Brigham and Women's Hospital
Founding Member, Mass General Brigham

ICU Nephrology and Continuous Renal Replacement Therapies

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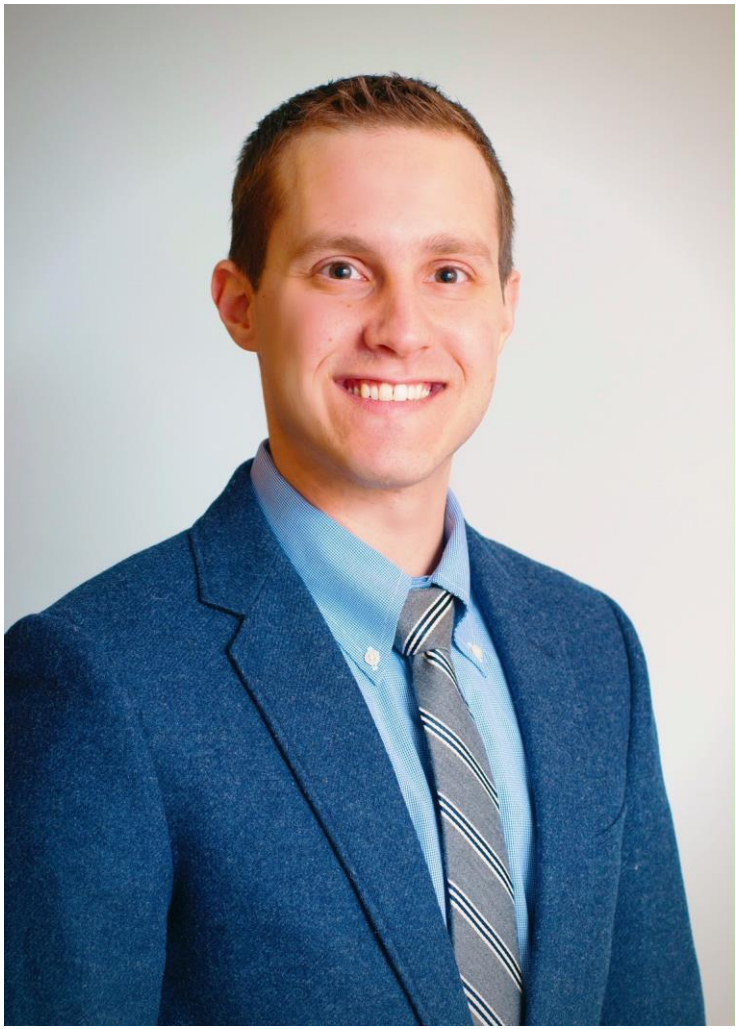

- Medical School: Brown University
- Residency: MGH
- Nephrology Fellowship: BWH/MGH
- Masters in Epidemiology: HSPH
- Current Roles:
  - Associate Professor of Medicine, HMS
  - Director of ICU Nephrology, MGH
  - Principal Investigator, MGH Kidney Research Center
  - Co-chair, HRS-HARMONY research collaborative
- Areas of Interest
  - AKI in cirrhosis, hepatorenal syndrome
  - Critical Care Nephrology

Disclosures

Consulting: Mallinckrodt Pharmaceuticals, Bioporto, Acta Pharmaceuticals, PharmaIN

DMSB: Astrazeneca

Research Support: NIH K23 DK128567

Objectives

1. To review one nephrologist's approach to acute kidney injury in the intensive care setting.
2. To understand indications, timing, and modality of renal replacement therapy for acute kidney injury in the ICU.

Acute Renal Failure in Critically Ill Patients
A Multinational, Multicenter Study

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for the Beginning and Ending

Context Although acute renal failure (ARF) is believed to be common in the setting of critical illness and is associated with a high risk of death, little is known about its epidemiology and outcome or how these vary in different regions of the world.

Objectives To determine the period prevalence of ARF in intensive care unit (ICU) patients in multiple countries; to characterize differences in etiology, illness severity, and clinical practice; and to determine the impact of these differences on patient outcomes.

Design, Setting, and Patients Prospective observational study of ICU patients who either were treated with renal replacement therapy (RRT) or fulfilled at least 1 of the predefined criteria for ARF from September 2000 to December 2001 at 54 hospitals in 23 countries.

Main Outcome Measures Occurrence of ARF, factors contributing to etiology, illness severity, treatment, need for renal support after hospital discharge, and hospital mortality.

Results Of 29 269 critically ill patients admitted during the study period, 1738 (5.7%; 95% confidence interval [CI], 5.5%-6.0%) had ARF during their ICU stay, including 1260 who were treated with RRT. The most common contributing factor to ARF was

Overall hospital mortality was 60.3% (95% CI, 58.0%-62.6%). Dialysis dependence at hospital discharge was 13.8% (95% CI, 11.2%-16.3%) for survivors.

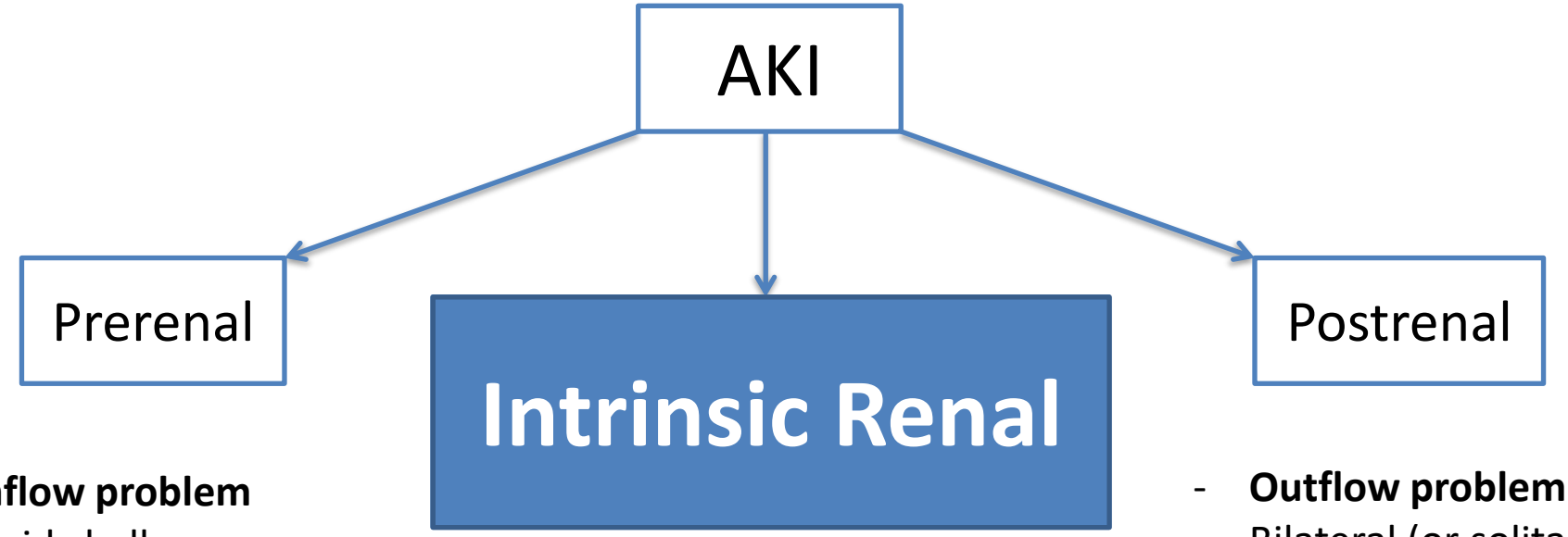
lation (OR, 2.11; 95% CI, 1.58-2.82; $P<.001$), septic shock (OR, 1.36; 95% CI, 1.03-1.79; $P=.03$), cardiogenic shock (OR, 1.41; 95% CI, 1.05-1.90; $P=.02$), and hepatorenal syndrome (OR, 1.87; 95% CI, 1.07-3.28; $P=.03$).

Conclusion In this multinational study, the period prevalence of ARF requiring RRT in the ICU was between 5% and 6% and was associated with a high hospital mortality rate.

JAMA. 2005;294:813-818 www.jama.com

Outline

1. Causes, Considerations, and Clinical Update for AKI in the ICU
2. Renal Replacement Therapy
   - Timing
   - HD vs CRRT: Modality choices



- **Inflow problem**
- Fluid challenge
- HRS, CHF
- Vascular disease

- **ATN (>80%)**: ischemic or nephrotoxic
- AIN (NSAIDs, antibiotics)
- Cholesterol Emboli
- Glomerulonephritis

- **Outflow problem**
- Bilateral (or solitary kidney) obstruction
- Neurogenic bladder
- BPH
- Tumor
- Hemorrhage
- Usually relieved with foley

AKI: Definition

		RIFLE criteria	
		sCreatinine	Urine output criteria
Increasing severity	**R**isk	↑ sCrea × 1.5	< 0.5 ml/kg per h × 6 h
	Injury	↑ sCrea × 2	< 0.5 ml/kg per h × 12 h
	Failure	↑ sCrea × 3 or ⩾ 0.5 mg/dl if baseline sCrea ↑ > 4.0 mg/dl	< 0.3 ml/kg per h × 24 h or anuria × 12 h
Outcome	**L**oss	Complete loss of renal function > 4 weeks	
	End-stage	End-stage renal disease	

		AKIN criteria	
		sCreatinine	Urine output criteria
Increasing severity	Stage 1	↑ sCrea × 1.5 or ↑⩾0.3 mg/dl in sCrea	< 0.5 ml/kg per h × 6 h
	Stage 2	↑ sCrea × 2	< 0.5 ml/kg per h × 12 h
	Stage 3	↑ sCrea × 3 or ↑⩾0.5 mg/dl if baseline sCrea > 4.0 mg/dl	< 0.3 ml/kg per h × 24 h or anuria × 12 h
Patients who receive RRT are considered to have met stage 3 criteria, irrespective of the stage they are in at the time of RRT			

KI 2012; 81: 819

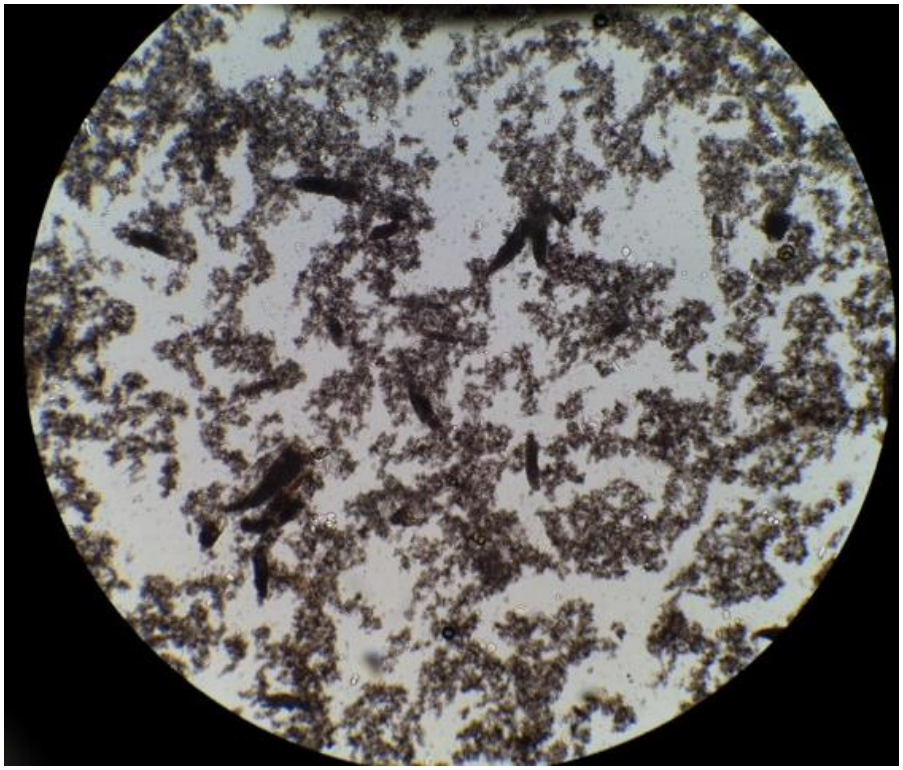
AKI: Definition

- RIFLE, AKIN, KDIGO criteria
  - Updated KDIGO criteria expected 2026, draft includes cystatin C and injury biomarkers
- Pitfalls:
  - Tiny person (low muscle mass) Cr ~ 0.4 can triple to 1.2 but still be “normal”
  - Need **steady state** to calculate eGFR (not AKI)
  - Large fluid admin. can dilute and lower Cr
- If UOP <10 cc/hr, GFR <10 for drug dosing

CJASN 2008; 3: 844 & *KI Suppl* 2012; 2: 19

Workup

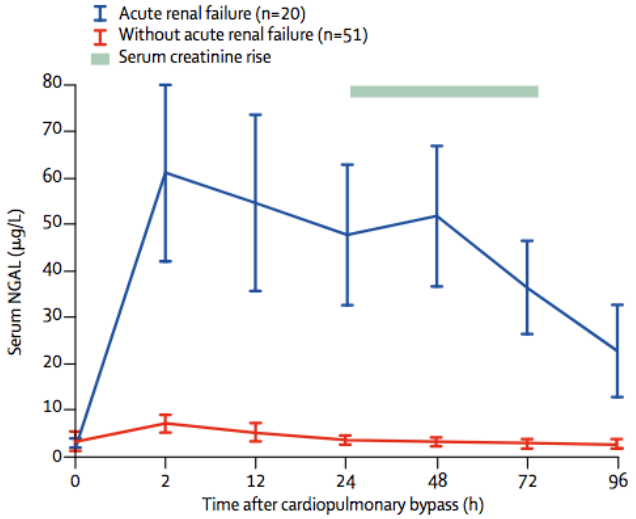
- History and Physical
  - Contrast, NSAIDs, ACE/ARB
  - Operative VS for HoTN
- Useful: CMP, volume exam, UOP, sediment
- Not useful: FE_{Na} (FE_{Urea}), urine eos (sens/spec 30%), BUN/Cr ratio
- Maybe useful: spot prot/Cr ratio, renal US



Lancet 2012; 380: 756

Newer AKI Biomarkers

- Cr is a late biomarker of AKI
- Does not reflect prerenal vs. ATN
  - May help fluid management
  - Early marker may anticipate renal consult, RRT, need for ICU



Type	Examples	Testing	Timing to Expression	Issues
Functional	Cystatin-C	Serum (urine)	12-24 hours	Less data in AKI than CKD
Tubular Injury	NGAL, KIM-1, IL-18, L-FABP, NAG	Urine (serum)	1-12 hours	No adult FDA approval
Cell cycle arrest	TIMP-2/IGFBP-7 [Nephrocheck]	Urine	<12 hours	FDA approved, not at MGH

Lancet 2005; 365: 1231 & *Br J Anaesth* 2012; 109: 843

Management Goals for AKI

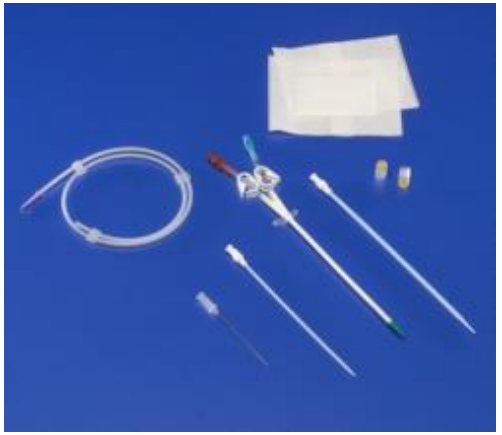
- Prevention
- Supportive care (common sense)
- Reverse underlying injury
- Maintain **euvolemia**, normotension
  - Volume is controllable and closely tied to mortality in AKI
- Minimize other nephrotoxins
- Adjust medications and nutrition
- Renal replacement (if indicated)
- When to call nephrology?
  - Before RRT is needed (if possible)

Timing of starting RRT

- Classic Indications: AEIOU
  - Acidemia
  - Electrolyte abnormalities
  - Intoxication (lithium, aspirin, methanol, ethylene glycol)
  - Overload (volume)
  - Uremia (encephalopathy, pericarditis, platelet function)
- Goals: balance fluid status, clear life-threatening toxins (potassium), management of life-threatening uremia (pericarditis)
  - No data to support acute dialysis decreases bleed risk
  - DDAVP an option pre-op, safe & fast acting
- TRAJECTORY

Access: Temp Lines

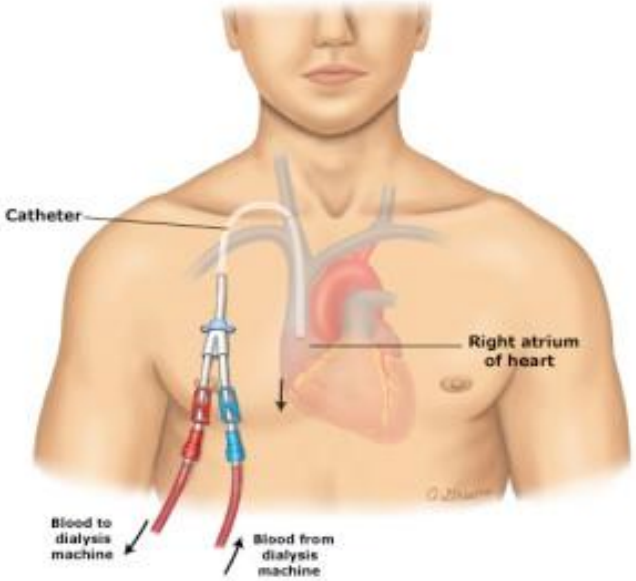
1. Internal Jugular: preferred
   - Right (**16 cm**) > Left (**20 cm**)
   - Right is straight shot into SVC/RA
2. Femoral (**24 cm**)
3. Subclavian (20 cm)



- ~12 French
- HD ports have citrate dwell – avoid pushing meds without drawing out 2 cc blood from each port (codes only)
  - Risk: acute hypocalcemia
- Third med port available but adds turbulence to circuit (rarely use)
- AVF/AVG not suitable for CRRT

Tunneled IJ Catheters

- Placed and pulled by IR
- Used like temp lines
- Lower infection rates in AKI
  - TDC: 2.9 per 1000 days
  - Temp IJ: 15.6 per 1000 days
  - Fem: 20.2 per 1000 days
- Need >48 hours neg. BCx, often deferred in ICU



J Vasc Interv Radiol 2009; 20:1578

Timing of RRT based on BUN

Year	Mode of RRT	Study Design	N	Bun at Initiation of RRT (mg%)		Survival %	
				Early	Late	Early	Late
1961	IHD	Retrospective	33	120-150	>200	75	12
1966	IHD	Retrospective	162	~150	>200	43	26
1972	IHD	Retrospective	500	<93	>163	73	58
1975	IHD	Prospective	18	<70	~150	64	20
1986	IHD	Prospective	34	<60	~100	41	53
1999	CRRT	Retrospective	100	<60 (42+/-13)	>60 (94+/-28)	39	20
2002	CRRT	Prospective	106	47 (30-66)	105(62-116)	72	75

- Primarily older, retrospective data
- Supports starting RRT prior to advanced uremia
- Meta analysis suggests early RRT a/w better survival

Seminars In Dialysis 2006; 19: 165 & *Crit Care* 15: R72, 2011

When to Start?

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

AKIKI, IDEAL-ICU, STARRT AKI Trials
2016, 2018, 2020

European/American Multicenter RCTs
Septic Shock population

VS

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Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

ELAIN Trial

German Single Center RCT
Mixed medical/surgical population

The NEW ENGLAND JOURNAL of MEDICINE

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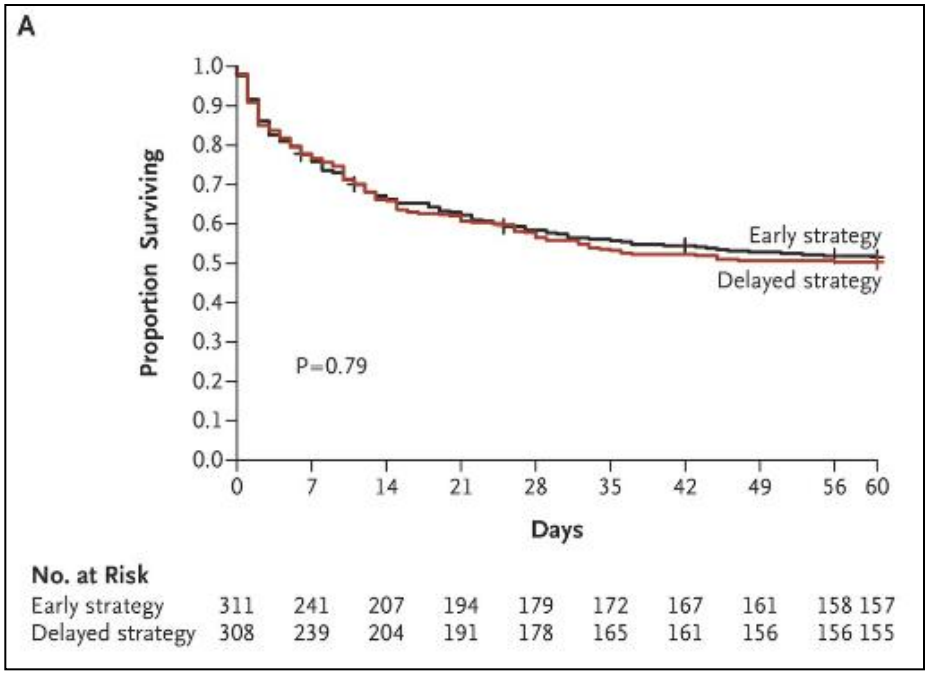
Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit



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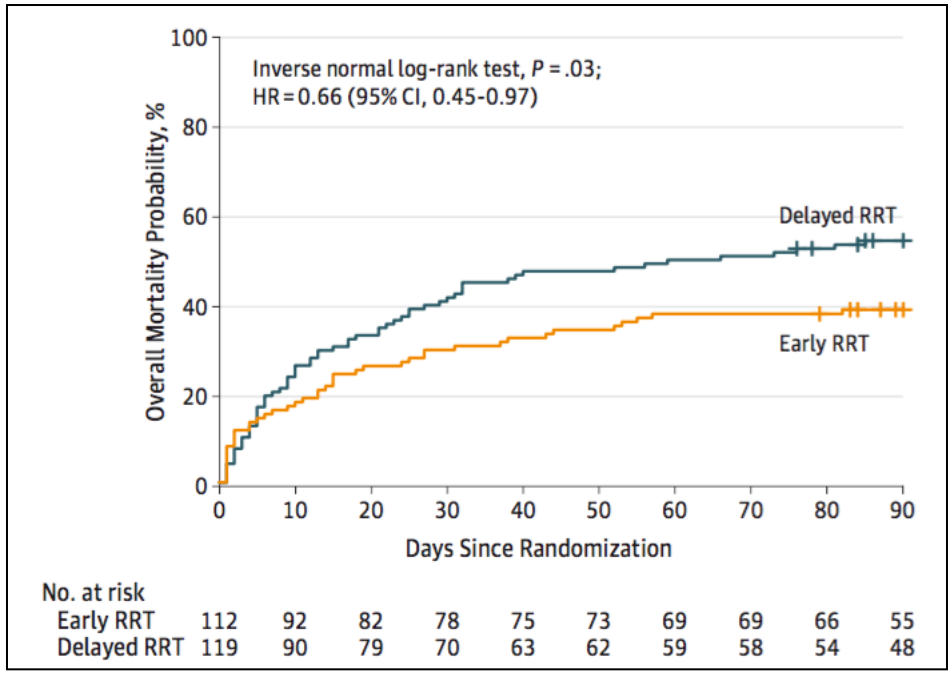
Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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



Does early initiation of Kidney Replacement Therapy (KRT) decrease mortality? A comparison of the RCTs

#NephJC

	ELAIN	AKIKI	IDEAL-ICU	STARRT-AKI
Design (all were RCTs)	Single-surgical center Germany N = 231	Multicenter France N = 620	Multicenter France N = 488	Multicenter Multinational N = 2927
AKI severity & Early KRT criteria	KDIGO Stage 2 AKI + NGAL >150ng/ml	KDIGO stage 3 on ventilator &/or vasopressors	RIFLE-F AKI Early septic shock	KDIGO stage 2 or 3 Critically ill
Time-frame early KRT start within...	8 hours	6 hours	12 hours	12 hours
% Received KRT (early vs late)	100% vs 91%	98% vs 51%	97% vs 62%	97% vs 62%
Mortality (early vs late)	90-day 39% vs 54%	60-day 49% vs 50%	90-day 58% vs 54%	90-day 44% vs 44%
Unique findings	Time on KRT, Kidney recovery, and ventilator time favored early group	61% of survivors did not receive KRT & fewer catheter infections in delayed group	Time on KRT, Kidney recovery, and ventilator time favored early group	Greater % adverse events, KRT dependence & rehospitalization in early (accelerated) group
ICU Length of stay	No difference	No difference	No difference	↓ accelerated group
Limitations & Critiques	Results potentially skewed as many early start patients may have recovered without KRT	Limited generalizability as ≅ 50% received iHD and 30% CRRT	Inconsistencies between KDIGO and RIFLE AKI criteria	Heterogeneity of KRT start time in delayed (standard) group
References	Zarbock et al. JAMA 2016	Gaudry et al. NEJM 2016	Barbar et al. NEJM 2018	Bagshaw et al. NEJM 2020

Visual abstract by @Sophia_Kidney

Early vs. Late RRT Conclusions

- Four excellent large critical care RCTs
- AKIKI/IDEAL-ICU/STARRT-AKI trials better represents our patient population and practice patterns
- No mortality difference when waiting for “absolute indications” for RRT
- May spare RRT with delayed strategy
- However, no harm with early RRT strategy, so individualized care is appropriate when considering patient trajectory

HD vs. CRRT

Nephrol Dial Transplant (2009) 24: 512–518
doi: 10.1093/ndt/gfn560
Advance Access publication 14 October 2008

Original Article

NDT
Nephrology Dialysis Transplantation

Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial

Robert L. Lins[1], Monique M. Elseviers[2], Patricia Van der Niepen[3], Eric Hoste[4], Manu L. Malbrain[5], Pierre Damas[6] and Jacques Devriendt[7] for the SHARF investigators

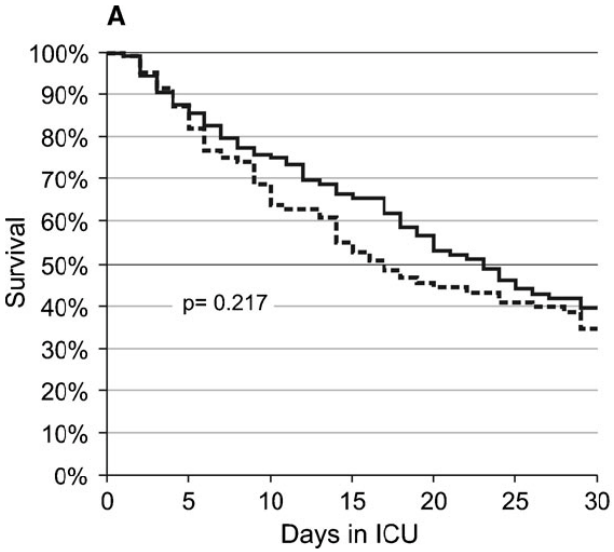
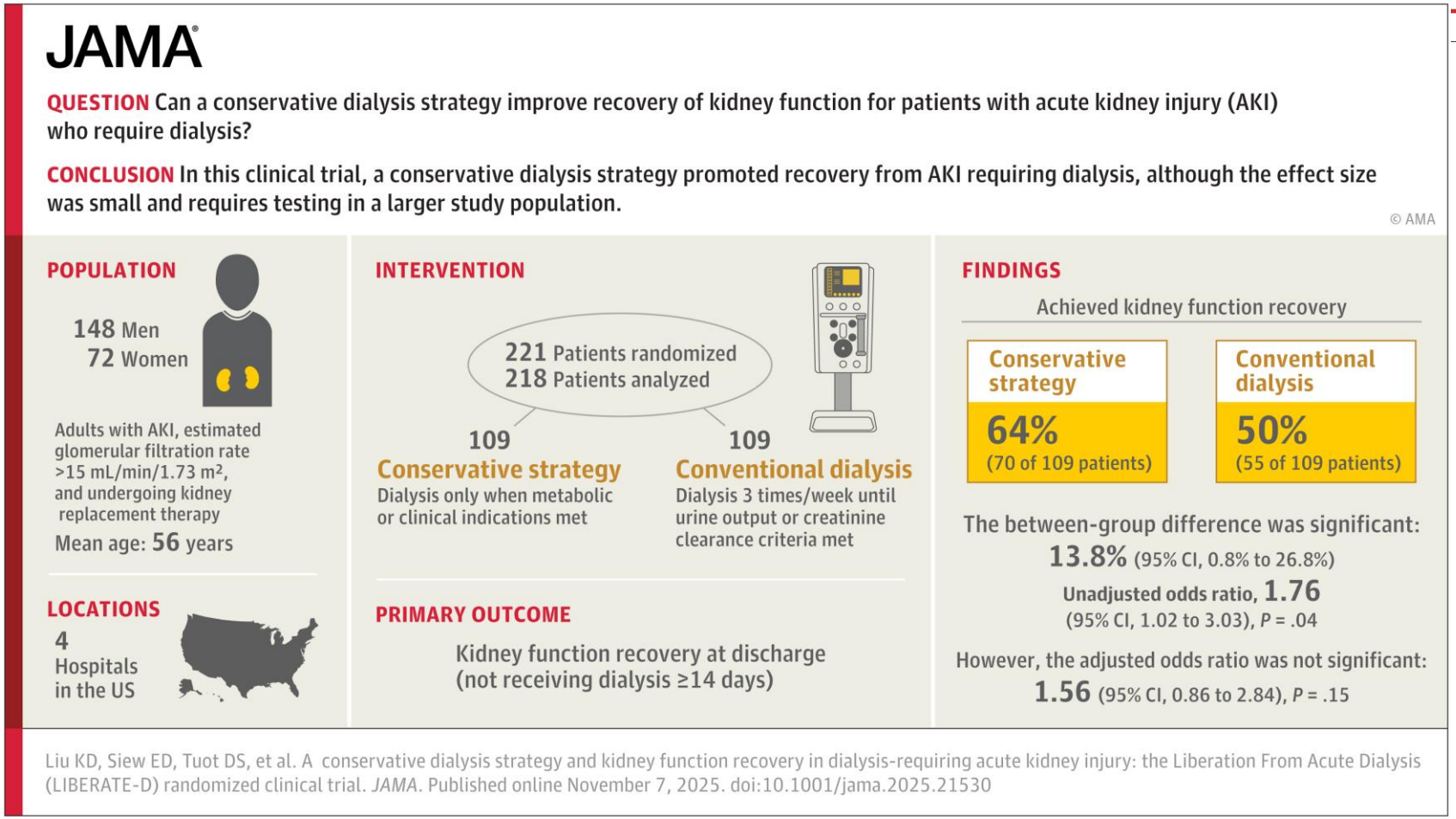


Fig. 3. Survival curves in patients randomized to intermittent (IRI hospital mortality. Life table analysis was performed with Cox re scores.

- Cochrane Review 2007 (Rabindranath et al) – No difference
- **Hard to design an RCT:** strong provider bias, high cross over
- **Theoretical advantages:** less variable MAP, "cytokine filtration," tighter volume control
- **Likely reality**: critical illness is a great equalizer
- Median cost difference: $321/day CVVH > HD [range -$420 to +$4032] in 2014 USD

Crit Care 2010; 14: R46

LIBERATE-D: Frequency of RRT for AKI



N.B. Pressors/Intubation were exclusionary

Liu et al. JAMA 2025.

ESTABLISHED IN 1812 JULY 3, 2008 VOL. 359 NO. 1

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*

20 mL/kg/hr vs 35 mL/kg/hr

RF = 1.6 L/hr vs RF = 2.8 L/hr

ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

25 mL/kg/hr vs 40 mL/kg/hr

RF = 2.0 L/hr vs RF = 3.2 L/hr

ESTABLISHED IN 1812 JULY

Intensity of Renal Suppor with Acute K

The VA/NIH Acute Renal

Table 3. Primary and Secondary Outcomes.*

Outcome	Intensive Strategy (N=563)	Less-Intensive Strategy (N=561)	Odds Ratio or Mean Difference (95% CI)†	P Value
Death from any cause by day 60 — no. (%)	302 (53.6)	289 (51.5)	1.09 (0.86 to 1.40)	0.47
In-hospital death — no. (%)	288 (51.2)	269 (48.0)	1.15 (0.90 to 1.47)	0.27
Discharged to home, off dialysis, by day 60 — no./no. with data (%)	88/560 (15.7)	92/561 (16.4)	0.95 (0.68 to 1.32)	0.75
Recovery of kidney function by day 28 — no./no. with data (%)‡			0.03 (0.02 to 0.07)	0.24
Complete	85/553 (15.4)	102/555 (18.4)		
Partial	49/553 (8.9)	50/555 (9.0)		
None	419/553 (75.8)	403/555 (72.6)		

ESTABLISHED IN 1812

Intensity of Coı i

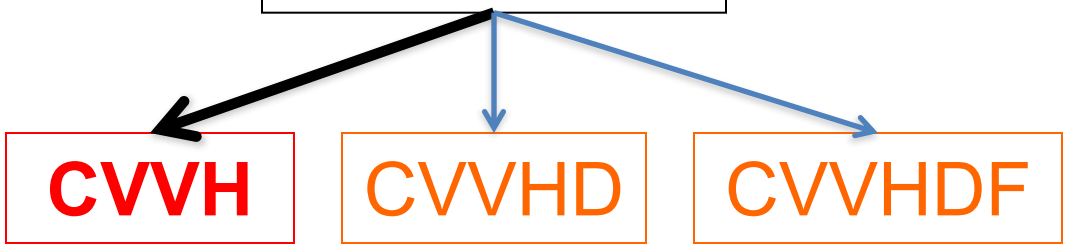
The REN

Table 3. Primary and Secondary Outcomes.*

Outcome	Higher-Intensity CRRT	Lower-Intensity CRRT	Odds Ratio	P Value†
Death — no./total no. (%)				
By day 90	322/721 (44.7)	332/743 (44.7)	1.00 (0.81–1.23)	0.99
By day 28	278/722 (38.5)	274/743 (36.9)	1.07 (0.87–1.32)	0.52
Place of death — no./total no. (%)				
ICU	251/722 (34.8)	254/743 (34.2)	1.026 (0.827–1.273)	0.81
Hospital ward	68/722 (9.4)	76/743 (10.2)	0.913 (0.647–1.288)	0.60
Outside hospital, after discharge	3/722 (0.4)	2/743 (0.3)	1.546 (0.258–9.279)	0.63
RRT dependence among survivors				
At day 28	64/443 (14.4)	57/469 (12.2)	1.22 (0.83–1.79)	0.31
At day 90	27/399 (6.8)	18/411 (4.4)	1.59 (0.86–2.92)	0.14

Terminology

CRRT — Continuous Renal Replacement Therapy



CVVH

Continuous Venovenous Hemofiltration

CVVHD

Continuous Venovenous Hemodialysis

CVVHDF

Continuous Venovenous Hemodiafiltration

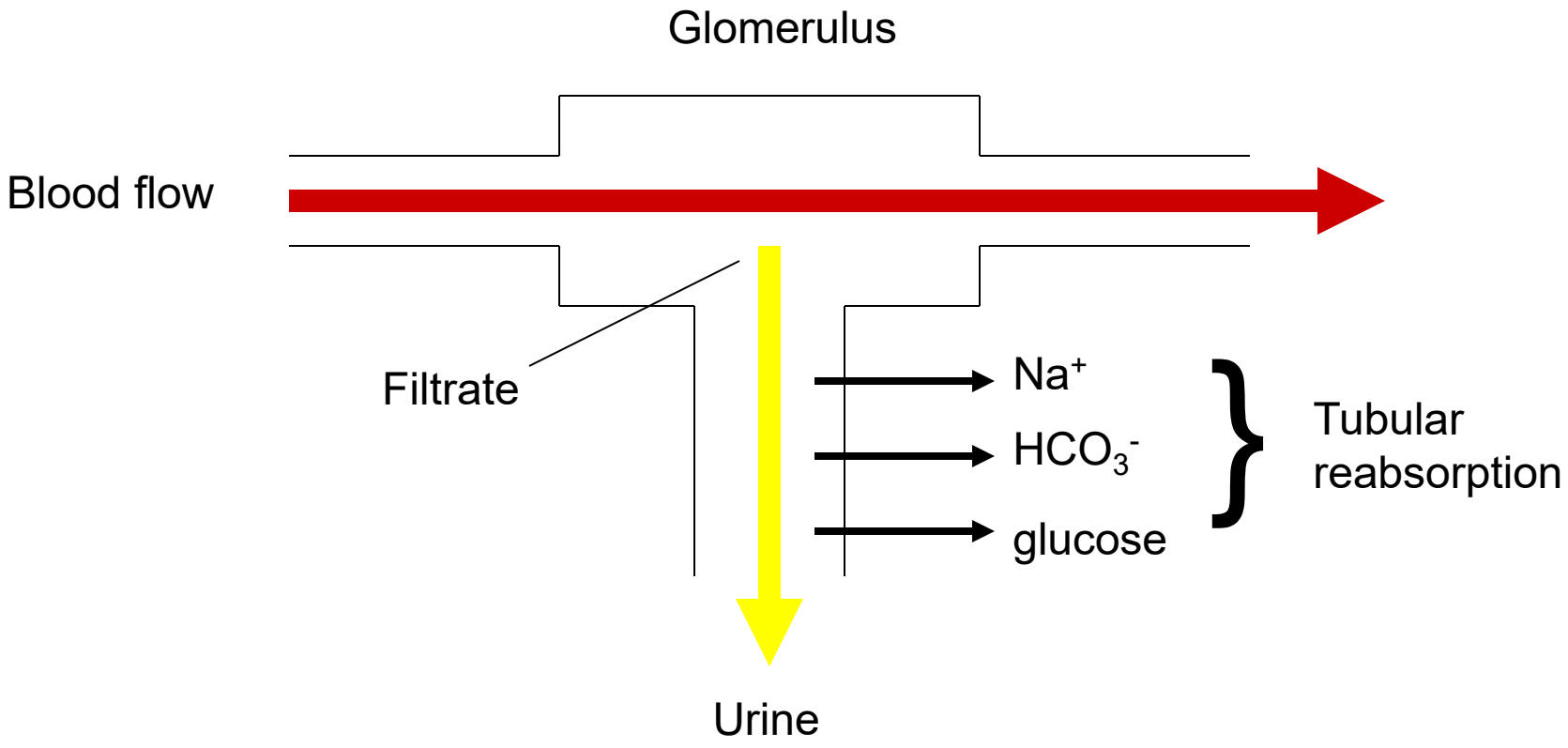
AVVH (Accelerated CVVH) – aka PIRRT

SCUF

Slow Continuous UF
(fluid removal only)

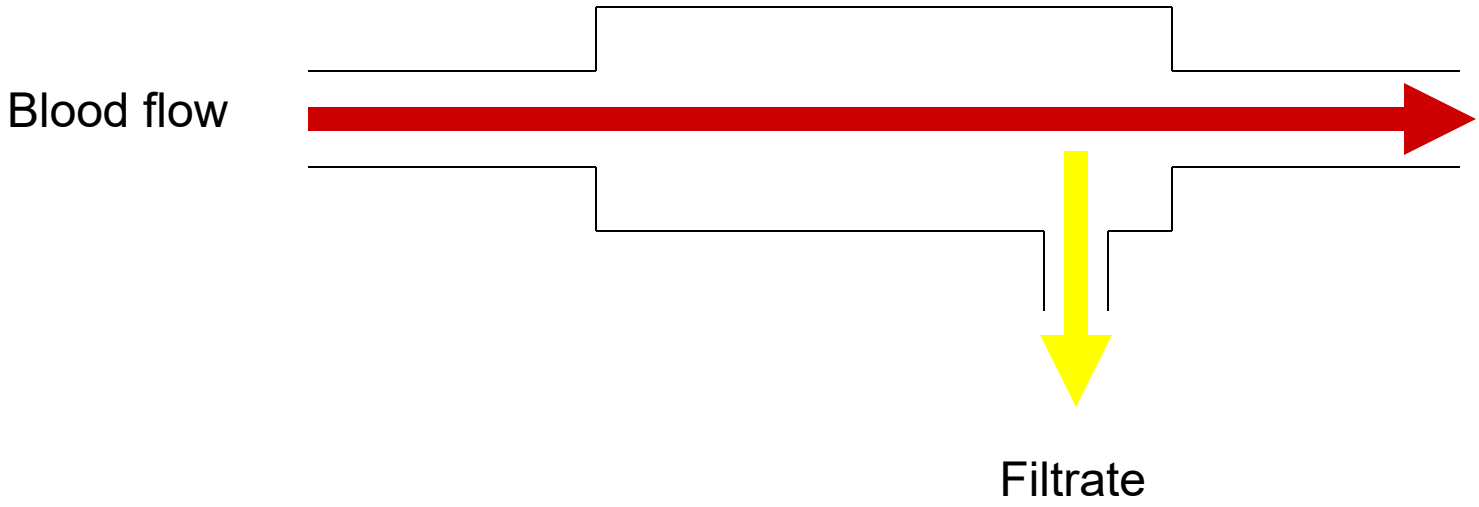
SLE(D)D — Sustained Low Efficiency (Daily) Dialysis
[i.e. slow hemodialysis]

The Kidney

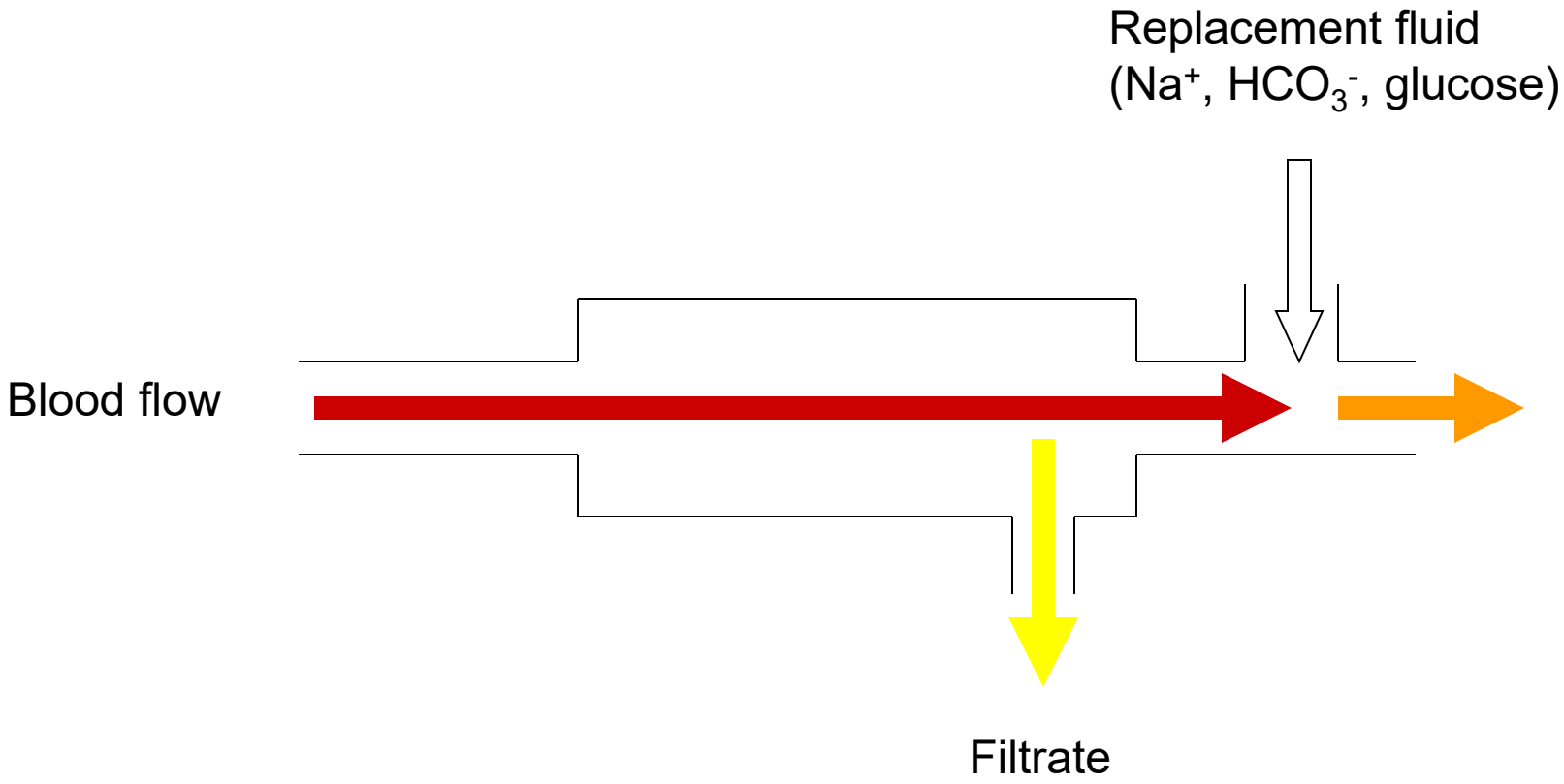

Glomerulus
Blood flow
Filtrate
Na^+
HCO_3^-
glucose
Tubular reabsorption
Urine

CVVH

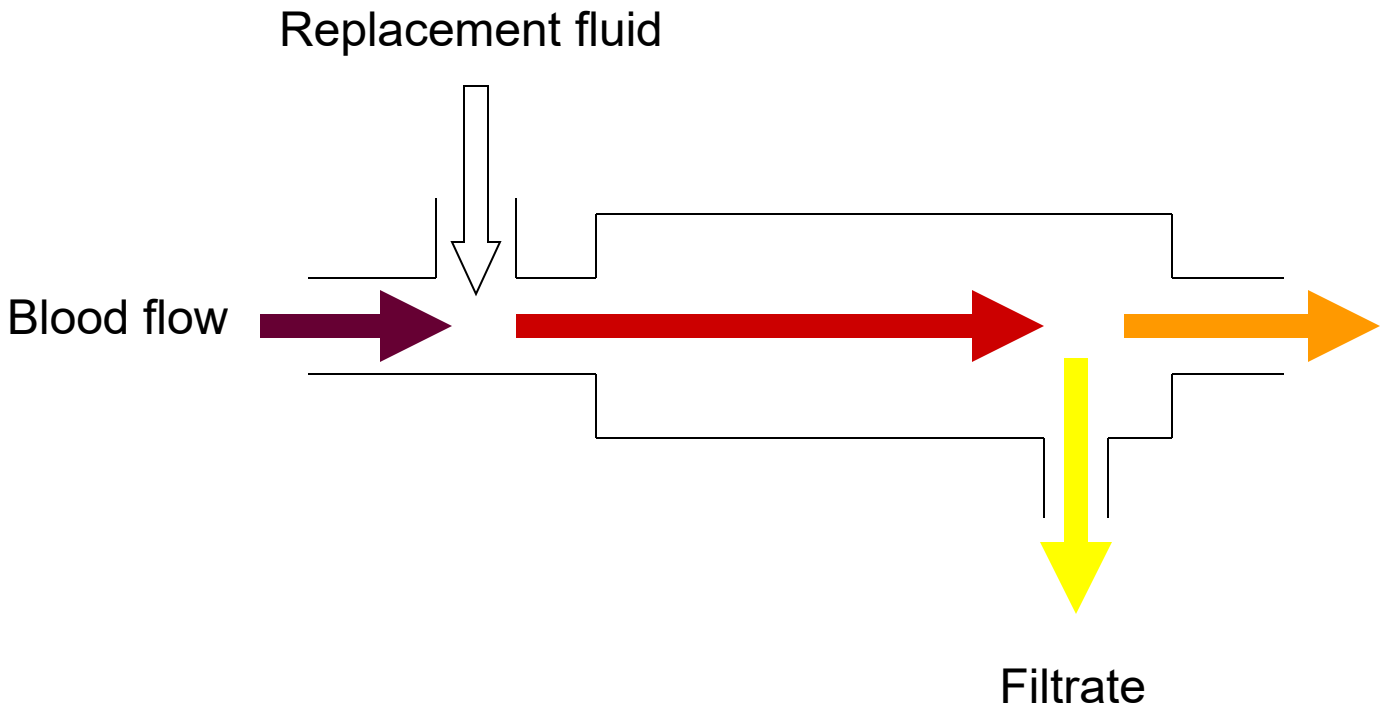
Filtration, but no tubular reabsorption



Post-filter replacement fluid

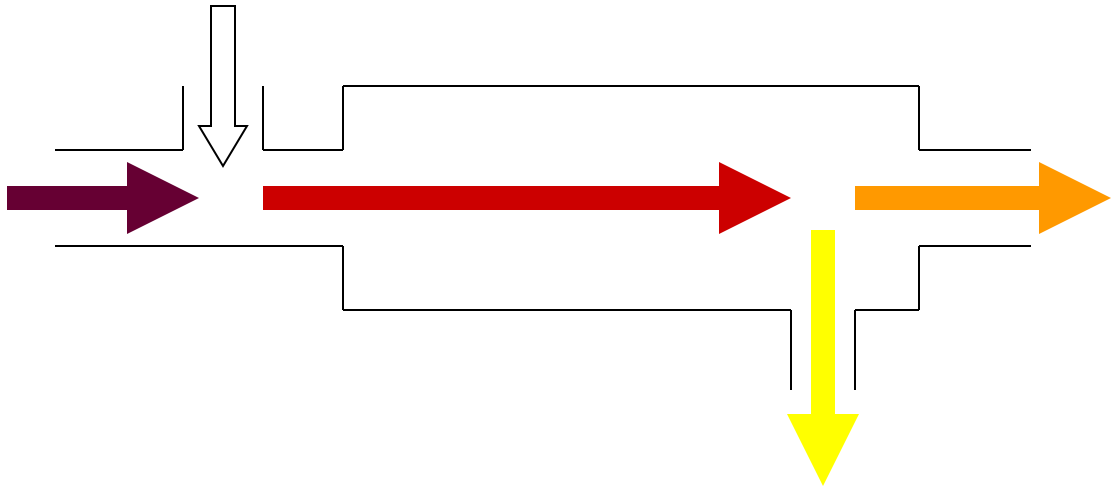


Pre-filter replacement fluid

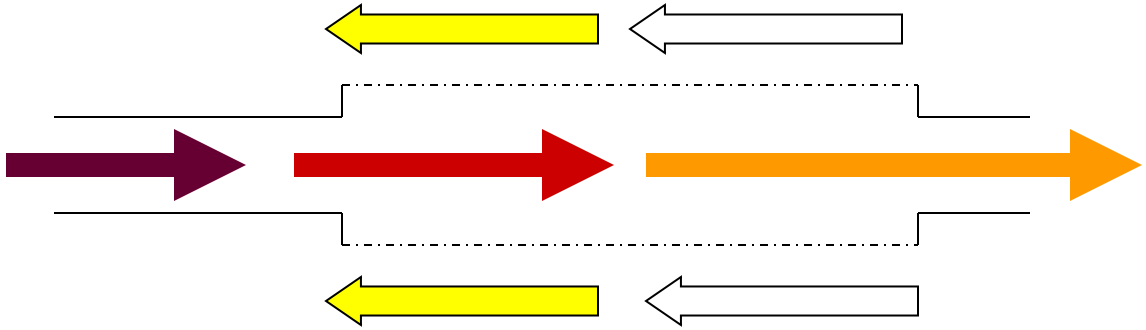


CVVH vs HD

CVVH
filtration
convection



HD
dialysis
diffusion



CVVH vs HD

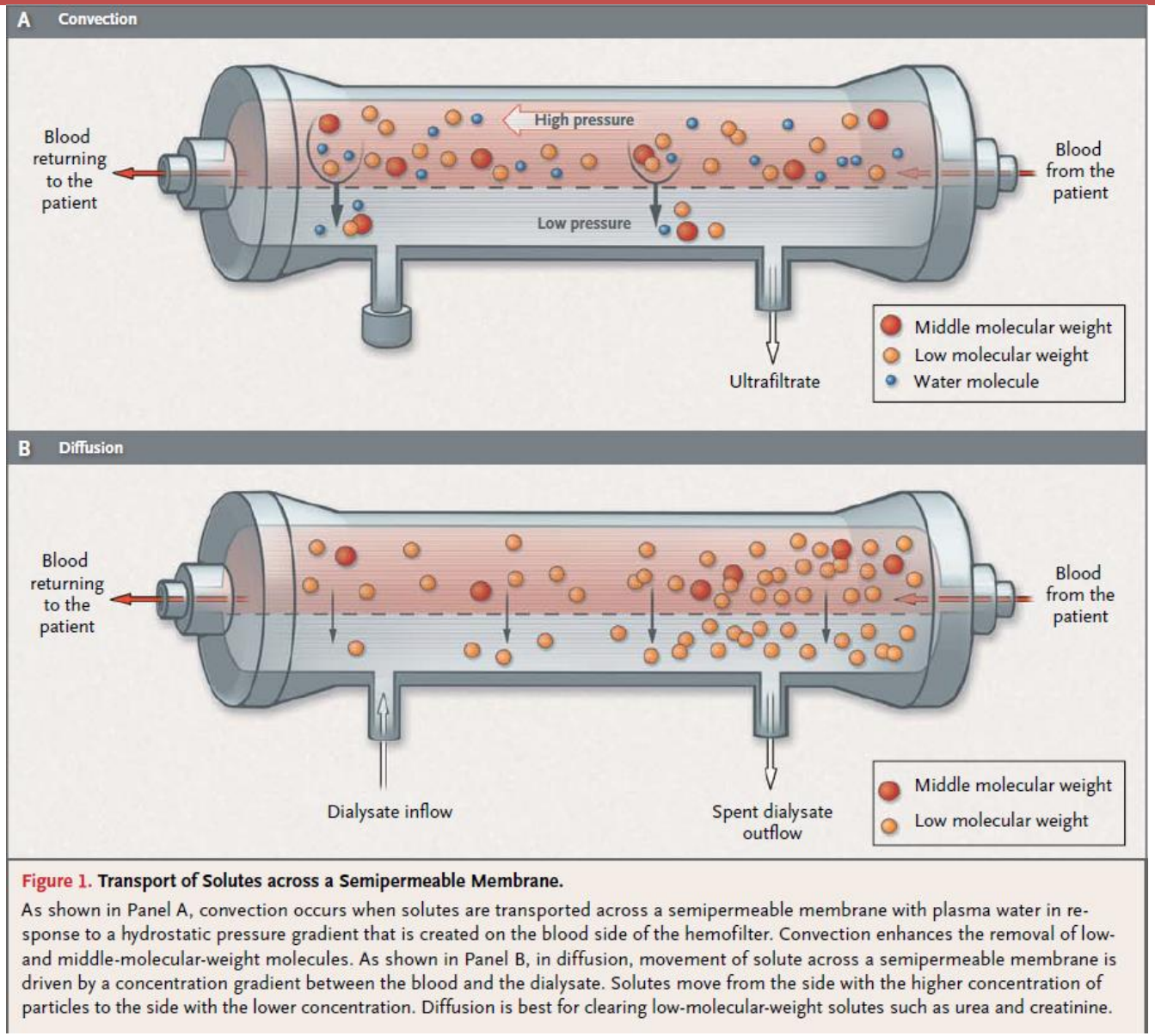
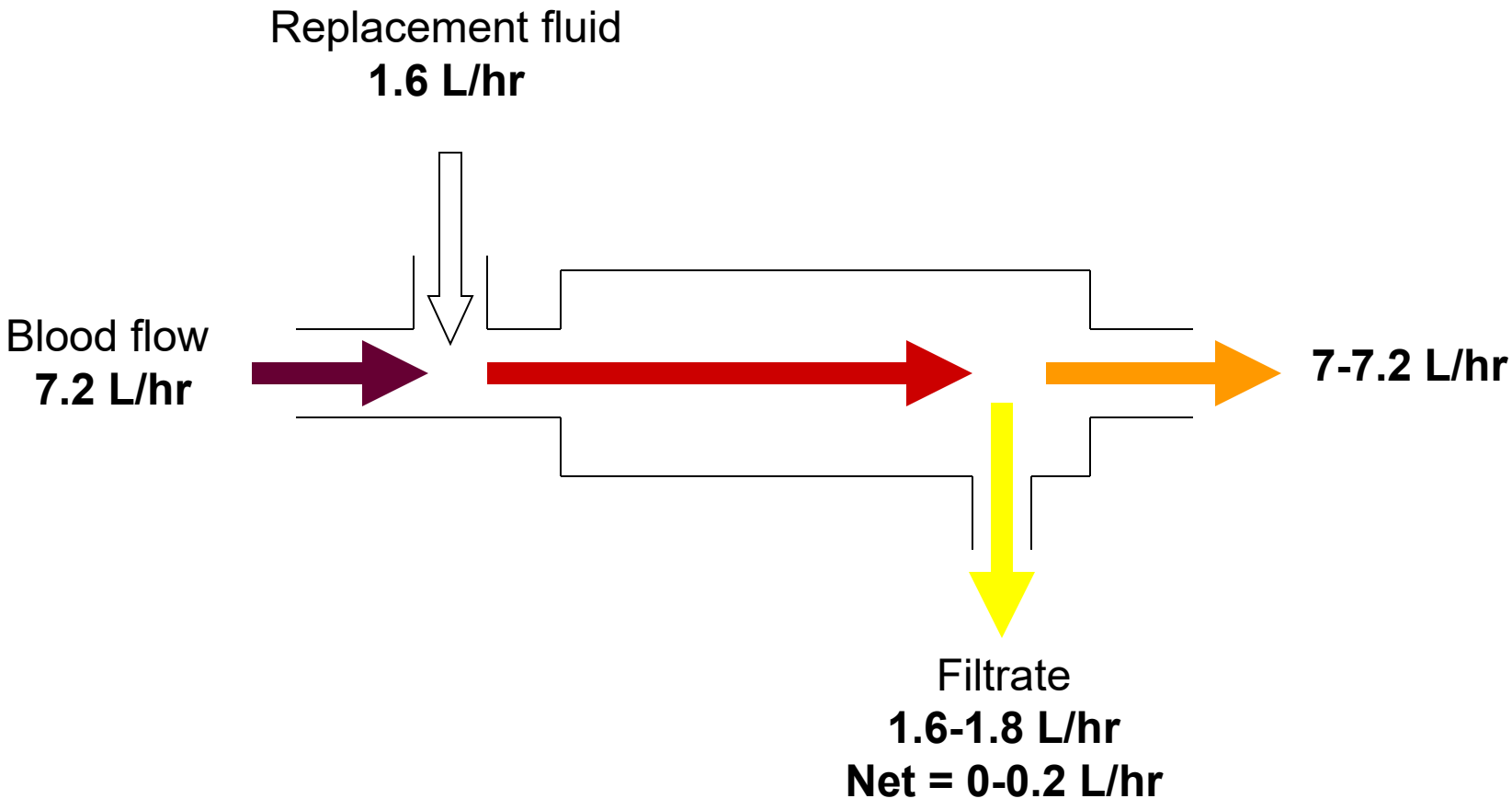


Figure 1. Transport of Solutes across a Semipermeable Membrane.

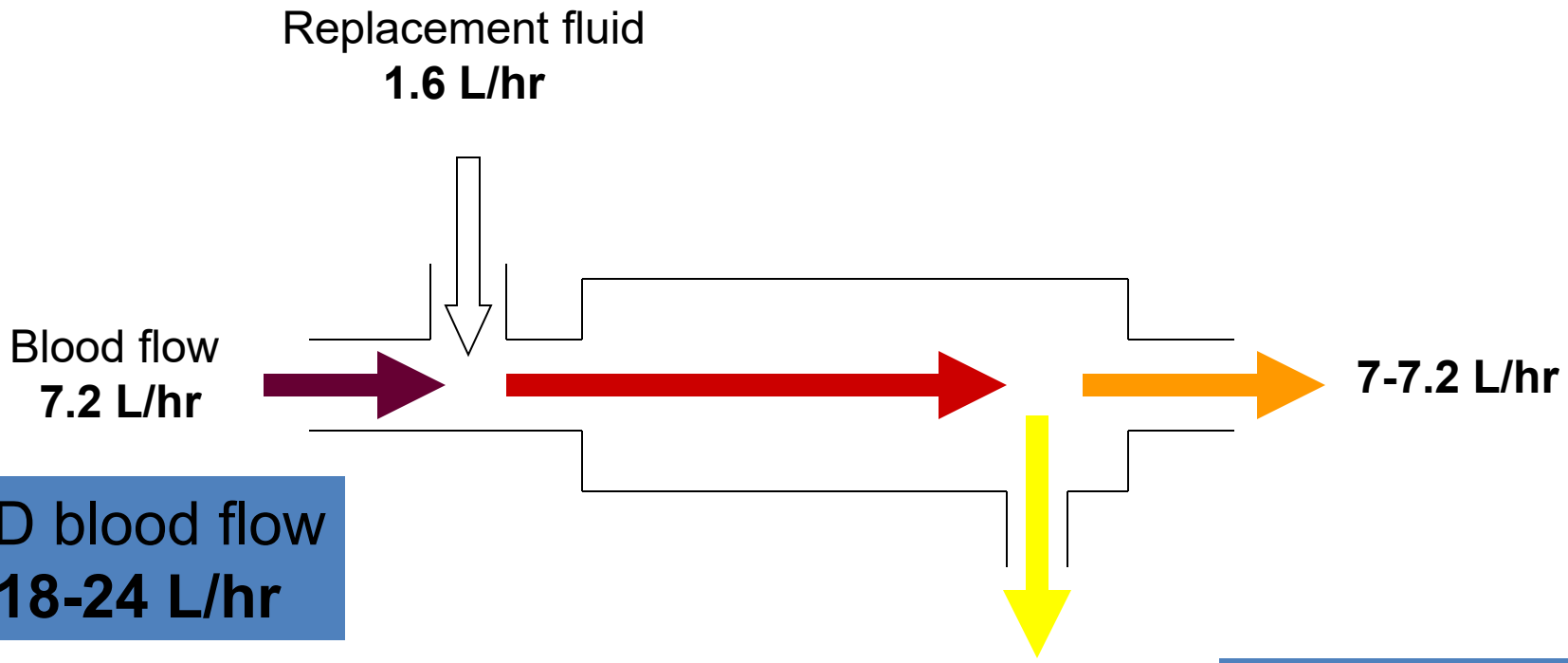
As shown in Panel A, convection occurs when solutes are transported across a semipermeable membrane with plasma water in response to a hydrostatic pressure gradient that is created on the blood side of the hemofilter. Convection enhances the removal of low- and middle-molecular-weight molecules. As shown in Panel B, in diffusion, movement of solute across a semipermeable membrane is driven by a concentration gradient between the blood and the dialysate. Solutes move from the side with the higher concentration of particles to the side with the lower concentration. Diffusion is best for clearing low-molecular-weight solutes such as urea and creatinine.

NEJM 2012; 367: 26

CVVH overview – flow rates



blood flow vs HD



HD blood flow
18-24 L/hr

HD net filtrate
0.5-1 L/hr

CVVH – indications

Advanced renal failure (acute or chronic)

+

CVVH – indications

Advanced renal failure (acute or chronic)

+

Hemodynamic instability

and/or

Significant volume overload

and/or

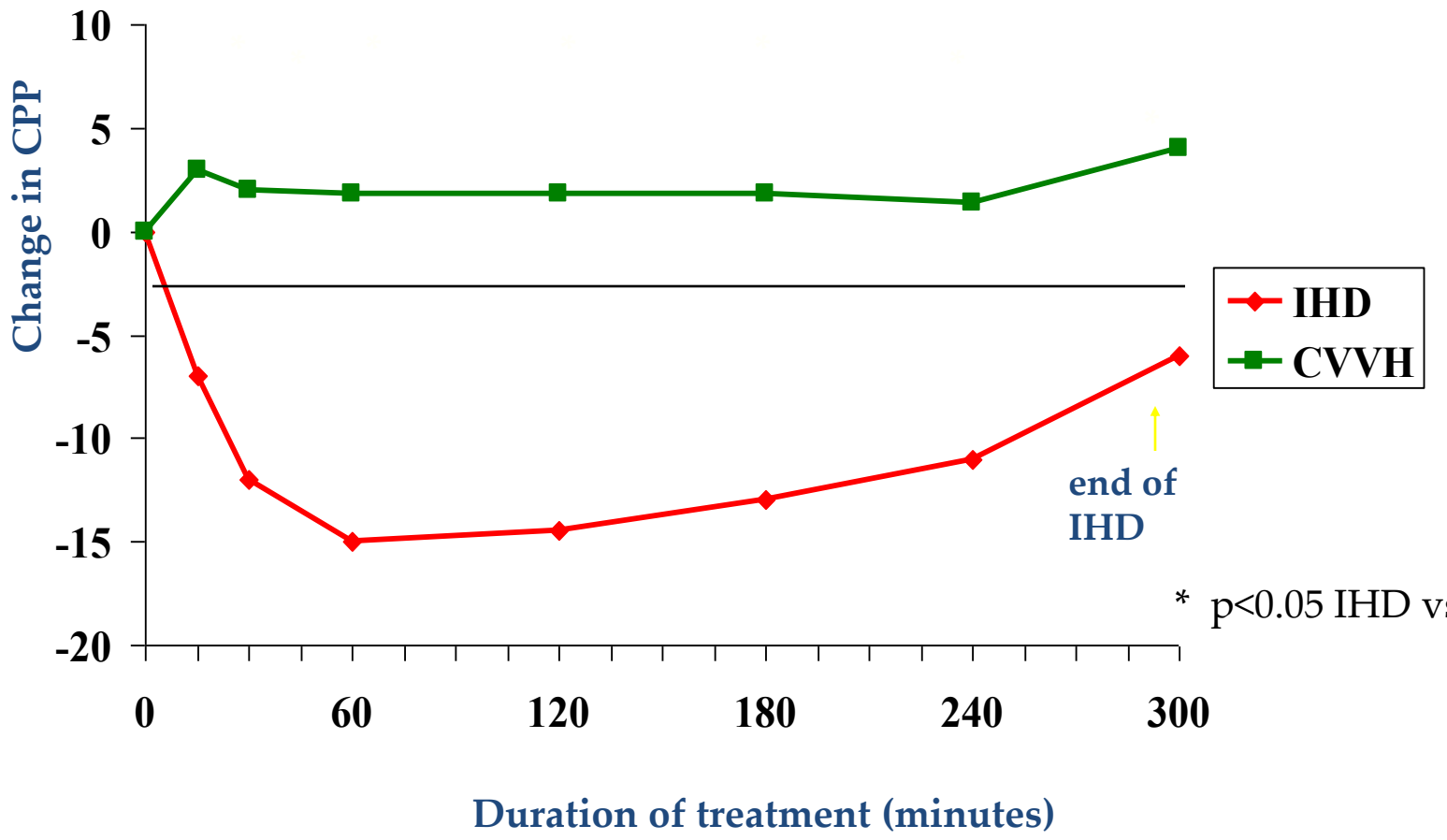
Ongoing, high-volume inputs

and/or

Significant acidosis

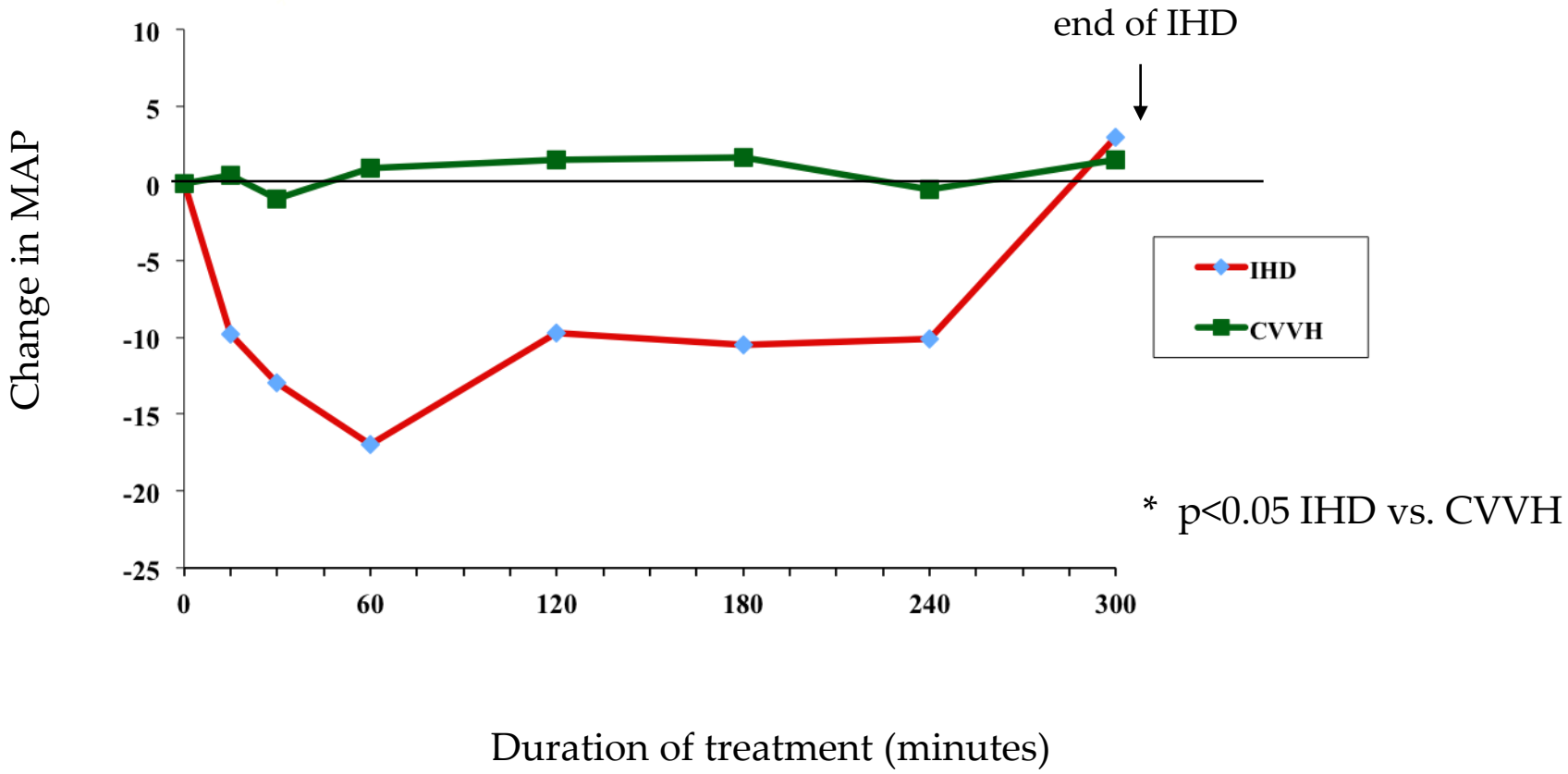
(? Cerebral edema – acute liver failure, head trauma?)

Cerebral perfusion pressure



Davenport, KI, 1993

Changes in MAP



Davenport, KI, 1993

AVVH – transition from CVVH to HD

Premise: high bounce back rate to ICU when transitioning to HD, may be able to accelerate CVVH as intermediate RRT modality

	CVVH	**AVVH**
Access	Catheter	Catheter
Blood flow (mL/min)	250	350-400
Replacement Fluid (L/hr)	1.6	4.0
Time (hr/day)	24	10
Replacement Fluid (L/day)	40	40
Ultrafiltration Rate (mL/hr)	~100	~200
Ultrafiltration Rate (mL/day)	~2000	~2000

When to Stop RRT

- Clinical judgment
- If UOP >1000 cc/day, consider RRT holiday
  - Can measure 12 or 24 hr urine Cr collection to estimate GFR (>15 mL/min usually d/c RRT)
- Chance of recovery ≈ degree of pre-injury CKD
- Any AKI leaves all patients with less reserve and CKD even if Cr normalizes

Crit Care 2012; 16:R107 & *JASN* 2012; 23: 967

CVVH – contraindications

Life-threatening hyperkalemia

Drug ingestions (lithium, ethylene glycol, methanol, metformin)

Futility

When to Start?

Data-driven ICU Care:

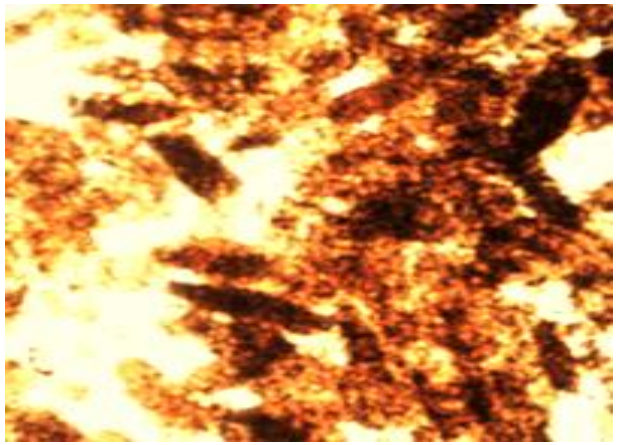
- Early goal-directed therapy
  - Central line CVP
- Lung protective ventilation
  - Control acidosis
- Conservative fluid management
  - Tight volume control despite inputs
  - TRAJECTORY

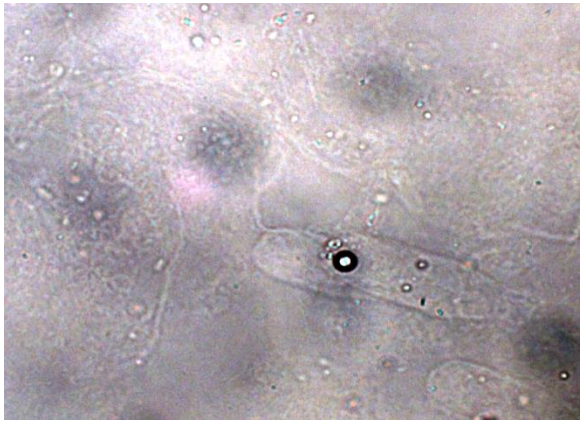
Trajectory

Hemodynamics

Urine output – lasix responsiveness

Urine sediment





Thank You