A Protocol-Based Furosemide Stress Test to Evaluate Renal Recovery During Continuous Renal Replacement Therapy (FST-STOP): A Pilot Randomized Controlled Trial

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Background

- Continuous renal replacement therapy (CRRT): commonly used to manage critically ill patients with acute kidney injury (AKI)
- Prolonged CRRT → adverse events (hypotension, acid-base & electrolyte imbalances, hypothermia, infection, thrombocytopenia/anemia, & arrhythmia)
- Unclear optimal timing for CRRT discontinuation

Trial	AKIKI NEJM 2016	ELAIN JAMA 2016	IDEAL-ICU NEJM 2018	STARRT-AKI NEJM 2020	AKIKI 2 LANCET 2021
Safety	• CRBSI 10% vs 5% • hypoP 22% vs 15%	NA	• infection 22% vs 18%	• CRBSI 0.5% vs 0.1% • hypoP 7.5% vs 4.2%	• CRBSI 13% vs 11% • hypoP 13% vs 15%
Criteria to stop CRRT	• urine >1,000 ml • urine>2,000 ml with diuretic • decline Cr	CrCl >20 + • urine >400 ml • urine>2,100 with diuretic	• urine >1,000 ml • urine >2,000 ml with diuretic • decline Cr	NA	• urine >1,000 ml • urine >2,000 ml with diuretic • decline Cr

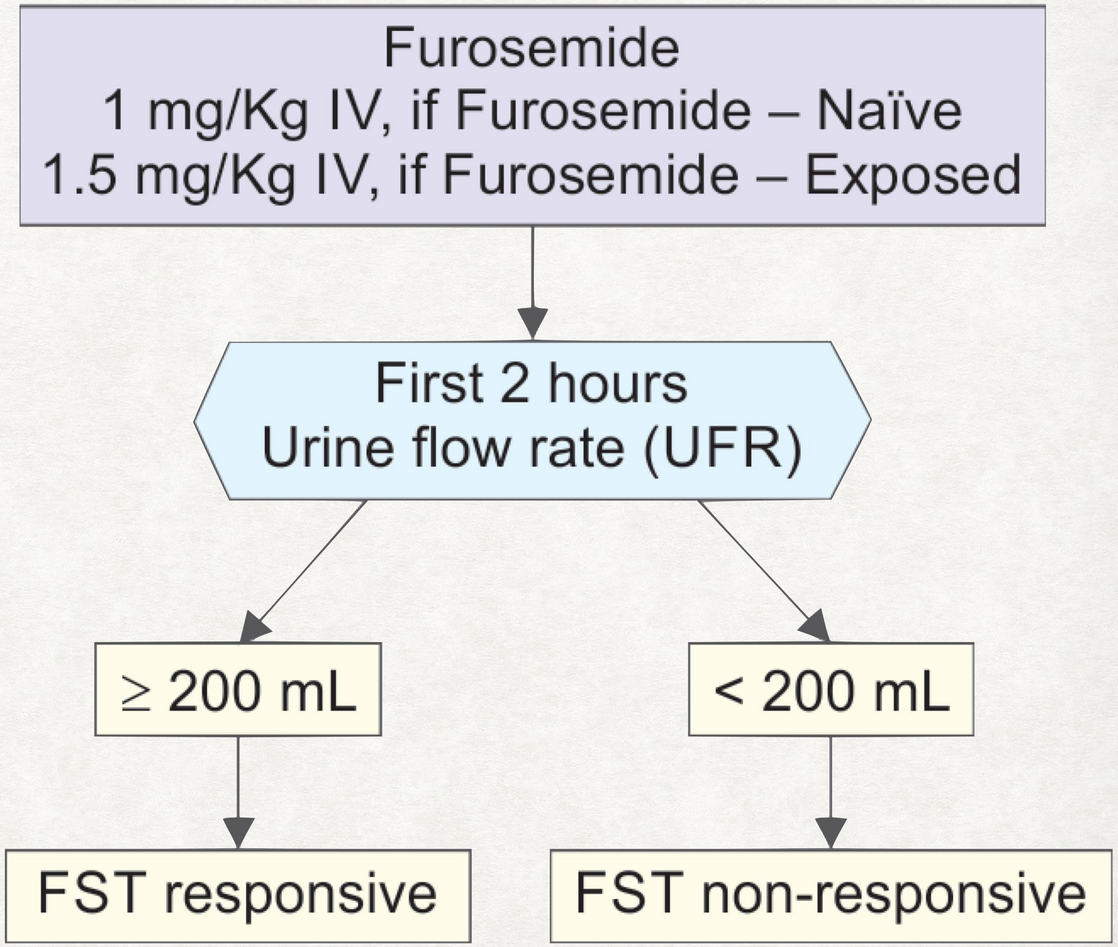
Akhoundi A, et al. Blood Purif. 2015;39(4):333-9, Zarbock A, et al. JAMA. 2016;315(20):2190-9, Gaudry S, et al. N Engl J Med. 2016;375(2):122-33.
Barbar SD, et al. N Engl J Med. 2018;379(15):1431-42, Bagshaw SM, et al. N Engl J Med. 2020;383(3):240-51, Gaudry S, et al. Lancet. 2021;397(10281):1293-300.

Background

- Furosemide stress test (FST)
  - Often use to guide CRRT initiation in patients with AKI, especially those who are FST-nonresponsive
- Limited evidence supporting its role in assessing renal recovery

Objective

This study aimed to evaluate whether FST could facilitate CRRT discontinuation.



Chawla LS, et al. Crit Care. 2013;17(5):R207, Koyner JL, et al. J Am Soc Nephrol. 2015;26(8):2023-31, Lumlertgul N, et al. Crit Care. 2018;22(1):101.

Study Design

- Pilot, prospective, open-label, randomized controlled trial
- Randomized 1:1 using permuted blocks of size 4 without additional stratification to receive either protocol-based FST or standard care (Nephrologists & intensivists provided furosemide at any dose or not at all)

Inclusion criteria

- Adult age ≥18 years
- AKI stage 3 based on KDIGO classification
- Initiated CRRT ≥48 h in ICU at Chiang Mai University Hospital, Thailand

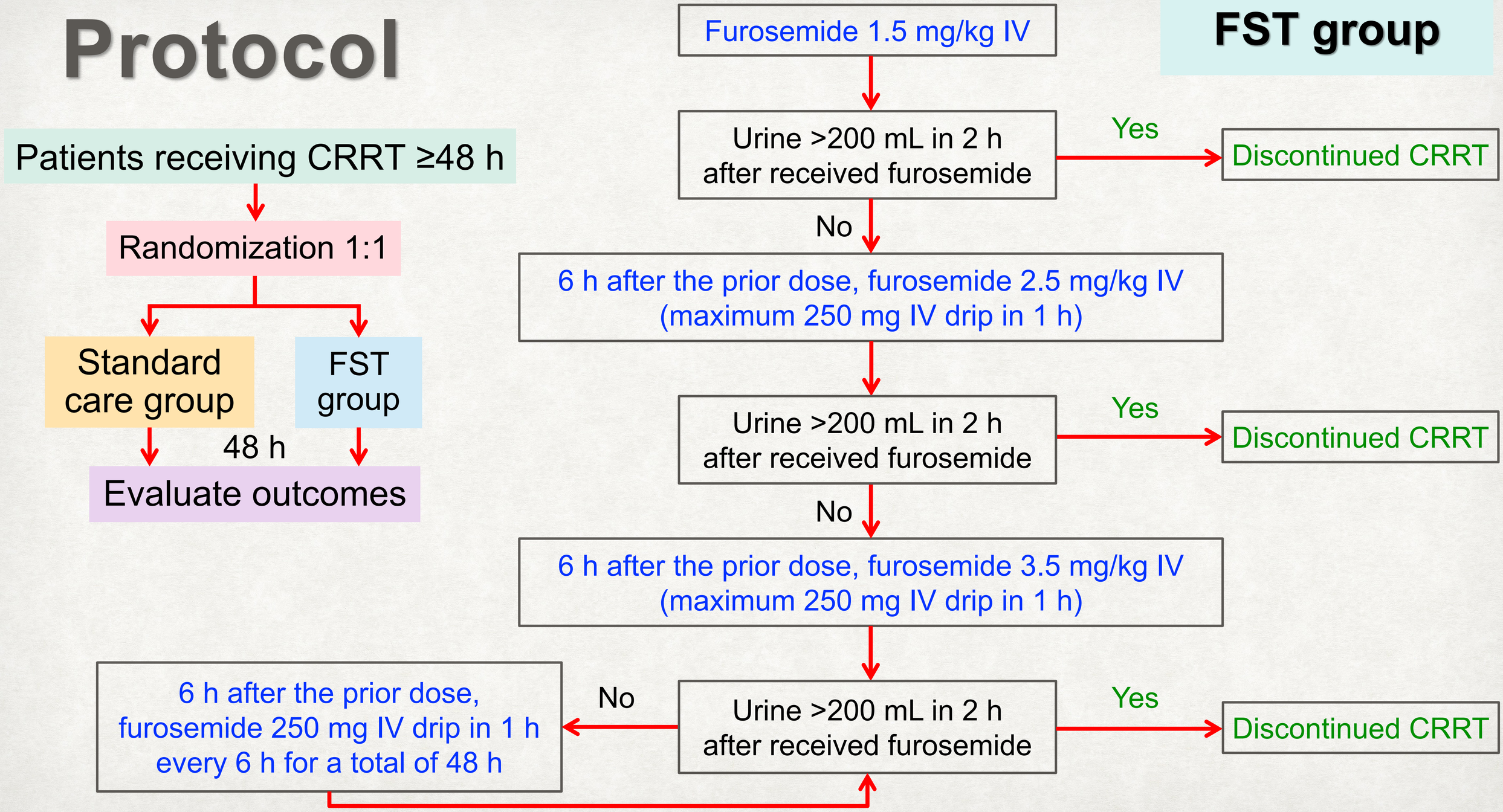
Exclusion criteria

- High-dose vasopressors (norepinephrine ≥0.5 mcg/kg/min, epinephrine ≥0.5 mcg/kg/min, dopamine ≥10 mcg/min)
- Severe electrolyte imbalance (K ≥6.5 or ≤2.5, HCO_3 ≤12 mmol/L, pH ≤7.2)
- Urine output ≥2,100 mL/day
- Obstructive uropathy

Exclusion criteria

- CKD stage 5 or ESKD
- Kidney transplantation
- RRT during previous 14 days
- RRT for eliminating drugs or toxins
- Furosemide use during CRRT
- CVP ≤5 mmHg or PPV ≥13%
- Expected death in 24 h
- Pregnancy & breastfeeding

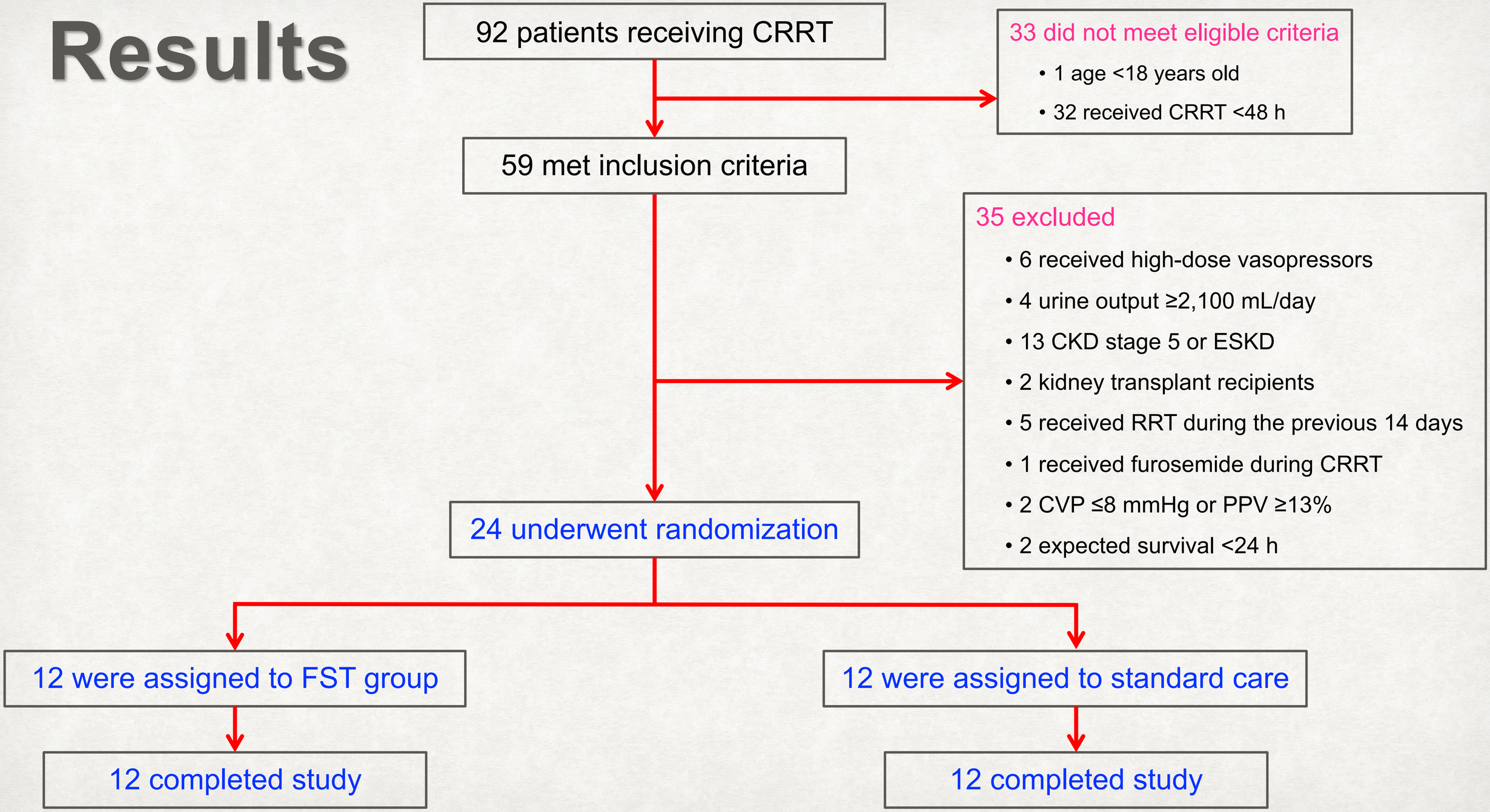
Protocol


Patients receiving CRRT ≥48 h
Randomization 1:1
Standard care group
FST group
48 h
Evaluate outcomes
FST group
Furosemide 1.5 mg/kg IV
Urine >200 mL in 2 h after received furosemide
Yes
Discontinued CRRT
No
6 h after the prior dose, furosemide 2.5 mg/kg IV (maximum 250 mg IV drip in 1 h)
Urine >200 mL in 2 h after received furosemide
Yes
Discontinued CRRT
No
6 h after the prior dose, furosemide 3.5 mg/kg IV (maximum 250 mg IV drip in 1 h)
Urine >200 mL in 2 h after received furosemide
No
6 h after the prior dose, furosemide 250 mg IV drip in 1 h every 6 h for a total of 48 h
Yes
Discontinued CRRT

Outcomes

- **Primary endpoint**
  - Number of patients successfully weaned from CRRT (stopping CRRT within 48 h after randomization while not reinitiating any RRT modality for the next 5 days)
- **Secondary endpoints**
  - Urine output on day 2 and 5 after randomization
  - 30-day all-cause mortality
  - Dialysis dependence at 30 days
  - Ventilator-free days
  - Length of ICU stay
  - Length of hospital stay
  - Adverse events

Results


92 patients receiving CRRT
33 did not meet eligible criteria
• 1 age <18 years old
• 32 received CRRT <48 h
59 met inclusion criteria
35 excluded
• 6 received high-dose vasopressors
• 4 urine output ≥2,100 mL/day
• 13 CKD stage 5 or ESKD
• 2 kidney transplant recipients
• 5 received RRT during the previous 14 days
• 1 received furosemide during CRRT
• 2 CVP ≤8 mmHg or PPV ≥13%
• 2 expected survival <24 h
24 underwent randomization
12 were assigned to FST group
12 were assigned to standard care
12 completed study
12 completed study

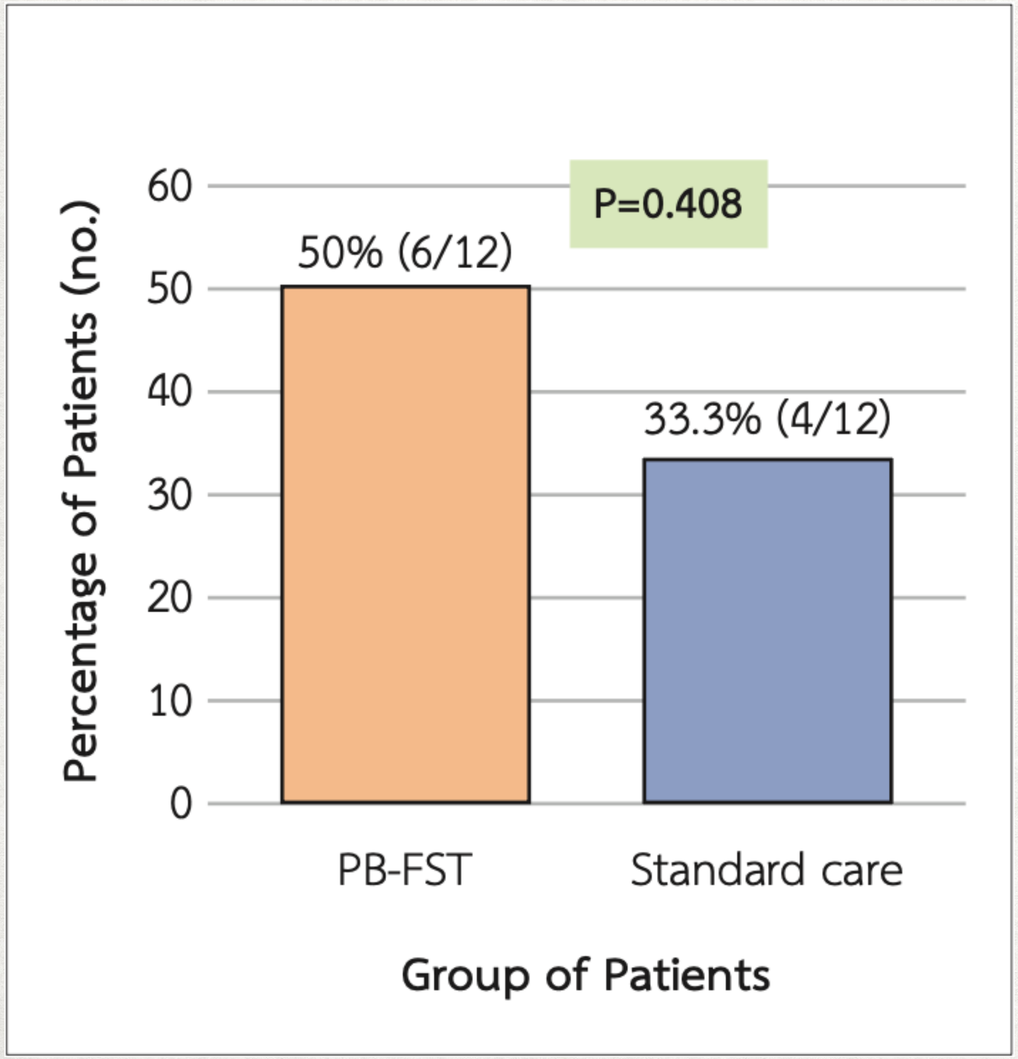
Baseline Characteristics

Parameters	FST group (n = 12)	Standard care (n = 12)
Age, years	72.8 ± 13.8	67.8 ± 17.6
Male, n (%)	9 (75.0)	8 (66.7)
BMI, kg/m²	23.2 ± 4.5	22.4 ± 2.9
Admission category, n (%) • Sepsis • Surgery • Coronary artery disease • COVID-19 infection	 5 (41.7) 3 (25.0) 2 (16.7) 2 (16.7)	 4 (33.3) 4 (33.3) 2 (16.7) 2 (16.7)
SOFA score	12.5 (11, 13.5)	14.5 (12, 18)
Mechanical ventilation, n (%)	12 (100.0)	10 (83.3)
Vasopressors, n (%)	5 (41.7)	8 (66.7)
CVP, mmHg	9.0 ± 2.1	10.2 ± 4.9
Urine volume, mL/day	295 (23, 480)	55 (28, 298)
6-h urine Cr clearance, n (%) • <12 mL/min • ≥12 mL/min	 9 (90.0) 1 (10.0)	 9 (90.0) 1 (10.0)

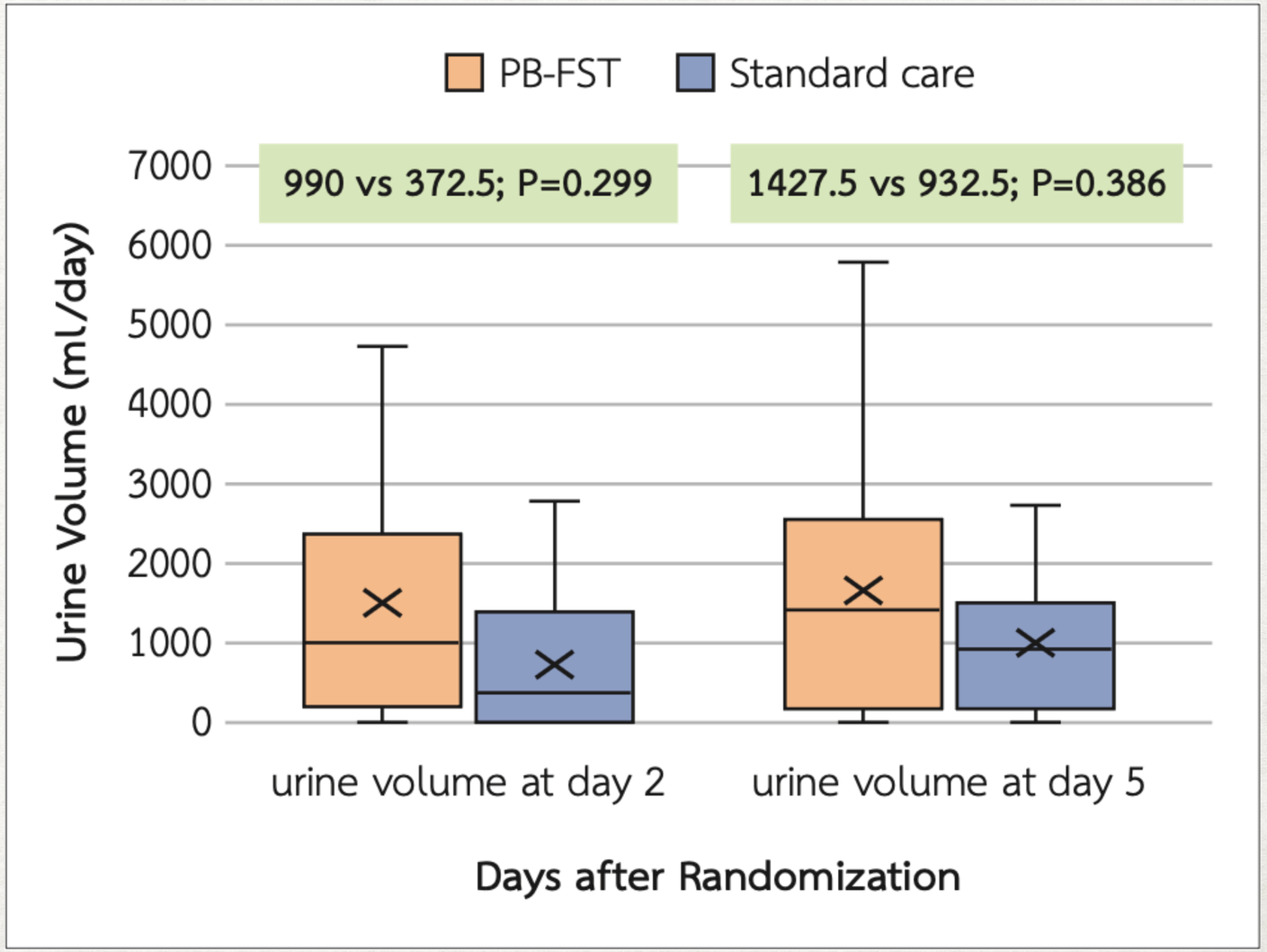
Parameters	FST group (n = 12)	Standard care (n = 12)
Laboratory investigation • BUN, mg/dL • Cr, mg/dL • eGFR, mL/min/1.73 m2 • Na, mmol/L • K, mmol/L • HCO_3, mmol/L	 26.5 (17.5, 32.0) 1.1 ± 0.3 60 (49.5, 82.0) 137.3 ± 2.5 3.7 ± 0.4 22.7 ± 3.3	 33.5 (26.5, 51.0) 1.4 ± 0.6 55 (37.0, 75.0) 136.3 ± 3.0 3.9 ± 0.6 20.7 ± 2.6
Indication for CRRT, n (%) • Volume overload • Uremia • Acidosis	 7 (58.3) 3 (25.0) 2 (16.7)	 7 (58.3) 3 (25.0) 2 (16.7)
Indication for CRRT, n (%) • CVVHDF • CVVHD • CVVH	 8 (66.7) 3 (25.0) 1 (8.3)	 9 (75.0) 1 (8.3) 2 (16.7)
Anticoagulation for CRRT, n (%) • No anticoagulation • Heparin • Regional citrate	 8 (66.7) 3 (25.0) 1 (8.3)	 7 (58.3) 2 (16.7) 3 (25.0)
Prescribed CRRT dose (mL/kg/h)	30.0 ± 4.3	30.0 ± 0.0

Primary Outcome

Successful discontinuation of CRRT



Urine volume at day 2 & 5



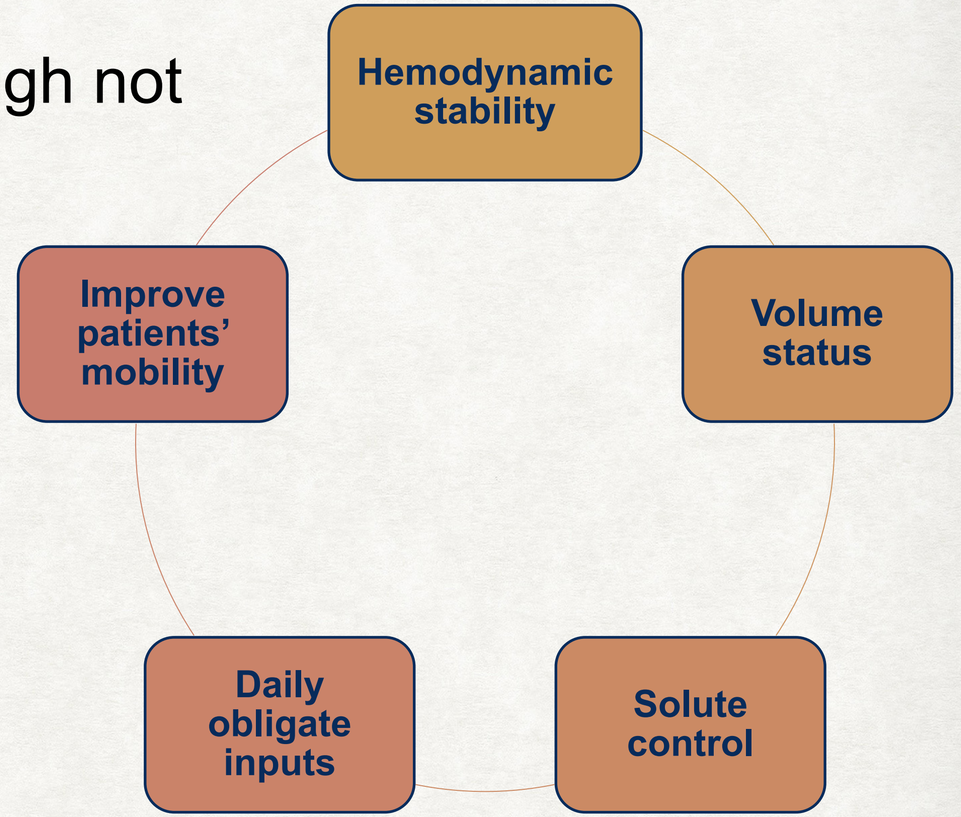
Secondary Outcomes

Outcomes	FST group (n = 12)	Standard care (n = 12)	P-value
30-day all-cause mortality, n (%)	8 (66.7)	8 (66.7)	1.000
RRT dependence at 30 days, n (%)	5 (41.7)	8 (66.7)	0.219
Duration of RRT, days	5 (4, 8)	6 (5, 10)	0.336
Length of ICU stay, days	24 (11, 30)	24 (14, 38)	0.773
Length of hospital stay, days	28 (18, 70)	30 (19, 40)	0.583
Ventilator-free day, days	5 (0, 29)	2.5 (0, 6)	0.401
Dose of furosemide during study, mg/day	1000 (525, 1000)	500 (0, 1000)	0.182

Adverse events, n (%)	FST group (n = 12)	Standard care (n = 12)	P-value
CRBSI	0 (0.0)	1 (8.3)	1.000
Hyponatremia			
• Day 2	3 (25.0)	3 (25.0)	1.000
• Day 5	3 (25.0)	5 (41.7)	0.386
Hypernatremia			
• Day 2	2 (16.7)	0 (0.0)	0.478
• Day 5	4 (33.3)	0 (0.0)	0.093
Hypokalemia			
• Day 2	5 (41.7)	4 (33.3)	0.673
• Day 5	4 (33.3)	1 (8.3)	0.317
Hypophosphatemia			
• Day 2	3 (25.0)	4 (33.3)	0.653
• Day 5	2 (16.7)	2 (16.7)	1.000
Hypomagnesemia			
• Day 2	1 (8.3)	0 (0.0)	1.000
• Day 5	1 (8.3)	0 (0.0)	1.000

Discussion

- FST-STOP, a pilot randomized-controlled trial:
  FST group as compared with standard care (although not statistically significant)
  - >12% successful RRT discontinuation
  - ↑ urine volume at day 2 & 5
  - ↑ ventilator-free days
  - ↓ RRT dependence
  - ↓ days of RRT use
  - ↓ length of hospital stay
  - No significant adverse events
- Support recent retrospective observational cohort findings that furosemide enhanced ventilator-free & RRT-free time among patients with sepsis-associated AKI receiving RRT



Li C, et al. BMJ Open. 2023;13(7):e074046.

Discussion

- **Strength**
  - First RCT that used FST during CRRT in a wide spectrum of baseline CKD, which assisted in stopping CRRT earlier
- **Limitation**
  - Small number of participants due to the short inclusion period, resulting in a non-significant outcome
  - Several other factors that impact critically ill patients, such as sepsis state or volume status, which affect mortality, hospital outcome, and urine volume

Conclusion

- In this pilot trial, FST appeared feasible for assessing kidney recovery during CRRT without adverse events.
- However, larger populations are needed to confirm and enhance statistical power of the findings.

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