Karolinska intensive care nephrology group

CRRT-behandling, timing/indikationer

Akut nefrologi och dialys inom intensivvården 2021

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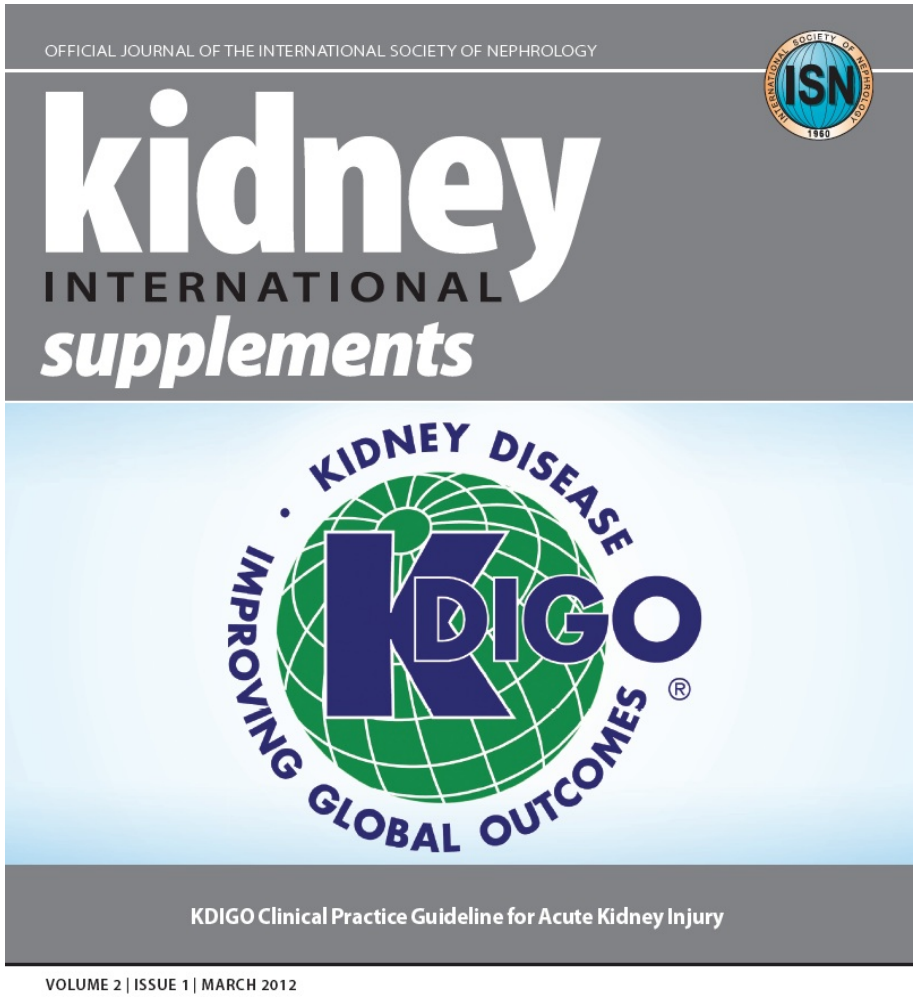
Vilka är våra val, vad kan vi påverka?

- **Modalitet**, CRRT eller intermittent (IHD, SLEDD)
- **Timing**, när ska vi starta behandlingen?
- **Dosen** av behandlingen, inklusive **vätskeborttag**
- **Filterval, vätskeval, antikoagulantia**
- **Behandlingslängd**(…dose), när avsluta?
- Under behandlingen kan vi justera (eller inte) **drogdosering**, särskilt viktigt gällande **antibiotikadosering**
- **Undvikande av nefrotoxiska droger**
- Optimering av **hemodynamik,** optimering av **nutrition**
- Vi kan – men ska vi? – **välja vilka patienter** vi behandlar med RRT

KDIGO


OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY
kidney
INTERNATIONAL
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IMPROVING GLOBAL OUTCOMES
KDIGO
KDIGO Clinical Practice Guideline for Acute Kidney Injury
VOLUME 2 | ISSUE 1 | MARCH 2012

KDIGO

Chapter 5.1: Timing of renal replacement therapy in AKI

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)

Indikationer, AKIN

Gibney N, et al. Timing of Initiation and Discontinuation of Renal Replacement Therapy in AKI: Unanswered Key Questions. Clin J Am Soc Nephrol.

Table 1. The indications for renal replacement therapy in patients with AKI

Indication	Characteristics	Absolute/Relative
Metabolic abnormality	BUN > 76 mg/dl (27 mmol/L)	Relative
	BUN > 100 mg/dl (35.7 mmol/L)	Absolute
	Hyperkalemia > 6 mEq/L	Relative
	Hyperkalemia > 6 mEq/L with ECG abnormalities	Absolute
	Dysnatremia	Relative
	Hypermagnesemia > 8 mEq/L (4 mmol/L)	Relative
	Hypermagnesemia > 8 mEq/L (4 mmol/L) with anuria and absent deep tendon reflexes	Absolute
Acidosis	pH > 7.15	Relative
	pH < 7.15	Absolute
	Lactic acidosis related to metformin use	Absolute
Anuria/oliguria	RIFLE class R	Relative
	RIFLE class I	Relative
	RIFLE class F	Relative
Fluid overload	Diuretic sensitive	Relative
	Diuretic resistant	Absolute

Indikationer, ADQI

- *Anuri - Oliguri* (diures ≤ 200 ml på 12 h)
- Svår metabol acidos (pH < 7.10)
- *Höga Urea och Kreatinin nivåer* (hur höga?)
- Hyperkalemi (K+ ≥ 6,5 mmol/L)
- Kliniska tecken på uremi
- Svår Dysnatremi (Na + ≤ 115 o ≥ 160 mmol/L)
- Hypertermi
- *Stora ödem eller uttalat vattenöverskott*
- *Multipel organsvikt med njurpåverkan*
- SIRS, Sepsis eller Septisk chock med renal dysfunktion

B.E.S.T. Kidney

Indikationer, gammal lärobok

Table 1. Conventional indications for renal replacement therapy in acute kidney injury

Intravascular volume overload unresponsive to diuretic therapy
Hyperkalemia refractory to medical management
Metabolic acidosis refractory to medical management
Concomitant intoxication with dialyzable drug or toxin
Overt uremic symptoms
Encephalopathy
Pericarditis
Uremic bleeding diathesis
Progressive azotemia in the absence of specific symptoms

Problems of RRT-timing research

- Presentation: de-novo AKI or acute on chronic?
- Definition of timing: temporal, biomarkers, parameters, fluid balance
- Widely varying practice
- Study design and quality:lack of randomized trials

Risks with RRT

- Catheter problems, bleeding, infections/sepsis
- Pro-inflammatory effect of exposure to the filter
- Hypotension (IHD, uncommon with CRRT)
- Anticoagulants (bleeding)
- Loss of trace elements, vitamins, nutrients
- Loss of heat
- Increased clearance of drugs/ underdosing of antibiotics

Är timing viktigt?

	ATN	RENAL
Commenced on CRRT	69.7%	100%
CRRT mode	Pre-dilution CVVHDF	Post-dilution CVVHDF
CRRT high-dose effluent target	35 mL/kg per hour	40 mL/kg per hour
CRRT low-dose effluent target	20 mL/kg per hour	25 mL/kg per hour
Time from ICU admission to first study RRT	6.7 days	2.1 days
Urea at study enrolment	23.8 mmol/L	24.2 mmol/L
Achieved dose of CRRT (high dose)	27.1 mL/kg per hour[a]	33.4 mL/kg per hour
Achieved dose of CRRT (low dose)	17.5 mL/kg per hour[a]	22 mL/kg per hour
Mean daily urea on CRRT (high dose)	11.7 mmol/L	12.7 mmol/L
Mean daily urea on CRRT (low dose)	16.8 mmol/L	15.9 mmol/L
Daily fluid balance on therapy	+130 mL	−20 mL
Survival at day 60	47.5%	Not reported
Survival at day 90	Not reported	55.3%
Percentage of survivors dependent on RRT		
At day 28	45.2%	13.3%
At day 60	24.6%	Not reported
At day 90	Not reported	5.6%

RENAL vs ATN trials (AUS vs USA, 1500 vs 1100 patients)

Är timing viktigt?

Table 5

Characteristics of patients with acute renal failure, stratified by time of initiation of renal replacement therapy (RRT)

Characteristic	Early RRT n = 213	Late RRT n = 65	*P* value
Age	62.3 ± 15.5	64.6 ± 15.0	0.30
Male gender	126 (59.4)	44 (68.8)	0.18
SAPS II	49.7 ± 17.5	45.3 ± 18	0.04
SOFA score	9.2 ± 4.1	8.2 ± 3.5	0.04
Mechanical ventilation	166 (77.9)	61 (93.8)	<0.01
Type of admission			
Medical	87 (40.8)	38 (58.5)	0.01
Surgical	126 (59.2)	27 (41.5)	0.01
Urine output, L/24 hours	0.18 (0.03–0.50)	0.47 (0.09–1.74)	<0.001
Creatinine, mg/dL	3.99 (2.57–6.17)	3.29 (2.10–5.00)	0.06
ICU stay, days	6.1 (2.5–14.8)	12.2 (8.0–26.5)	<0.001
Hospital stay, days	25.0 (8.0–46.0)	27.0 (17.0–45.0)	0.10
ICU mortality, number (percentage)	84 (39.4)	40 (61.5)	<0.01
60-day mortality, number (percentage)	94 (44.8)	42 (64.6)	<0.01

Data represent mean ± standard deviation, number (percentage), or median (interquartile range). ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA, sequential organ failure assessment.

Data from SOAP, Payen 2008

Är timing viktigt? (Mortalitet – ja, jo, tja)

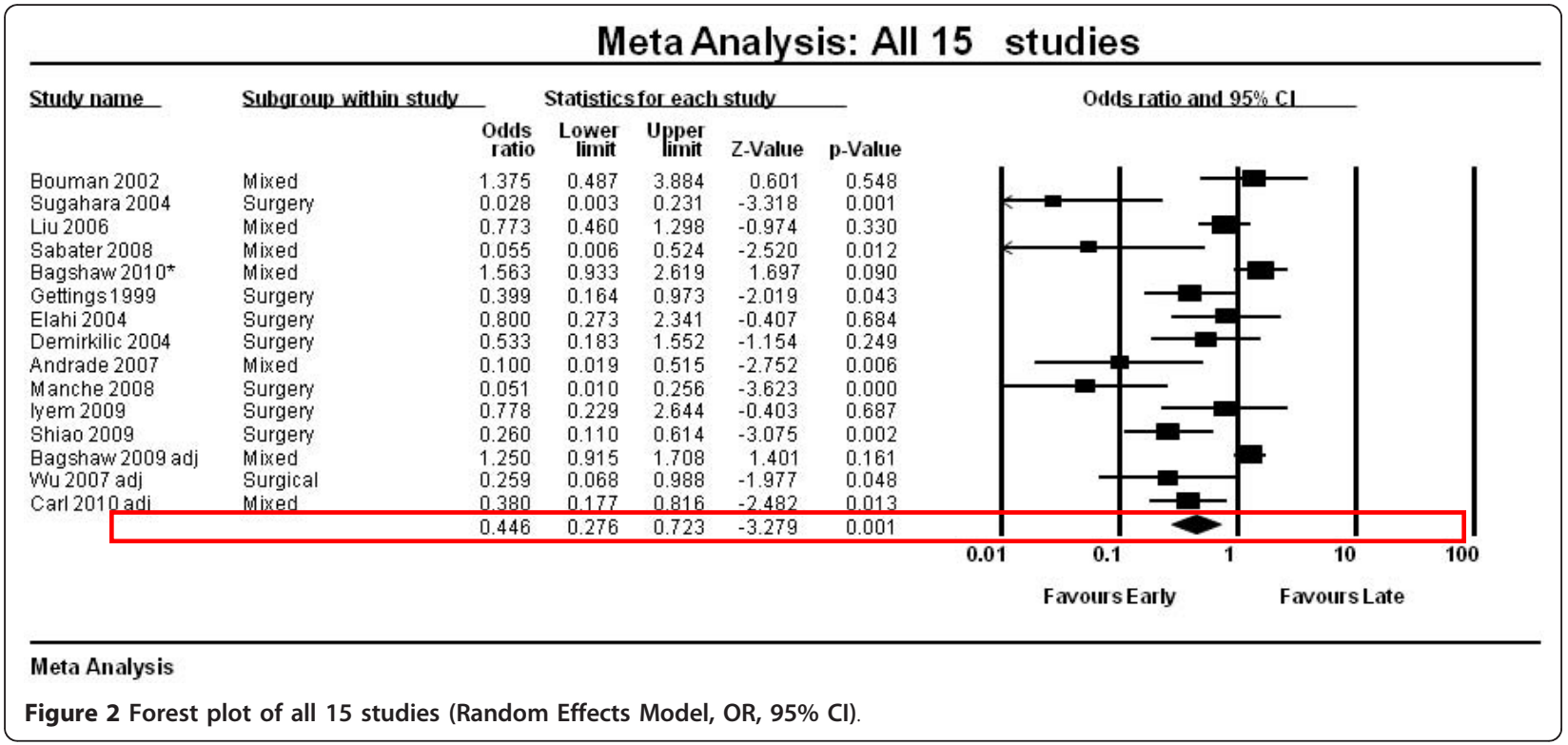


Figure 2 Forest plot of all 15 studies (Random Effects Model, OR, 95% CI).

Äldre studier där urea använts som biomarkör för timing

Table 2. Summary of studies evaluating the timing of initiation of renal replacement therapy (RRT)

Study	Yr	Mode of RRT	Study Design	No.	Criteria for Initiation of RRT		Survival (%)	
					Early	Late	Early	Late
Parsons et al (20)	1961	IHD	Retrospective	33	BUN 120–150 mg/dL	BUN >200 mg/dL	75	12
Fischer et al (21)	1966	IHD	Retrospective	162	BUN ~150 mg/dL	BUN >200 mg/dL	43	26
Kleinknecht et al (22)	1972	IHD	Retrospective	500	BUN <93 mg/dL	BUN >163 mg/dL	73	58
Conger (23)	1975	IHD	RCT	18	BUN <70 mg/dL or S_{Cr} <5 mg/dL	BUN ~150 mg/dL, S_{Cr} ~10 mg/dL, or clinical indications	64	20
Gillum et al (24)	1986	IHD	RCT	34	S_{Cr} 8 mg/dL Treatment goal: BUN <60 mg/dL, S_{Cr} <5 mg/dL	BUN ~100 mg/dL or S_{Cr} ~9 mg/dL	41	53
Gettings et al (25)	1999	CRRT	Retrospective	100	BUN <60 mg/dL	BUN >60 mg/dL	39	20
Bouman et al (12)	2002	CRRT	RCT	106	<12 hrs after meeting AKI definition	BUN >112 mg/dL, S_K >6.5 mmol/L, or pulmonary edema	LV: 69 HV: 74	LV: 75
Demirkiliç et al (26)	2004	CRRT	Retrospective	61	UOP <100 mL/8 hr	S_{Cr} >5.0 mg/dL or S_K >5.5 mmol/L	77	45
Elahi et al (27)	2004	CRRT	Retrospective	64	UOP <100 mL/8 hr	BUN ≥4 mg/dL, S_{Cr} >2.8 mg/dL, or S_K >6 mmol/L	78	57
Piccinni et al (28)	2006	CRRT	Retrospective	80	<12 hrs after ICU admission	"Conventional" indications	55	28
Liu et al (29)	2006	IHD & CRRT	Observational	243	BUN ≤76 mg/dL	BUN >76 mg/dL	65	59

Nested observational cohort study
RENAL RCT

Jun, Bellomo Crit Care Med. 2014 Aug;42(8)

- 439 patients with AKI on ICU
- four groups of CRRT :

  < 7.1 hrs ≥ 7.1 to < 17.6,

  ≥ 17.6 to < 46.0, ≥ 46.0 hr)

<u>Result</u>

- earlier commencement of continuous renal replacement therapy was **not** associated with a significantly lower risk of death at 28 days or 90 days.

Studier där RIFLE / AKIN / KDIGO har utnyttjats

Bell *Nephrol Dial Transplant* **20**:354–360, 2005

7-year retrospective analysis 207 patients with AKI on RRT. Stratified by RIFLE class at RRT initiation.

RIFLE at RRT initiation	Crude 30 day mort %	Adjusted HR (F versus R or I)
Failure	57.9	3.4
Injury	22.0	
Risk	23.5	

Shiao *Crit Care* **13**:R171, 2009

- Early versus late using estimated GFR from RIFLE
- Early initiation: lower ICU+hospital mortality

Vaara ST Clin J Am Soc Nephrol. 2014 Sep 5;9(9):1577-85

239 patients AKI with RRT + 67 non RRT patients.

134 (56.1%) fulfilled at least one conventional indication before commencing RRT. Crude 90-day mortality 48.5%

pre-emptive RRT 105 Crude 90 day mortality 29.5%

Classic RRT was associated with a higher risk for mortality (adjusted OR, 2.05;)

44 patients with classic-delayed RRT showed higher crude mortality (68.2%) compared with patients with classic-urgent RRT, and this association persisted after adjustment for known confounders (OR, 3.85

Crude 90-day mortality of 67 1:1 matched patients with pre-emptive RRT was 26.9%, and it was 49.3%; P=0.01) for their non-RRT matches

Early vs. Delayed RRT - A Comparison of the Different Trials				
		ELAIN	**AKIKI**	**IDEAL ICU**
Design		RCT	RCT	RCT
Setting		Single ICU, Germany (predominately surgical including 47% cardiac)	31 ICUs in France (80% medical patients)	24 ICUs in France
Population	Inclusion criteria	KDIGO stage 2 (2* increase in Cr or UO <0.5ml/kg/hr for 12 hours despite optimal resuscitation	KDIGO stage 3 (Cr >354 or >3* baseline, anuria for >12 hours, or UO <0.3ml/kg/hr for 24 hours)	RIFLE (3* increase in Cr; Cr >354 with acute increase of >44; UO <0.3ml/kg/hr for >24 hrs or anuria for >12hrs)
		NGAL >150ng/ml (only 3 patients excluded as NGAL <150)		
		Critically unwell (severe sepsis, norad/adrenaline >0.1µg/kg/min, refractory fluid overload, proression of nonrenal organ dysfunction (SOFA score ≥2)	Critically unwell (mechanical ventilation or vasopressors)	1st 48 hours of septic shock
	Exclusion criteria	Pre-existing renal disease (eGFR <30ml/min)	Pre-existing renal failure (CrCl<30ml/min)	Chronic RRT
	Number of patients randomised	231	620	864
Baseline characteristics	SOFA score (early vs. delayed)	15.6 vs. 16	10.9 vs. 10.8	
	APACH II (early vs. delayed)	30.6 vs. 32.7	NR	
Intervention	Early RRT	Within 8 hours of stage 2 AKI	Within 6 hours of stage 3 AKI	Within 12 hours of meeting inclusion criteria
Control	Delayed RRT	Within 12 hours of stage 3 AKI (UO <0.3ml/kg/hr for >24 hours, or 3* increase in Cr or Cr >354 with acute increase of 44 within 48 hours, or UO <200ml/12 hours, urea >100mg/dL, K >6, organ edema with resistance to diuretics)	If developed: Urea >40mmol/l, K>6, pH <7.15, acute pulmonary oedema, oliguria/anuria >72 hours	48-60 hours post meeting inclusion criteira, unless recovers normal renal function
	% of patients in delayed group that received RRT	91% at a median of 25.5hrs post randomisation	51% at a median of 57hrs post randomisation	TBA
Method of RRT		CVVHDF	Physician discretion (55% initially intermittent RRT)	Physician discretion
Primary outcome	Mortality	90 days	60 days	90 days
	early vs. delayed	39.3% vs. 54.7%	48.5% vs. 49.7%	TBA
	p	0.03	0.79	TBA
	Fragility index	3 patients	-18 patients	TBA
Secondary outcomes	Duration of RRT (median, days)	9 vs. 25, p=0.04	NR	TBA
	Number of RRT sessions by day 28 (median)	NR	All patients 3 vs. 4, p=0.15; patients alive at day 60: 3 vs. 6, p=0.009	TBA
	Ongoing Requirement for RRT	At day 90: 13% vs. 15%, p=0.8	AT day 60: 2% vs. 5%, p=0.12	TBA

TABLE 1: Comparison between recent randomized clinical trials addressing early vs delayed initiation of RRT in critically ill patients with AKI

Characteristics	AKIKI Trial	ELAIN Trial	IDEAL Trial
Participating sites	31 (France)	1 (Germany)	29 (France)
Total number of participants	620	231	488
Early RRT definition	KDIGO stage 3	KDIGO stage 2	KDIGO stage 3
Delayed RRT definition	BUN >112, K >6, pH <7.15, pulmonary edema, oliguria for >72 h	<12 h KDIGO stage 3 or absolute indications	>48 h KDIGO stage 3 or absolute indications
Timing from randomization to initiation of RRT, median	2 h (early) vs 57 h (delayed)	6 h (early) vs 25.5 h (delayed)	7.6 h (early) vs 51.5 h (delayed)
SOFA score, mean	11	16	12
CKD, %	10	41	15
Septic shock, %	67	32	100
Surgical intervention, %	21	97	–
RRT modality at initiation	HD, SLED, or CRRT	CRRT	HD, SLED, or CRRT
Primary endpoint	60-day mortality	90-day mortality	90-day mortality
Mortality – Early, %	49	39	58
Mortality – Delayed, %	50	55	54
Received RRT in delayed arm, %	51	91	62

Note: KDIGO = Kidney Disease: Improving Global Outcomes; HD = hemodialysis; SLED = sustained low-efficiency dialysis.

ELAINE vs AKIKI, who did they study

AKIKI was primarily studying medical patients in multiple centres with sepsis (SOFA scores ~11) whilst

ELAIN was studying surgical patients in one centre (SOFA scores ~16).

- The pathophysiology between these two cohorts is probably different.
- *Surgical patients*: possibly reduced renal blood flow related with stress response pathophysiology
- *Medical patients*: possibly increased renal blood flow with significant immune complex / toxaemia

ELAINE vs AKIKI, what did they study

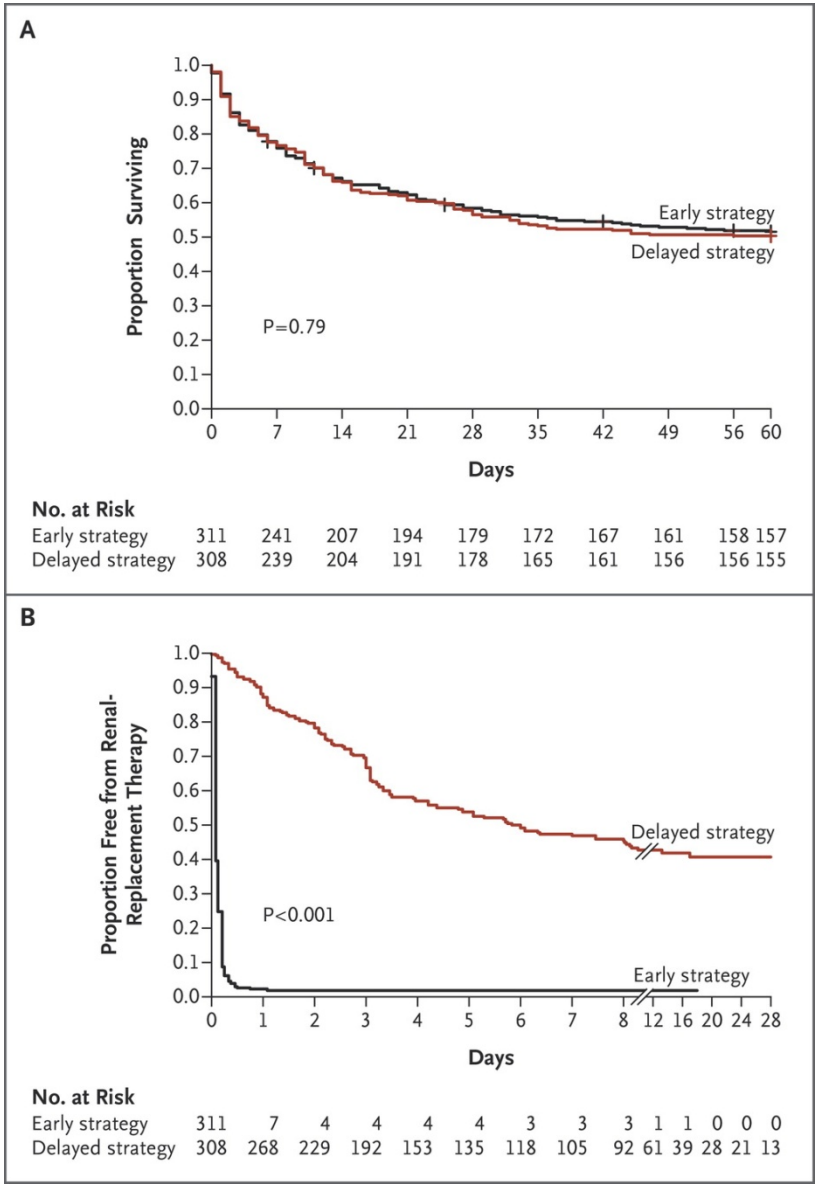
Timing of RRT

- Both trials defined criteria for the early intervention: these differed slightly such that **ELAIN** was *really early*(KDIGO stage 2) and **AKIKI** was just *early* (KDIGO stage 3).
- The control groups were slightly different too:
  the **ELAIN** trial used KDIGO stage 3 (85% patients) or metabolic derangement (15% patients) as the indication for RRT, but the **AKIKI** trial used metabolic derangement only. This means that the control group in **ELAIN** was actually a very similar treatment to the**AKIKI** intervention group.
- So **ELAIN** was *really*
  early vs *early* and **AKIKI** was *early* vs *conventional*.

ELAINE vs AKIKI, delivery of RRT

- **AKIKI** allowed unblinded clinicians to go ahead with whatever mode of RRT they wanted, at whatever dosage. *This was mixed intermittent and / or continuous RRT for a median of 4 days.* Given that intermittent mode RRT was used extensively, it may be difficult to extrapolate the findings to ICUs where continuous mode RRT is used almost exclusively. *The exact modalities and dosages delivered were not published*. Only 51% of the delayed group actually received RRT.
- In contrast, **ELAIN** defined the RRT modality and dose: continuous vena-venous haemodiafiltration (CVVHDF) at 30 ml/kg/hr with 100% pre-dilution and 1:1 dialysate to replacement fluid. 91% of the delayed group received RRT – a much higher proportion than the AKIKI trial's delayed group.

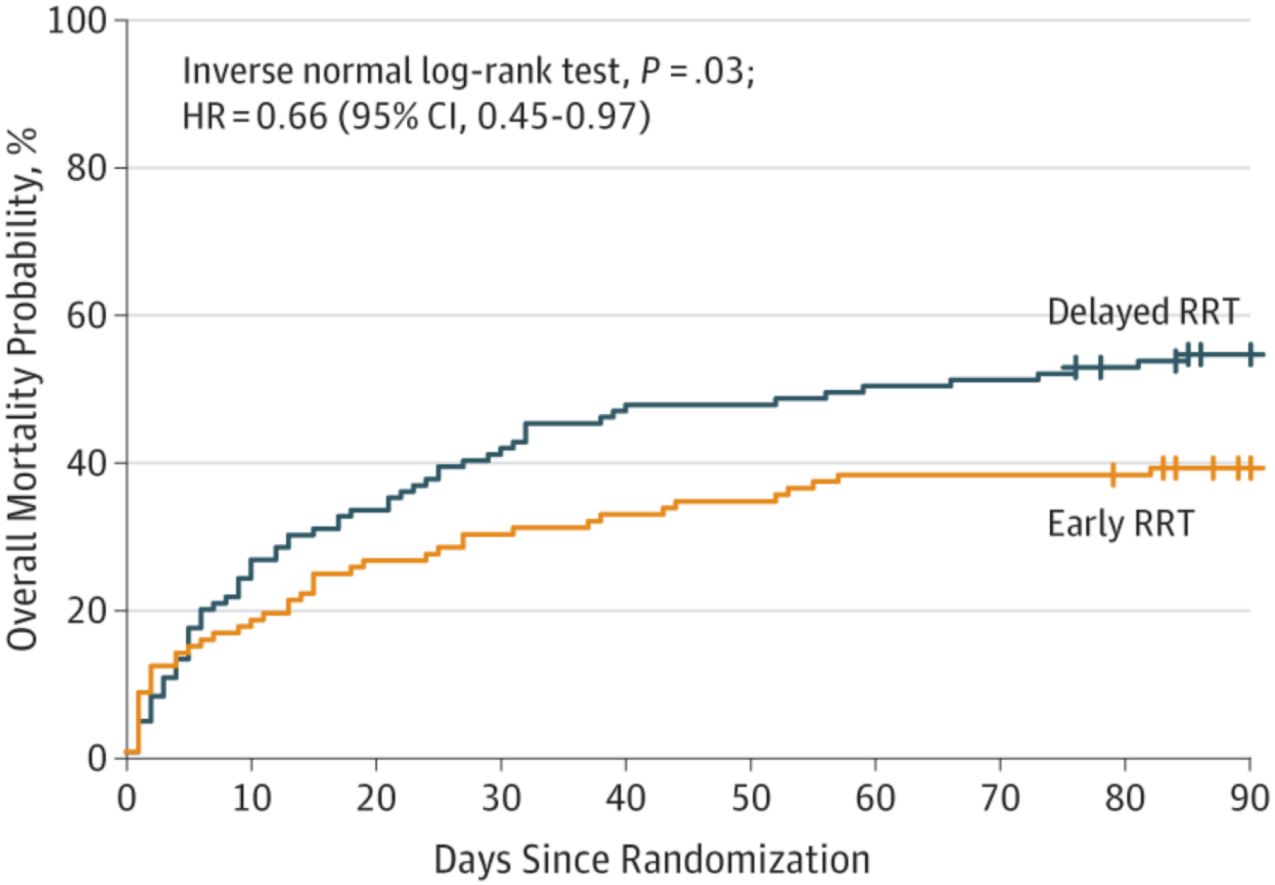
AKIKI, results



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

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
Alexander Zarbock et al
JAMA. 2016;315(20):2190-2199.
doi:10.1001/jama.2016.5828

ELAINE, results



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

AKIKI vs ELAINE, take home

- **AKIKI**: In sick patients that are medical or surgical with sepsis, then *I don't know* if early or delayed RRT is the right therapy.
- **ELAIN**: In really sick patients on a surgical intensive care unit, then *I cautiously think* very early CVVHDF is the right therapy.

Editorial: The Bottom Line: Early vs Late Renal Replacement Therapy
June 17, 2016 Duncan Chambler

IDEAL ICU

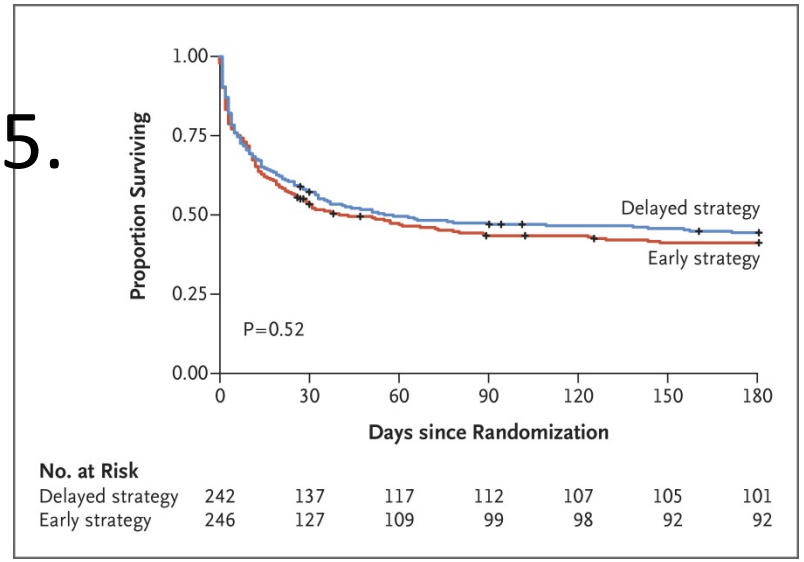
October 11, 2018
N Engl J Med 2018; 379:1431-1442
DOI: 10.1056/NEJMoa1803213

RCT initiation RCT early versus delayed in severe septic AKI

864 patients

Outcome 90 day mortality

Recruitment 2012-May 2015.



STARRT-AKI

168 hospitals in 15 countries, 3019 patients

Randomised to "accelerated" or "standard" initiation.

- Early = within 12 hrs of fulfilling criteria
- Standard = monitor 7 days, start if potassium ≥6.0 mmol/L, bicarb ≤10 mmol/L, severe resp. failure (PaO_2/FiO_2<200) or persisting AKI for ≥72 hours

Inclusion

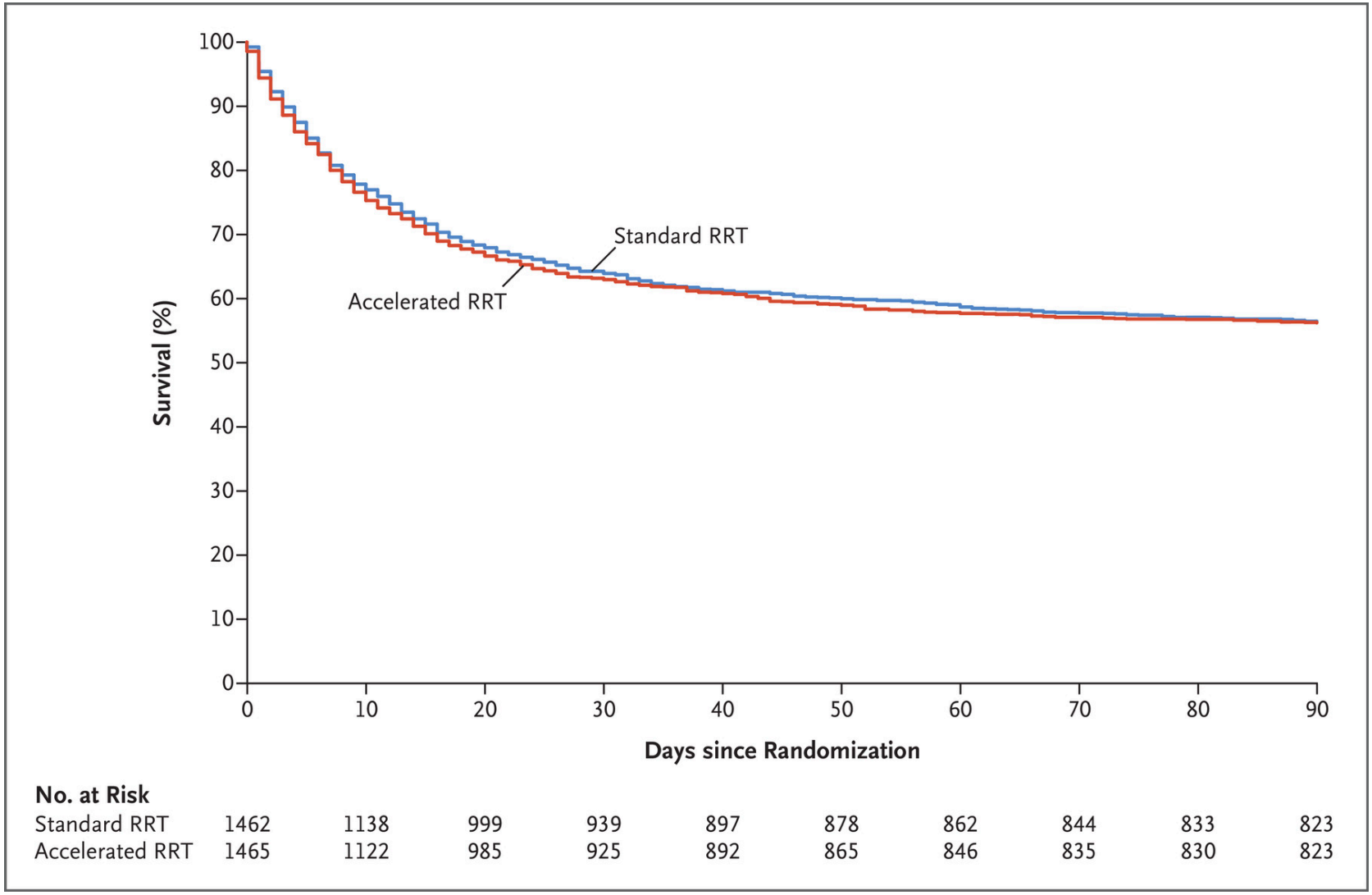
- RIFLE Injury
- Oliguria as defined by urine output <6 mL/kg over the preceding 12 i.
- If only 1 of 2 above criteria are met a whole-blood (NGAL) ≥400 ng/mL.

Exclusion:

- Clinician(s) caring for patient believe(s) that immediate RRT is absolutely mandated or that deferral of RRT initiation is mandated.

They screened 11,852 pat.

No meaningful difference



No. at Risk

Standard RRT	1462	1138	999	939	897	878	862	844	833	823
Accelerated RRT	1465	1122	985	925	892	865	846	835	830	823

Slutsatser. Vad kan vi påverka?

- **Modalitet**, CRRT eller intermittent (IHD, SLEDD)
- **Timing**, när ska vi starta behandlingen?
- **Dosen** av behandlingen, inklusive **vätskeborttag**
- **Filterval, vätskeval, antikoagulantia**
- **Behandlingslängd**(…dos), när avsluta?
- Under behandlingen kan vi justera (eller inte) **drogdosering**, särskilt viktigt gällande **antibiotikadosering**
- **Undvikande av nefrotoxiska droger**
- Optimering av **hemodynamik,** optimering av **nutrition**
- Vi kan – men ska vi? – **välja vilka patienter** vi behandlar med RRT

Hur ”brukar” man göra?

- Man tar hänsyn till sin egen uppfattning om patientens status
- Man tittar på patientkarakteristika
  - Det akuta insjuknandet, den akuta indikationen
  - Andra, samtidiga, sjukdomar
  - Ålder
  - Severity of illness, APACHE II/SAPSIII/SOFA etc
- Man bedömer organisationen
  - Vilken kompetens finns på plats
  - Vilka apparater finns