Updates in Kidney Dysfunction Among Cirrhosis Patients

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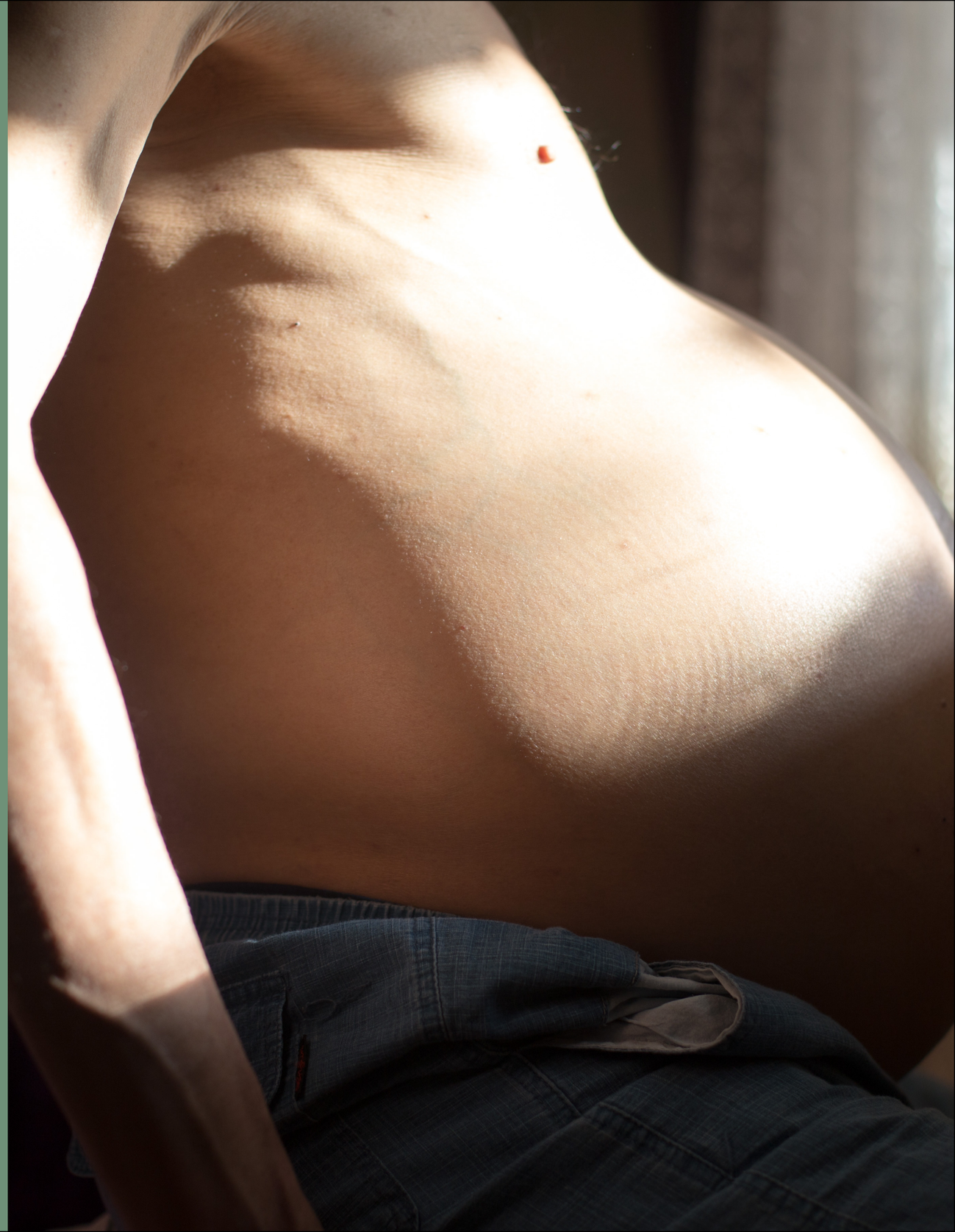
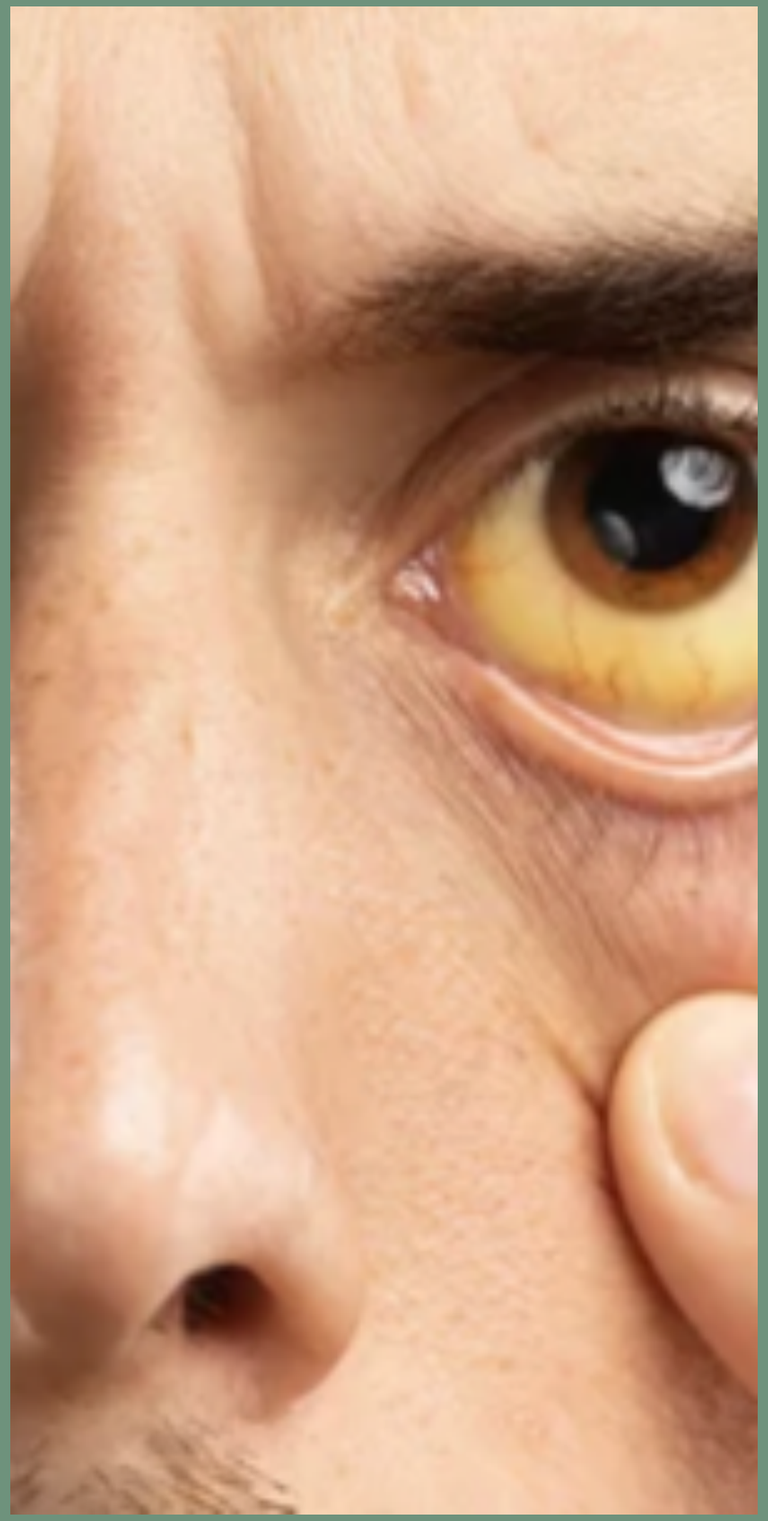
A hospitalized patient with cirrhosis and kidney dysfunction:



This Patient:

- HCV, 50 Years Old
- Previous Hypertension, DM
- Baseline Creatinine (7-90 days before) 0.7 mg/dl
- Admission Labs: sCr 2.0 mg/dL, TB 8 mg/dL, INR 2.0, MELDNA 29, UNa<20, no RBCs, no proteinuria



To Be Reviewed:

How do we define AKI? HRS-AKI?

What could have predicted AKI? HRS-AKI?

How do we define AKI Reversal?

What are the predictors of AKI Reversal?

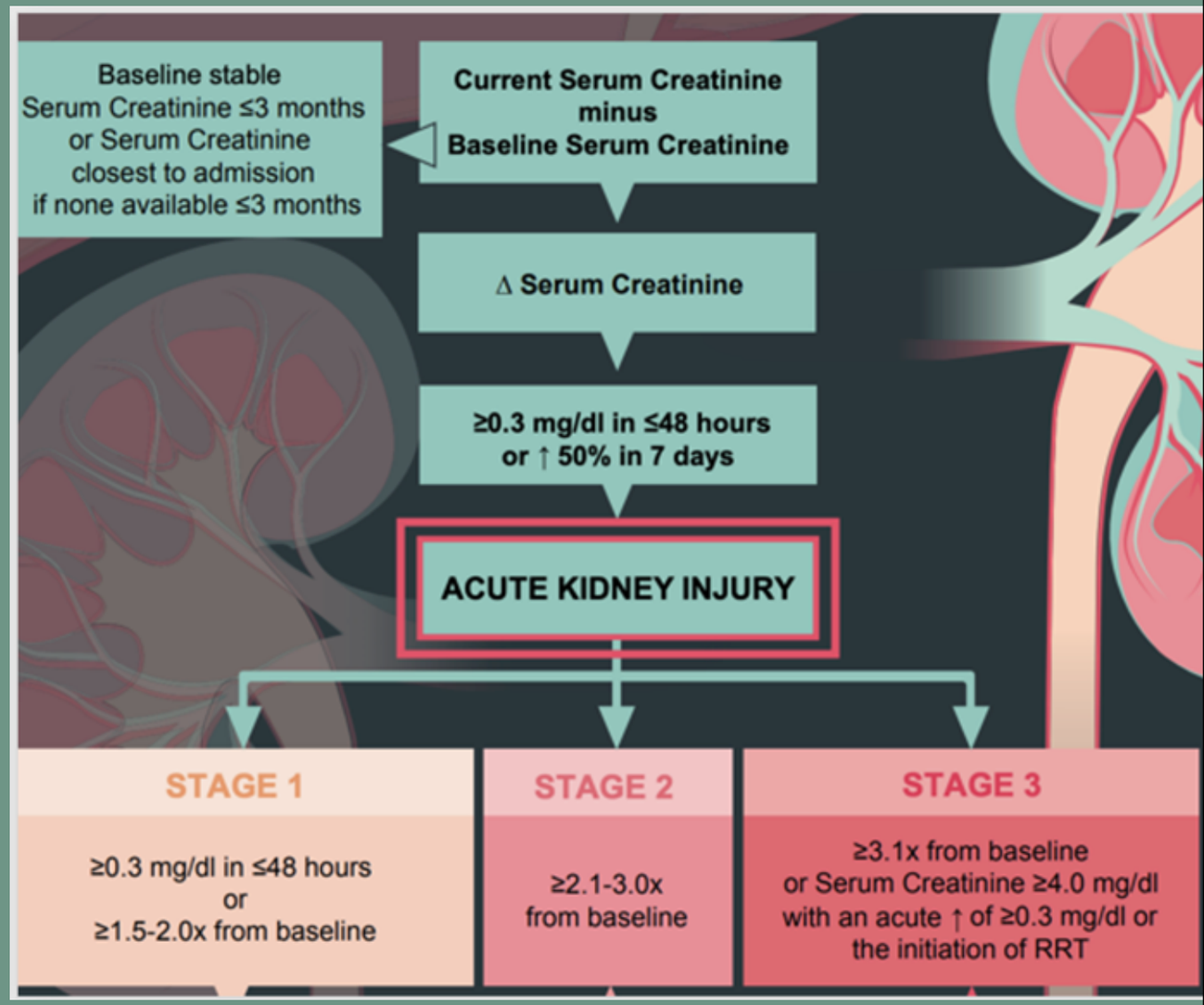
What are the treatments for AKI? HRS-AKI?

What are the implications of an episode of AKI? HRS-AKI

How do we define AKI?

HRS-AKI?

Stages of AKI:



HRS-AKI

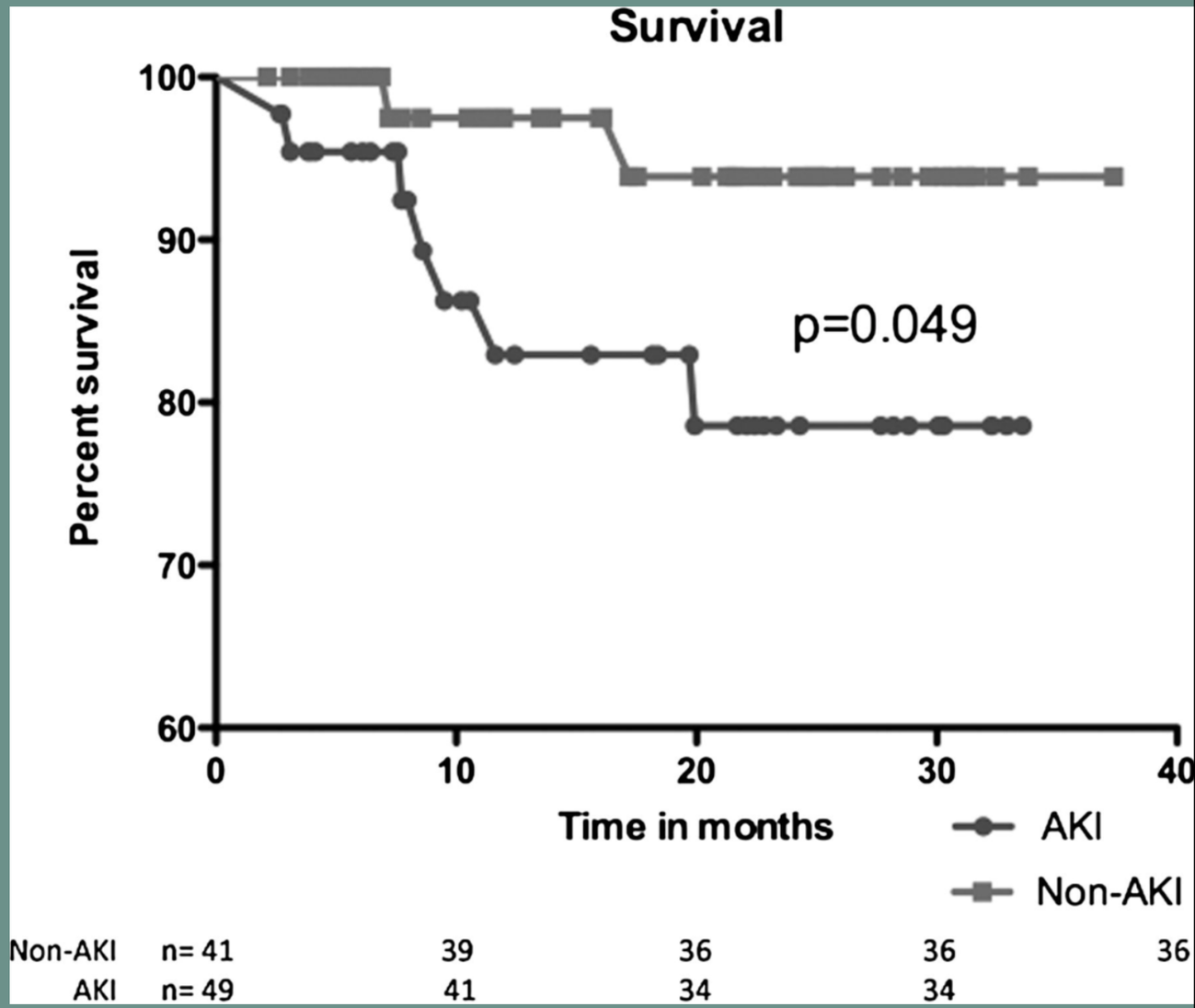
AKI in the setting of:

portal hypertension

bland urine

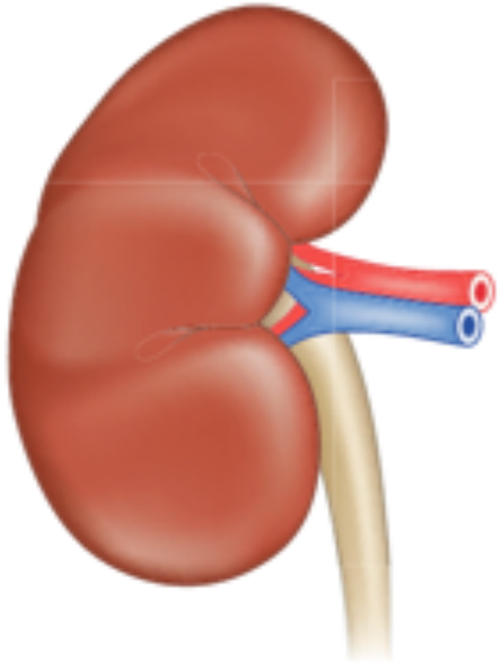
no response to volume expansion

Is a cut-off of 0.3 mg/dL too low?



Prerenal
- Laxatives for HE
- Diuretics for ascites
- Decreased PO intake
- HCRS-1

Renal vein congestion
- ACS
- PoPHTN, CCM



HRS-1

Acute glomerulonephritis
- HCV-MPGN, HBV-GN
- IgAN

Interstitial nephritis
- FQ for SBP
- PCN, PPI

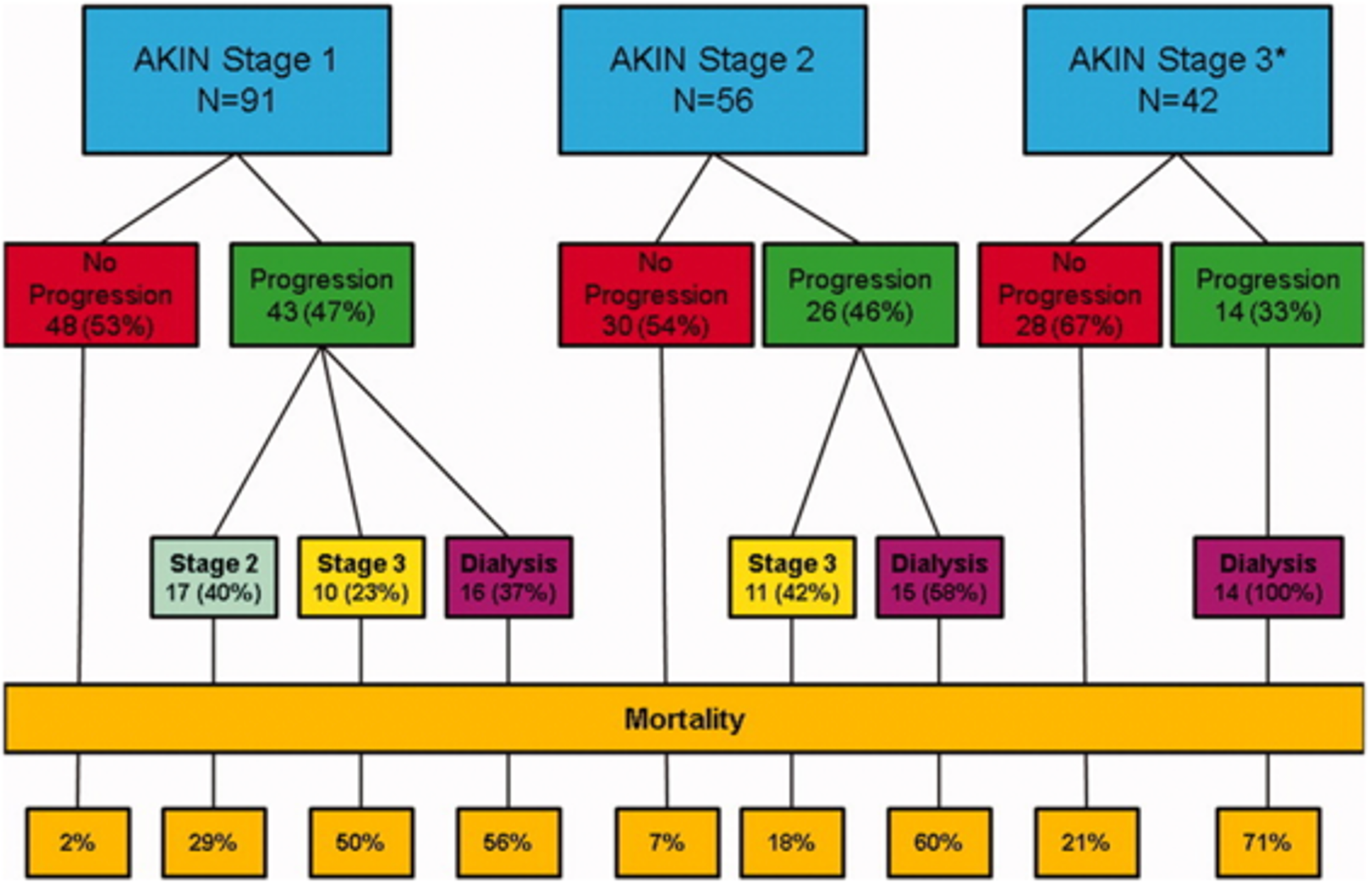
Toxic ATI
- Cholemic
- FQ for SBP
- Vancomycin

Ischemic ATI
- Prolonged prerenal
- Hemorrhagic shock (GIB)
- Septic shock (SBP)

Obstructive uropathy
- Midodrine-induced

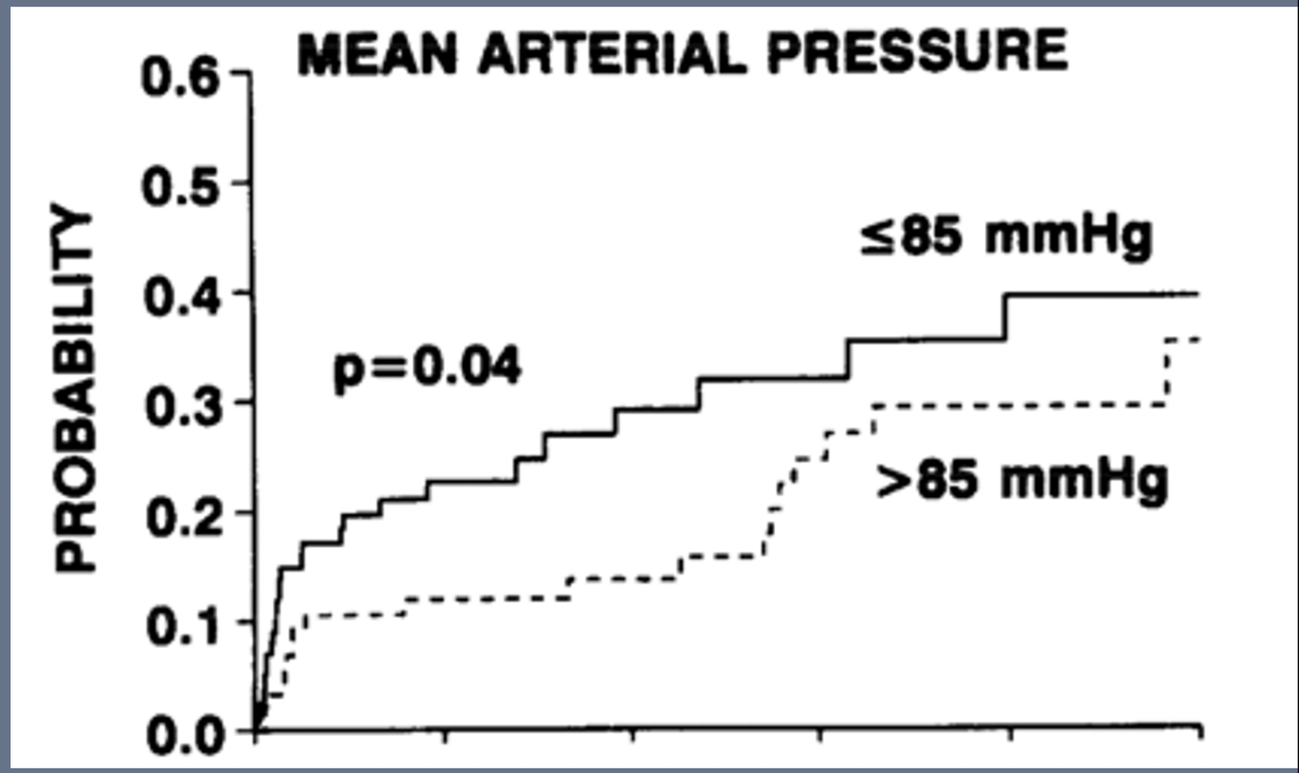
What matters more, the diagnosis or the clinical course?

Association of AKI With mortality and complications in hospitalized patients with cirrhosis

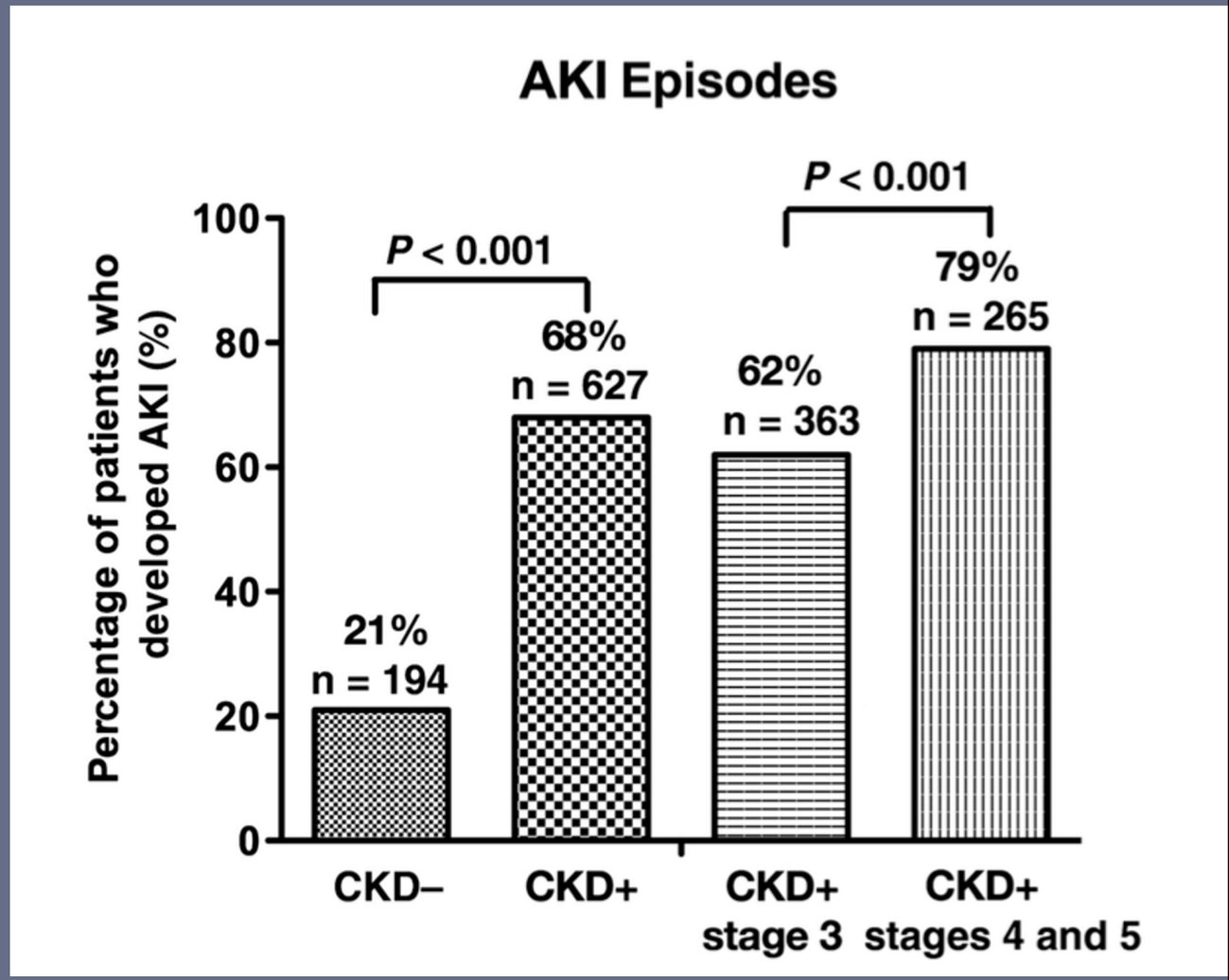


What could have predicted AKI? HRS-AKI?

Patients with worse portal hypertension and those with a low MAP:



Those with Baseline Chronic Kidney Disease are more susceptible to AKI:



How do we define AKI Reversal?

Full: Return of sCr to a value within 0.3 mg/dl (26.5 µmol/L) of the baseline value

Partial: Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 µmol/L) above the baseline value

None: Neither of the above

Predictors of AKI Reversal

Worsening hyperbilirubinemia

Baseline CKD
Congestive nephrology

Increase in mean arterial blood pressure

HRS-AKI reversal

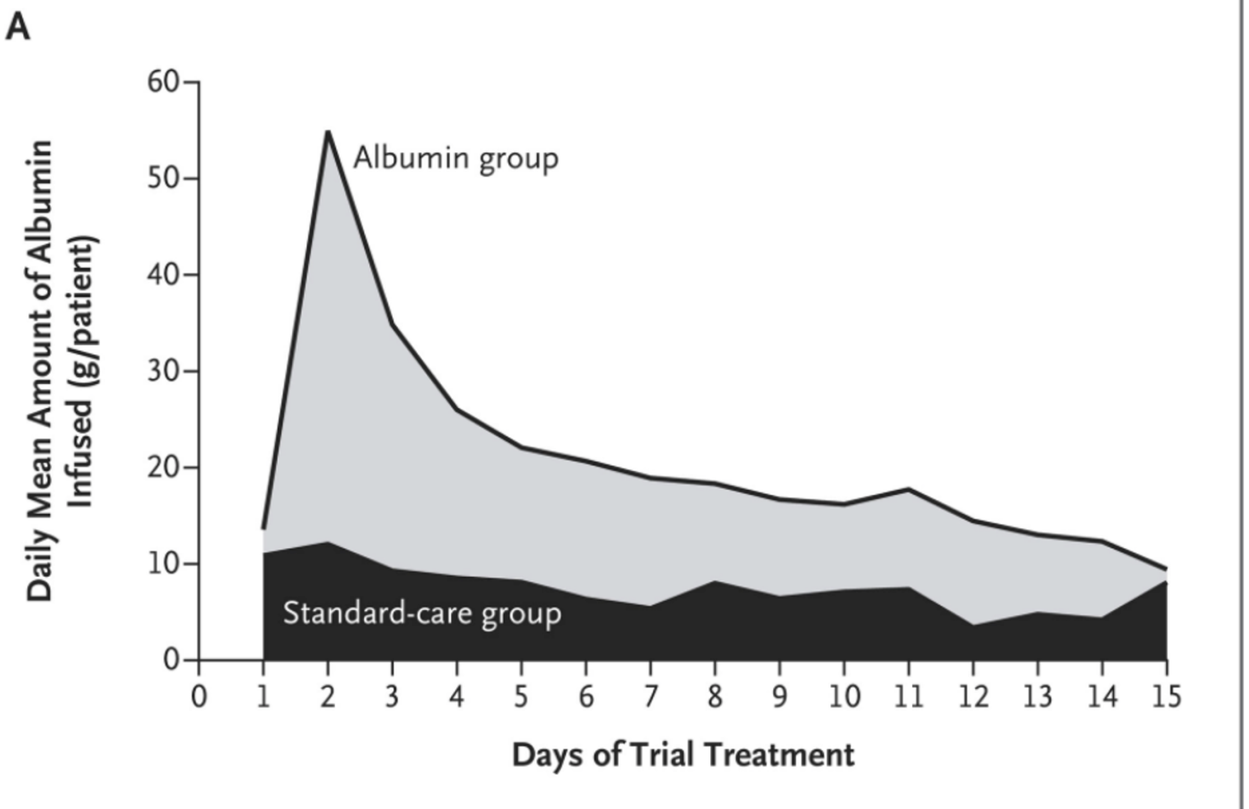
Removal of trigger
Improved acute-on-chronic liver failure

Cirrhosis
Cardiomyopathy

What are the treatments for AKI? HRS-AKI?

1. Albumin challenge, but not *too* much.

Albumin has been investigated both for prevention and treatment.



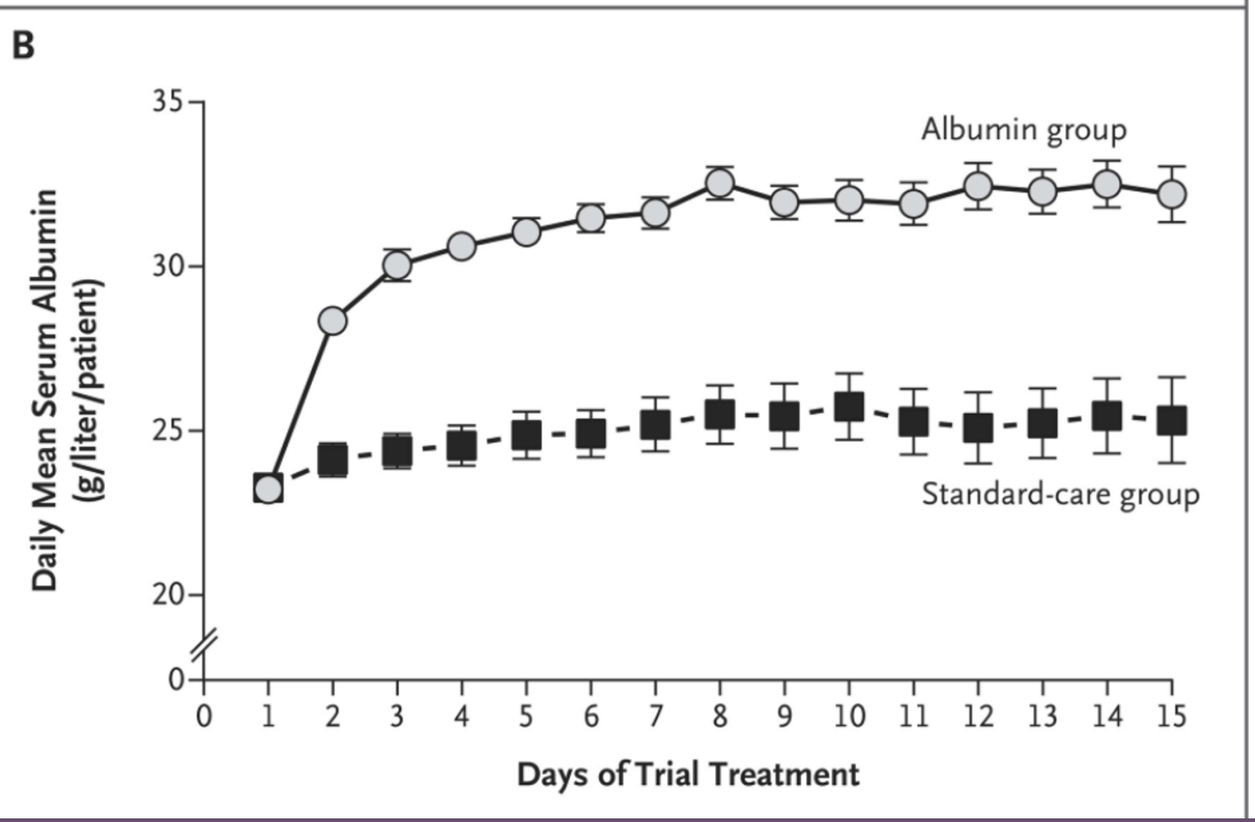


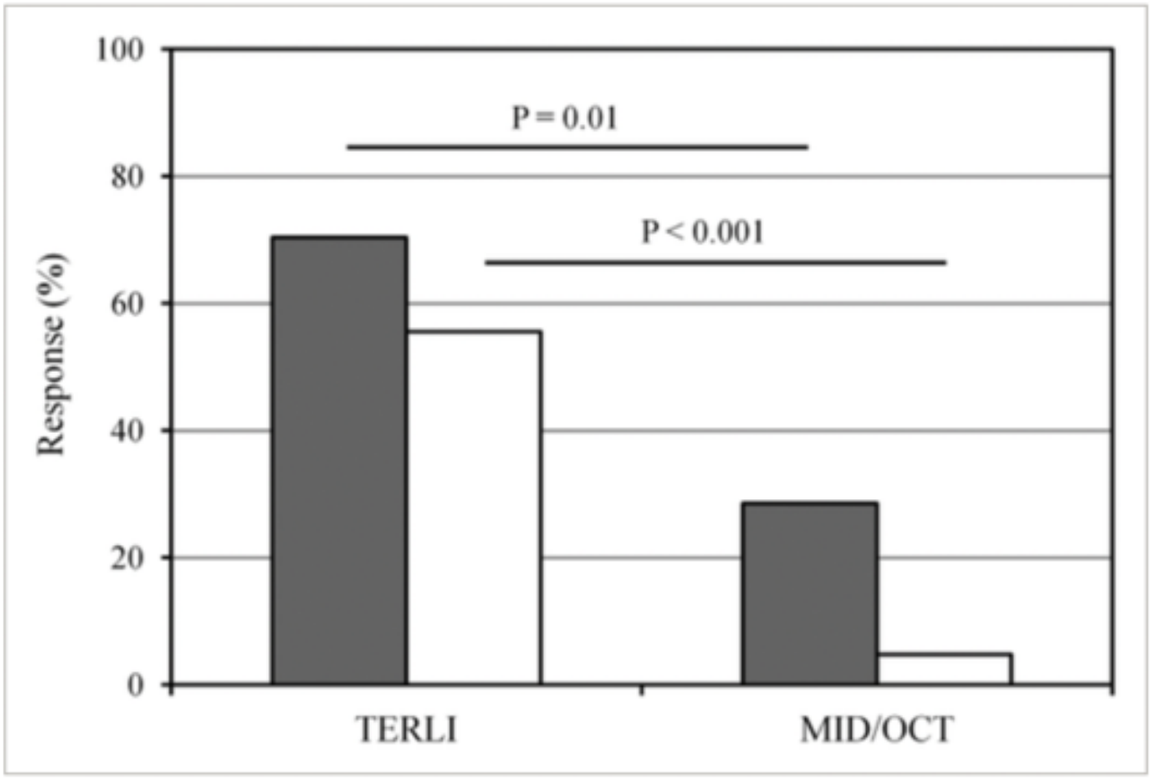
Table 3. Serious Adverse Events.*

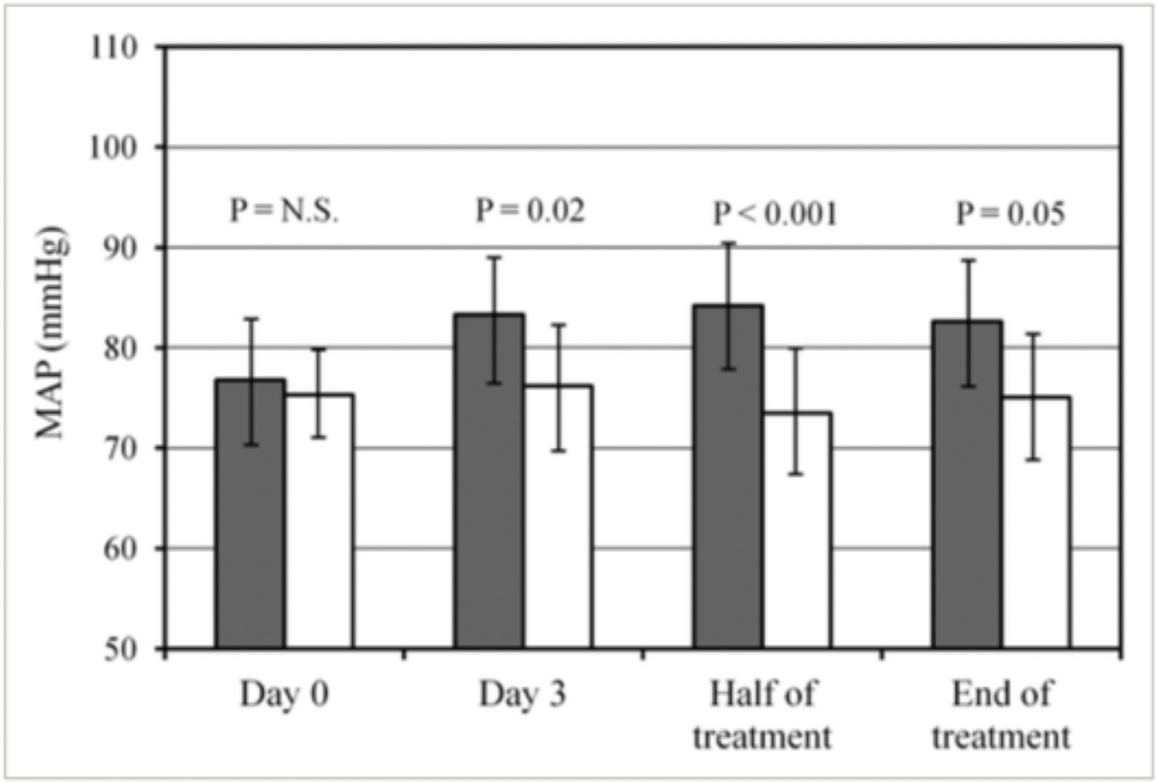
Event	Albumin Group (N=380)	Standard-Care Group (N=397)	All Patients (N=777)
		number of events	
Serious adverse event			
Grade 3: severe event	28	11	39
Grade 4: life-threatening event	17	13	30
Grade 5: death	42	48	90
All events	87	72	159
Individual serious adverse events occurring in >1 patient†			
Anemia	1	1	2
Esophageal varices hemorrhage	5	6	11
Gastric hemorrhage	5	4	9
Multiorgan failure	23	31	54
Other infections and infestations: spontaneous bacterial peritonitis	0	5	5
Lung infection	15	8	23
Sepsis	4	3	7
Encephalopathy	4	1	5
Acute kidney injury	2	0	2
Adult respiratory distress syndrome	0	2	2
Hypoxia	1	1	2
Pleural effusion	1	1	2
Pulmonary edema	15	4	19
All serious adverse events that included pulmonary edema or gastrointestinal bleeding‡			
Any pulmonary edema or fluid overload	23	8	31
Any gastrointestinal bleeding	11	13	24

Who should receive albumin?

Those with serum albumin ≤3.0 mg/dL, but be judicious, use clinical judgement and not as reflexive.

2. Increase the MAP.


100
80
60
40
20
0
Response (%)
P = 0.01
P < 0.001
TERLI
MID/OCT


110
100
90
80
70
60
50
MAP (mmHg)
P = N.S.
P = 0.02
P < 0.001
P = 0.05
Day 0
Day 3
Half of treatment
End of treatment

3. Terlipressin for floor patients with HRS-AKI.

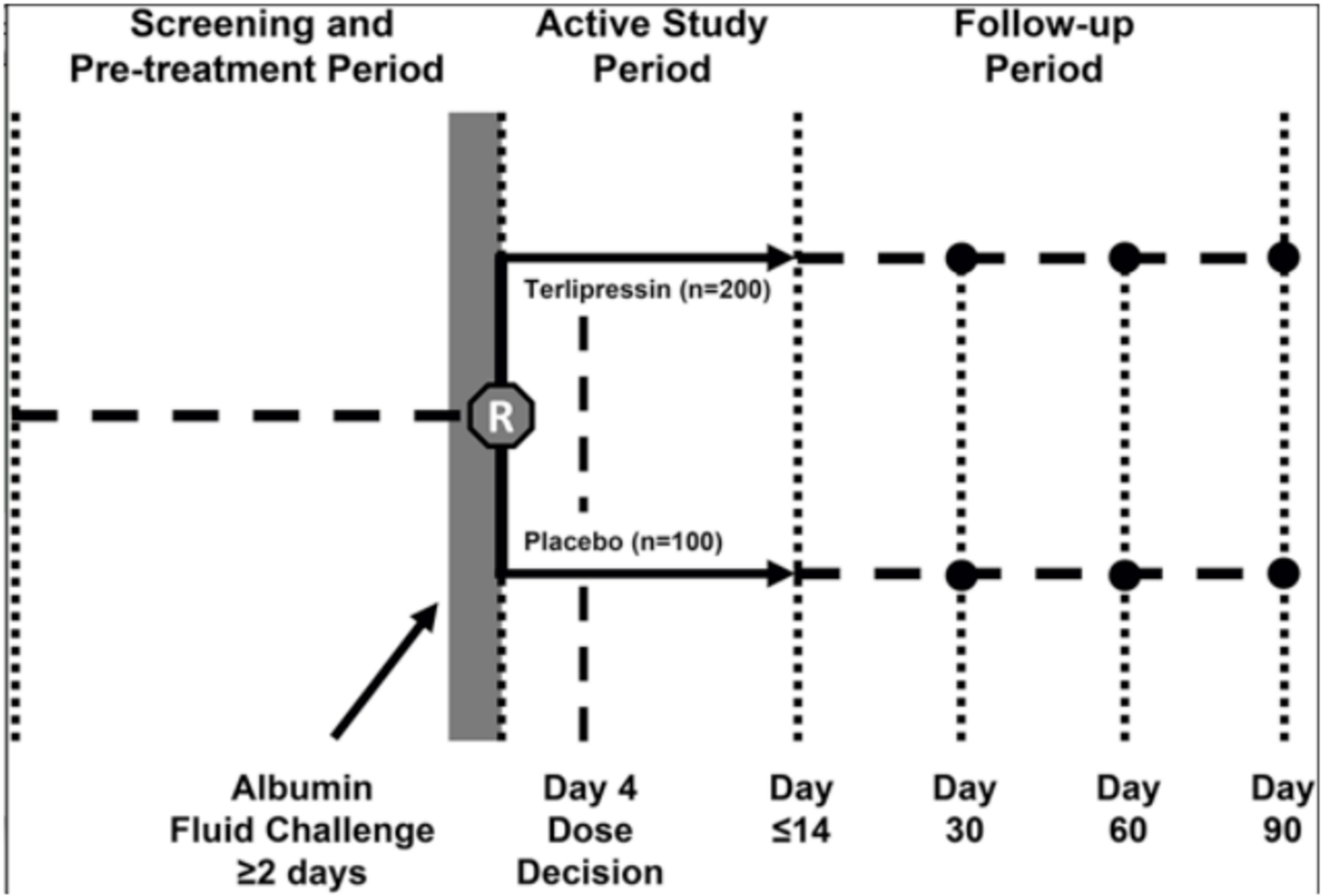

Screening and Pre-treatment Period
Active Study Period
Follow-up Period
Terlipressin (n=200)
R
Placebo (n=100)
Albumin Fluid Challenge ≥2 days
Day 4 Dose Decision
Day ≤14
Day 30
Day 60
Day 90

Table 2. Primary and Four Secondary End Points Included in Multiplicity Adjustment.*

End Point	Terlipressin	Placebo	P Value
	number/total number of patients (percent)		
Primary end point of verified reversal of HRS†			0.006
Clinical success	63/199 (32)	17/101 (17)	
Clinical failure	121/199 (61)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	
Secondary end points included in multiplicity adjustment			
HRS reversal§			<0.001
Clinical success	78/199 (39)	18/101 (18)	
Clinical failure	105/199 (53)	79/101 (78)	
Competing event‡			
Liver transplantation	11/199 (6)	4/101 (4)	
Death	5/199 (3)	0/101	
HRS reversal with no renal-replacement therapy through 30 days			0.001
Clinical success	68/199 (34)	17/101 (17)	
Clinical failure	116/199 (58)	80/101 (79)	
Competing event‡			
Liver transplantation	10/199 (5)	3/101 (3)	
Death	5/199 (3)	0/101	
HRS reversal in patients with systemic inflammatory response syndrome			<0.001
Clinical success	31/84 (37)	3/48 (6)	
Clinical failure	45/84 (54)	43/48 (90)	
Competing event‡			
Liver transplantation	4/84 (5)	1/48 (2)	
Death	5/84 (6)	0/48	
Verified reversal of HRS with no recurrence through 30 days			0.08
Clinical success	52/199 (26)	17/101 (17)	
Clinical failure	131/199 (66)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	

Table 4. Adverse Events in the Safety Population.*

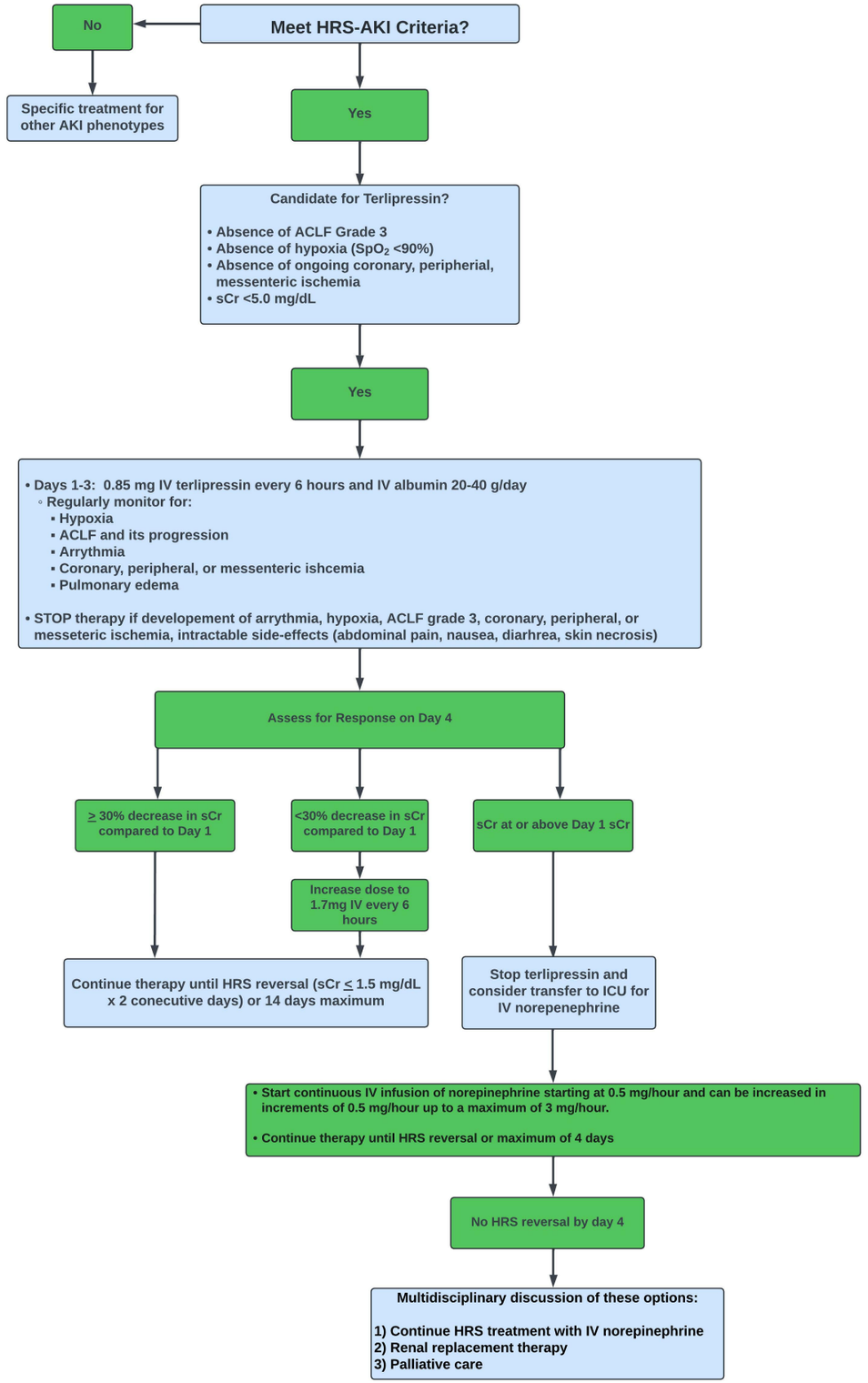
Event	Terlipressin (N=200)	Placebo (N=99)
	number of patients (percent)	
Adverse events of any grade†	176 (88)	88 (89)
Adverse events leading to discontinuation of the trial regimen	24 (12)	5 (5)
Serious adverse events with an incidence of ≥3% in either trial group‡		
Any	130 (65)	60 (61)
Cardiac disorders	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)

Who should receive Terlipressin:

1. HRS-AKI Diagnosis
2. sCr<5 mg/dL
3. No Hypoxemia

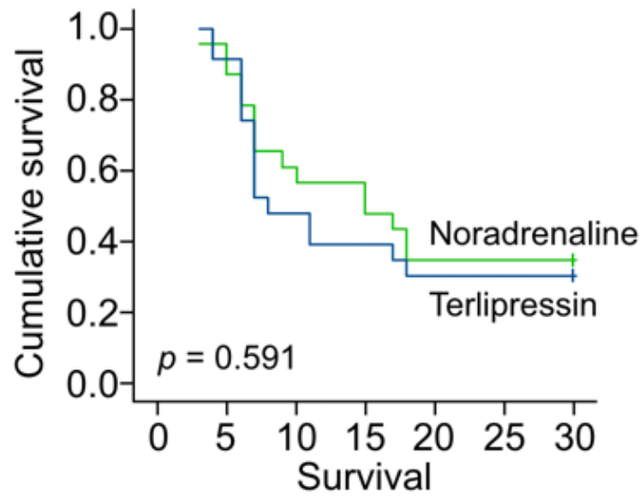
Be mindful in those with ACLF and with MELDNa ≥ 35

Management of Hepatorenal Syndrome-Acute Kidney Injury



In the ICU, should you use terlipressin or norepinephrine?

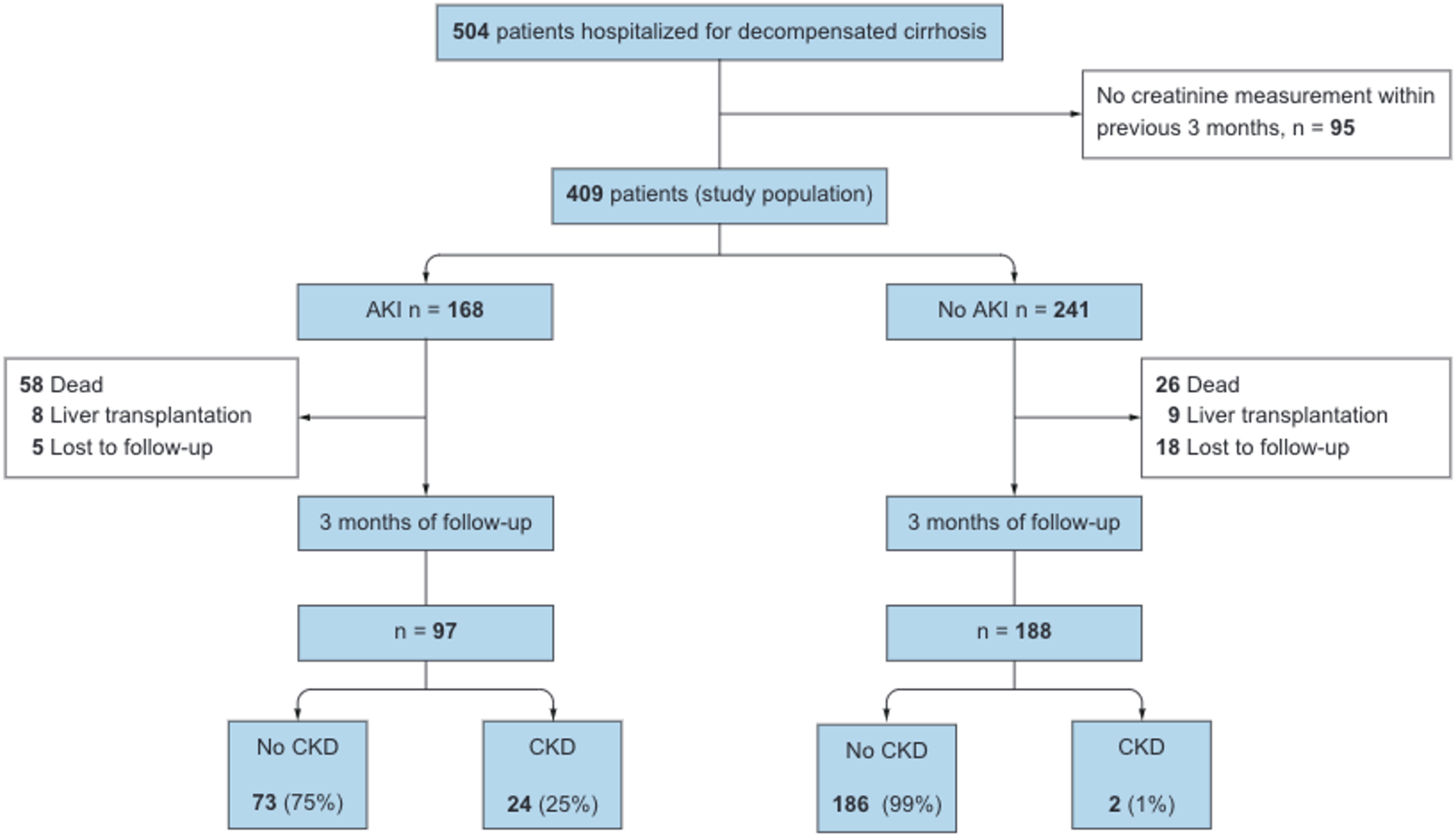
There are few randomized trials. Those that have been done are poorly designed.



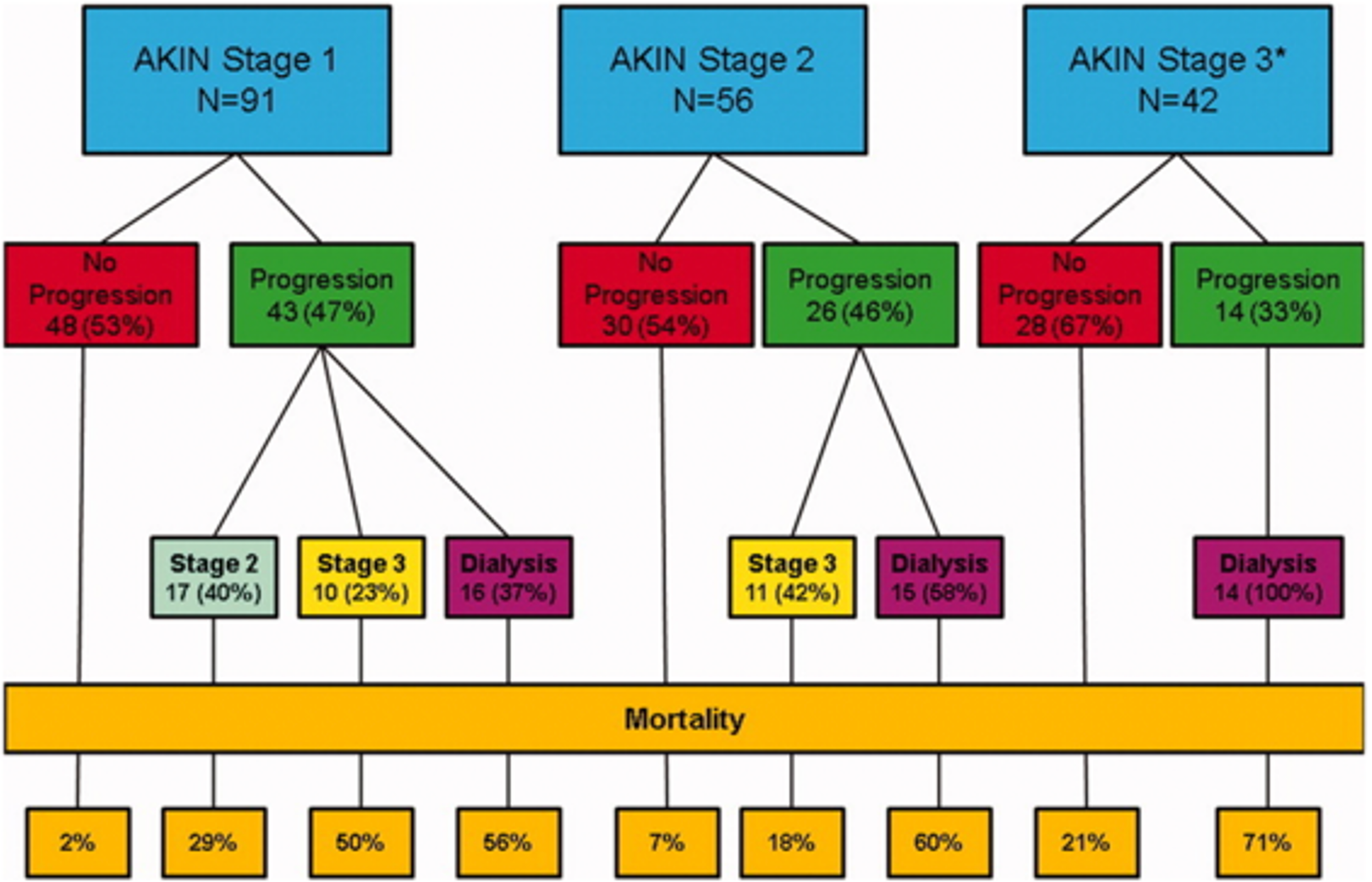
Patients at risk	Day					
	5	10	15	20	25	30
Terlipressin group (n = 23)	20	11	9	7	7	7
Noradrenaline group (n = 23)	21	13	11	8	8	8

Fig. 1. Kaplan–Meier curve showing the cumulative probability of survival of patients treated with terlipressin and noradrenaline.

Implications of AKI:


504 patients hospitalized for decompensated cirrhosis
No creatinine measurement within previous 3 months, n = 95
409 patients (study population)
AKI n = 168
No AKI n = 241
58 Dead
8 Liver transplantation
5 Lost to follow-up
26 Dead
9 Liver transplantation
18 Lost to follow-up
3 months of follow-up
3 months of follow-up
n = 97
n = 188
No CKD
73 (75%)
CKD
24 (25%)
No CKD
186 (99%)
CKD
2 (1%)

Association of AKI With mortality and complications in hospitalized patients with cirrhosis



AKI often triggers a vicious cycle - where ascites worsens; diuretics are no longer tolerated; malnutrition and physical frailty play larger factors; ultimately, a common cause of death.

Conclusions