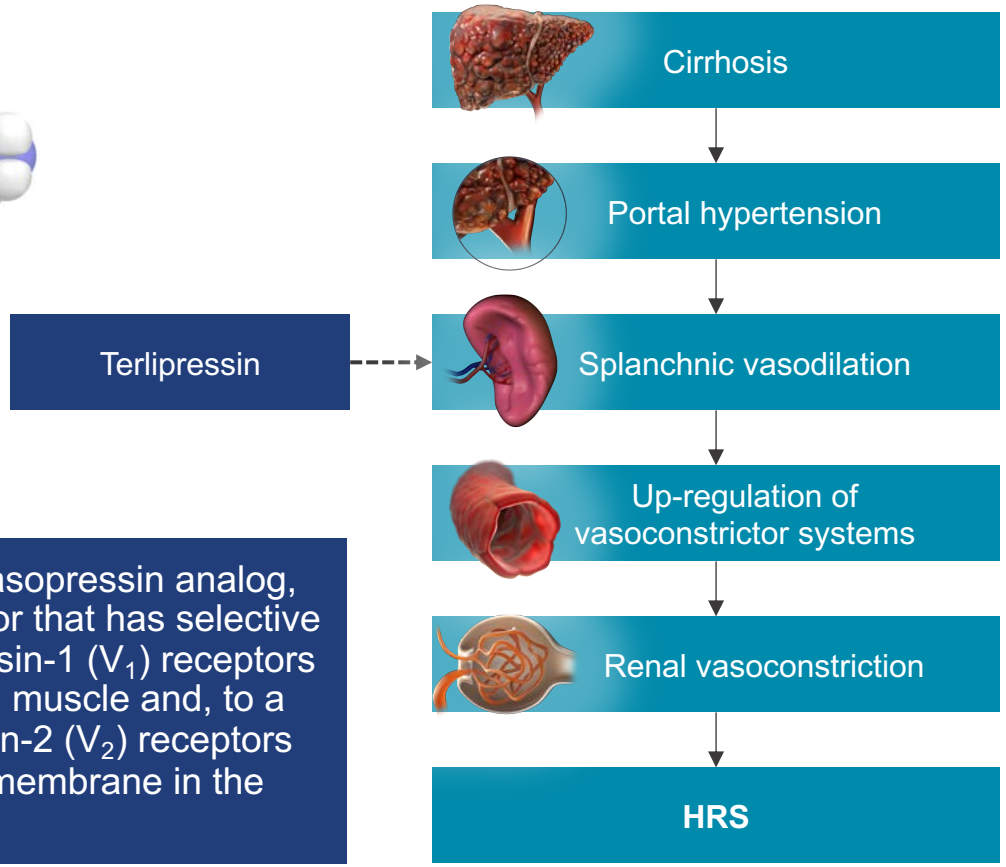
Terlipressin in HRS-1





Terlipressin, a synthetic vasopressin analog, is a systemic vasoconstrictor that has selective agonist activity at vasopressin-1 (V_1) receptors located on vascular smooth muscle and, to a lesser extent, at vasopressin-2 (V_2) receptors located on the basolateral membrane in the kidney[1]

Vasoconstrictors such as terlipressin counteract the extreme vasodilation in splanchnic arteries that occurs due to portal hypertension in patients with HRS-1

Treatment-related improvement in circulatory function leads to suppression of endogenous vasoconstrictor systems and improvement in renal blood flow[2]

1. Jamil K, et al. *J Exp Pharmacol.* 2018;10:1-7. 2. Gines P, et al. *Lancet.* 2003;362:1819-1827.

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Terlipressin in HRS-1 (cont'd)

- Three randomized, placebo-controlled phase 3 studies have demonstrated the efficacy of terlipressin for improving renal function in patients with HRS-1[1–3]
- The objectives of the current post hoc analyses were to assess the incidences of renal replacement therapy (RRT) among survivors in the CONFIRM study (NCT02770716) and to examine pooled data from the 3 phase 3 studies of terlipressin (OT-0401 [NCT00089570], REVERSE [NCT01143246], and CONFIRM) to assess 90-day RRT-free survival rates

1. Sanyal AJ, et al. *Gastroenterology.* 2008;134:1360-1368. 2. Boyer TD, et al. *Gastroenterology.* 2016;150:1579-1589. 3. Wong F, et al. Abstract presented at: AASLD, November 8–12, 2019, Boston, MA.

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Overview of Terlipressin Phase 3 Study Designs

	OT-0401[1] (NCT00089570)	REVERSE[2] (NCT01143246)	CONFIRM[3] (NCT02770716)
Design	All Phase 3, randomized, double-blind, placebo-controlled, multicenter trials		
Randomization rate	1:1	1:1	2:1
No. of subjects/sites	112/35	196/52	300/60
Treatment	Albumin and terlipressin 4–8 mg/day (IV q6h) or placebo		

HRS-1, hepatorenal syndrome type 1; IV, intravenous; LVP, large-volume paracentesis; q6h, every 6 hours; SCr, serum creatinine.

1. Sanyal AJ, et al. *Gastroenterology*. 2008;134:1360-1368. 2. Boyer TD, et al. *Gastroenterology.* 2016;150:1579-1589. 3. Wong F, et al. Abstract presented at: AASLD, November 8–12, 2019, Boston, MA.

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Primary Efficacy Endpoint in CONFIRM and 3 Pooled Randomized Controlled Trials of Terlipressin

	CONFIRM[1, 2]	Pooled Data From OT-0401, REVERSE, CONFIRM[3,4]
Primary efficacy endpoint	Verified HRS reversal (multi-component endpoint)* • Two consecutive SCr ≤1.5 mg/dL at least 2 hours apart while on treatment by Day 14 or discharge • Without RRT at Day 10 after verified HRS reversal • Alive at Day 10 after verified HRS reversal	HRS reversal • Percentage of all patients with SCr ≤1.5 mg/dL while on treatment up to 24 hours after the final dose of study drug, by Day 14, or discharge
Additional efficacy endpoint	• **Percentage of patients with RRT through Day 90**	

*Patients had to meet all criteria in order to meet the primary efficacy endpoint.

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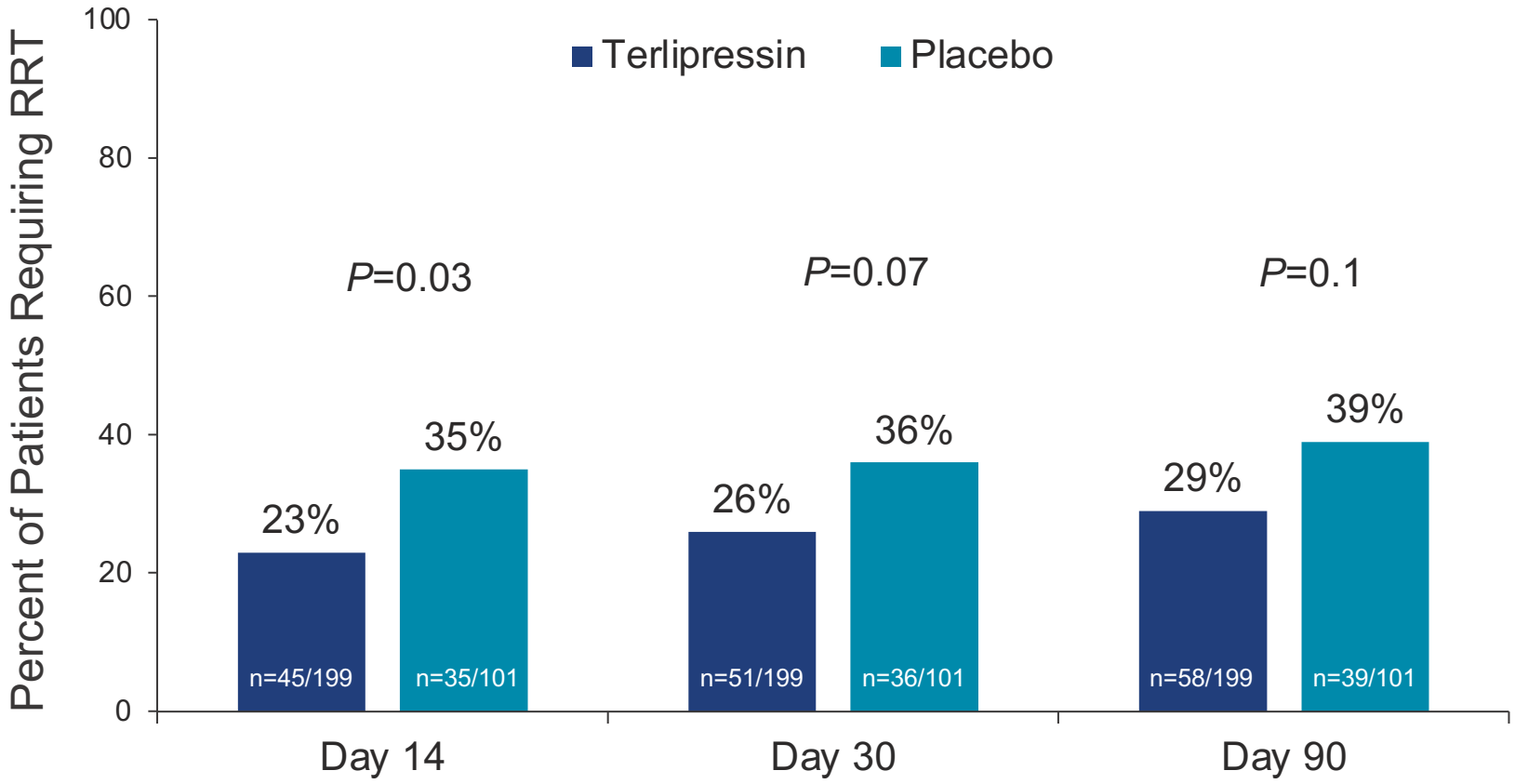
HRS, hepatorenal syndrome; RRT, renal replacement therapy; SCr, serum creatinine.

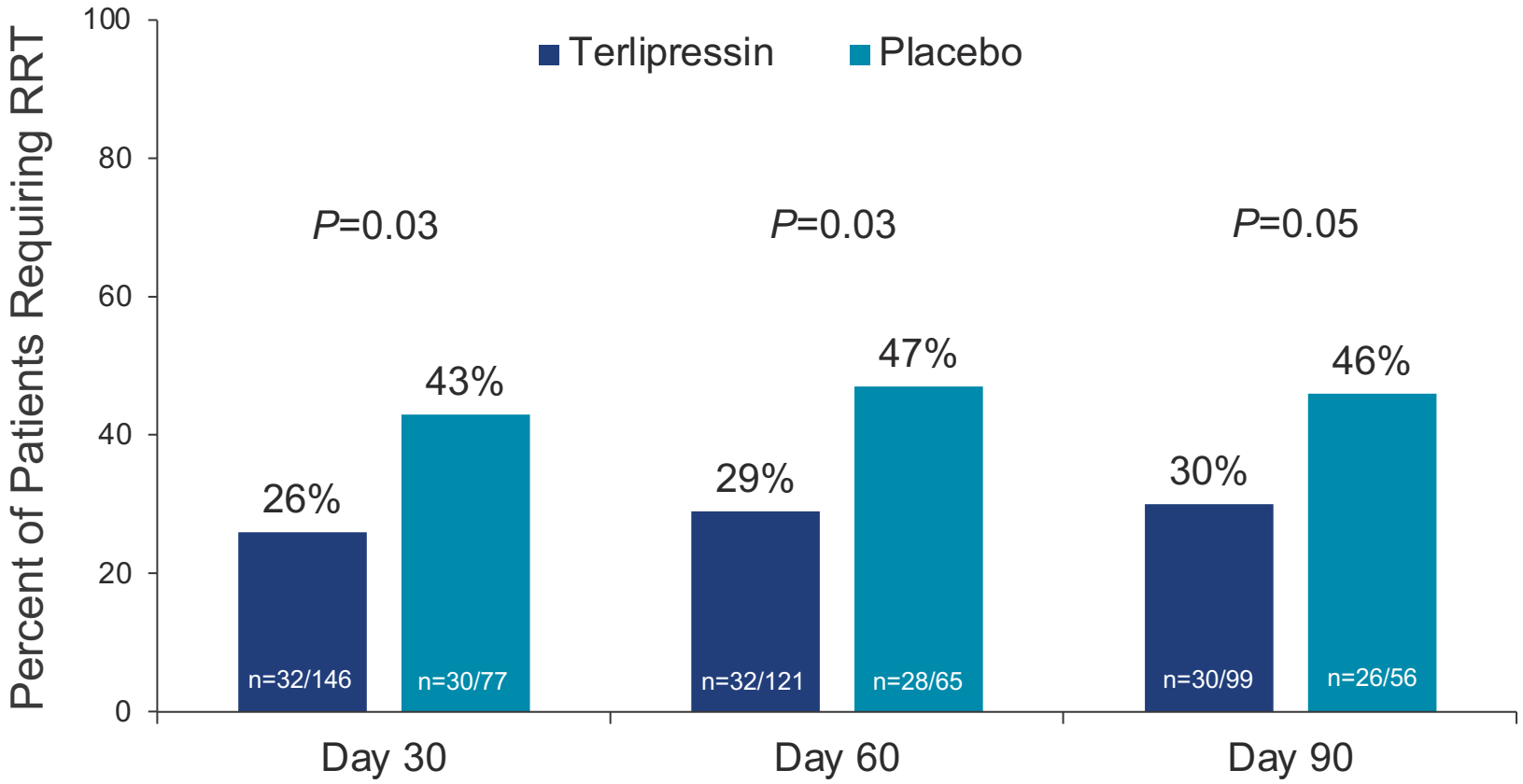
1. Wong F, et al. Abstract presented at: AASLD, November 8–12, 2019, Boston, MA. 2. Jamil K, et al. *J Clin Trials.* 2019;11:67-73. 3. Sanyal AJ, et al. *Gastroenterology.* 2008;134:1360-1368.
4. Boyer TD, et al. *Gastroenterology.* 2016;150:1579-1589.

Cumulative Incidence of Need for RRT in CONFIRM



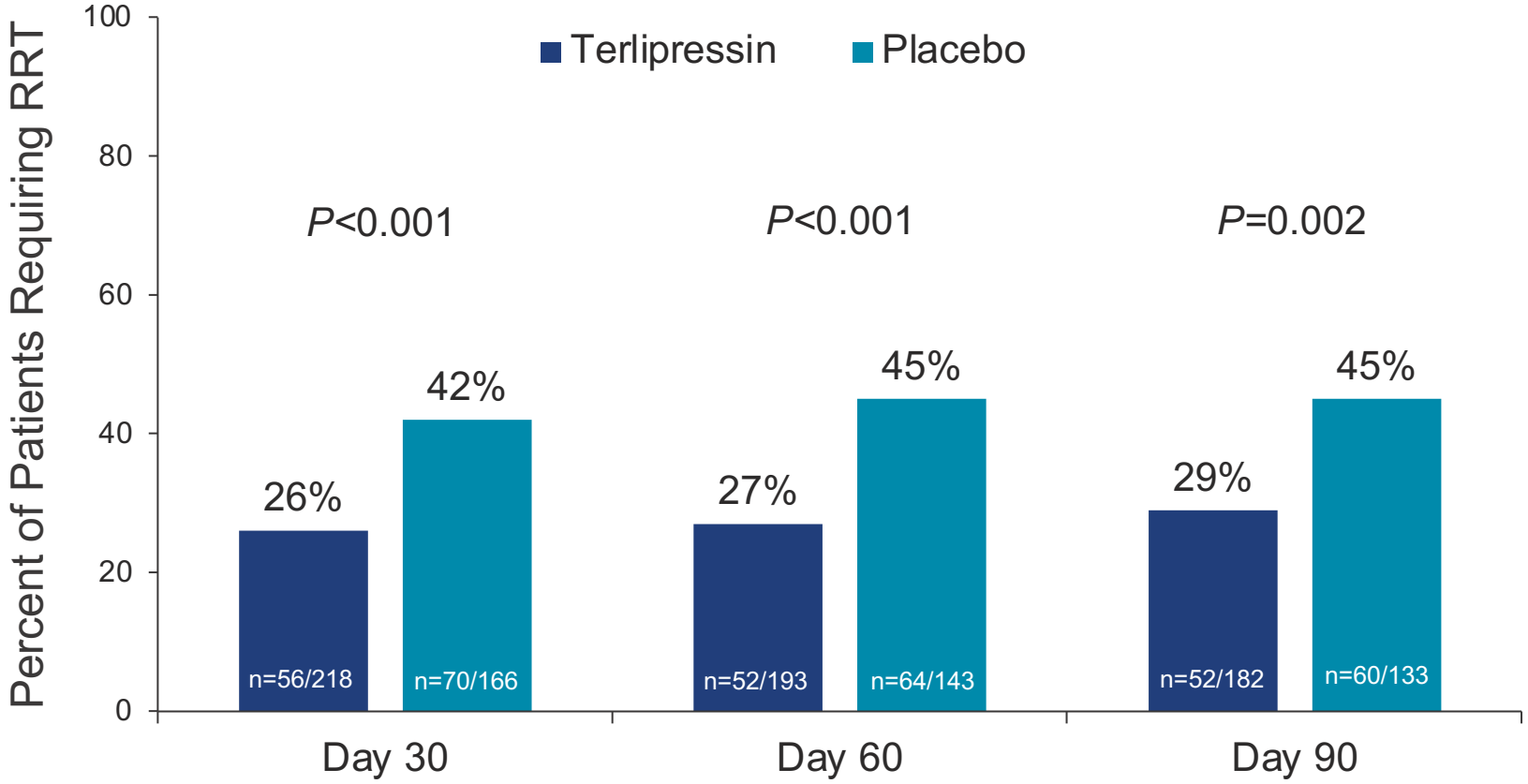
RRT, renal replacement therapy.

Need for RRT Through Day 90 Among Survivors in CONFIRM



RRT, renal replacement therapy.

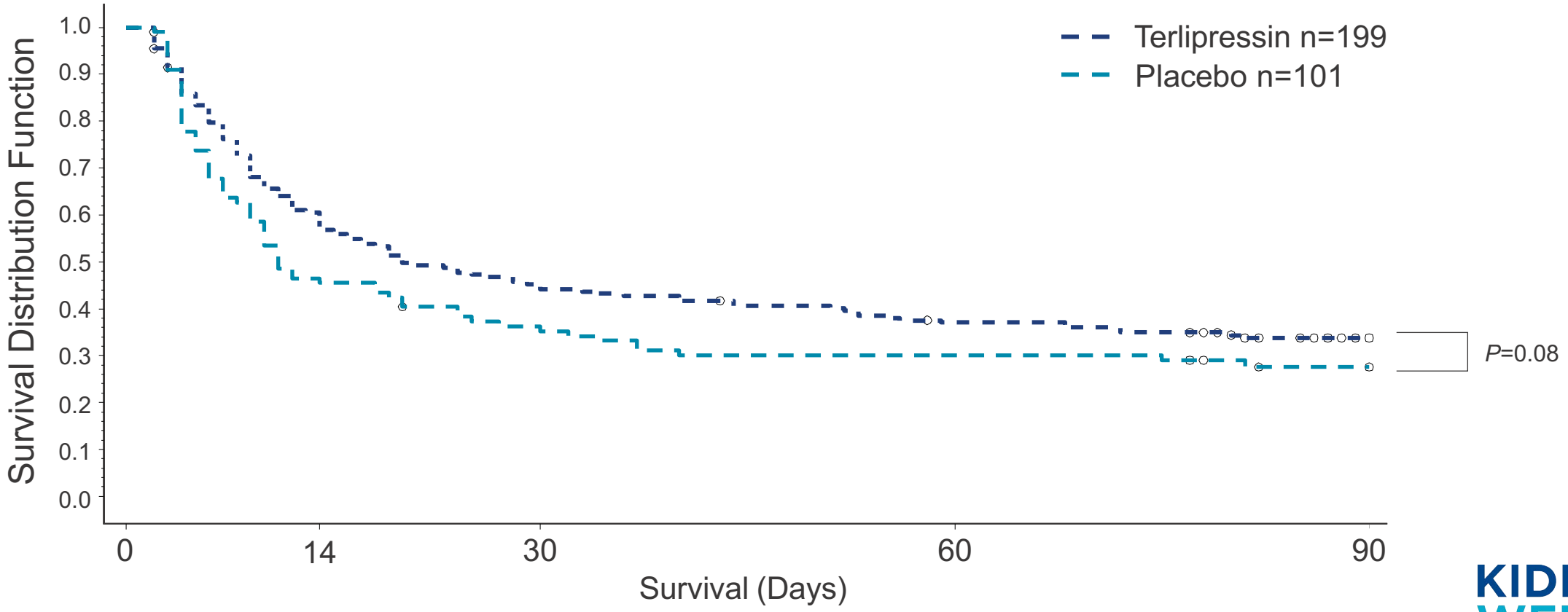
Need for RRT Through Day 90 Among Survivors in 3 Pooled Randomized Controlled Trials of Terlipressin



RRT, renal replacement therapy.

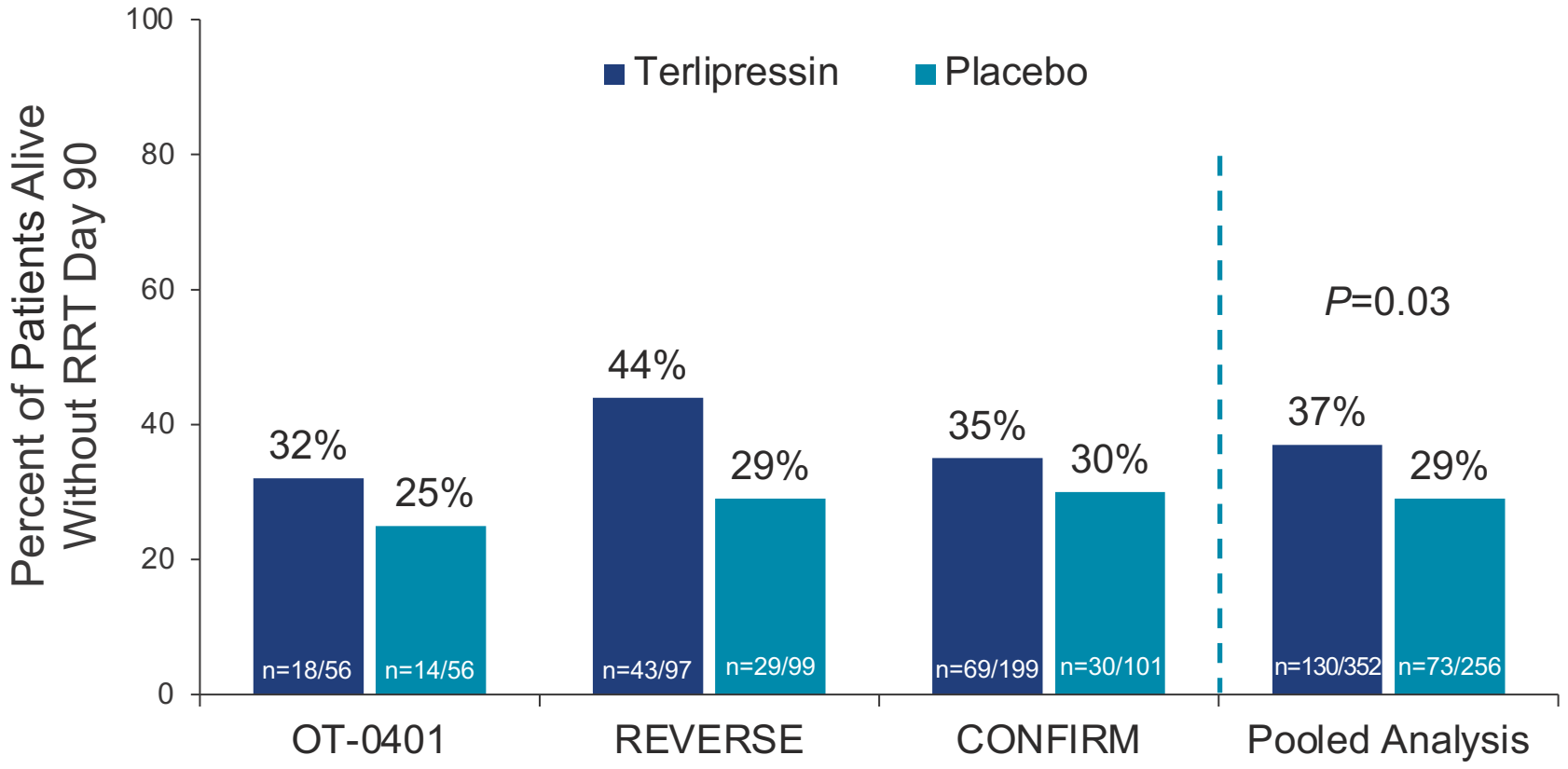
RRT-Free 90-Day Survival in CONFIRM

- Median survival was 20.0 days in the terlipressin group versus 11.0 in the placebo group



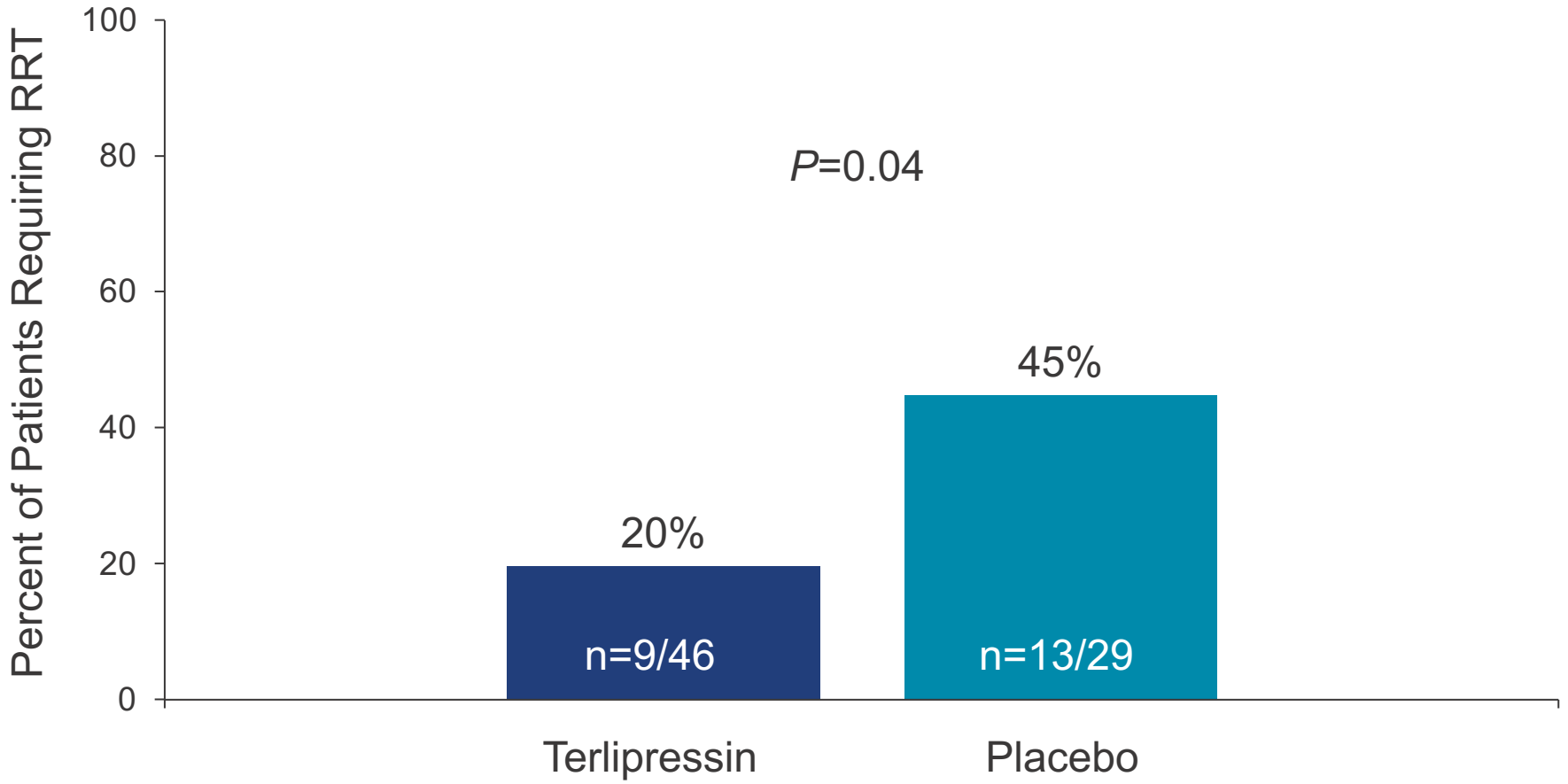
RRT, renal replacement therapy.

RRT-Free 90-Day Survival in CONFIRM, OT-0401, REVERSE, and Pooled Analysis



RRT, renal replacement therapy.

Patients Requiring RRT Following Liver Transplant in CONFIRM



RRT, renal replacement therapy.

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Conclusions

- These post hoc analyses showed treatment with terlipressin added to albumin decreased the rate of RRT and improved RRT-free survival in patients with HRS-1
- Terlipressin is the first pharmacologic intervention proven to reduce the need for RRT in patients with HRS-1
- Because of the significant impact of RRT on quality of life, this observation expands the clinical benefit of terlipressin plus albumin and enhances the reported efficacy of terlipressin in inducing HRS-1 reversal

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HRS-1, hepatorenal syndrome type 1; RRT, renal replacement therapy.