Timing of Renal Replacement Therapy

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Potential Conflicts of Interest

Speaker

- Fresenius
- Baxter
- Braun
- CLS Behring
- Biomerieux

Consultant

- Baxter
- Fresenius
- Novartis
- Sandoz
- AmPharma
- Takeda

…steering committee member of STARRT-AKI

Criteria for Initiation of RRT

CHAPTER 5.1: TIMING OF RENAL REPLACEMENT THERAPY

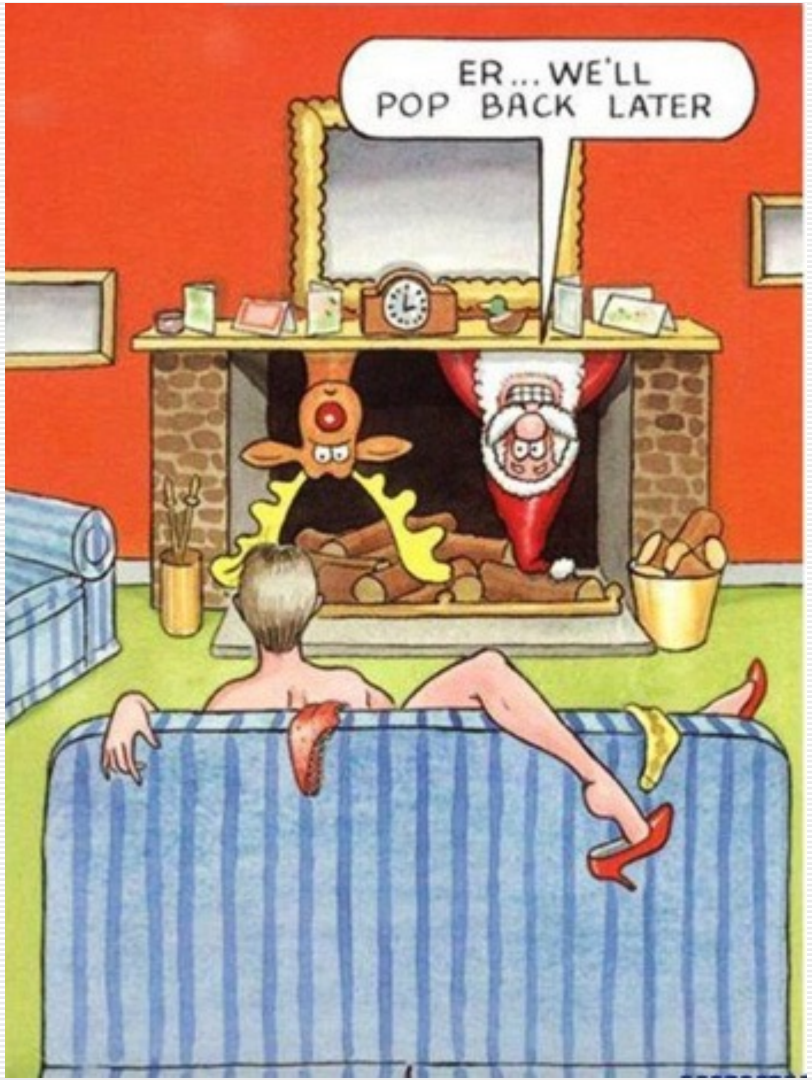
- 5.1.1: Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist (Not Graded)
- 5.1.2: Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT (Not Graded)

Kidney Int 2012, Suppl. 2012, 2: 1-138

Kidney Disease: Improving Global Outcomes

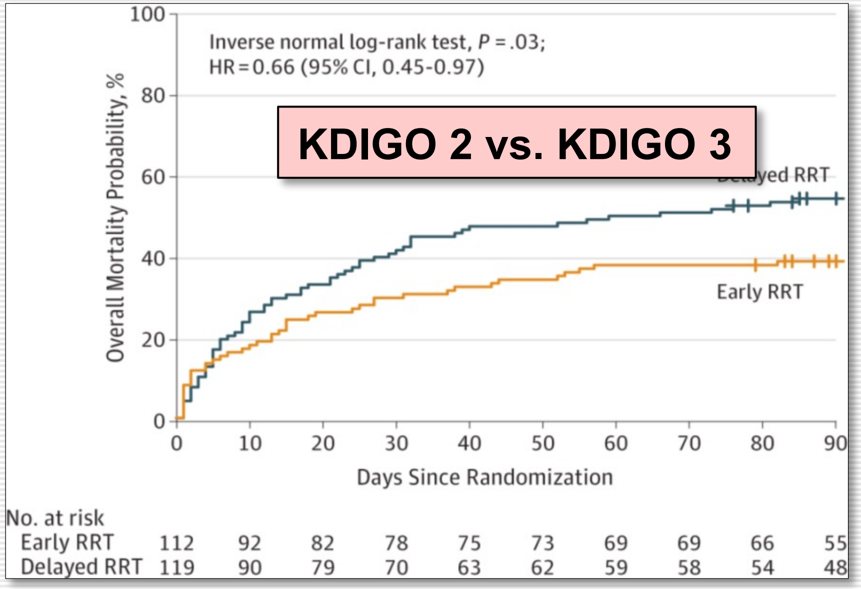
WWW.KDIGO.ORG

Optimal Timing….?



Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial

The JAMA Network

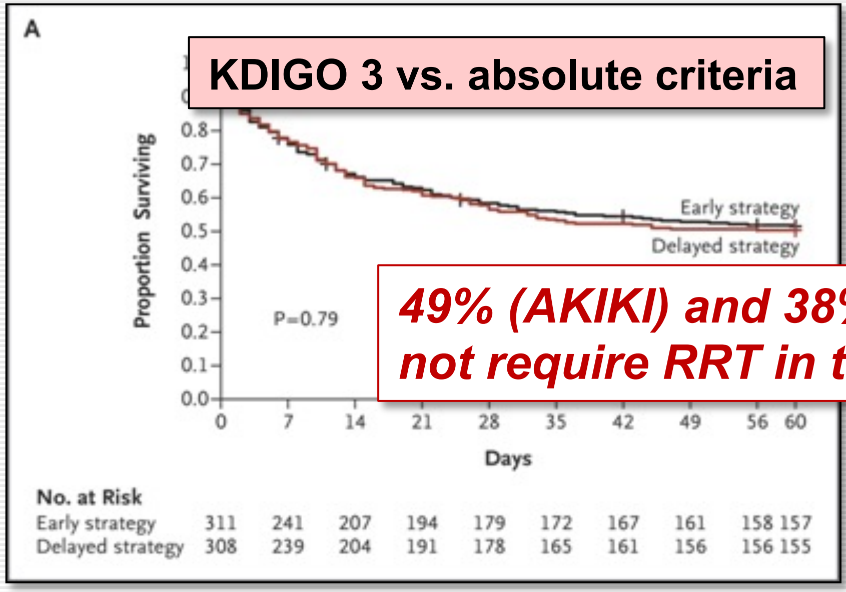


Zarbock A et al, JAMA. 2016;315(20):2190-2199

Single Centre
N= 231
95% surgical
100% CVVHDF
Time difference: 21.5h
Cumulative fluid balance ~ +6.5 L
Fragility index = 3

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit (AKIKI trial)

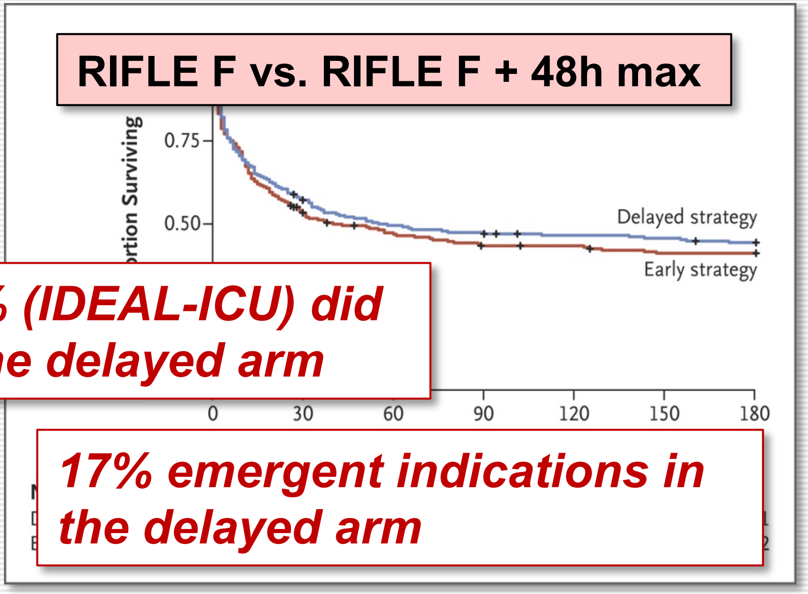
The NEW ENGLAND JOURNAL of MEDICINE



Gaudry S et al. N Engl J Med 2016;375:122-133

Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis (IDEAL-ICU)

The NEW ENGLAND JOURNAL of MEDICINE



49% (AKIKI) and 38% (IDEAL-ICU) did not require RRT in the delayed arm

17% emergent indications in the delayed arm

Barbar SD et al. N Engl J Med 2018;379:1431-1442

Multicentre
N= 619
80% medical/(75% Sepsis)
55% IHD (!)
Time difference: 57h
Cumulative fluid balance ?

Multicentre
N= 488
100% early septic shock
55% IHD (!)
Time difference: 44h
Cumulative fluid balance + 2.7L
Terminated for futility

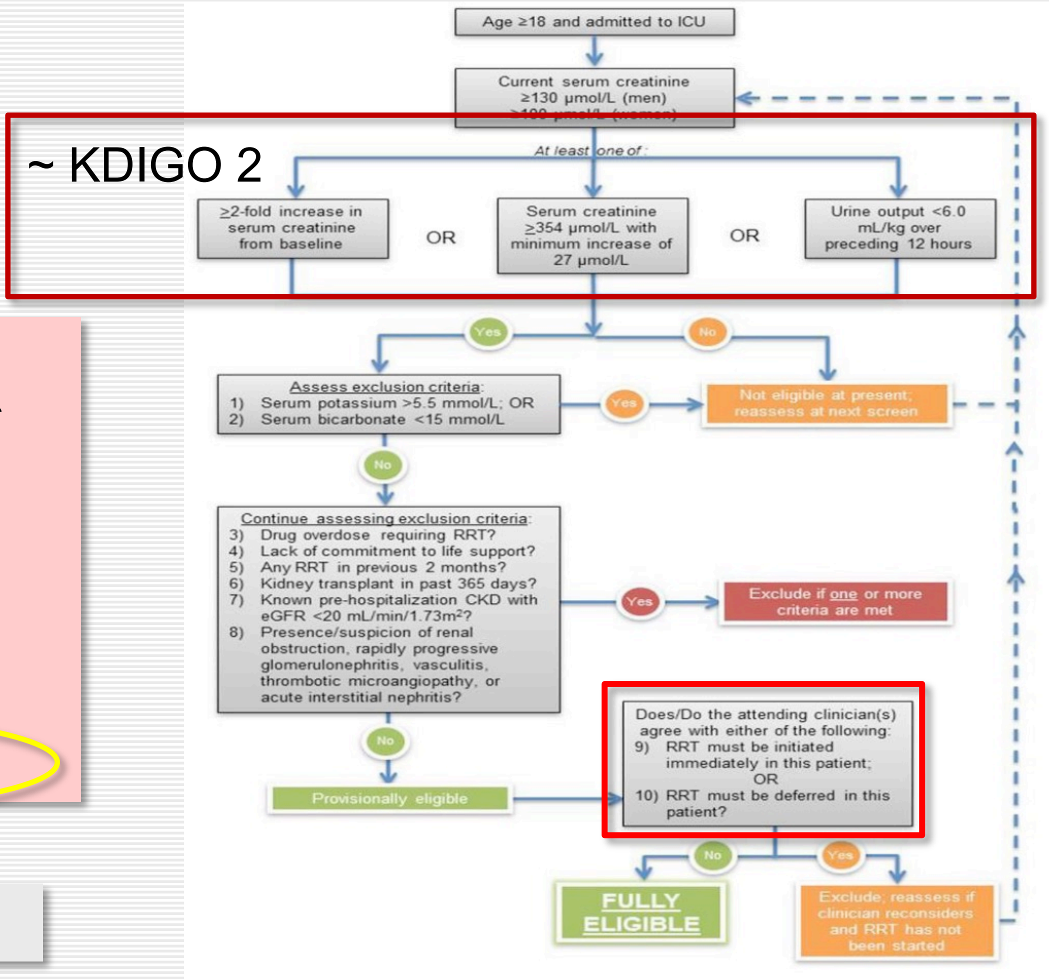
Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI trial)

Randomised controlled trial
15 countries, 168 centres, 3019 patients

Accelerated strategy:
RRT $\leq$ 12 hours after meeting eligibilty criteria

Standard strategy:
RRT discouraged ***unless***

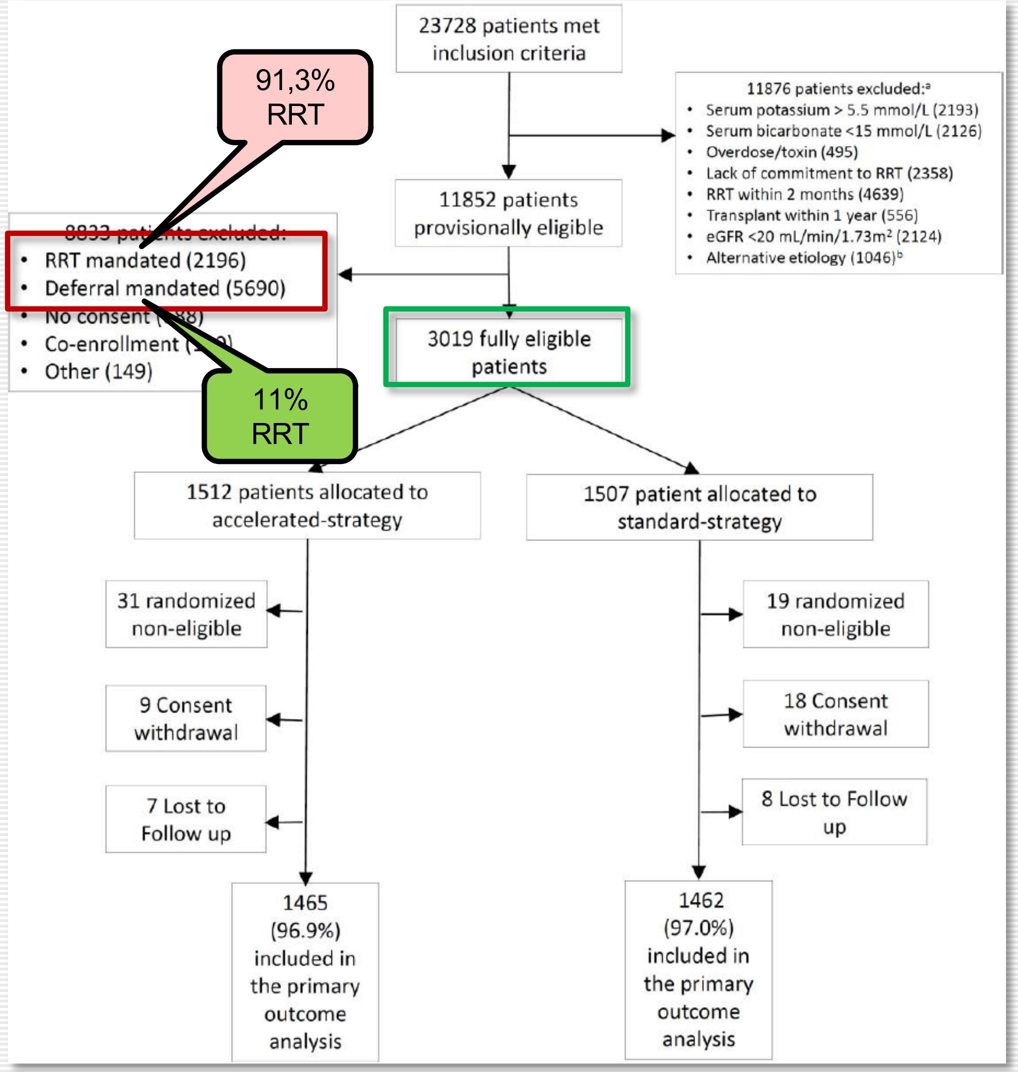
- K$\geq$6 mmol/l,
- pH $\leq$ 7.2
- HCO3 $\leq$ 12 mmol/l
- paO2/FiO2 $\leq$ 200
- volume overload
- **persistent AKI $\geq$ 72h**



Primary outcome: all cause mortality at 90 days

The STARRT-AKI Investigators. N Engl J Med 2020;383:240-251.

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI trial)



Patient characteristics:

CKD	44% (1284)
Surgical patients	33% (965)
Medical patients	67% (1962)
Sepsis	58% (1689)
Septic shock	44% (1284)

Modality:

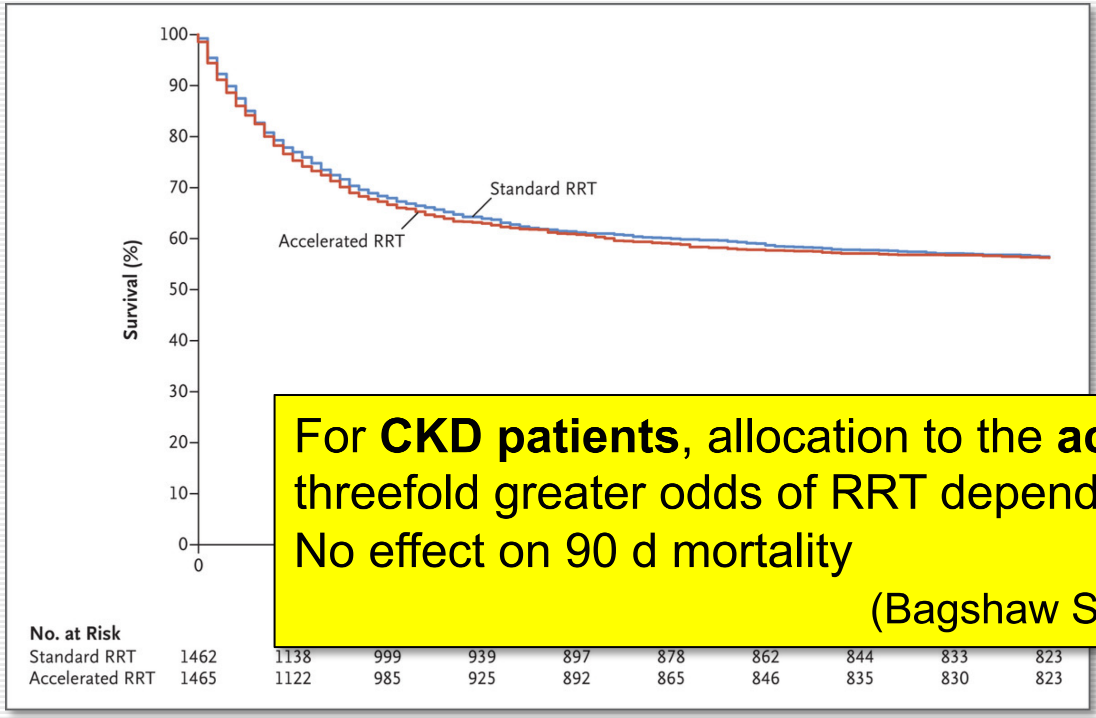
CRRT	70% (1590)
IHD	26% (606)
SLED	4% (101)

The STARRT-AKI Investigators. N Engl J Med 2020;383:240-251.

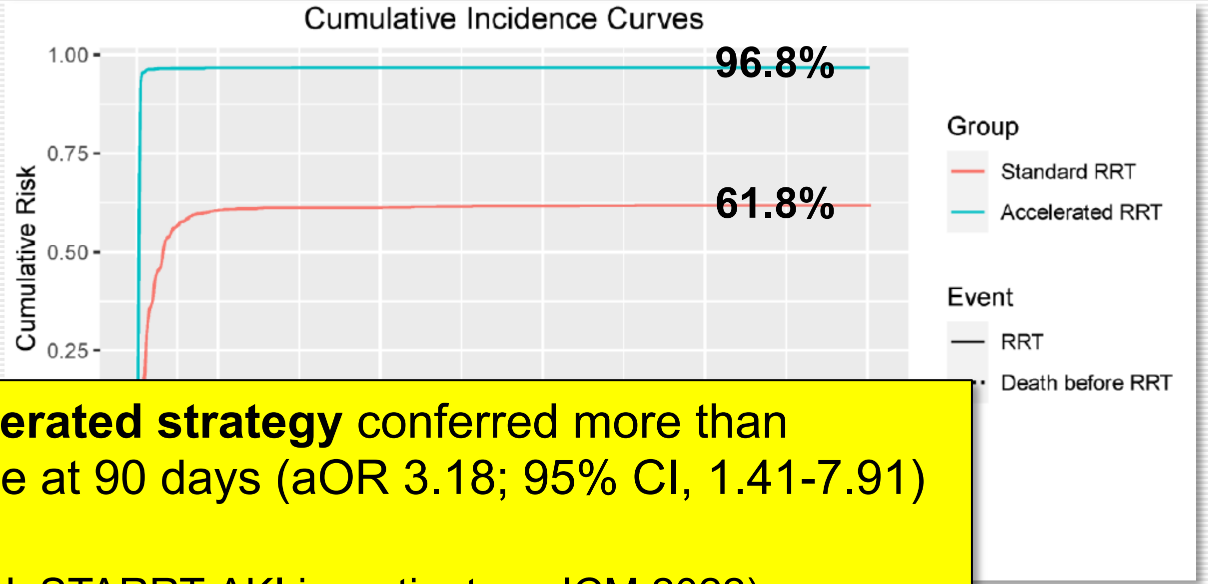
Wald R *et al., Am J Respir Crit Care Med 2021, 204(2):234-237*

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI trial)

Kaplan–Meier Estimates of Survival at 90 Days



Renal Replacement Therapy



For **CKD patients**, allocation to the **accelerated strategy** conferred more than threefold greater odds of RRT dependence at 90 days (aOR 3.18; 95% CI, 1.41-7.91)
No effect on 90 d mortality

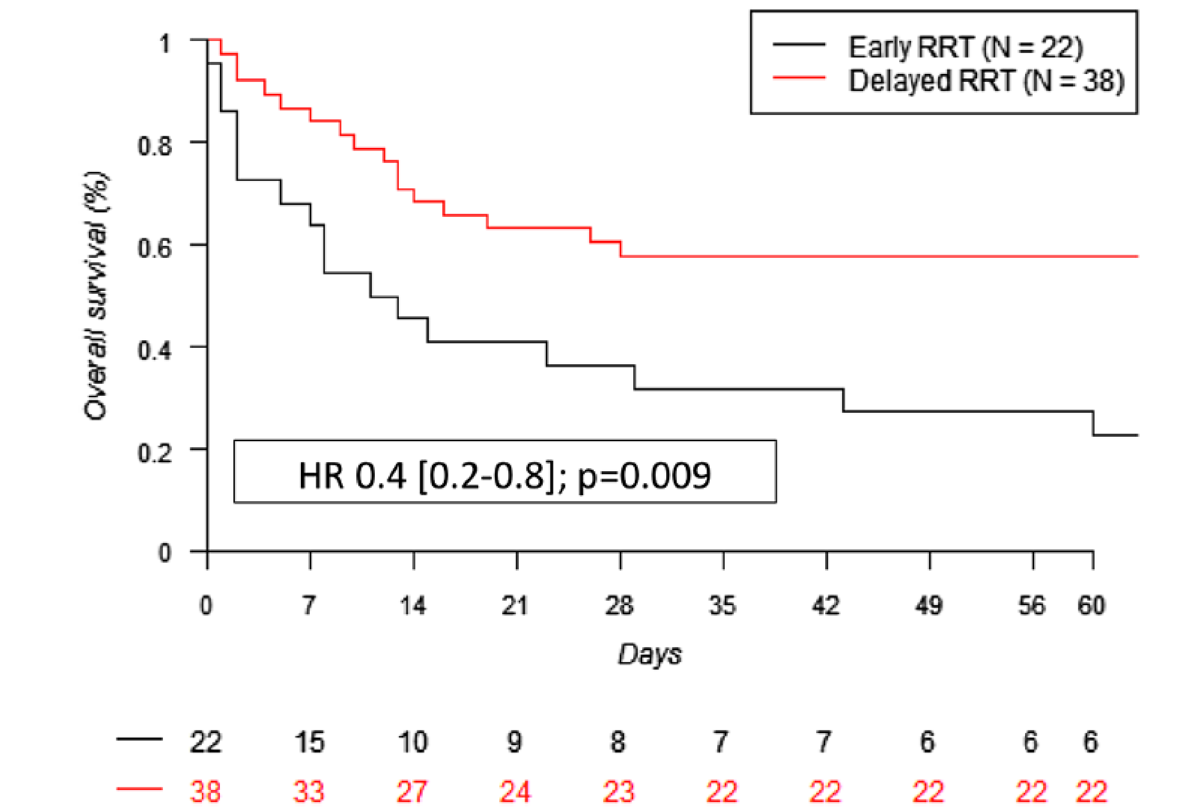
(Bagshaw S et al, STARRT-AKI investigators, ICM 2022)

Adverse events	Accelerated Group	Standard Group
Hypotension	**131 (8.7%)**	**83 (5.6%)**
Hypophosphatemia	**112 (7.5%)**	**62 (4.2%)**
Dependence on RRT, survivors 90d (814/815)	**85 (10.4%)**	**49 (6.0%)**

The STARRT-AKI Investigators.
N Engl J Med 2020;383:240-251.

Hypothesis: early renal replacement therapy increases mortality in critically ill patients with acute on chronic renal failure. A post hoc analysis of the AKIKI trial

60 of 619 with CKD (GFR 30-60 ml/min)



Gaudry S et al, Intensive Care Med (2018) 44:1360–1361

„Avoiding‘ RRT by a „Watch and Wait“ Strategy?

„Early“ vs. „late“ initiation of RRT

no RRT in the delayed arm in + reduced RRT dependency at 90d

- AKIKI 49%
- IDEAL-ICU 38%
- STARRT-AKI 38% 6% (vs. 10.4%) CKD

BUT…

How long can/should we wait?

Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial

multicentre, open-label, randomised, controlled trial in 39 ICUs (France)

n= 747
AKI KDIGO 3 patients requiring **vasopressors/mechanical ventilation**

n=127 emergency indication for RRT
n=352 did not fulfil criteria for
domisation/no RRT

„more-delayed" strategy:
79% RRT
HR for death 1,65 (95% KI: 1.09-2.50, p=0.018)

n=137
„delayed strategy":
RRT ≤ 12 h after fulfilling criteria for randomisation

n= 141
„more delayed strategy":
RRT if
- K≥6 mmol/l,
- pH ≤ 7.15
- Lung edema/hypoxemia/ respiratory support
- BUN > 140 mg/dl

20%

60%

Primary endpoint: RRT free days

Gaudry S et al, Lancet 2021; 397: 1293–300

Any objection against a „watch and wait“ strategy in patients with AKI?

No..

- As long as there is no absolute indication,
- a delayed strategy for RRT in patients with AKI and **oliguria $\leq$ 72h** or **BUN < 112 mg/dl** providing **tight monitoring/control of metabolic situation and volume status** may be pursued

Conditions for a „watch and wait " strategy

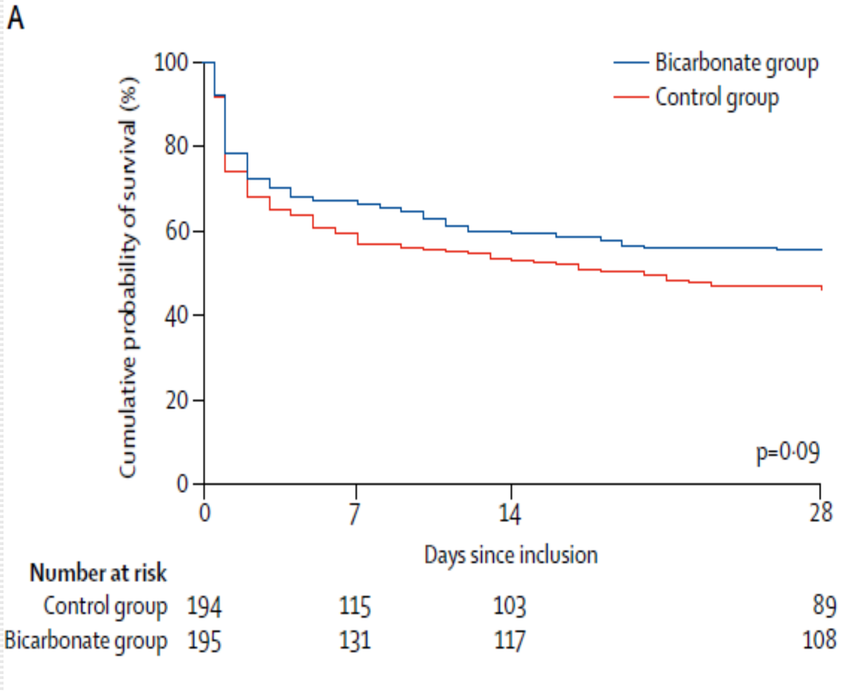
1. Optimise hemodynamics
2. Avoid nephrotoxins
3. Provide nutrition
4. Monitor volume status (obtain cumulative fluid-balance) -> **use diuretics, if needed**
5. Monitor electrolyte status (potassium, phosphate) -> **diuretics**
6. Monitor acid-base status (renal acidosis!) -> **bicarbonate substitution**
7. Monitor renal function
8. Monitor patient condition (e.g. neurologic status, vigilance)

Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial

26 French ICUs, 389 patients w. **metabolic acidosis**, (ph ≤ 7. 2, s-bicarb. < 20 mmol/l)
4.2% sodium bicarbonate to achieve pH >7.3, 125 -250 ml/30 min, max 1L/d vs. no sodium bicarbonate

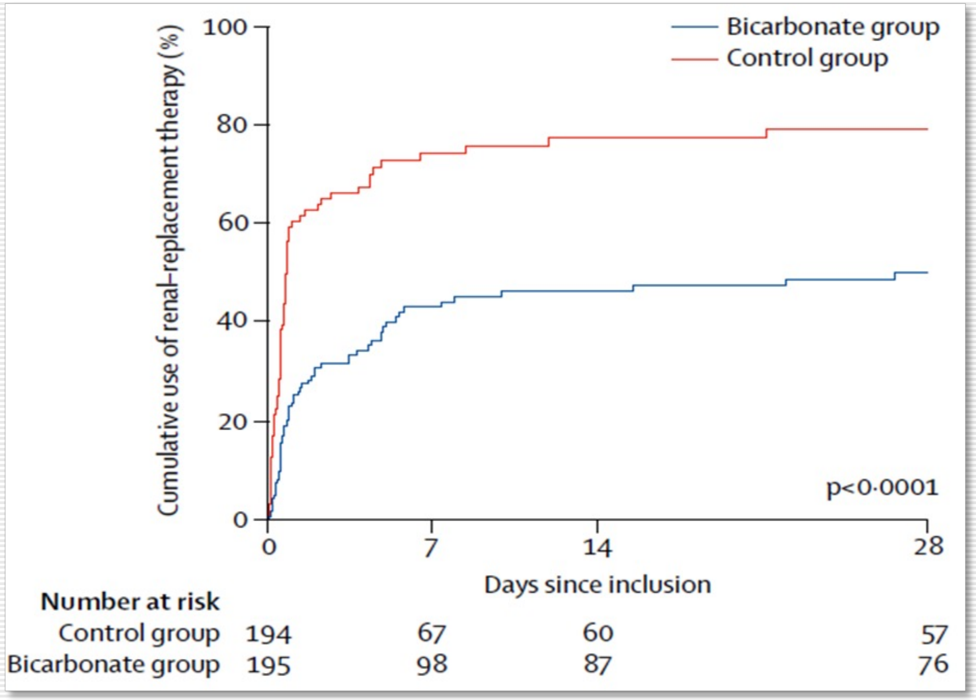
Cumulative fluid balance within first 24h: 3500 ml (co) vs. 3350 ml (Nabic), p=0.835
Average amount of NaBic within first 24: 500 ml (250-750)

Overall cohort



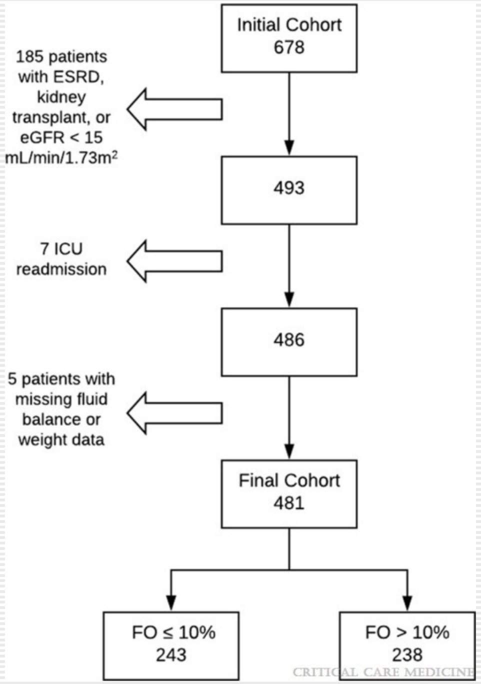
AKI stages 2-3 (pre-specified)

Use of RRT



Saber J. et al, *Lancet 2018; 392: 31–40*

Fluid Overload Associates With Major Adverse Kidney Events in Critically Ill Patients With Acute Kidney Injury Requiring Continuous Renal Replacement Therapy



Study Outcomes	Whole Cohort (n = 481)	FO ≤ 10% (n = 243)	FO > 10% (n = 238)	p
Major adverse kidney event[a] (%)	363 (75.5)	174 (71.6)	189 (79.4)	0.047
Hospital mortality (%)	290 (60.3)	133 (54.7)	157 (66.0)	0.012
ICU-free days[b], median (25–75th percentile)	9 (2–17)	10 (2.25–17)	9 (1–17)	0.485
Ventilator-free days[c], median (25–75th percentile)	17 (8–22)	19 (11.25–23)	15 (6–21)	0.017

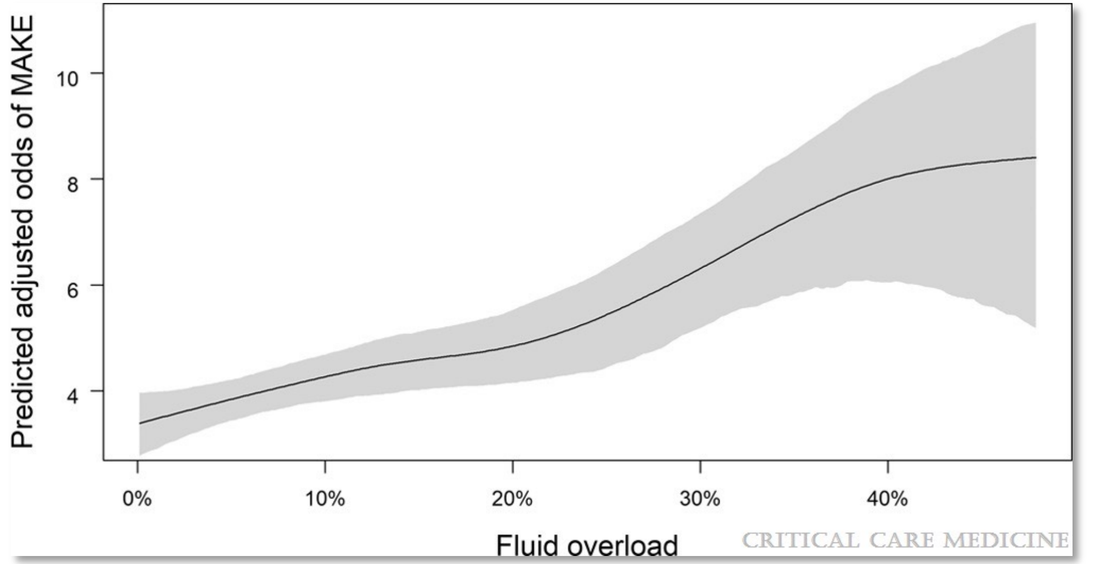
FO = fluid overload.

[a]Major adverse kidney event, which includes mortality at or within 90 d of discharge, continued rena an inability to recover more than 50% of baseline estimated glomerular filtration rate within 90 d of

[b]ICU-free days was defined as 28 d minus the length of the ICU stay, with a score of 0 being assig hospital discharge.

[c]Ventilator-free days was defined as the number of days in which a ventilator was not used during th counted as ventilator-free. Data reported only for patients surviving to hospital discharge.

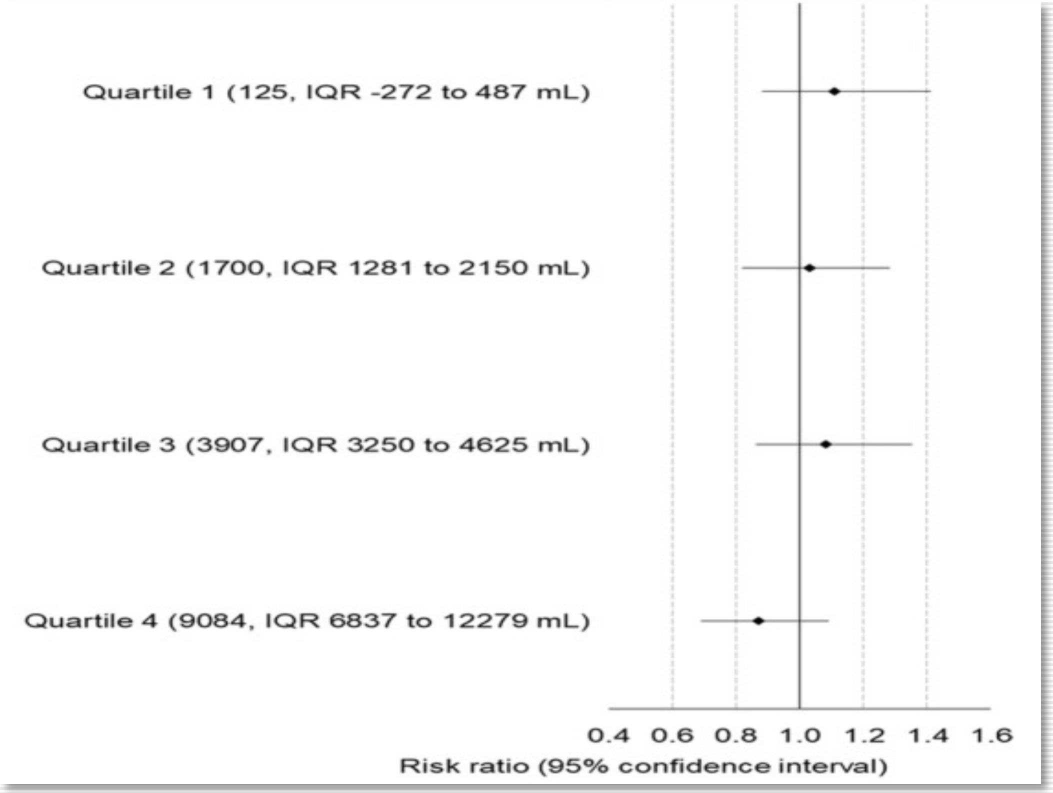
$$FO = \sum (\text{fluid intake - fluid output}) / (\text{admission weight}) \times 100\%$$



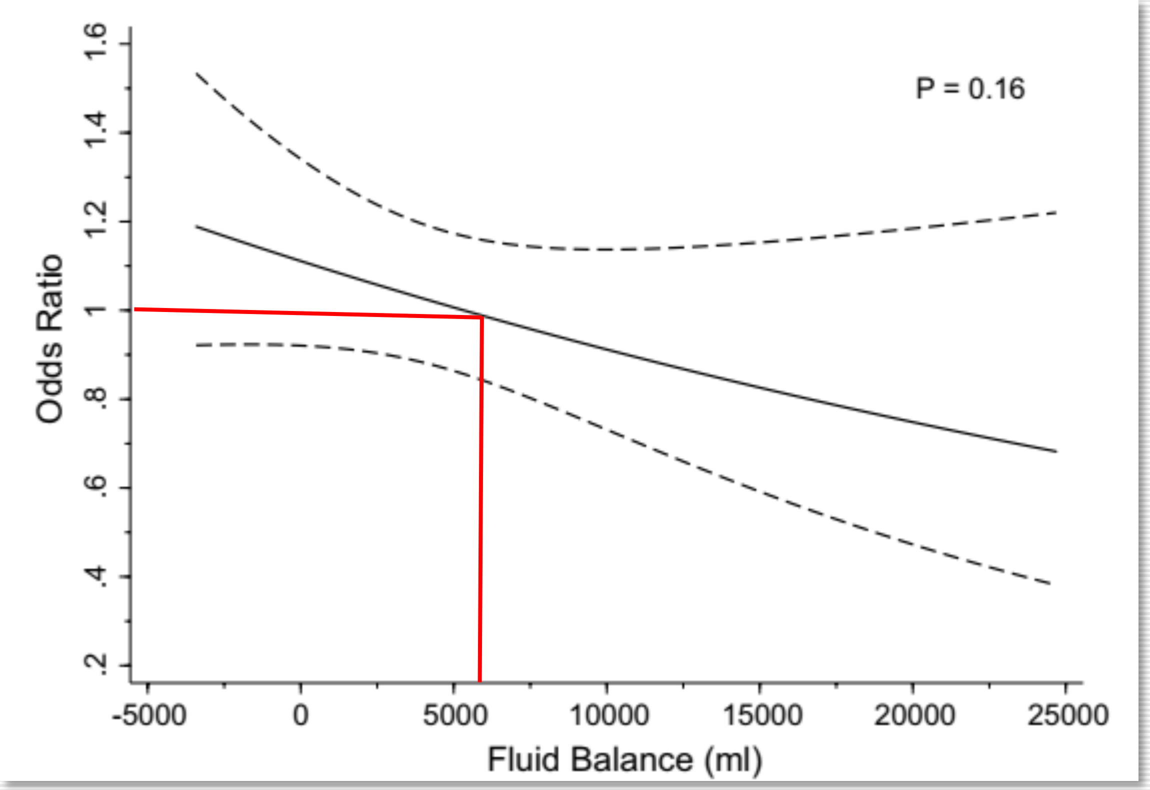
Woodward C et al, *Critical Care Medicine47(9):e753-e760, September 2019*

Fluid balance and renal replacement therapy initiation strategy: a secondary analysis of the STARRT-AKI trial

The effect of **accelerated** versus standard RRT initiation on 90-day mortality across quartiles of cumulative fluid balance at randomization



The effect of **accelerated RRT initiation**, as compared to standard RRT initiation, on all-cause mortality across the spectrum cumulative fluid balance at randomization



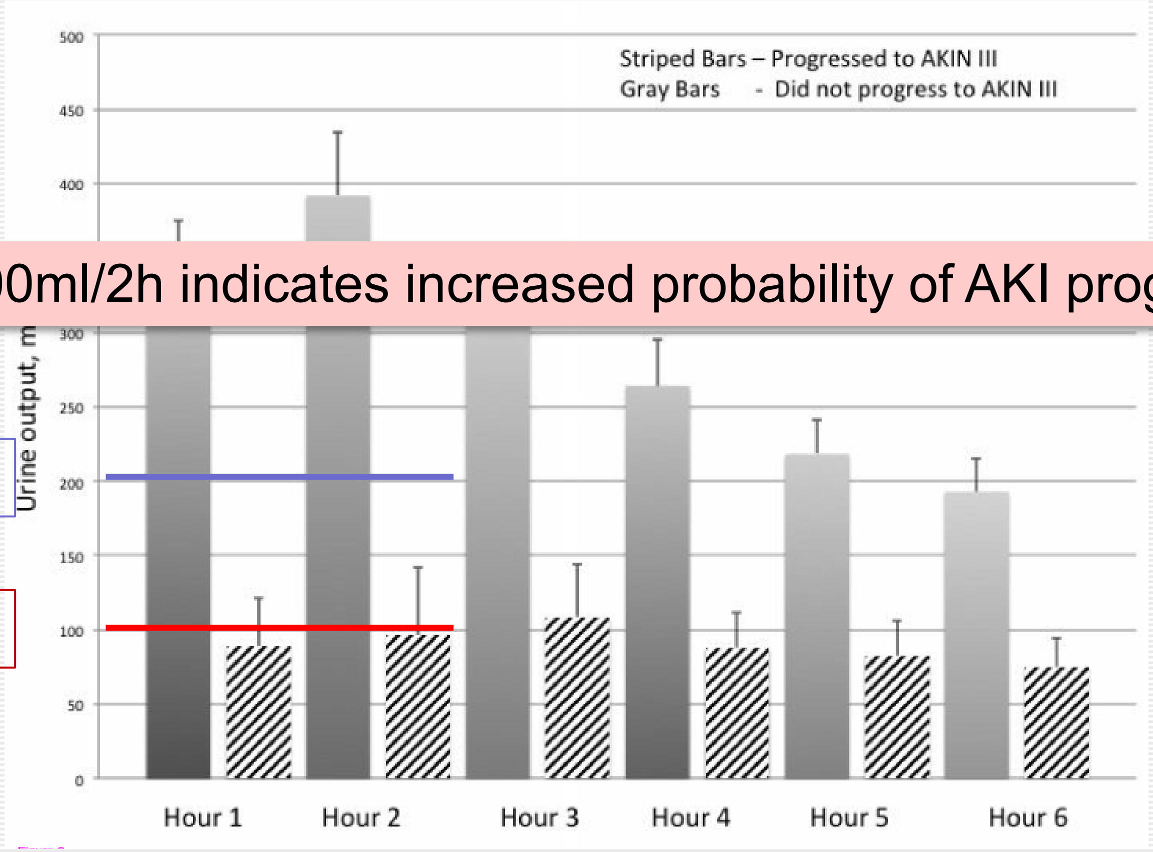
Wald *et al. Critical Care (2022) 26:360*

Optimal Timing of RRT

Which biomarkers may help in decision making?

Development and standardization of a furosemide stress test to predict the severity of acute kidney injury

Urinary Output response to 1.0-1.5 mg/kg furosemide in patients with AKI stage I or II



UO < 200ml/2h indicates increased probability of AKI progression

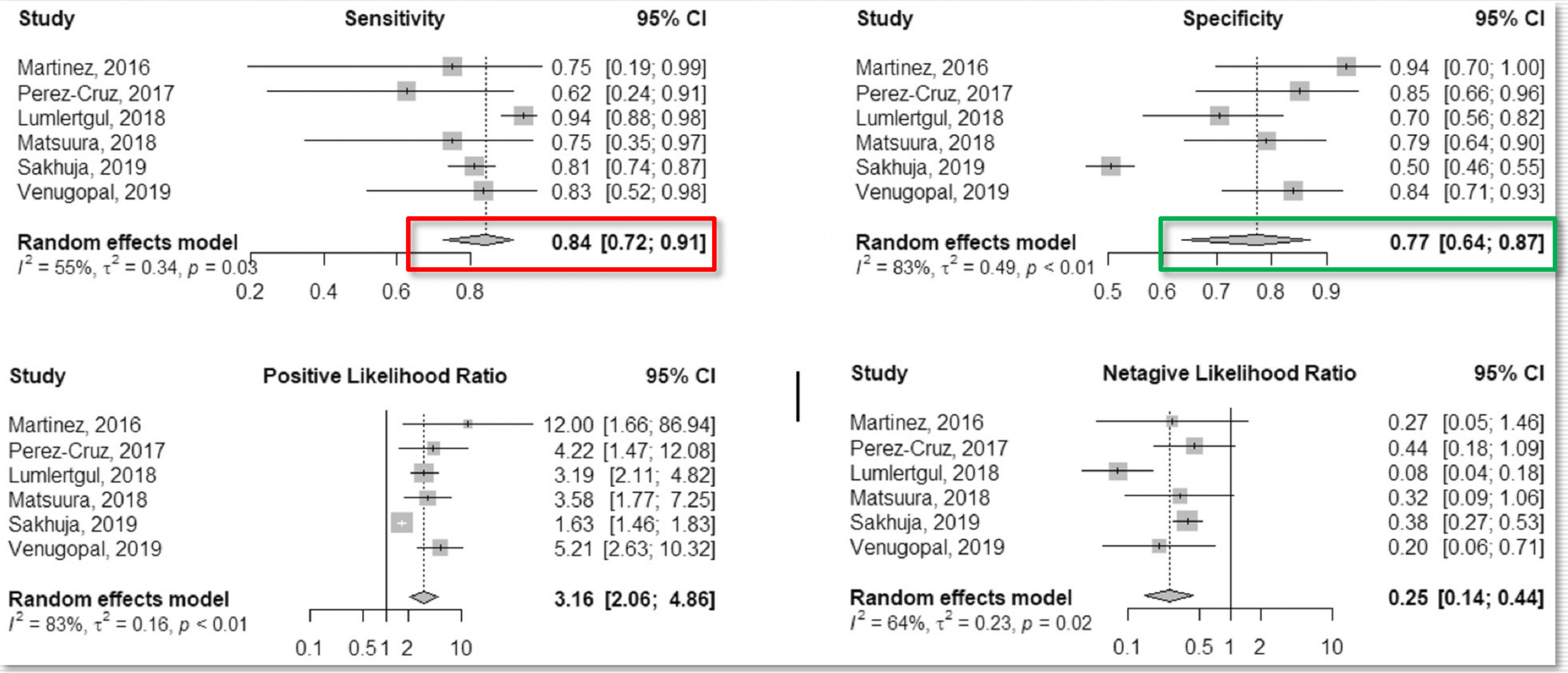
Sensitivity 87%

Sensitivity 84%

Chawla LS et al, Crit Care 2013, 17:R207

Furosemide stress test as a predictive marker of acute kidney injury progression or renal replacement therapy: a systemic review and meta-analysis

11 trials / 1366 patients:
AKI stage progression reported in 517 patients, renal replacement therapy reported in1017 patients



Chen et al. Critical Care (2020) 24:202

Biomarkers of persistent severe AKI

Prediction of persistent AKI
(= AKI stage 3 >72h)

C-C motif chemokine ligand 14 (CCL14)

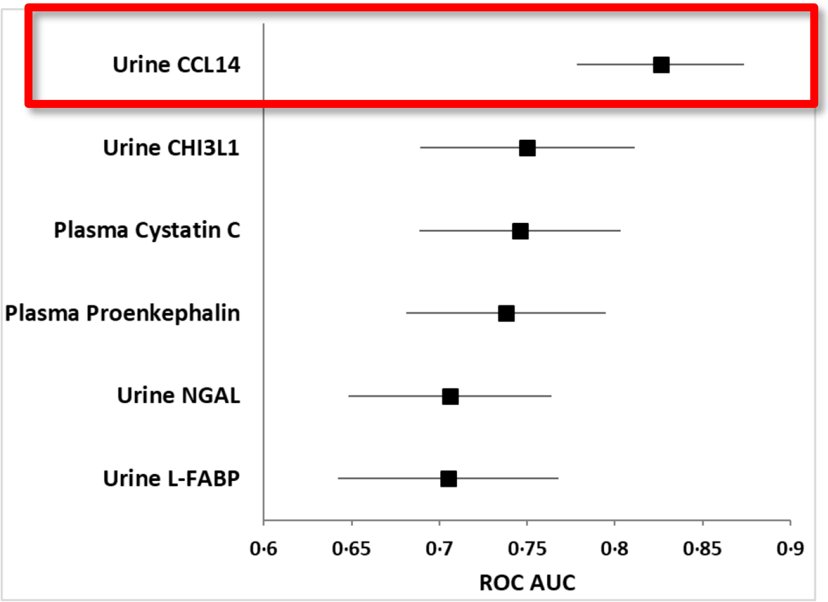
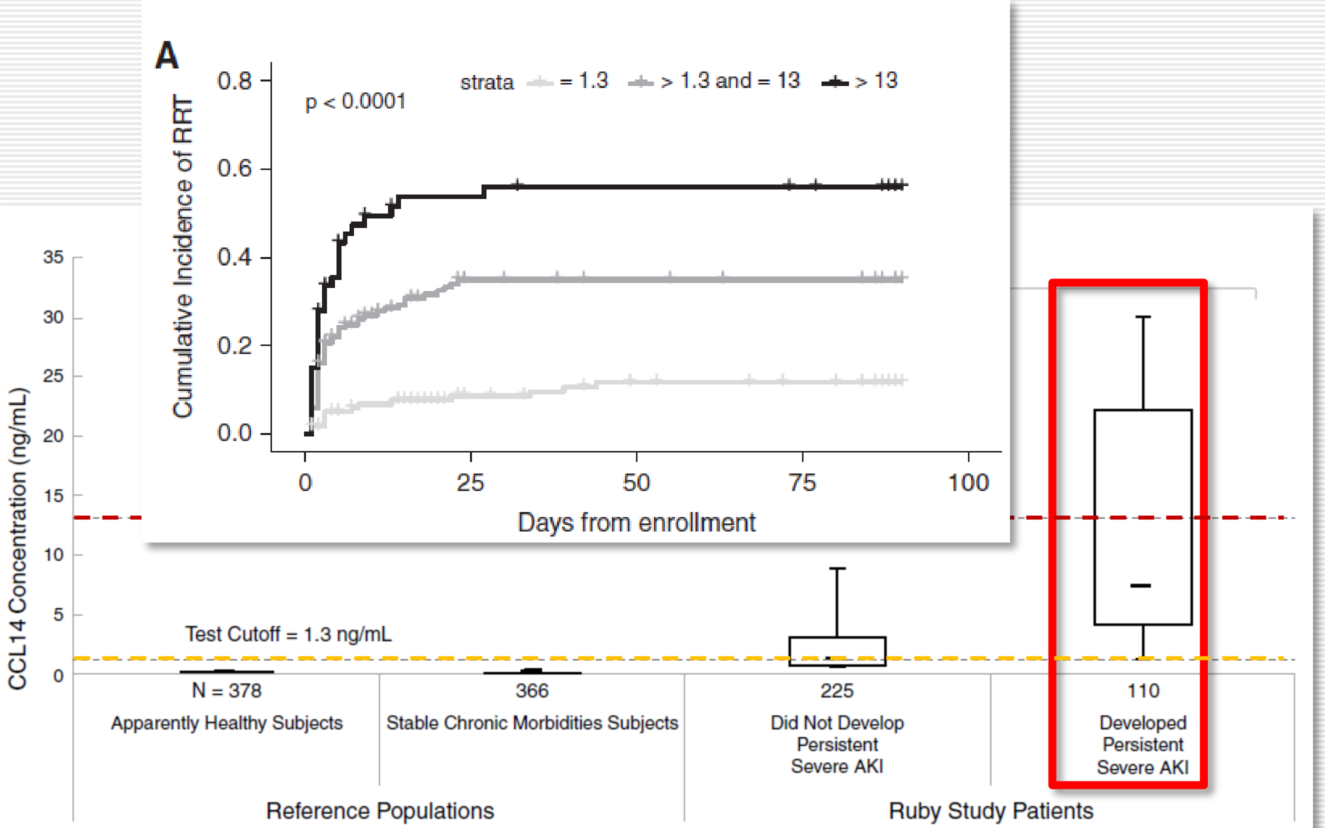


Figure 2. Area under the ROC curve (AUC) for prediction of persistent stage 3 AKI by urine CCL14 and other AKI biomarkers. Biomarker concentrations were measured in urine and plasma samples collected at enrolment. The AUC for urine CCL14 was significantly (p<0·05) greater than for all other biomarkers shown.



Endpoint	Cutoff (ng/mL)	% below	% above	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value	Negative Likelihood Ratio	Positive Likelihood Ratio
Persistent severe AKI	1.3	37.0	63.0	91% 84% – 96%	51% 44% – 57%	92% 86% – 96%	47% 40% – 54%	0.18 0.10 – 0.33	1.84 1.59 – 2.13
	13	83.9	16.1	35% 27% – 45%	93% 89% – 96%	75% 69% – 80%	72% 58% – 84%	0.69 0.60 – 0.80	5.32 3.07 – 9.22

E. Hoste et al, Intensive Care Med (2020) 46:943–953

Koyner J. et al, KIDNEY360 3: 1158–1168, 2022.

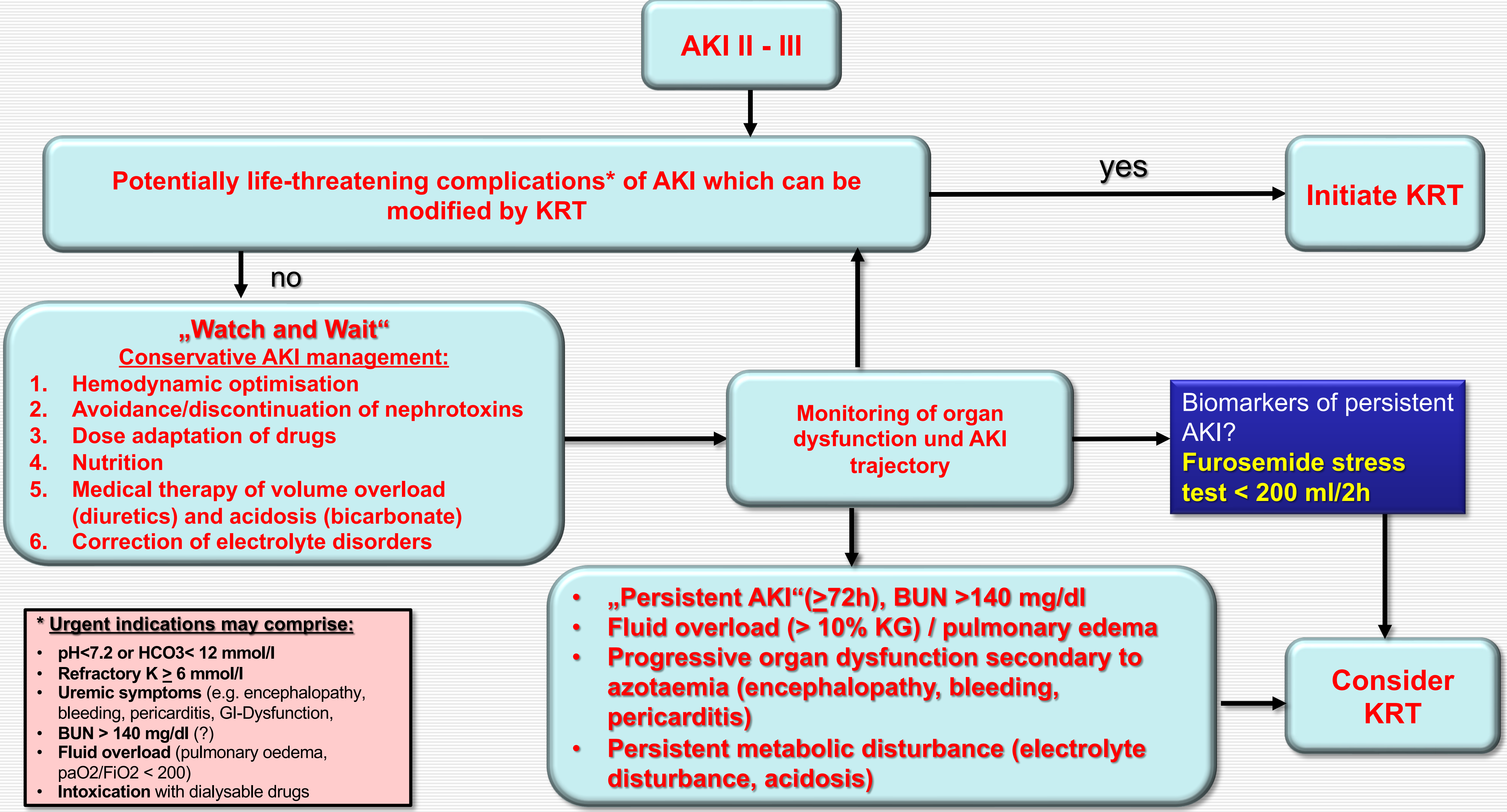
Predicting the Development of Renal Replacement Therapy Indications by Combining the Furosemide Stress Test and Chemokine (C-C Motif) Ligand 14 in a Cohort of Postsurgical Patients

Prospective observational cohort study: critically ill adult patients with an oliguric stage 2 AKI were (n=208). At study inclusion, patients had to be either mechanically ventilated and/or receiving vasopressors.
Exclusion CKD < 20 ml/min/1.73 m²

Biomarker	FST Negative (UO < 200 mL/2 hr), AUC (95% CI)	FST Positive (UO > 200 mL/2 hr), AUC (95% CI)	*p*[a]
Chemokine (C-C motif) ligand 14	0.855 (0.770–0.940)	0.658 (0.517–0.800)	0.019
Neutrophil gelatinase-associated lipocalin	0.716 (0.614–0.819)	0.718 (0.602–0.834)	0.98
Dipeptidyl peptidase 3	0.697 (0.568–0.826)	0.707 (0.572–0.843)	0.91

CCL14 : AUC 0.83 (95% CI, 0.77–0.89)
FST : AUC 0.79 (95% CI, 0.74–0.85)
Combination of FST and CCL14: AUC 0.87 (95% CI, 0.82–0.92)

Meersch M et al. Critical Care Med (2023) 51 EPUB


AKI II - III
Potentially life-threatening complications* of AKI which can be modified by KRT
yes
Initiate KRT
no
„Watch and Wait"
Conservative AKI management:
1. Hemodynamic optimisation
2. Avoidance/discontinuation of nephrotoxins
3. Dose adaptation of drugs
4. Nutrition
5. Medical therapy of volume overload (diuretics) and acidosis (bicarbonate)
6. Correction of electrolyte disorders
Monitoring of organ dysfunction und AKI trajectory
Biomarkers of persistent AKI?
Furosemide stress test < 200 ml/2h
„Persistent AKI"(≥72h), BUN >140 mg/dl
Fluid overload (> 10% KG) / pulmonary edema
Progressive organ dysfunction secondary to azotaemia (encephalopathy, bleeding, pericarditis)
Persistent metabolic disturbance (electrolyte disturbance, acidosis)
Consider KRT
* Urgent indications may comprise:
pH<7.2 or HCO3< 12 mmol/l
Refractory K ≥ 6 mmol/l
Uremic symptoms (e.g. encephalopathy, bleeding, pericarditis, GI-Dysfunction,
BUN > 140 mg/dl (?)
Fluid overload (pulmonary oedema, paO2/FiO2 < 200)
Intoxication with dialysable drugs

Accuracy of clinicians' ability to predict he need for renal replacement therapy: a prospective multicenter study

Prospective observational multi-centre trial
649 patients admitted to the ICU, 270 developed AKI, 77 required RRT

RRT prediction at ICU admission

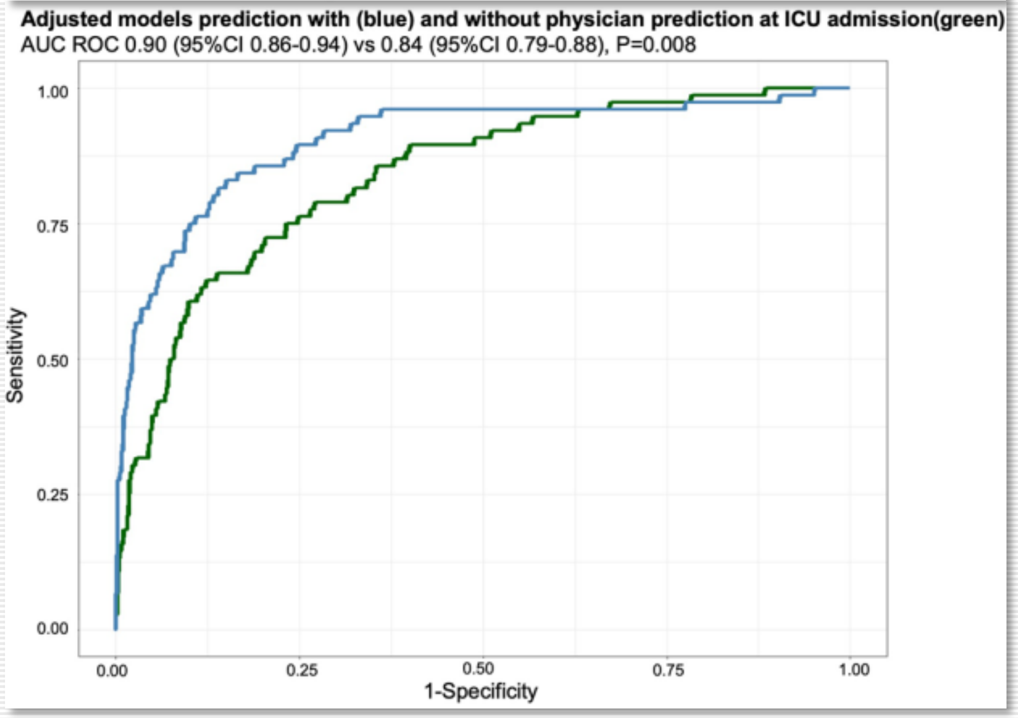
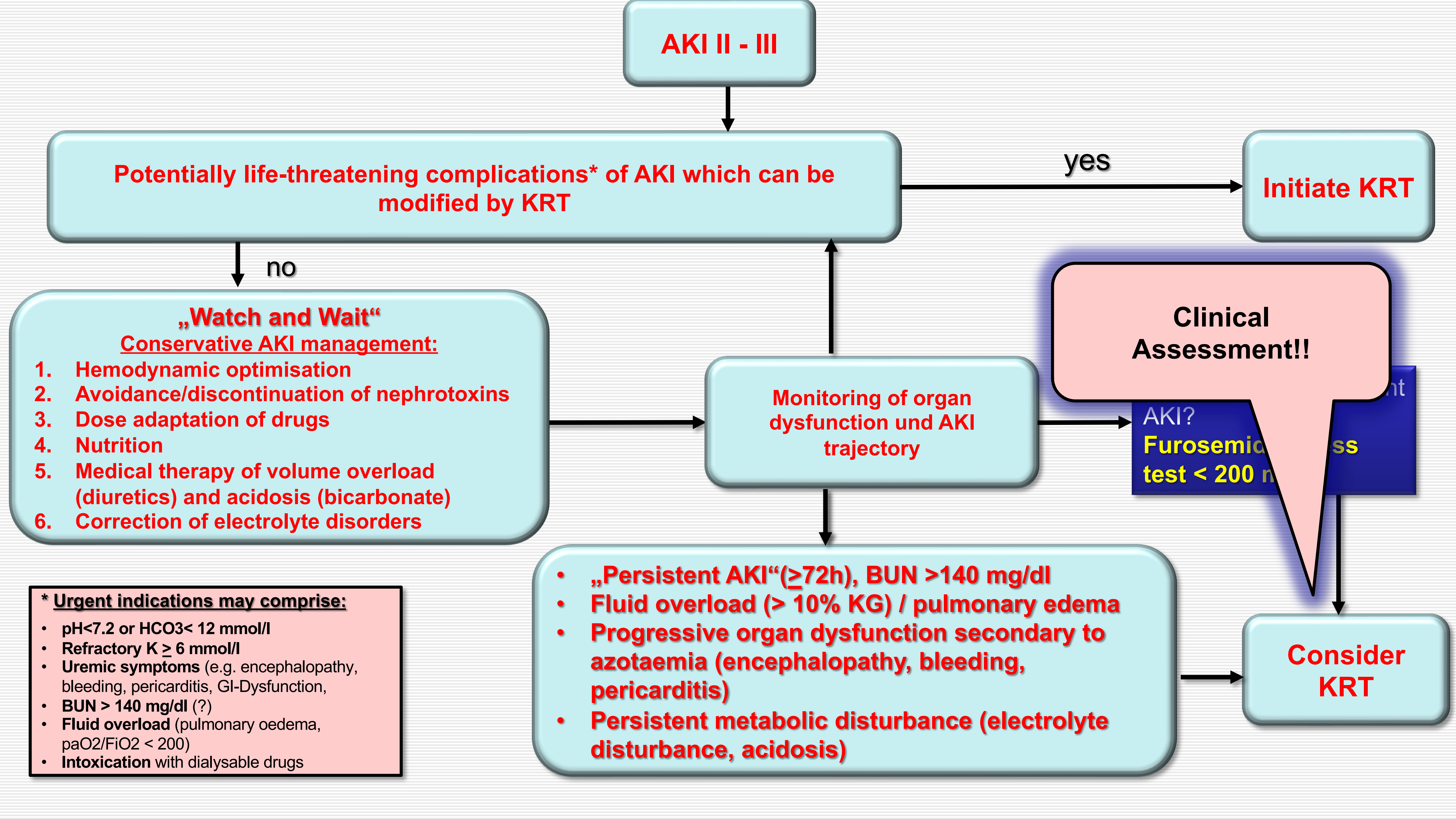


Table 3 Physician's prediction of need of RRT at AKI

Variables	OR [95% CI]	*P* value
SOFA score at AKI diagnosis	0.93 [0.85–1.02]	0.14
Serum creatinine—per 100 µmol/l	0.99 [0.85–1.17]	0.94
Urinary output at admission—ml/kg/h	0.94 [0.63–1.41]	0.76
Physician's prediction at AKI diagnosis	1.06 [1.04–1.07]	< 0.001

SOFA Sequential Organ Failure Assessment, *AKI* acute kidney injury, *RRT* renal replacement therapy, *OR* odds ratio

Sitbon *et al. Annals of Intensive Care (2022) 12:95*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Thanks for your attention

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