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Renal Replacement Therapy – Choices and Outcomes

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Clinical Focus

- Lupus Nephritis
- ICU Nephrology

DISCLOSURES

- Consultant for GlaxoSmithKline, Apellis Pharma, Optum Consulting
- Research Support from Alexion Pharmaceuticals

AKI Epidemiology

KDIGO definition of AKI

- Serum Creatinine rises by 0.3mg/dl in 48 hours

OR

- Creatinine increases 1.5-fold from reference value

OR

- Urine Output is < 0.5 ml/kg/hr for >6 hours

Stages of AKI

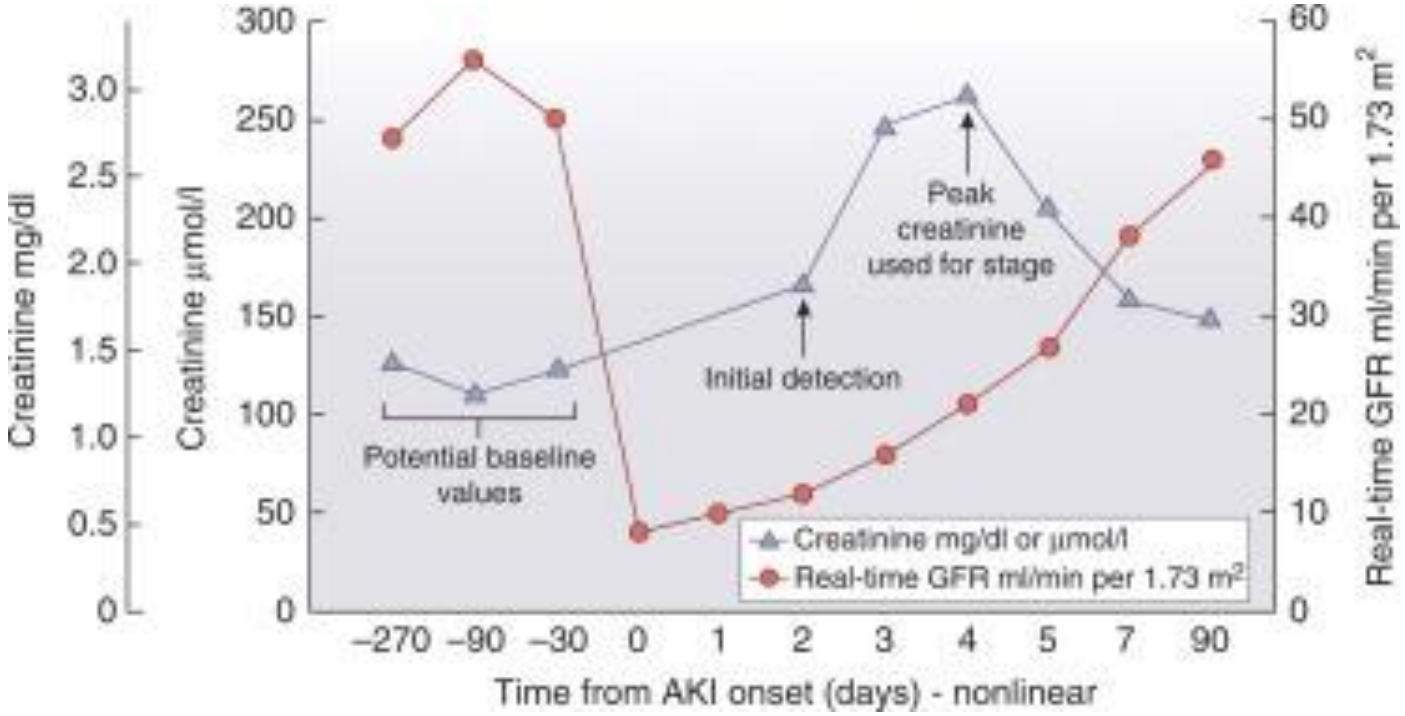
Stage 1
- Creatinine increase by 0.3 or 1.5-2 fold from baseline.

Stage 2
- Creatinine increase > 2-3 fold from baseline

Stage 3
- Creatinine >4 or initiated on RRT

AKI Epidemiology

- Limitations of creatinine as measure of renal function
  - Non-GFR determinants of creatinine
  - Late marker of AKI
  - Decrease in muscle mass with prolonged ICU stay
- Cystatin C may be a better measure of AKI in some ICU patients
  - Less affected by muscle mass
  - Other non-GFR determinants
- Need better markers of tubular injury!



Kid Int, 2015

AKI Epidemiology – Risk Factors

Chronic Risk Factors

- Old Age
- Diabetes
- Hypertension
- CKD
- CVD
- Chronic Liver Disease
- HIV
- Obesity

Acute Risk Factors

- Shock
- Sepsis
- Nephrotoxins
- Surgery
- Hyperuricemia
- Hypoalbuminemia
- Hyperglycemia
- Anemia

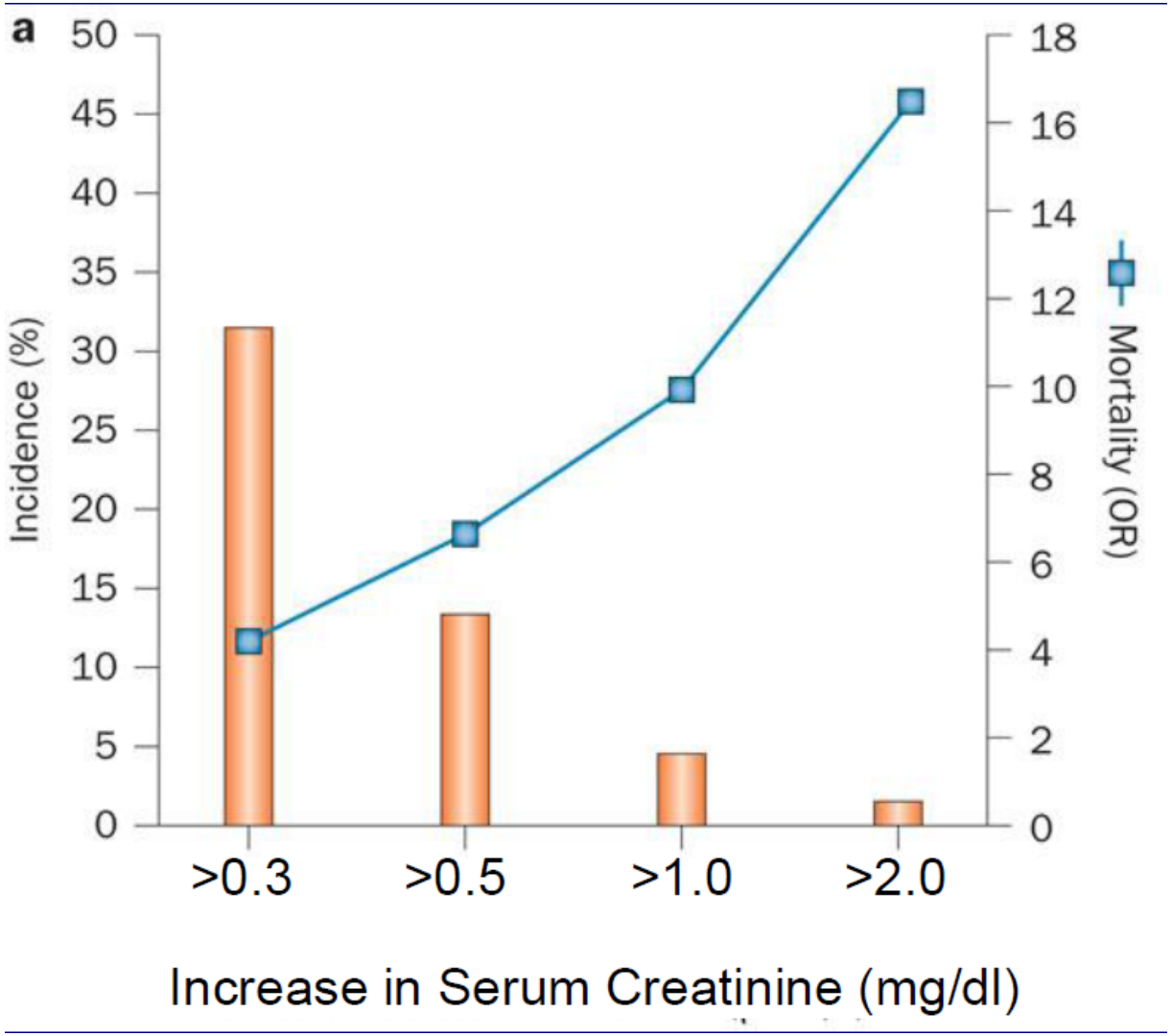
AKI Pathophysiology

Incidence/Prevalence

- Present in 5-7% of hospitalized patients
- Up to 25% of ICU admissions
- 6% of ICU admissions require RRT

Outcomes

- Mortality increases with AKI severity
- 50% mortality in patients requiring RRT in the ICU
- 90% of patients who recover survive the ICU stay do not need long term RRT
- Likelihood of renal recovery depends on baseline renal function



Nat Rev Neph, 2013

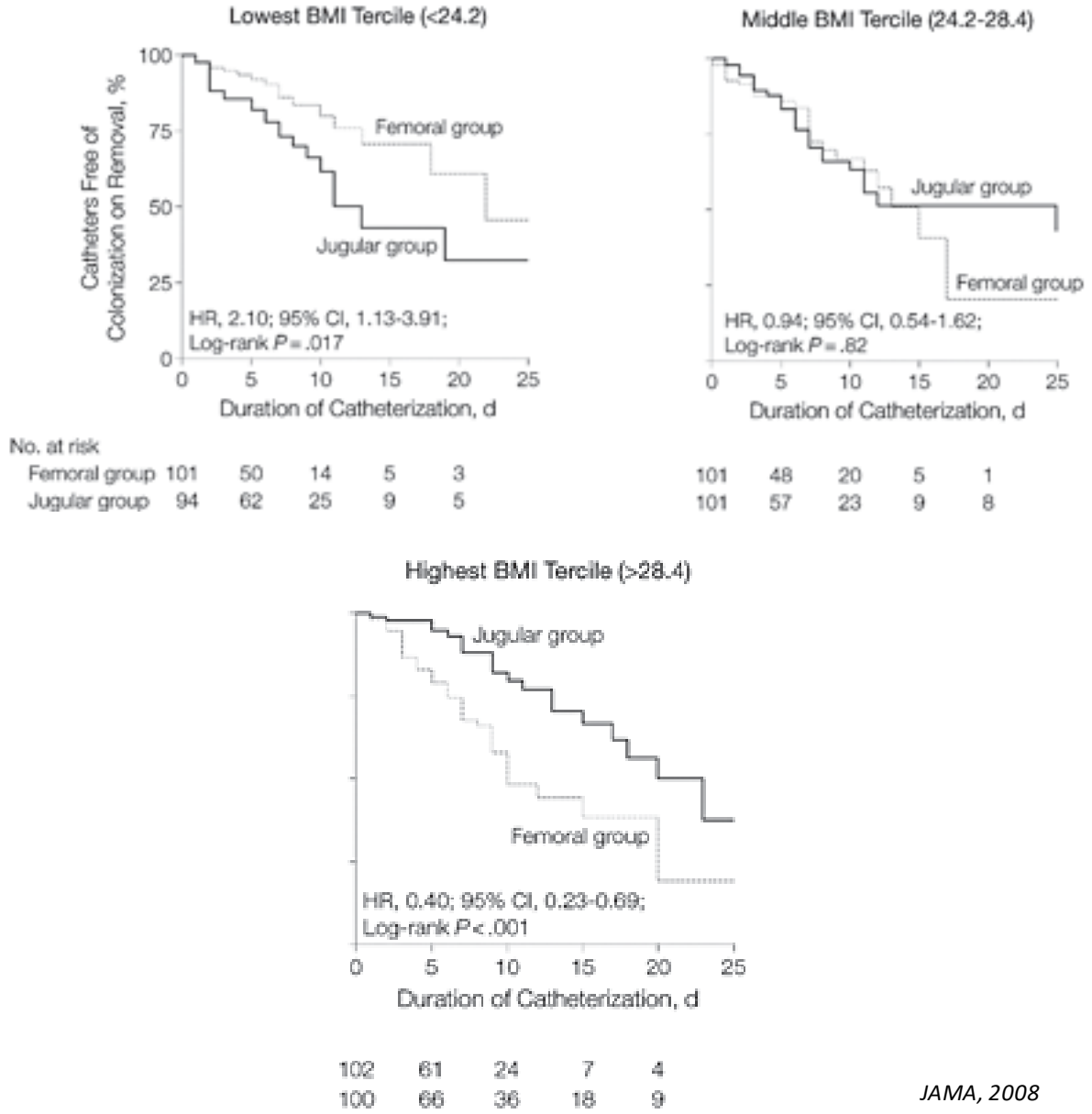
Components of RRT in the ICU

1. Vascular Access
2. Modality
3. Anticoagulation
4. Early vs Late Start
5. Dose
6. Complications

Vascular Access

- An uncuffed double-lumen catheter should be used at dialysis initiation
- Preferred site is RIJ -> Fem -> LIJ
- Failure rates
  - RIJ 6.6%
  - Fem 10.2%
  - LIJ 19%

- No greater risk of infection (catheter colonization) with femoral route except in patients in highest BMI tertile (>28)

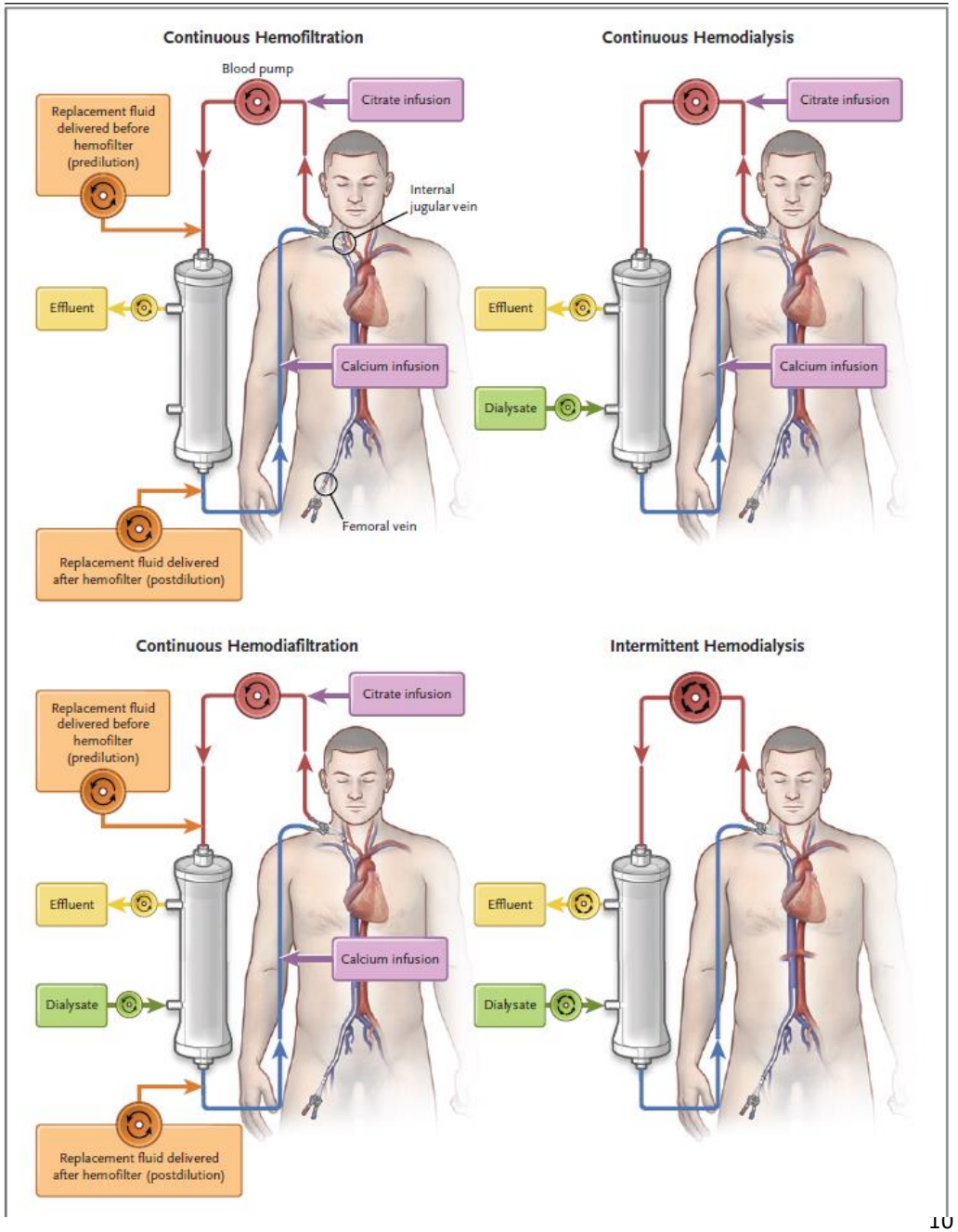


JAMA, 2008

Dialysis Modalities

- Choice of modality is based mostly on center experience.

- Main choices are:
  - CVVH
  - Intermittent HD
  - AVVH
  - SLED
  - Peritoneal Dialysis

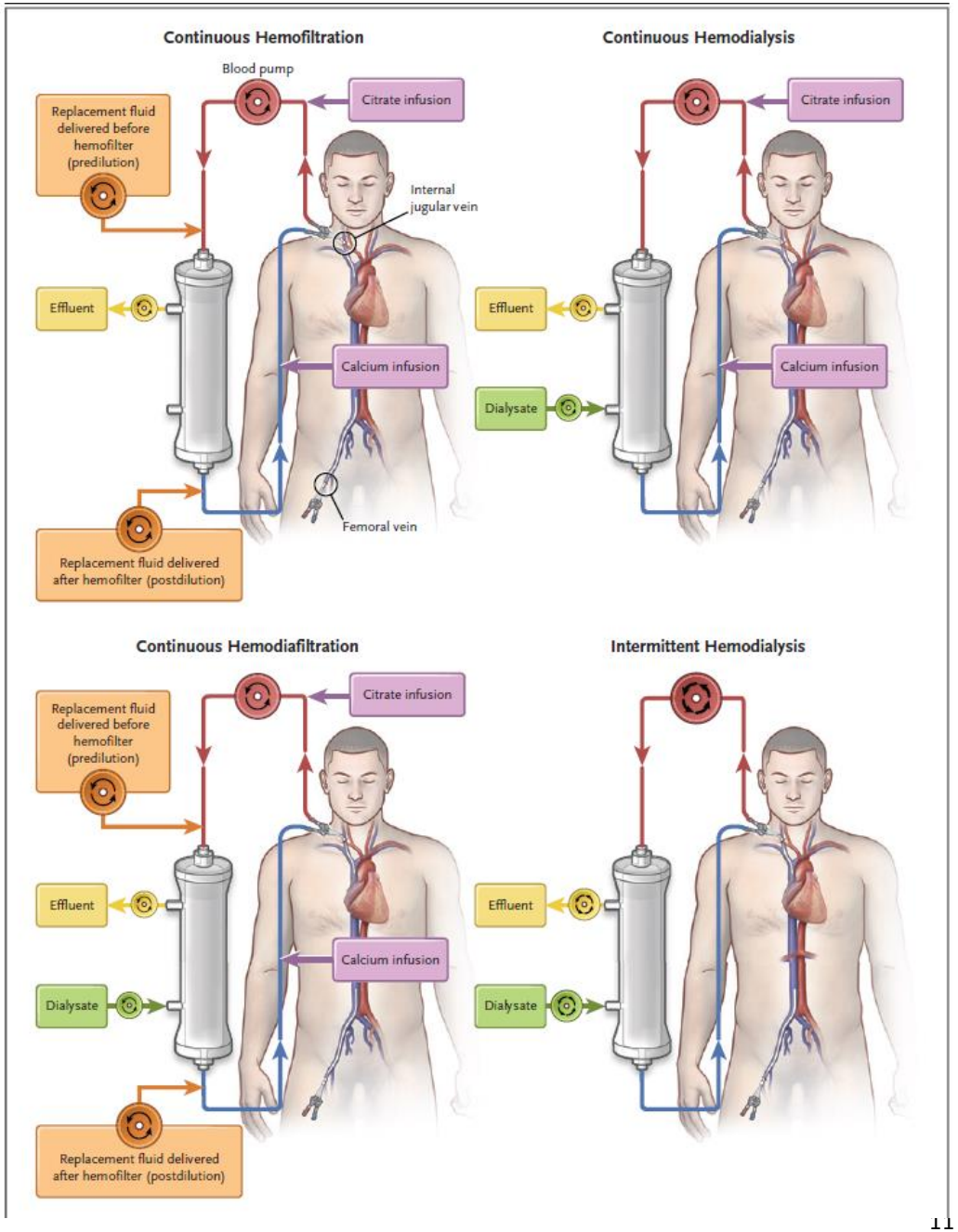


Gaudry et al, NEJM 2022

Dialysis Modalities

- Advantages of CVVH
  - Better control of fluid balance
  - Avoids rapid fluid shifts and hypotension (better cerebral perfusion)
  - Better for patients with suspected cerebral edema
  - Theoretically better renal recovery

- When HD is preferred
  - Rapid removal of poisons/toxins
  - Chronic HD patients with AV fistulae



Gaudry et al, NEJM 2022

Intermediate Therapies

Accelerated Veno-Venous Hemofiltration (AVVH)

- Clearance in CRRT determined by replacement fluid rate
- By markedly increasing RFR, can do dialysis for shorter periods and get the same dose.
- May not be hemodynamically tolerated.
- Bridge to HD

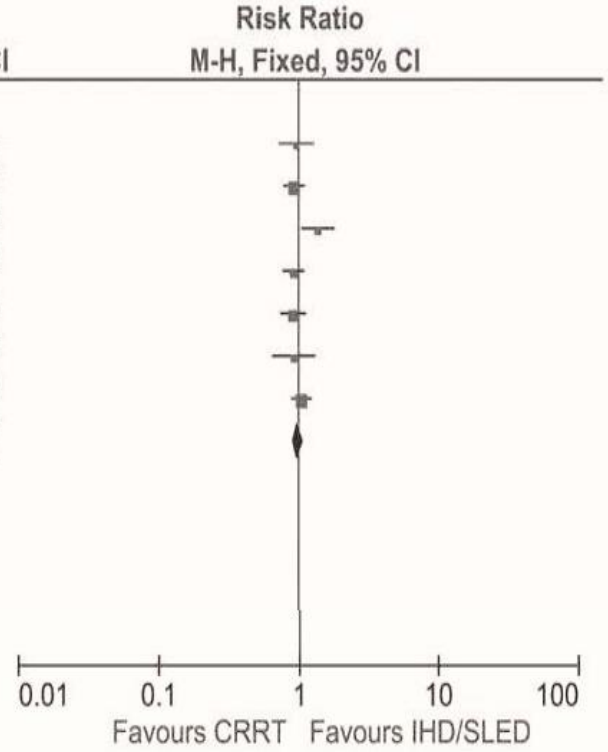
Slow Low Efficiency Dialysis (SLED)

- Standard iHD equipment
- 6-8 hours treatment
- Lower BFR and DFR
- Lower UF rate
- Requires dedicated dialysis nurse
- May not be tolerated in all patients

Meta-analysis of studies comparing CVVH to HD in the ICU: Mortality

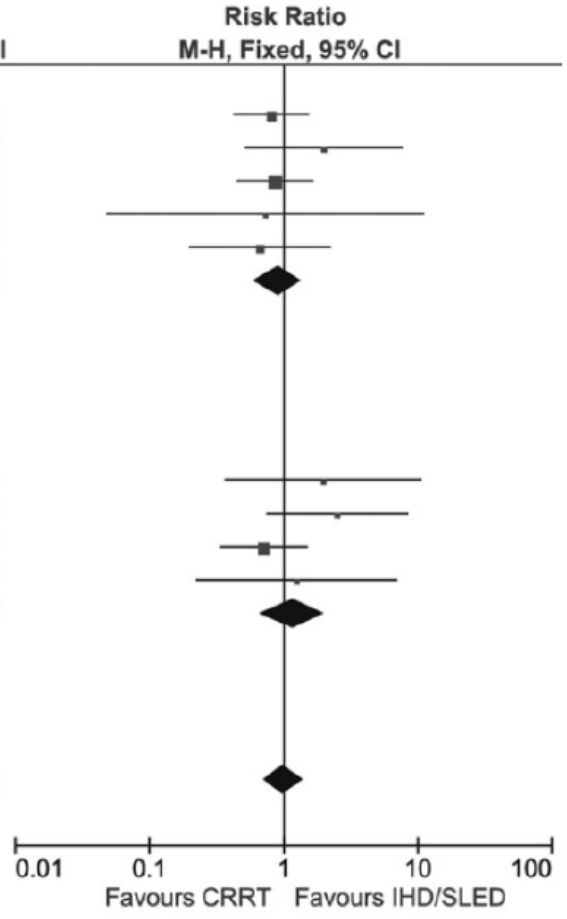
In-Hospital Mortality

Study or Subgroup	CRRT Events	CRRT Total	IHD or SLED Events	IHD or SLED Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 IHD						
Augustine 2004	27	40	28	40	5.5%	0.96 [0.72, 1.30]
Lins 2009	100	172	90	144	19.3%	0.93 [0.78, 1.11]
Mehta 2001	55	84	39	82	7.8%	1.38 [1.05, 1.81]
Noble 2006	49	64	44	53	9.5%	0.92 [0.77, 1.11]
Schefold	67	122	77	128	14.8%	0.91 [0.74, 1.13]
Uehlinger 2005	33	70	28	55	6.2%	0.93 [0.65, 1.33]
Vinsonneau 2006	107	175	107	184	20.6%	1.05 [0.89, 1.25]
Subtotal (95% CI)		**727**		**686**	**83.8%**	**1.00 [0.92, 1.09]**
Total events	438		413			
Heterogeneity: Chi² = 7.82, df = 6 (*P* = 0.25); I² = 23%						
Test for overall effect: Z = 0.01 (*P* = 0.99)						
Total events	540		494			

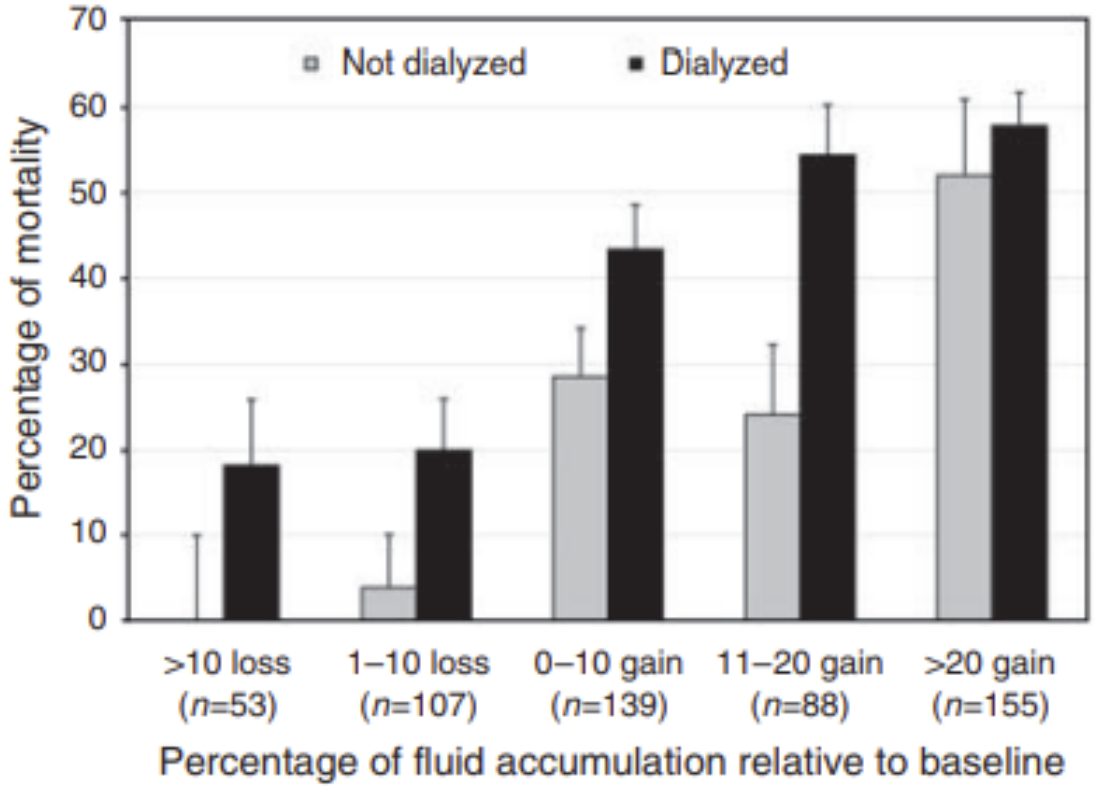


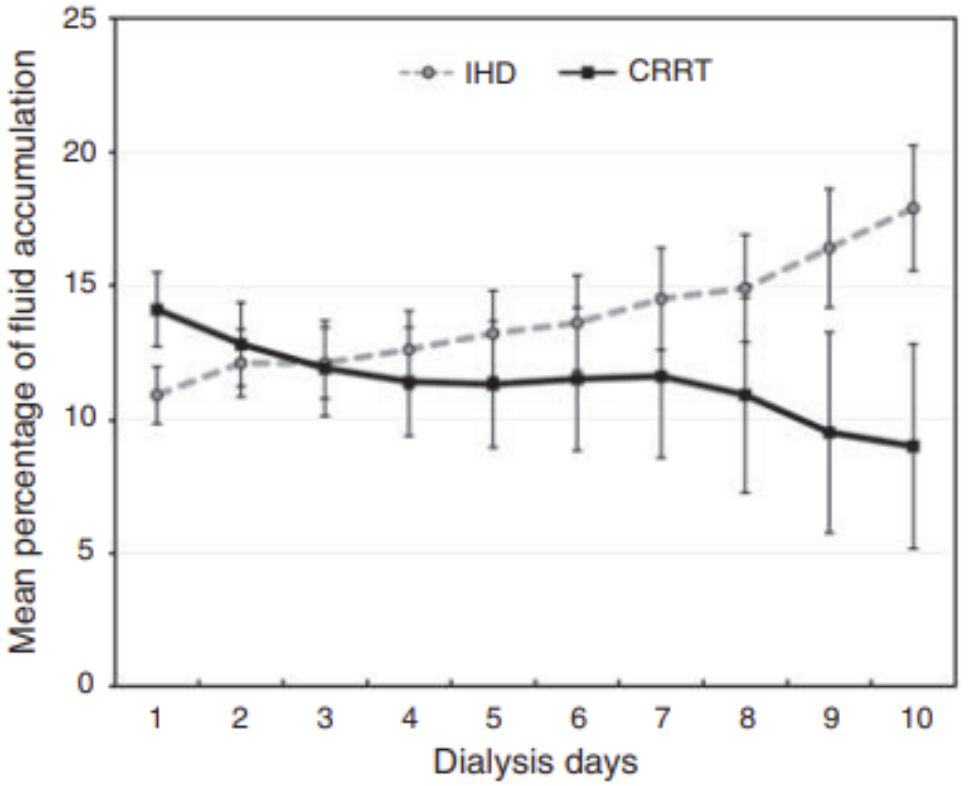
Meta-analysis of studies comparing CVVH to HD in the ICU: Renal Recovery

Study or Subgroup	CRRT Events	CRRT Total	IHD or SLED Events	IHD or SLED Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 IHD						
Augustine 2004	7	13	8	12	16.5%	0.81 [0.42, 1.54]
Mehta 2001	5	36	3	43	5.4%	1.99 [0.51, 7.77]
Schefold	13	57	14	53	28.7%	0.86 [0.45, 1.66]
Uehlinger 2005	1	37	1	27	2.3%	0.73 [0.05, 11.16]
Vinsonneau 2006	4	61	6	61	11.9%	0.67 [0.20, 2.25]
Subtotal (95% CI)		**204**		**196**	**64.8%**	**0.90 [0.59, 1.38]**
Total events	30		32			
Heterogeneity: Chi² = 1.69, df = 4 (*P* = 0.79); I² = 0%						
Test for overall effect: Z = 0.48 (*P* = 0.63)						
3.3.2 SLED						
Abe 2010	3	19	2	25	3.4%	1.97 [0.37, 10.66]
Abe 2011	6	16	3	20	5.3%	2.50 [0.74, 8.47]
Badawy 2013	8	31	12	33	23.0%	0.71 [0.34, 1.50]
Kumar 2004	2	8	2	10	3.5%	1.25 [0.22, 7.02]
Subtotal (95% CI)		**74**		**88**	**35.2%**	**1.15 [0.67, 1.99]**
Total events	19		19			
Heterogeneity: Chi² = 3.56, df = 3 (*P* = 0.31); I² = 16%						
Test for overall effect: Z = 0.52 (*P* = 0.61)						
Total (95% CI)		**278**		**284**	**100.0%**	**0.99 [0.71, 1.38]**
Total events	49		51			
Heterogeneity: Chi² = 5.71, df = 8 (*P* = 0.68); I² = 0%						
Test for overall effect: Z = 0.05 (*P* = 0.96)						
Test for subgroup differences: Chi² = 0.49, df = 1 (*P* = 0.48), I² = 0%						



Volume control is better with CVVH



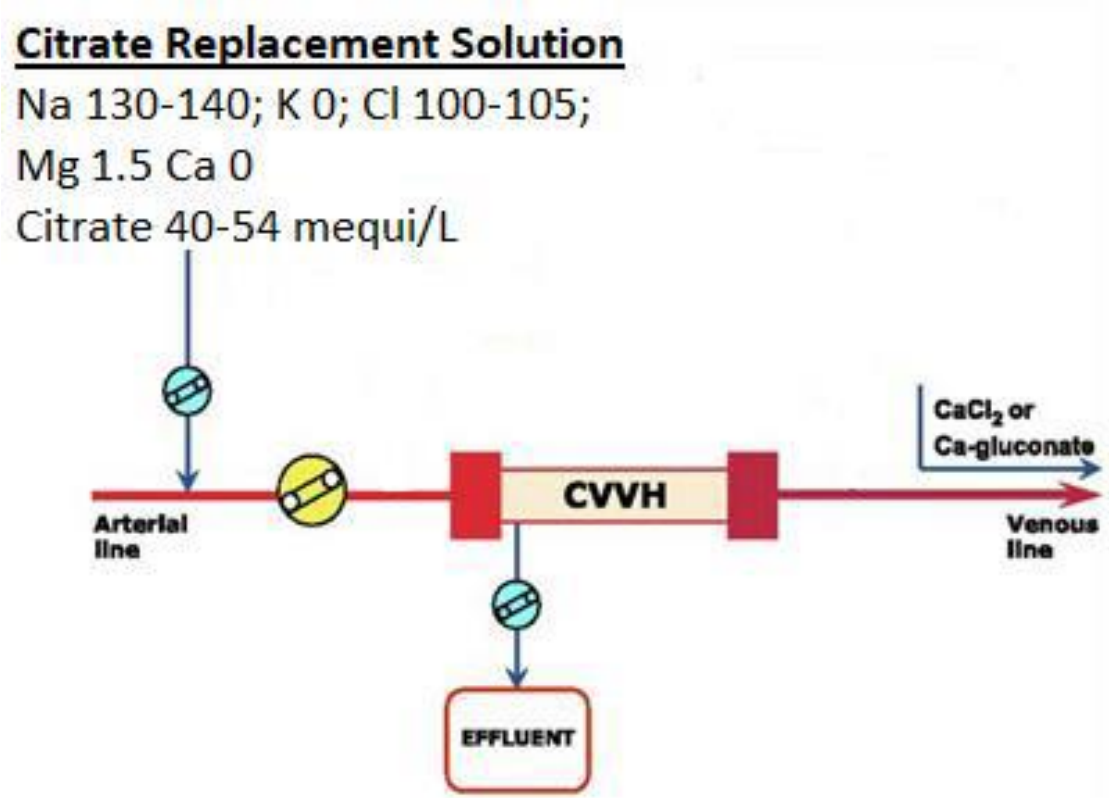


Bouchard et al, AJKD 2009

Anticoagulation for CVVH

Often required to prolong the life of CVVH filters
Biggest determinant of adequate dose is filter time

- Regional Heparinization
  - Difficult to monitor
  - Uncertain effectiveness
- Systemic Heparinization
  - Increased bleeding risk
- Citrate
  - Low bleeding risk
  - Risk for citrate toxicity



Citrate Anticoagulation

Citrate Protocol

- Can be given as replacement fluid or as a separate infusion
- Given pre-filter
- Chelates calcium inhibiting thrombin generation and preventing coagulation
- Lower Blood Flow Rate to maintain appropriate citrate concentration
- Needs post-filter calcium to reverse anticoagulant effect.
- Systemic citrate rapidly metabolized to bicarbonate (half life 5 mins)

Citrate Toxicity

- Due to accumulation of systemic citrate
- Low ionized calcium with high total calcium
- Elevated anion gap
- Increasing calcium requirements

- Most commonly seen in patients with liver disease. Can preclude the use of citrate
- Reduce RFR first before changing solution

Factors to Consider when Initiating RRT

Severity of AKI
- Creatinine trajectory
- Urine output/volume status
- Electrolyte derangements
- Acid-base status

Severity of Critical Illness
- Inciting event
- Non-renal organ dysfunction
- Pre-existing co-morbidities
- Likelihood of renal recovery

Potential Risks of RRT
- Line insertion
- Hypotension during RRT

Other Factors
- Availability of machines and staff
- Patient wishes
- Futility

Indications for RRT in Critically Ill Patients

- Start HD when an urgent indication exists
- Uremic complications rarely occur in patients with AKI.
- Metabolic encephalopathy is multifactorial in these patients and rarely responds to dialysis

ADQI/KDOGI guidelines on RRT Initiation
- Consider when metabolic and fluid demands exceed total kidney capacity
- Not based solely on renal function or AKI stage
- Consider the broader context – do not use a single BUN/Cr threshold***

Table 2. Indications for KRT in Critically Ill Patients.*

Urgent indications in patients with AKI

Refractory, severe hyperkalemia†
Refractory, severe metabolic acidosis†
Refractory, severe pulmonary edema†
Uremic complications: pericarditis, bleeding, and encephalopathy‡

Urgent indications in patients without AKI

Severe intoxication due to lithium, toxic alcohol poisoning (especially from ethylene glycol or methanol), metformin, or salicylate

Nonurgent indications

Persistent, severe AKI with blood urea nitrogen level >112 mg/dl, oliguria or anuria for more than 72 hr, or both§

No indications

Severe AKI (KDIGO stage 3) in the absence of complications¶
Sepsis in the absence of complicated AKI

Gaudry et al, NEJM 2022

Early vs Late Start RRT for AKI

Potential Advantages for Early Start

- Better volume control
- Better non-renal organ function
- Improved clinical outcomes based on observational studies (pre-2015)

- Early start generally defined by BUN or creatinine threshold accompanied by oliguria
- Absence of emergent indication for RRT

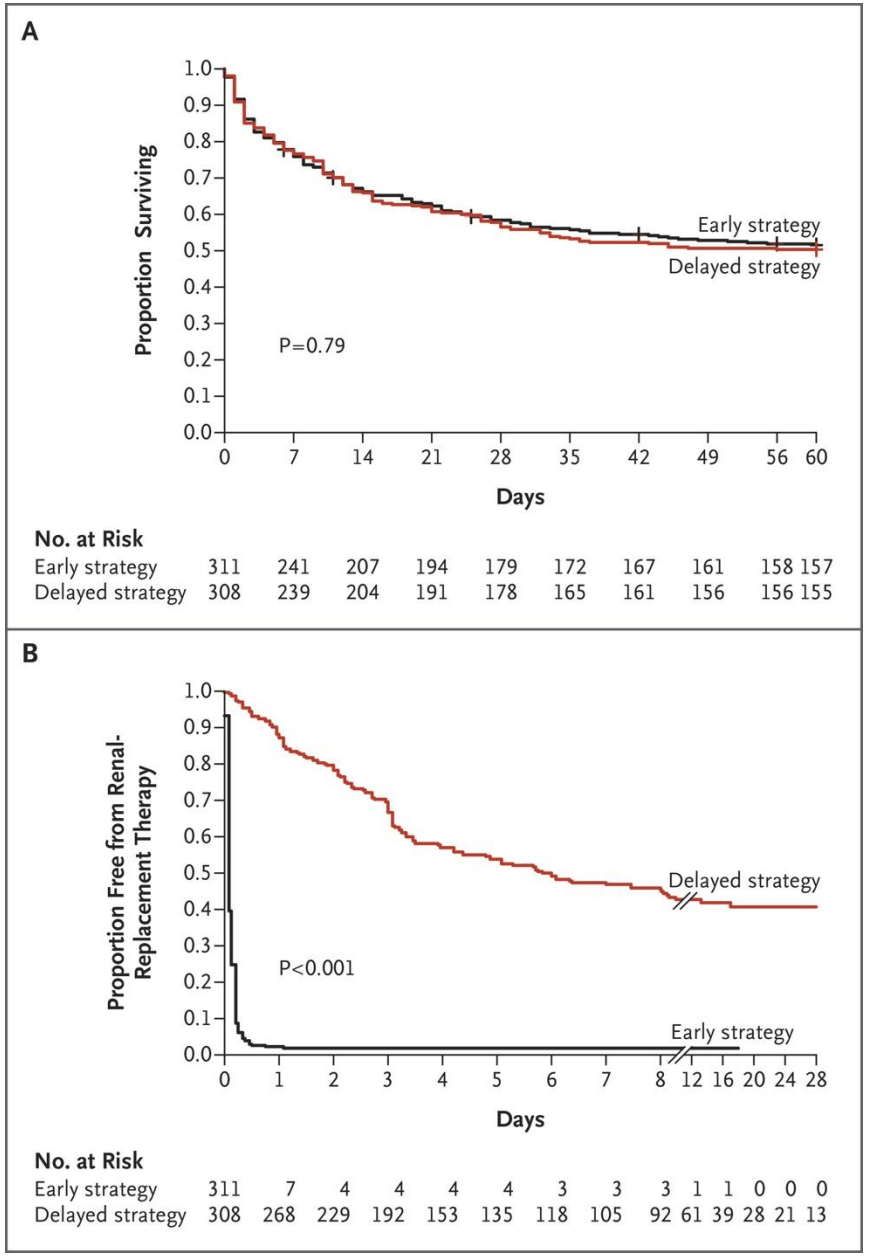
Disadvantages of Early Start

- Access
  - bleeding complications/infection
- Dialysis
  - Hemodynamic issues
  - Clotting and blood loss
  - Loss of nutrients
- Renal
  - Delayed renal recovery
  - Dialyzing patients who may not ultimately need it
- Increased cost

Early vs Late – AKIKI Study

Adult ICU – 620 patients
KDIGO AKI stage 3
Early – initiate with 6 hours of AKI
Late – BUN >100 or urgent need for RRT

Results
- No difference in mortality or dialysis dependence at 60 days
- Higher rates of infection and hypophosphatemia in the early group
50% of delayed group never received RRT
- Similar total time on RRT

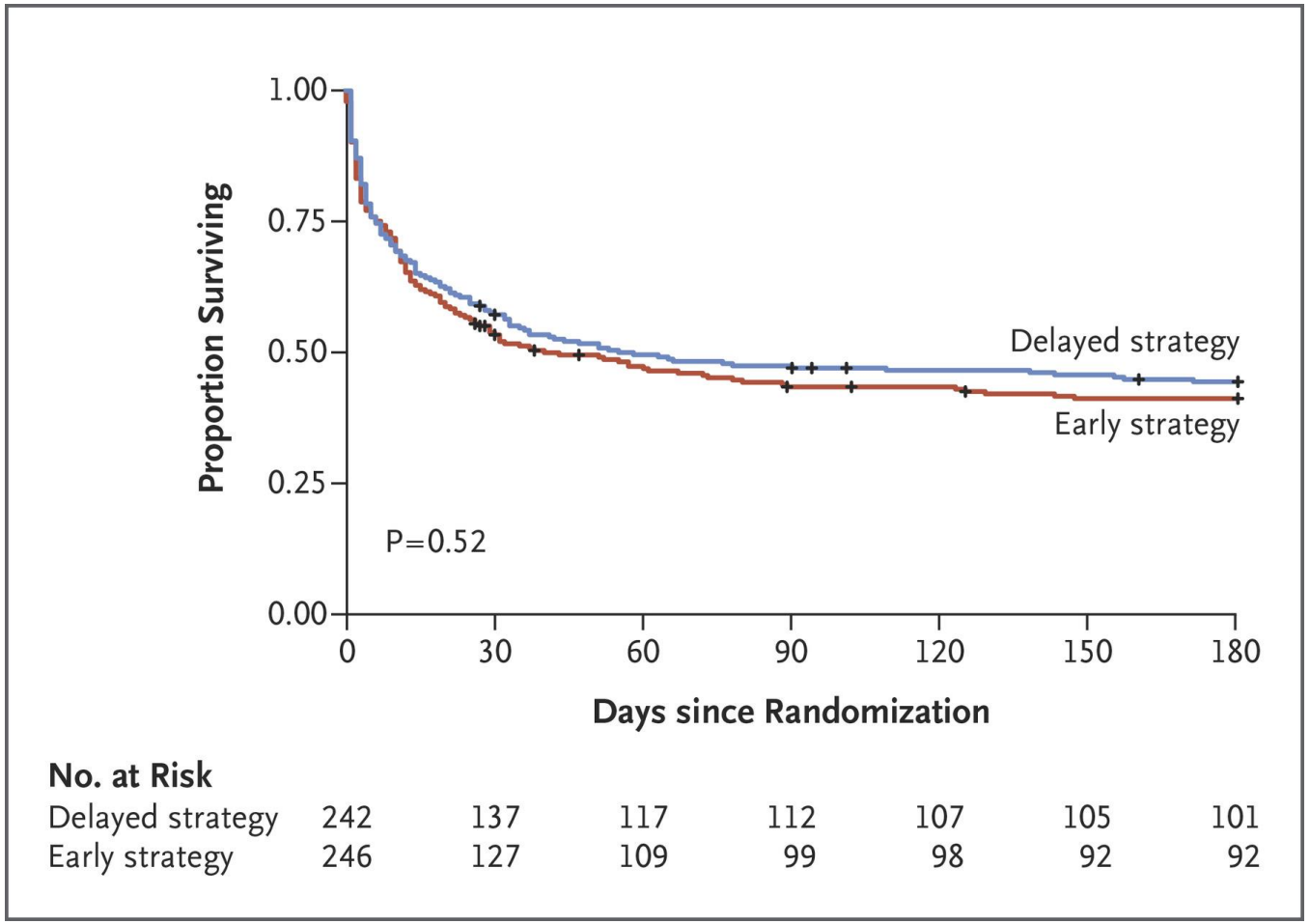


Guadry et al, MNEJM 2016

Early vs Late – IDEAL ICU

Multicenter RCT. 488 patients
KDIGO stage III
Early – initiate within 12 hours

Results
- No difference in mortality
- Trial stopped early after second interim analysis



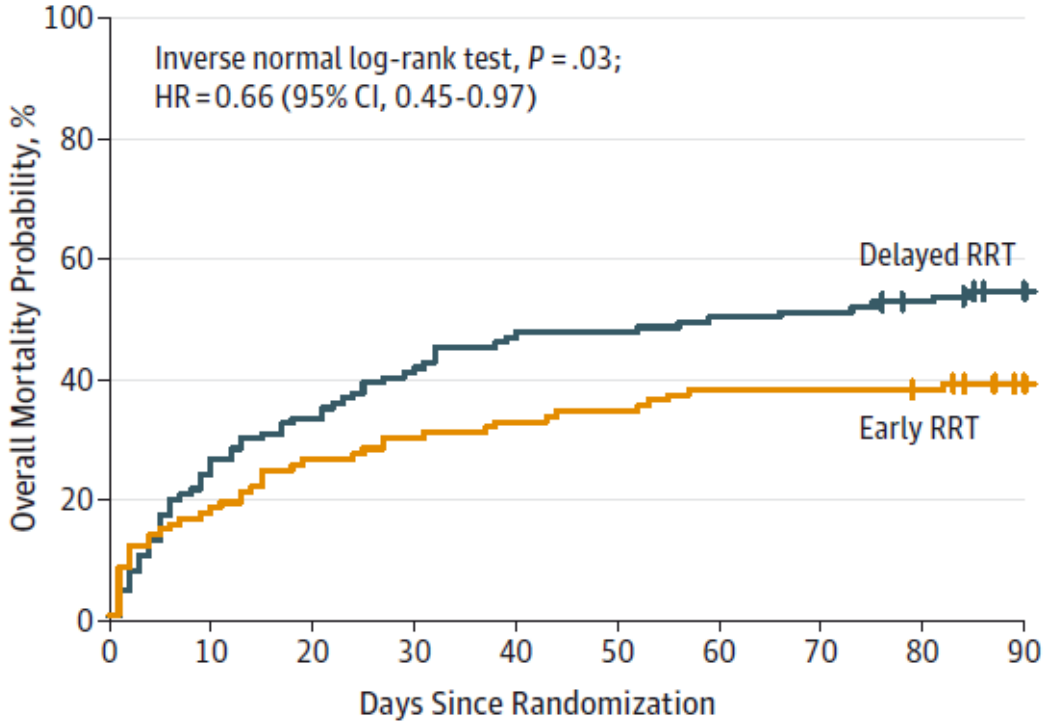
Early vs Late – ELAIN Study

Single Center KDIGO Stage II
Early – initiate within 8 hours
High proportion of surgical patients (particularly post cardiac surgery)

Results
- HR 0.66 for mortality in the early group
- Lower duration RRT, hospital stay and ventilation in early group

Thought that better volume control in post CT surgery patients may have led to the different results.

Figure 2. Mortality Probability Within 90 Days After Study Enrollment for Patients Receiving Early and Delayed Initiation of Renal Replacement Therapy (RRT)



No. at risk

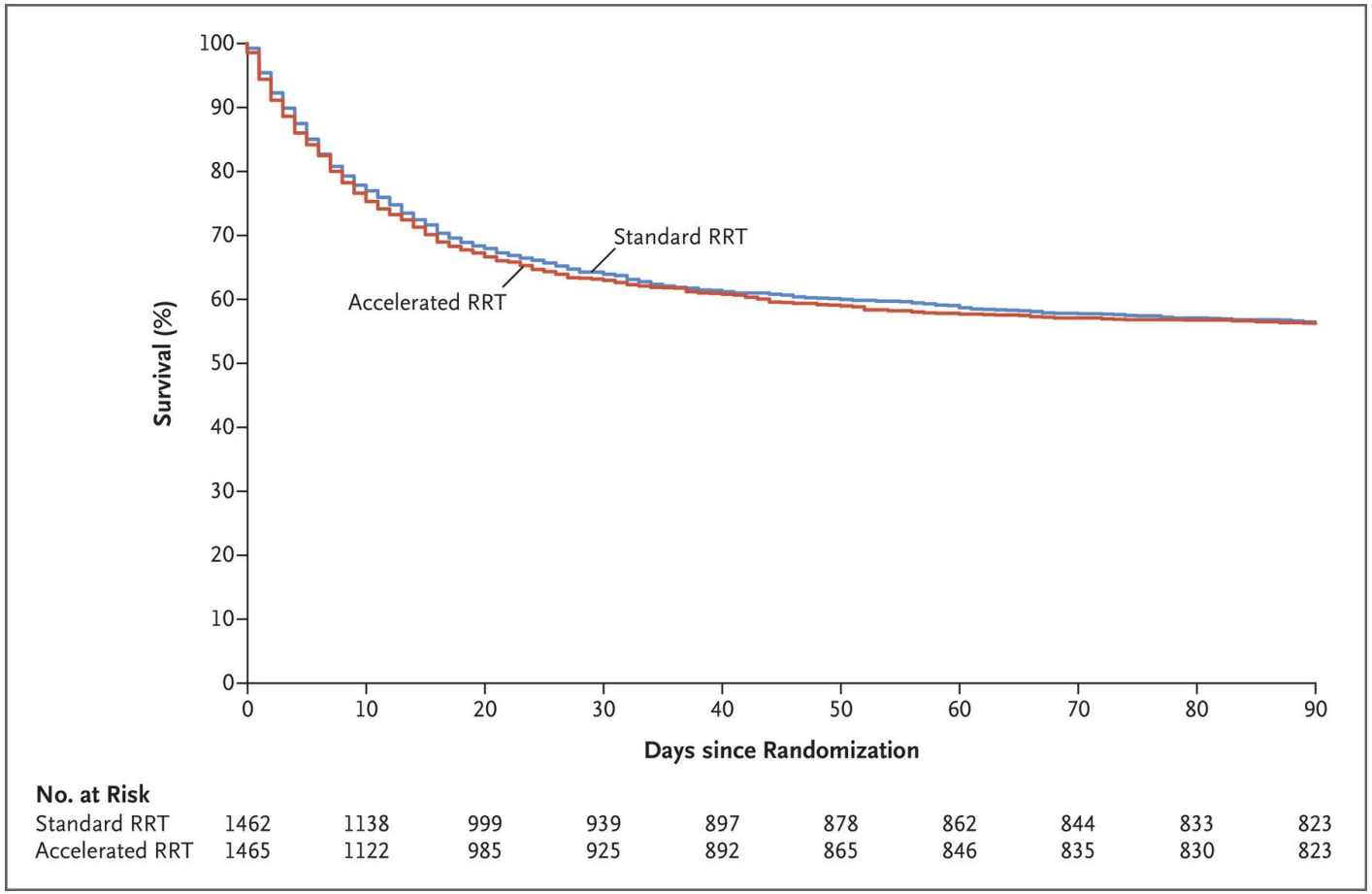
Early RRT	112	92	82	78	75	73	69	69	66	55
Delayed RRT	119	90	79	70	63	62	59	58	54	48

Zarbock et al, JAMA 2016

Early vs Late – STARRT AKI

Multicenter RCT
KDIGO Stage II
Early – initiate within 12h

Results:
- 62% of delayed group had RRT (median of 31h post randomization
- No difference in mortality
- More adverse events in the accelerated arm
- No difference in subgroups (medical vs surgical ICUs)



Delayed vs More Delayed – AKIKI2

Multicenter RCT
Compared delayed (BUN >112) vs more delayed (BUN>140 or urgent indication) strategy for RRT initiation in the ICU

Results
- Increased 60-day mortality in more delayed strategy (HR 1.65)
- No difference in complications or RRT-free days

May be a point at which RRT should not be delayed even if there is no "emergent" indication

Table 3. Multivariable analysis of risk factors for day-60 mortality

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
More-delayed strategy	1·34 (0·96–1·89)	0·13	1·65 (1·09–2·50)	0·018
Simplified Acute Physiology Score III	1·03 (1·02–1·05)	<0·0001	1·03 (1·01–1·05)	0·0005
Mechanical ventilation	2·90 (1·47–5·70)	<0·0001	3·44 (1·52–7·81)	0·0020
Catecholamine infusion	1·69 (1·17–2·44)	0·0080	1·13 (0·69–1·84)	0·64
Sepsis status	..	0·064	..	0·19
Sepsis	0·78 (0·47–1·30)	..	0·56 (0·28–1·12)	..
Septic shock	1·44 (0·98–2·12)	..	0·91 (0·51–1·64)	..
Time between ICU admission and acute kidney injury	0·69 (0·36–1·31)	0·24	0·70 (0·31–1·59)	0·39

Dialysis Intensity

CVVH dose is dependent on replacement fluid rate

- Standard blood flow rate = 250ml/min
- Filtration Rate = 1600 mls/hr = 27 mls/min

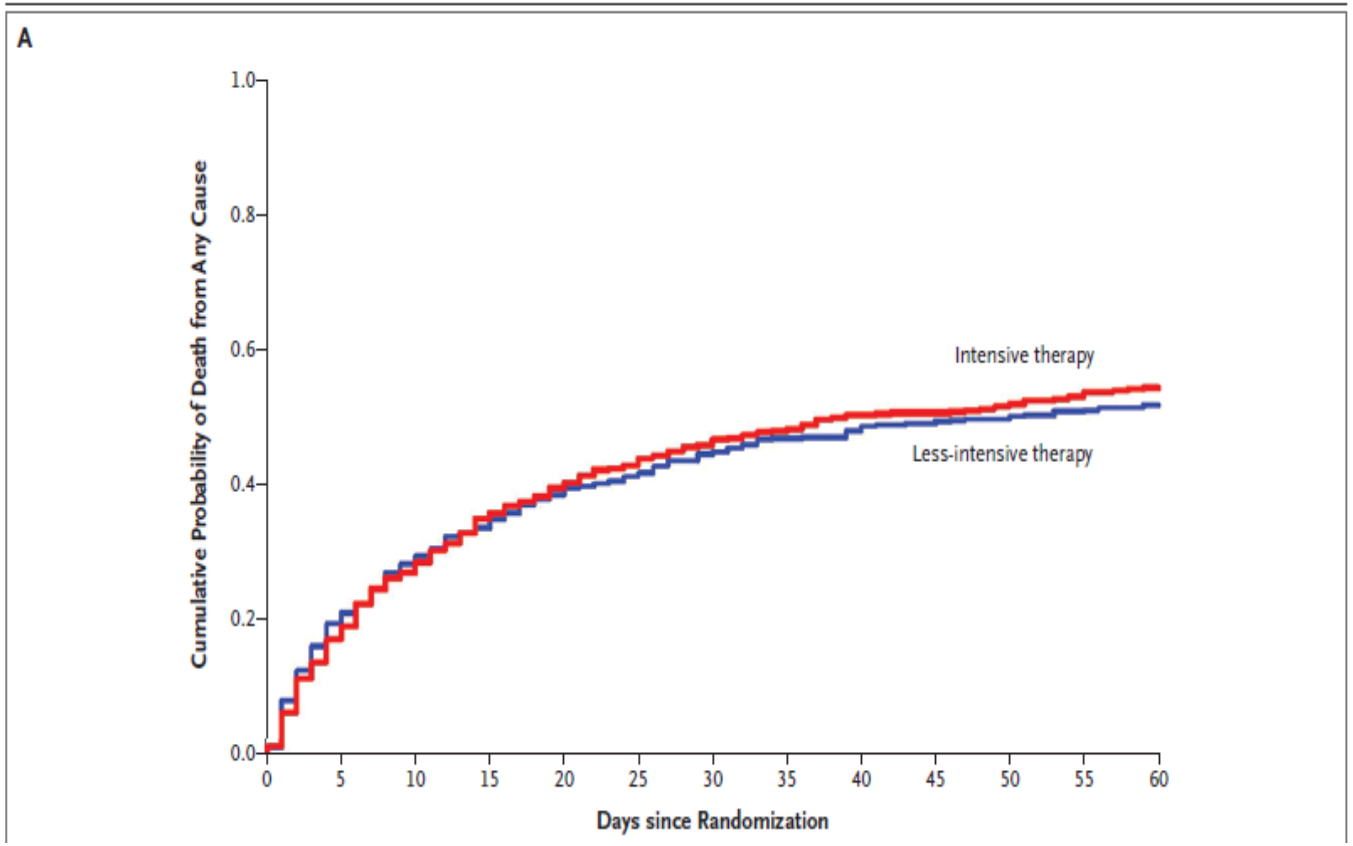
All current CVVH circuits use pre-dilution which reduces efficiency by 10-30% depending on the RFR

Correct dose of CVVH remains controversial
- Ronco study (1999) suggested higher dose CVVH was associated with better mortality

Dialysis Intensity – ATN study

Multicenter RCT
Randomized to intensive (HD x6/week or CVVH @ 35mls/kg/hr) vs less intensive (HD x3/week or CVVH @ 20 mls/kg/hr)

Results:
- No increase in mortality in the low intensity group
- Trend towards **higher** mortality in the high intensity group in patients with sepsis



ARF Trial Network, NEJM 2008

Dialysis Intensity – RENAL Trial

Multicenter RCT
1508 patients
Randomized to high (45mls/kg/hr) vs low (25 mls/kg/hr) CVVH

Results:
- No difference in mortality (44.7% in both groups)
- No difference in renal recovery among survivors (87%)
- More hypophosphatemia and prolonged ventilator times in high intensity groups.

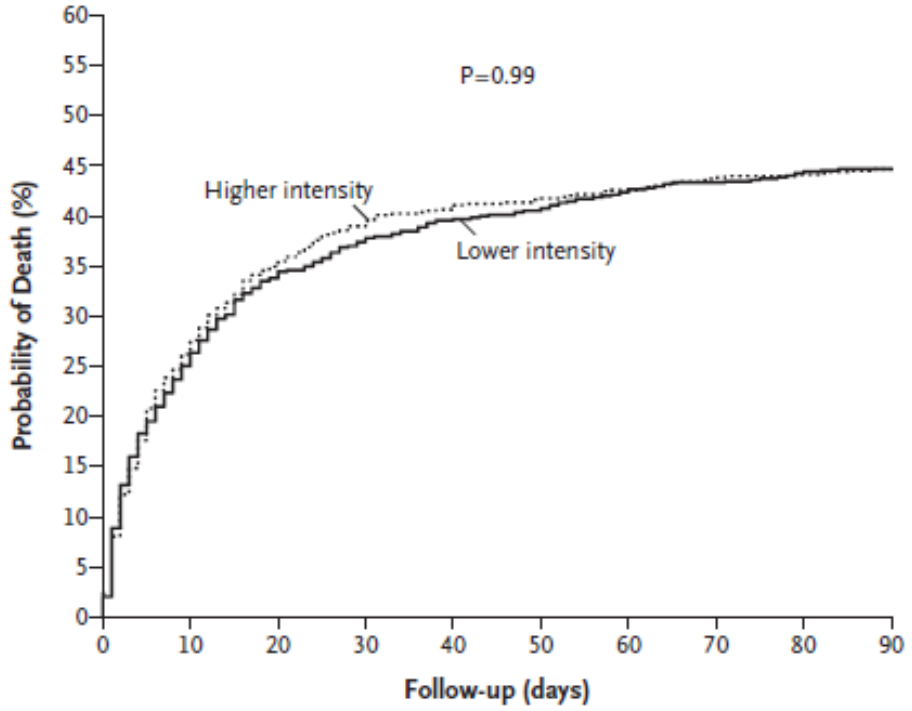


Figure 2. Kaplan–Meier Estimates of the Probability of Death.
Mortality at 28 days was similar in the higher-intensity and lower-intensity treatment groups (38.5% and 36.9%, respectively), and mortality at 90 days was the same (44.7%) in both groups.

Bellomo et al, NEJM 2009

Dialysis Intensity

Current Standard of Care

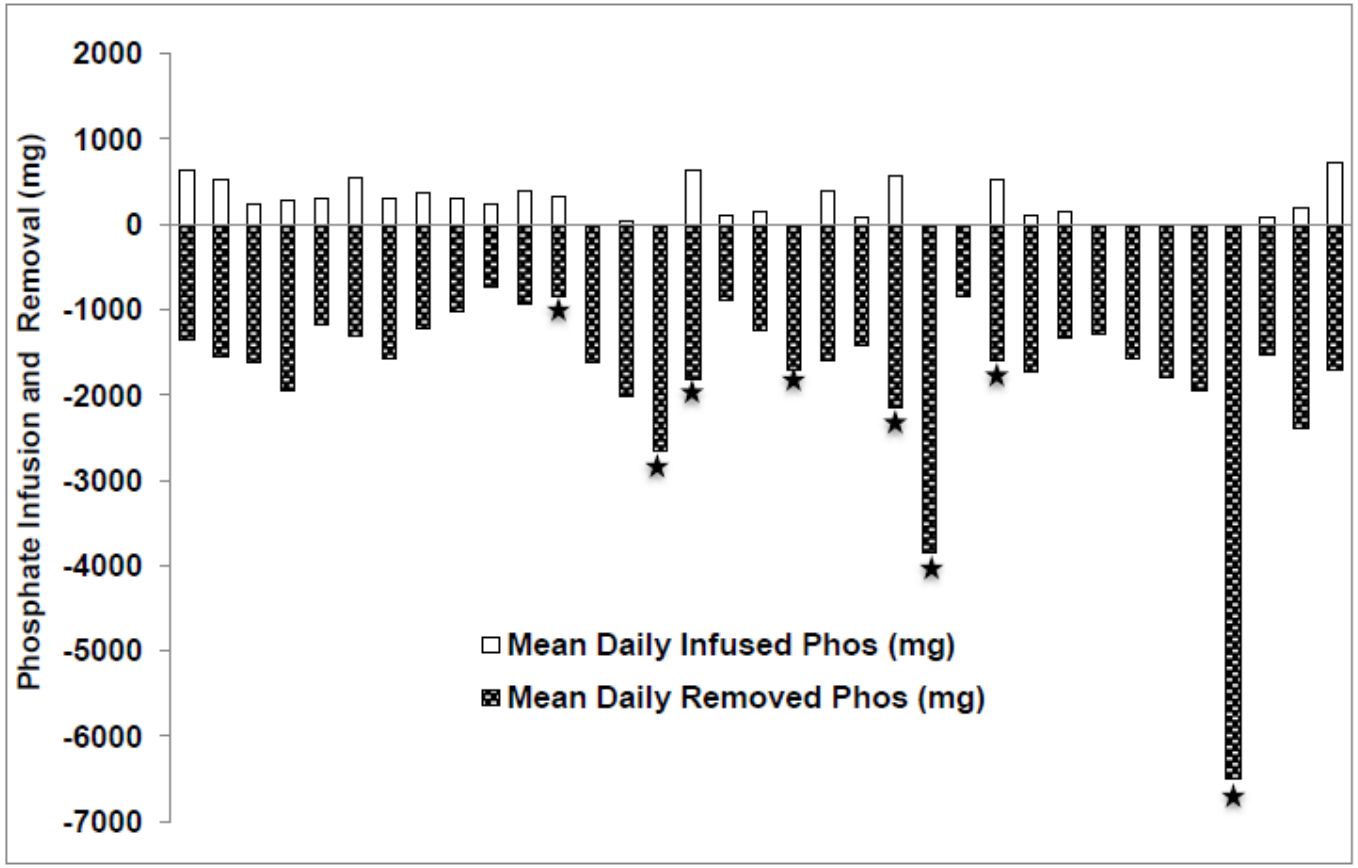
- HD x3/week
- CVVH @ 25mls/kg/hr

May be a role for higher intensity in patients with volume issues or >catabolism

Complications of CVVH - Hypophosphatemia

- Traditional CRRT causes severe PO4 depletion
  Net -9g over 7 days treatment
- Intracellular stores are depleted before serum levels fall
- Leads to muscle weakness and prolongs ventilator time
- PO4-containing fluids are preferred as a result

However – these do not contain dextrose so high risk of euglycemic acidosis



Sharma et al, AJKD 2013

TAKE HOME MESSAGES

AKI is common in the ICU with high morbidity and mortality

Modality

- No benefit for CRRT vs HD except hemodynamics, volume overload and increased ICP

Dose

- No need for high intensity RRT. Ensure adequate dosing

Initiation

- Initiate when clear indication
- May be role for earlier initiation in thoracic/cardiac surgery patients due to adverse consequences of volume overload

Anticoagulation

- Citrate preferred