RRT for AKI in the ICU: When & How?

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Objectives

At the end of this activity, the participant will be able to:

1. Understand the current equipoise related to timing of initiation renal replacement therapy for AKI
2. Choose when to initiate renal replacement therapy in a patient with acute kidney injury
3. Select a modality of renal replacement therapy for a patient with acute kidney injury

Differences Between Renal Support in AKI and ESRD

- Time-frame
  - days to weeks versus years
- Burden of concomitant illness
- Hemodynamic instability
- Recoverability of kidney function

Renal Replacement Therapy in Acute Kidney Injury

- When should renal replacement therapy be initiated in AKI?
- Which modality is most appropriate?
- What is the appropriate dose of therapy?

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Renal Replacement Therapy in Acute Kidney Injury

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Clinical Case 1

You are consulted for possible initiation of RRT for an 82-year-old man who has developed oliguric AKI following emergent CABG. He has a history of HTN, T2DM and COPD but has normal baseline kidney function with a plasma creatinine of 0.9 mg/dL (80 µmol/L). He presented to the hospital 5 days previously with severe chest pain, was diagnosed with a NSTEMI and underwent urgent coronary angiography which demonstrated severe 3-vessel disease. Surgical management was recommended and two days ago he underwent CABGx5. Post-operatively he was hypotensive, requiring vasopressor support with epinephrine and norepinephrine. His initial cardiac index was 1.3 $L/min/m^2$, increasing to 1.9 $L/min/m^2$ yesterday and 2.2 $L/min/m^2$ today. He has now been weaned off of epinephrine and has a BP of 110/60 mm/Hg on 0.03 mcg/kg/min norepinephrine.

Clinical Case 1, cont.

On exam, he is intubated, sedated, mechanically ventilated. He has decreased breath sounds over his left chest and has 1+ pedal/flank edema. His S_aO_2 is 98% on an F_iO_2 of 0.40 with PEEP of 5 cm H_2O.

His I/O and labs are summarized below:

	POD1	POD2	POD3
Intake/Output, (mL)	8,600/930	2,300/430	1,700/520
BUN mg/dL (mmol/L)	22 (7.9)	34 (12.1)	42 (15.0)
Creatinine, mg/dL (µmol/L)	1.3 (115)	2.4 (215)	3.1 (275)
Potassium, mmol/L	5.1	5.3	5.6
tCO_2, mmol/L	24	21	19

Audience Response 1

You are asked by the CT surgeon whether she should place a catheter so that you can begin RRT.

Which ONE of the following strategies should be followed?

A. Place a catheter and begin RRT immediately
B. Holding off on placement of the catheter for the time being.

Timing of Renal Replacement Therapy in AKI

"While there is increasing recognition of the value of earlier dialysis, the *published* consensus, and the practice in many centers at present, is still to apply dialysis to relatively ill rather than to relatively healthy patients"

-Teschan PE, et al: Ann Intern Med 1960; 53:992-1016

Timing of Renal Replacement Therapy in AKI

“**We would urge that dialyses applied to patients who might otherwise survive should not under any circumstances be considered to be superfluous**. Rather, the judgment of whether to undertake dialysis should also be made in view of the possible risks of *not* employing this procedure. We would question both the wisdom and the safety of subjecting patients to several days of avoidable nausea, vomiting, drowsiness and thirst, which not only implies significant discomfort to the patient but may also impose considerable risk of aspiration, pneumonia and other unexpected ‘complications’”

-Teschan PE, et al: Ann Intern Med 1960; 53:992-1016

Indications for Renal Support in Acute Kidney Injury

- Volume overload
- Metabolic acidosis
- Hyperkalemia
- Uremic state
  - encephalopathy
  - pericarditis
- Azotemia without uremic manifestations
- Oliguria

Retrospective Studies of Timing of Hemodialysis in AKI

	n	BUN pre Dialysis (mg/dL)		Survival (%)	
		Early	Late	Early	Late
Parsons et al Lancet 1961; 1:129-134	33	120-150	>200	75	12
Fischer et al Surg Gynecol Obstet 1966; 123:1019-1023	162	~150	>200	43	26
Kleinknecht et al Kidney Int 1972; 1:190-196	500	<93	>163	71	58

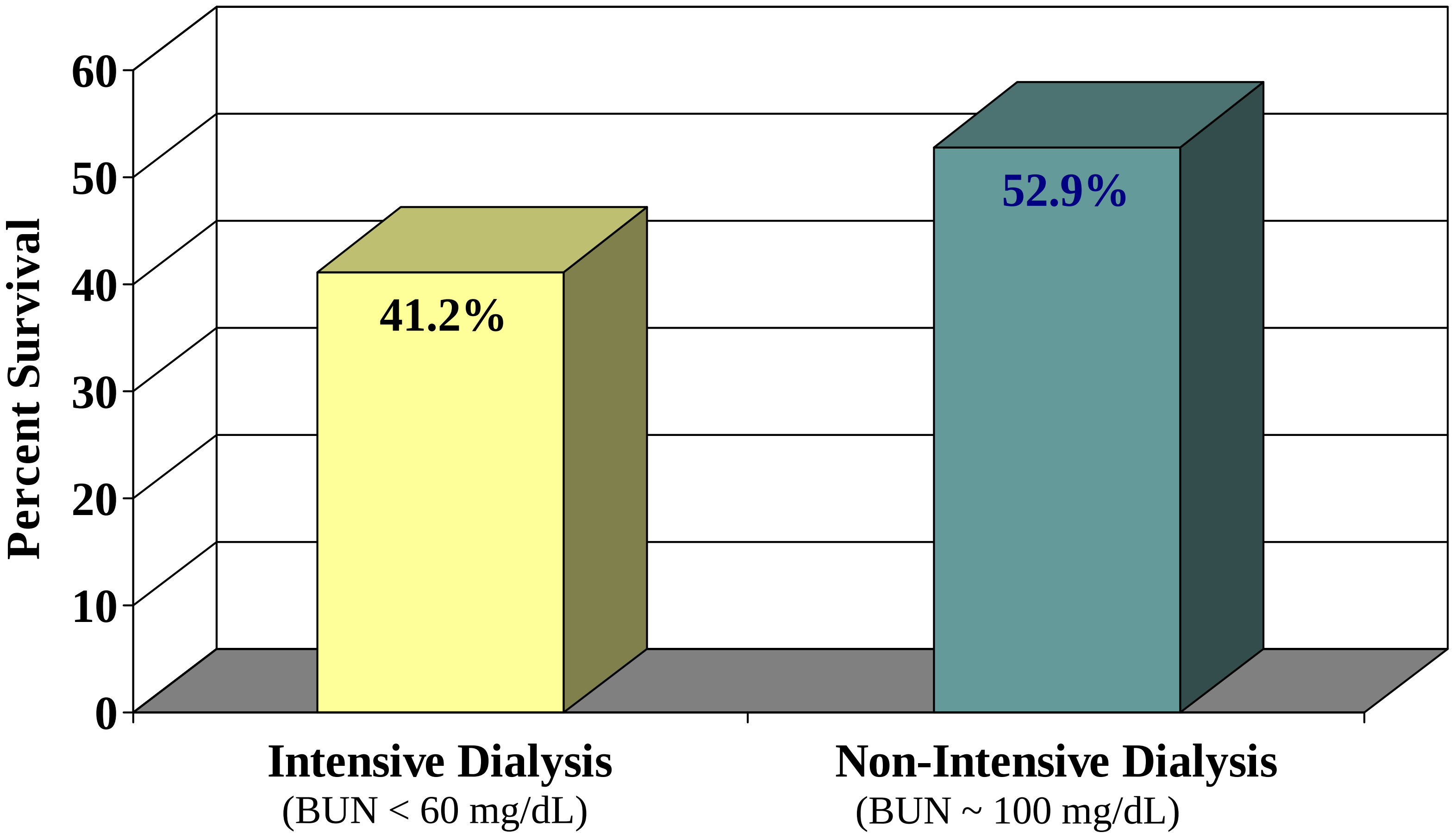
“Prophylactic” Dialysis in AKI

	Group A (n=8)	Group B (n=10)
Complications		
Septic		
Gr (-) sepsis	50%	80%
Peritonitis	36%	50%
Pneumonia	13%	20%
Meningitis	13%	10%
Hemorrhage	36%	60%
Seizures	13%	20%
ARDS	25%	30%
Survival	64%	20%

Group A: BUN < 70 mg/dL, creatinine < 5.0 mg/dL
Group B: BUN ~150 mg/dL, creatinine ~10 mg/dL

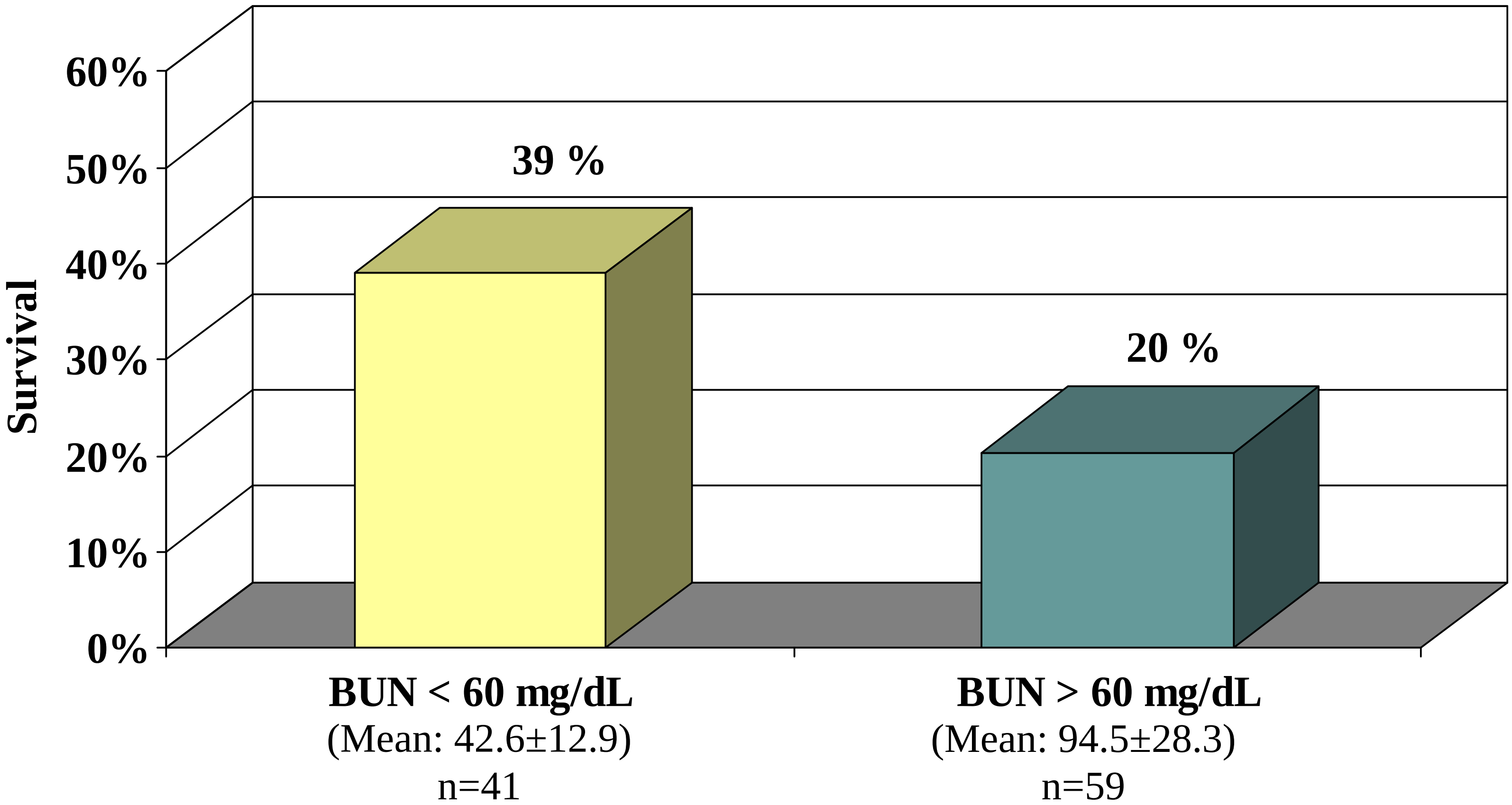
Conger JD: J Trauma 1975; 15:1056-1063

“Intensive” Dialysis in AKI



Gillum DM, et al: Clinical Nephrology 1986; 25:249-255

Timing of CVVH in Post-Traumatic AKI

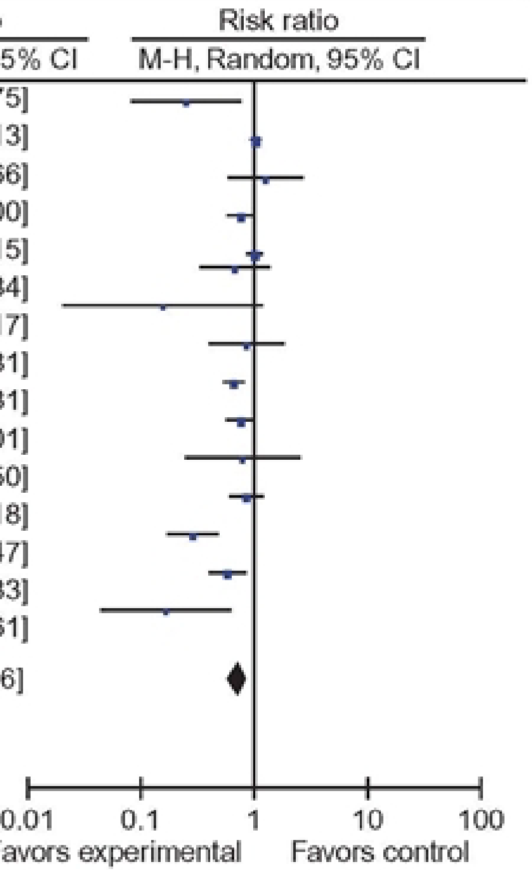


Gettings LG, et al: Intensive Care Med 1999; 25:805-813

2012 Meta-Analysis of Timing of Initiation of RRT in AKI: Survival

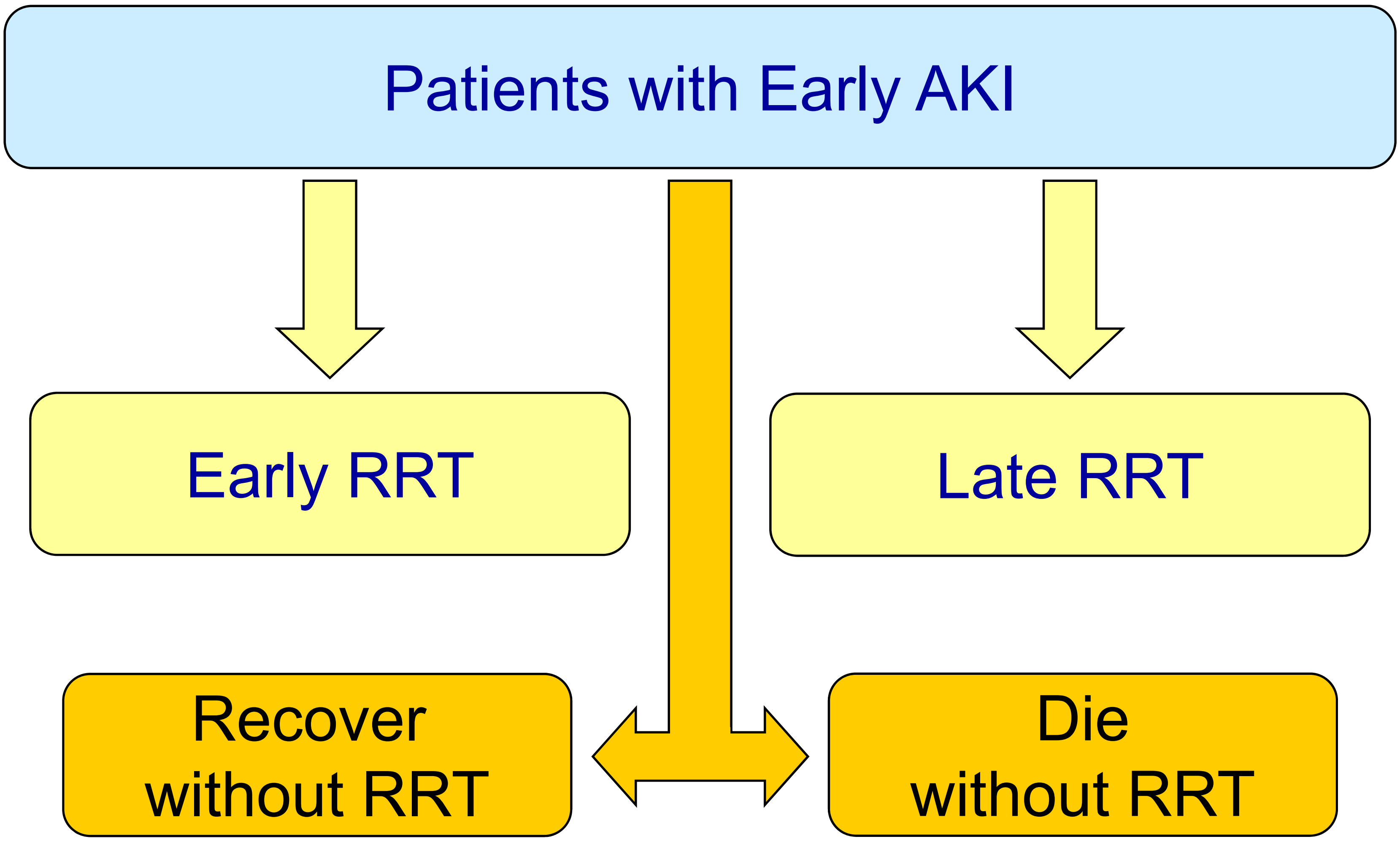
Study or subgroup	Early RRT Events	Early RRT Total	Late RRT Events	Late RRT Total	Weight (%)	Risk ratio M-H, Random, 95% CI
Andrade 2007	3	18	10	15	2.4	0.25 [0.08, 0.75]
Bagshaw 2009	392	618	380	619	12.3	1.03 [0.95, 1.13]
Bouman 2002	11	35	9	36	4.2	1.26 [0.59, 2.66]
Carl 2010	44	85	42	62	10.0	0.76 [0.58, 1.00]
Chou 2011	135	192	124	178	11.8	1.01 [0.88, 1.15]
Dermirkilic 2004	8	27	15	34	4.7	0.67 [0.34, 1.34]
Durmaz 2003	1	21	7	23	0.8	0.16 [0.02, 1.17]
Elahi 2004	8	28	12	36	4.2	0.86 [0.41, 1.81]
García-Fernández 2011	59	111	74	92	11.0	0.66 [0.54, 0.81]
Gettings 1999	25	41	47	59	9.9	0.77 [0.58, 1.01]
Iyem 2009	5	95	6	90	2.2	0.79 [0.25, 2.50]
Liu 2006	43	122	50	121	9.2	0.85 [0.62, 1.18]
Manche 2008	14	56	13	15	6.7	0.29 [0.18, 0.47]
Shiao 2009	22	51	35	47	8.7	0.58 [0.41, 0.83]
Sugahara 2004	2	14	12	14	1.8	0.17 [0.05, 0.61]
Total (95% CI)		1514		1441	100.0%	0.71 [0.59, 0.86]
Total events	772		836			

Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 67.42$, df = 14 ($p < 0.00001$); $I^2 = 79\%$
Test for overall effect: $Z = 3.55$ ($p = 0.0004$)

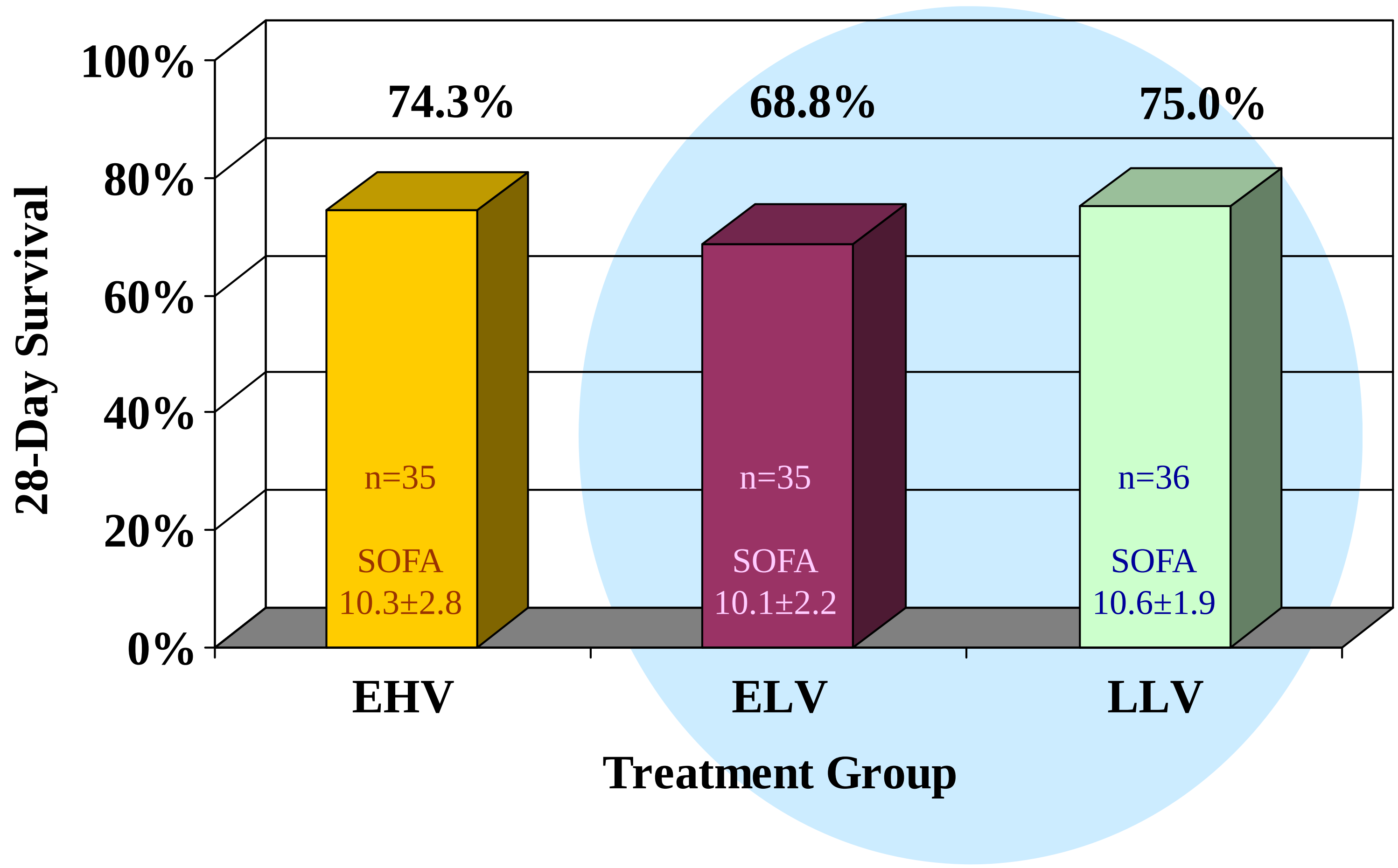


Wang X, et al. Renal Fail 2012; 34: 396-402

Timing of RRT in AKI

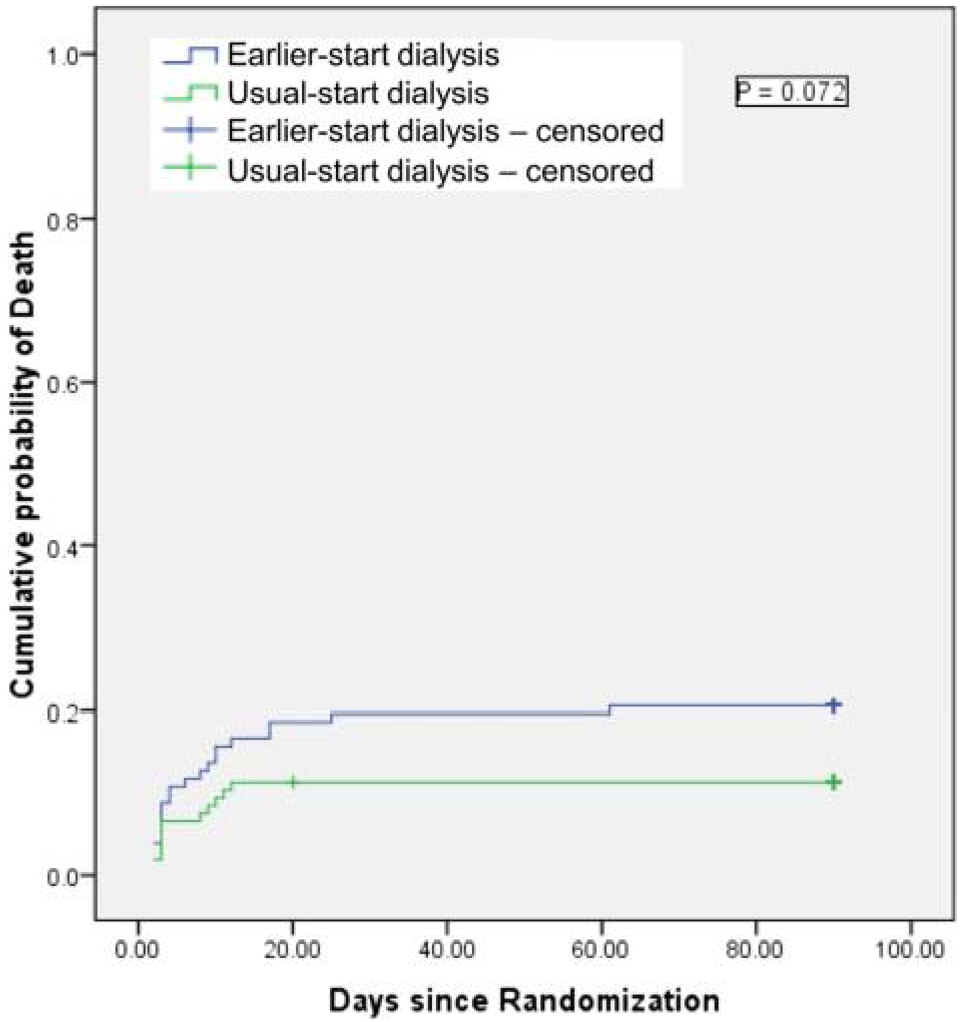


Timing and Dose of CVVH in AKI



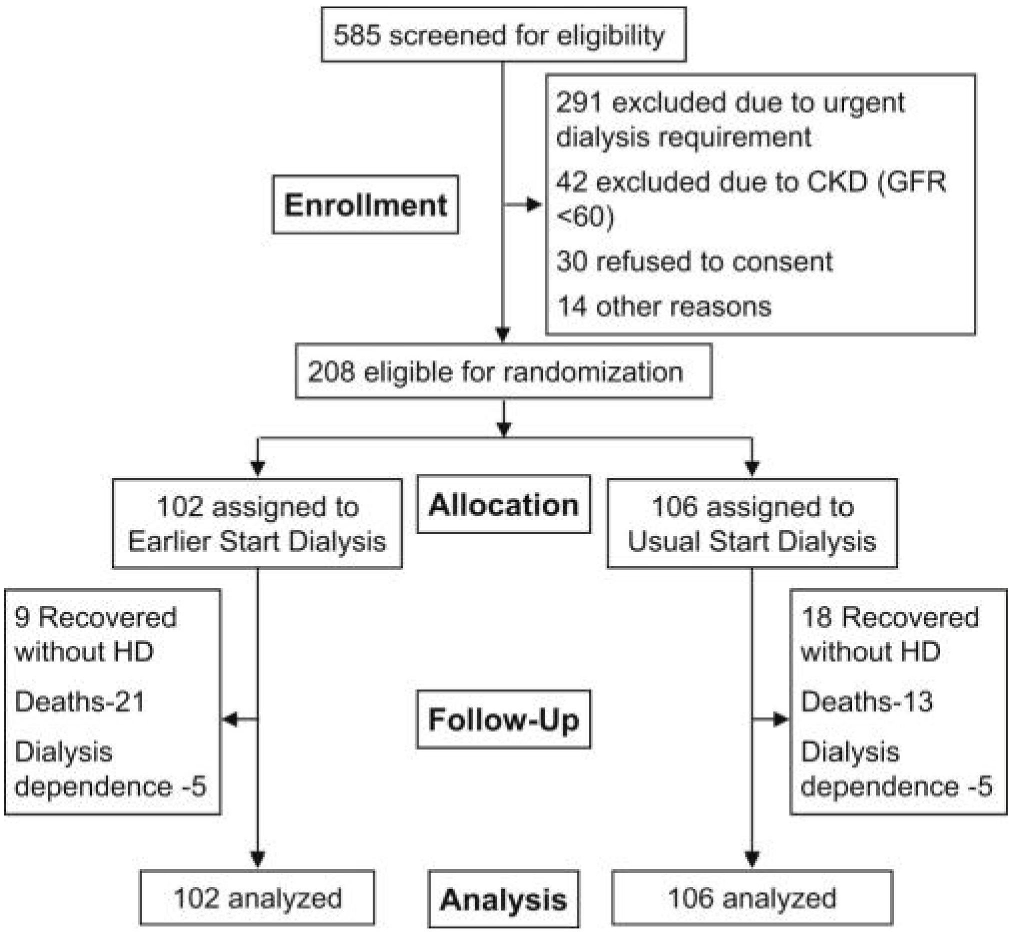
Bouman CS, et al. Critical Care Med 2002; 30:2205-2211

Earlier versus Usual Start of RRT in Community-Acquired AKI



Jamale TE, et al. Am J Kidney Dis 2013; 62:1116-1121

Earlier versus Usual Start of RRT in Community-Acquired AKI



Baseline Data

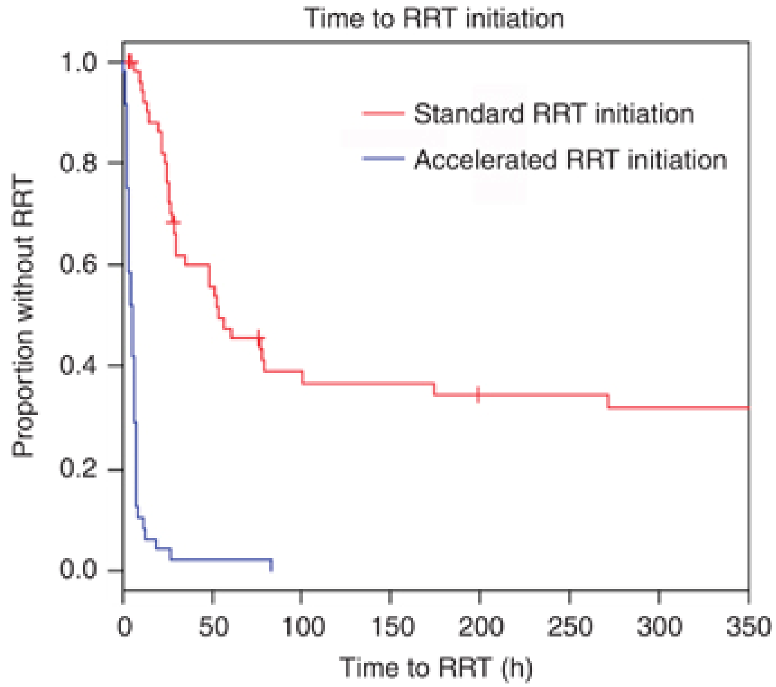
	Early Start	Usual Start
BUN (mg/dL)	71.7±21.7	100.9±32.6
Creatinine (mg/dL)	7.4±5.3	10.4±3.3

Jamale TE, et al. Am J Kidney Dis 2013; 62:1116-1121

STARRT-AKI Pilot

Eligibity Criteria

- Presence of severe AKI (2 of the following)
  - twofold increase in serum creatinine from baseline
  - urine output <6 ml/kg in the preceding 12 h, or
  - whole-blood NGAL ≥400 ng/ml)
- <48 hours since doubling of serum creatinine
- Absence of urgent indications for RRT initiation (serum K^+≤5.5 mmol/l and HCO_3^-≥15 mmol/l)
- Low likelihood of volume-responsive AKI (defined CVP≥8 mm Hg).
- Exclusions:
  - Lack of commitment to ongoing life support;
  - presence of an intoxication requiring RRT
  - RRT within the previous 2 months;
  - clinical suspicion of renal obstruction, RPGN or AIN
  - prehospitalization eGFR<30 ml/min per 1.73 m^2;
- Equipoise among treating team (attending intensivist and nephrologist)
  - Did treating physicians believe believed that either immediate RRT initiation or RRT deferral was mandated.



Wald R, et al. Kidney Int 2015; 88: 897-904

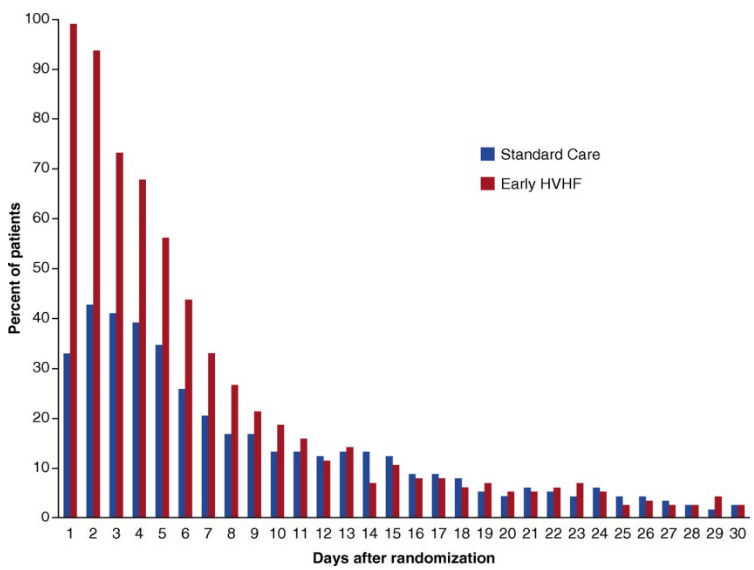
STARRT-AKI Pilot

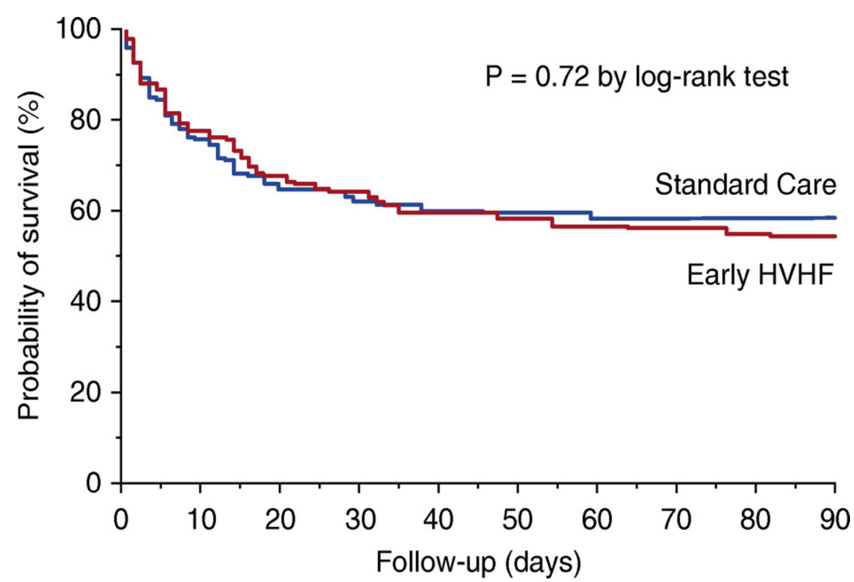
Treatment Group	90-day Mortality
Accelerated Initiation of RRT (n=48)	37.5%
Standard Initiation of RRT (n=52)	36.5%
Received RRT (n=33)	*39.4%*
Did not receive RRT (n=19)	*31.6%*

Wald R, et al. Kidney Int 2015; 88: 897-904

HEROICS Trial

	Early HVHF (N=112)	Delayed CVVHDF (N=112)	OR (95% CI)
Number receiving RRT	111 (99%)	64 (57%)	
30-day mortality	36%	36%	1.00 (0.58-1.73)
90-day mortality	46%	38%	1.34 (0.79-2.28)





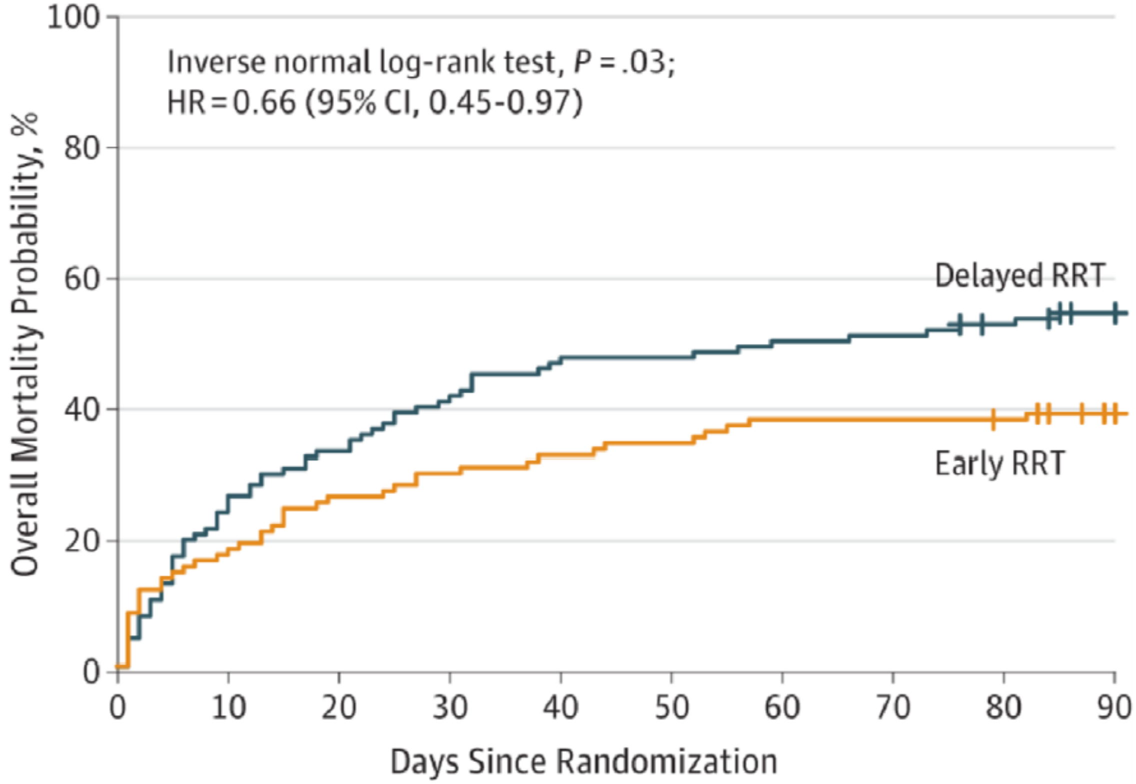
Combes, A et al. Am J Respir Crit Care Med 2015;192: 1179-1190

ELAIN Trial

	Early (N=112)	Late (N=119)	Difference, HR or OR (95% CI)	*P*-value
Received RRT	112 (100%)	108 (91%)		
Median time from stage 2 AKI to RRT (h)	6.0 (4.0-7.0)	25.5 (18.8-40.3)	Difference: -21.0 (-24.0 - -18.0)	<0.001
Serum creatinine at RRT initiation (mg/dL)	1.9±0.6	2.4±1.0	Difference: -0.5 (-0.7 - -0.3)	<0.001
28-day mortality	30.4%	40.3%	OR: 0.64 (0.37-1.11)	0.11
60-day mortality	38.4%	50.4%	OR: 0.61 (0.36-1.03)	0.07
90-day mortality	39.3%	54.7%	HR: 0.66 (0.45-0.97)	0.03

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

ELAIN Trial



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 A, et al. JAMA 2016; 315: 2190-2199

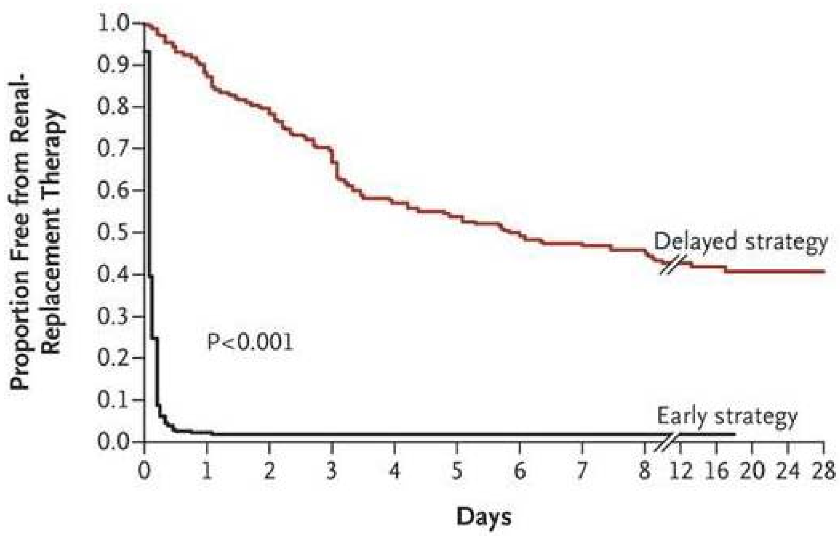
AKIKI Trial

	Early (N=311)	Late (N=308)	HR (95% CI)	*P*-value
Received RRT	305 (98%)	157 (51%)		
Median time from stage 3 AKI to RRT (h)	4.3 (2.7-5.9)	57 (28-83)		<0.001
Serum creatinine at RRT initiation (mg/dL)	3.3±1.4	5.3±2.3		<0.001
Total number of RRT sessions	1665	943		
Median number of RRT sessions per patient	3 (2-7)	4 (2-8)		0.15
28-day mortality	41.6%	43.5%		
60-day mortality	48.5%	49.7%	1.03 (0.82-1.29)	0.79

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

AKIKI Trial

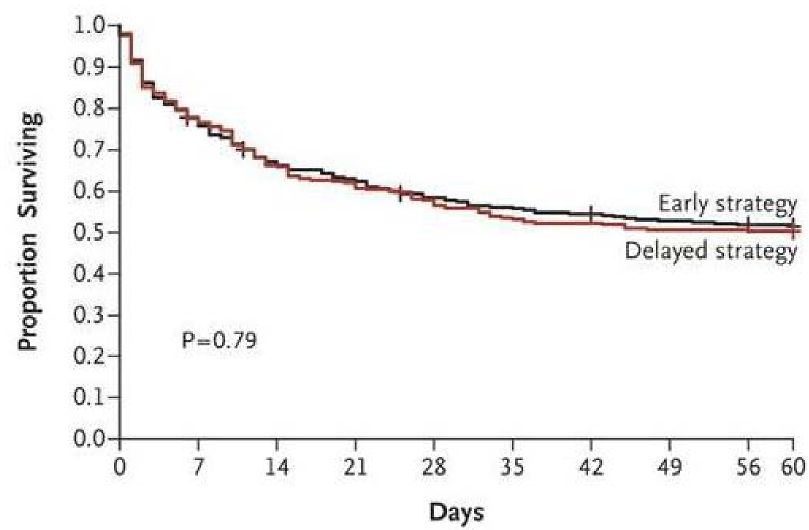
Time to Initiation of RRT



No. at Risk

	0	1	2	3	4	5	6	7	8	12	16	20	24	28
Early strategy	311	7	4	4	4	4	3	3	3	1	1	0	0	0
Delayed strategy	308	268	229	192	153	135	118	105	92	61	39	28	21	13

Survival



No. at Risk

	0	7	14	21	28	35	42	49	56	60
Early strategy	311	241	207	194	179	172	167	161	158	157
Delayed strategy	308	239	204	191	178	165	161	156	156	155

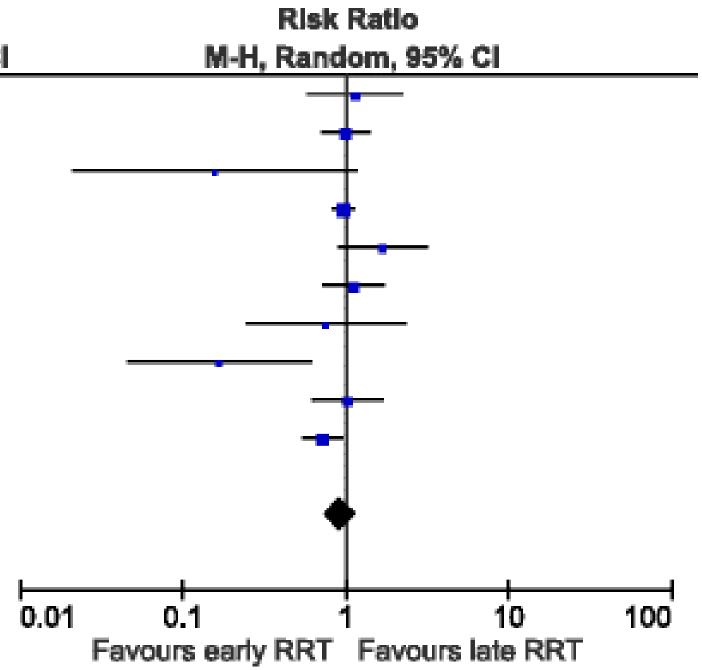
Gaudry S, et al. N Engl J Med 2016; 375: 122-133

Meta-Analysis of Trials of Timing of RRT in AKI

	Early RRT		Late RRT			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Bouman 2002	20	70	9	36	7.2%	1.14 [0.58, 2.25]
Combes 2015	40	112	40	112	15.2%	1.00 [0.70, 1.42]
Durmaz 2002	1	21	7	23	1.1%	0.16 [0.02, 1.17]
Gaudry 2016	150	312	153	308	22.6%	0.97 [0.82, 1.14]
Jamale 2013	21	102	13	106	7.8%	1.68 [0.89, 3.17]
Payen 2009	20	37	19	39	12.4%	1.11 [0.72, 1.72]
Pursnani 1997	4	18	5	17	3.1%	0.76 [0.24, 2.35]
Sugahara 2004	2	14	12	14	2.4%	0.17 [0.05, 0.61]
Wald 2015	18	48	19	52	10.4%	1.03 [0.62, 1.71]
Zarbock 2016	44	112	65	119	17.8%	0.72 [0.54, 0.95]
Total (95% CI)		**846**		**826**	**100.0%**	**0.93 [0.75, 1.15]**
Total events	320		342			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 17.93$, df = 9 (P = 0.04); $I^2 = 50\%$

Test for overall effect: Z = 0.67 (P = 0.50)

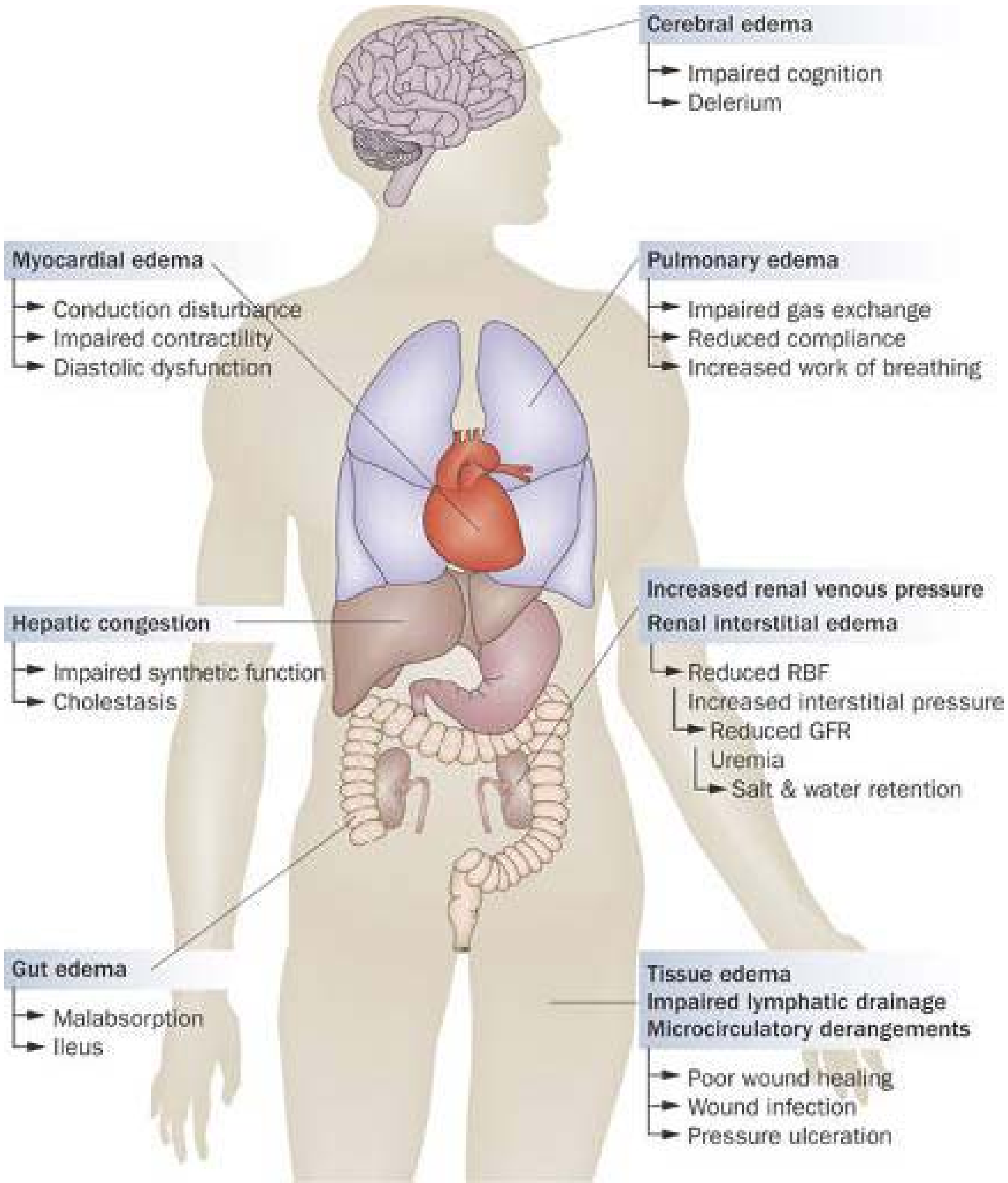


Bhatt GC, Das RR. BMC Nephrol 2017; 18:78

Ongoing RCTs of Timing of RRT in AKI

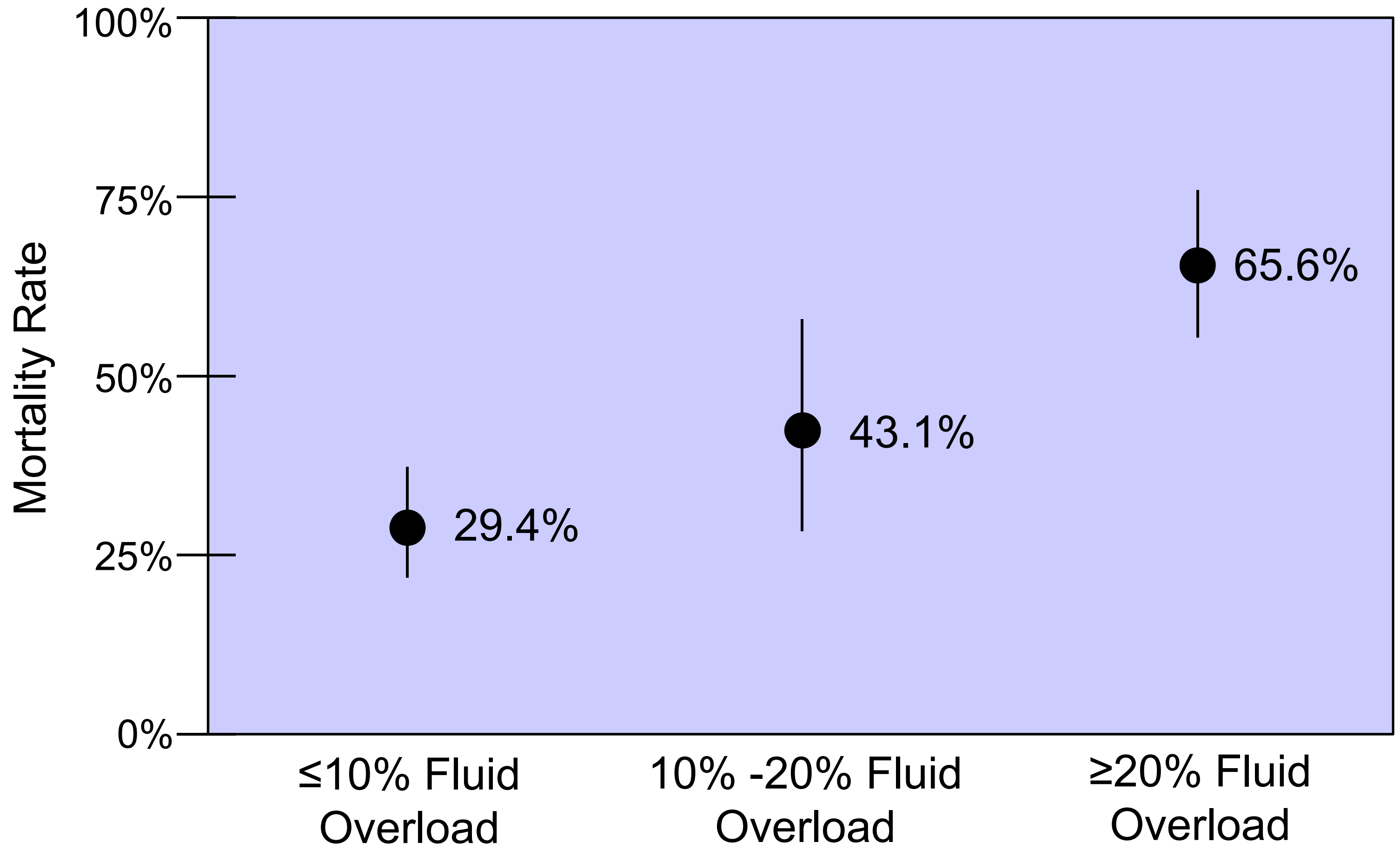
Study	Location	Start Date	Target Enrollment
Initiation of Dialysis Early Versus Late in Intensive Care Unit (IDEAL-ICU)	France	July 2012	824
Standard Versus Accelerated Initiation of Dialysis in Acute Kidney Injury (STARRT-AKI)	Multinational	Fall 2015	2,866

Sequelae of Fluid Overload



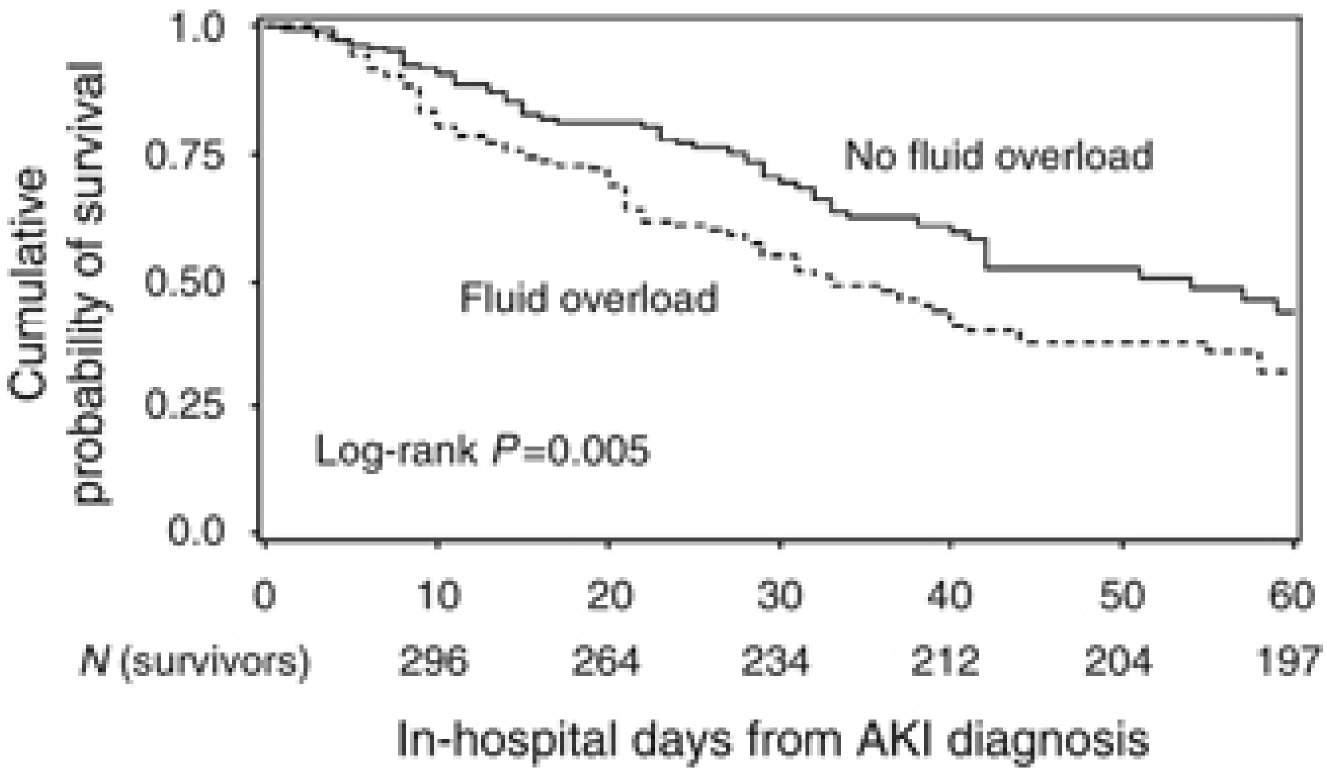
Prowle JR, et al. Nat Rev Nephrol 2010; 6:107-115

Mortality and Fluid Overload in Pediatric CRRT Patients



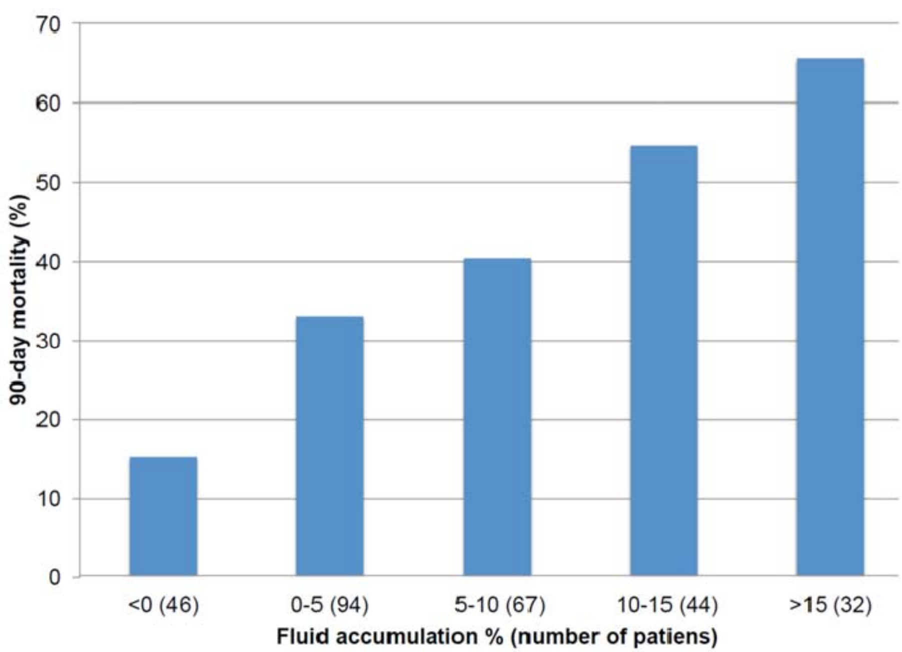
Sutherland SM, et al. Am J Kidney Dis 2010; 55:316-325

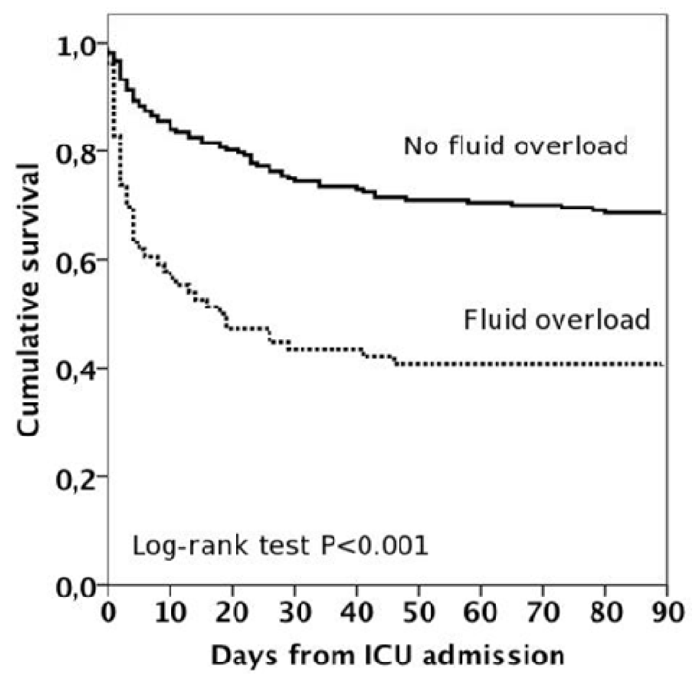
PICARD Study: Impact of Fluid Overload at Initiation of RRT



Bouchard J, et al. Kidney Int 2009; 76: 422-427

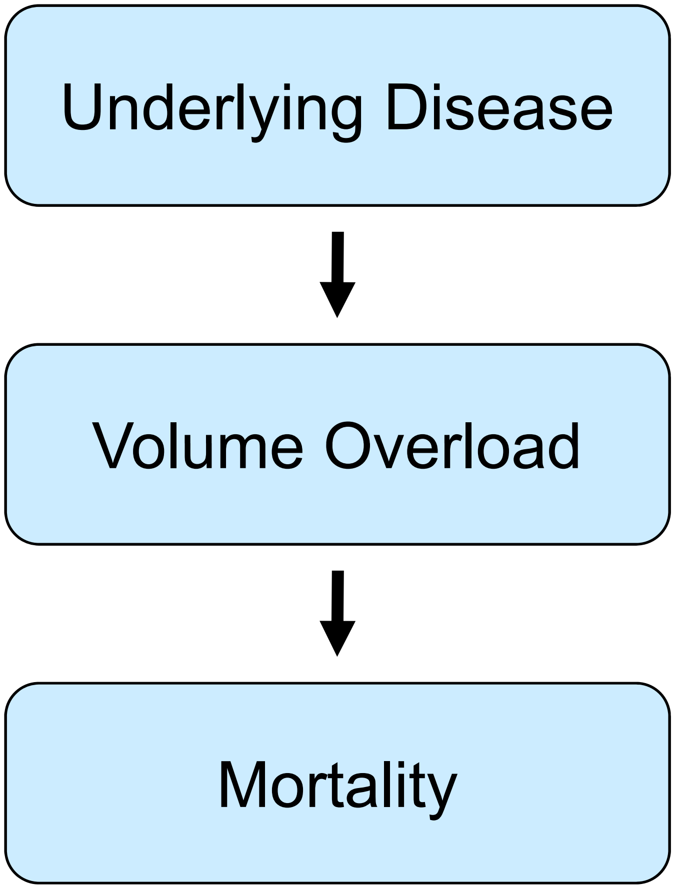
FINNAKI Study: Volume Overload at RRT Initiation and Mortality



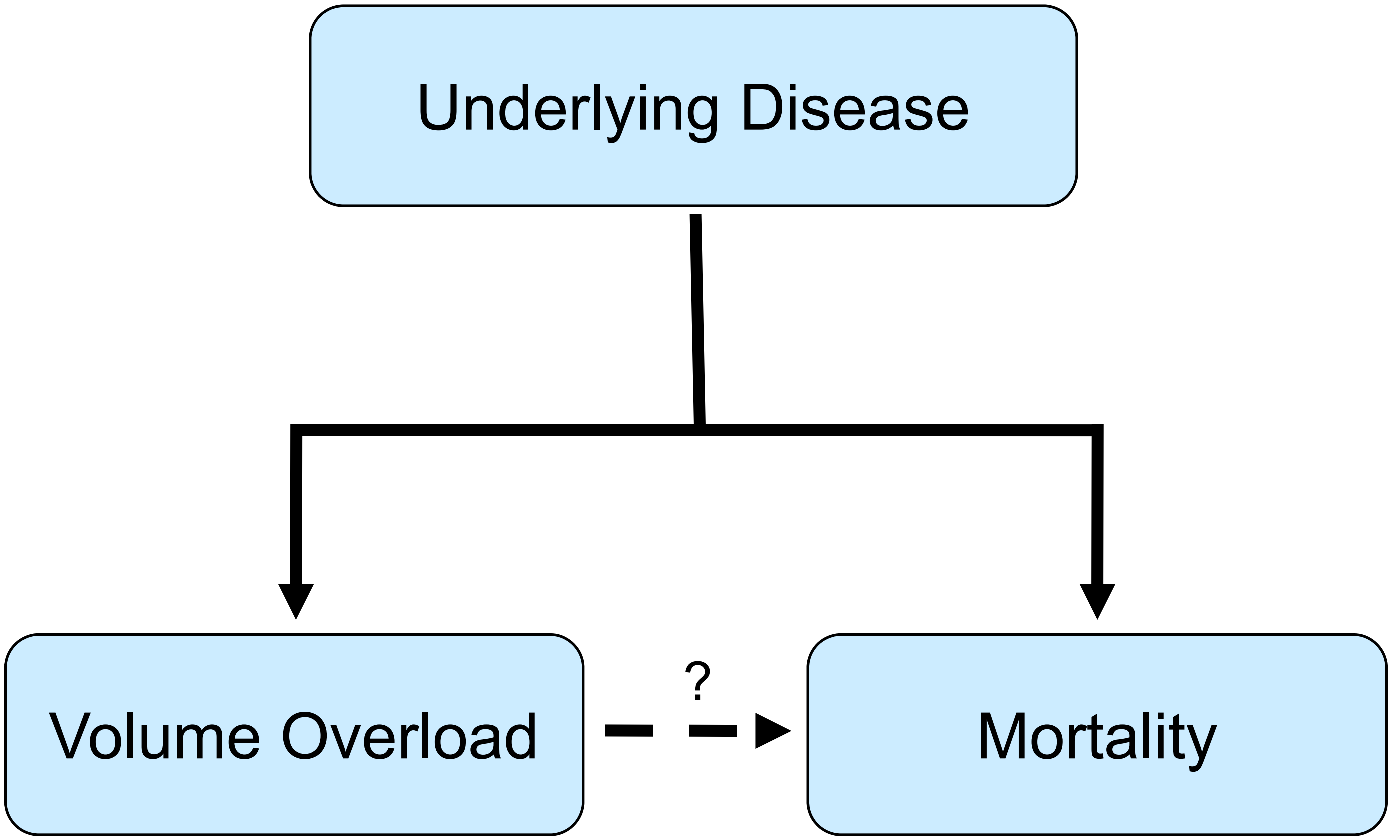


Vaara et al. Crit Care 2012, 16:R197

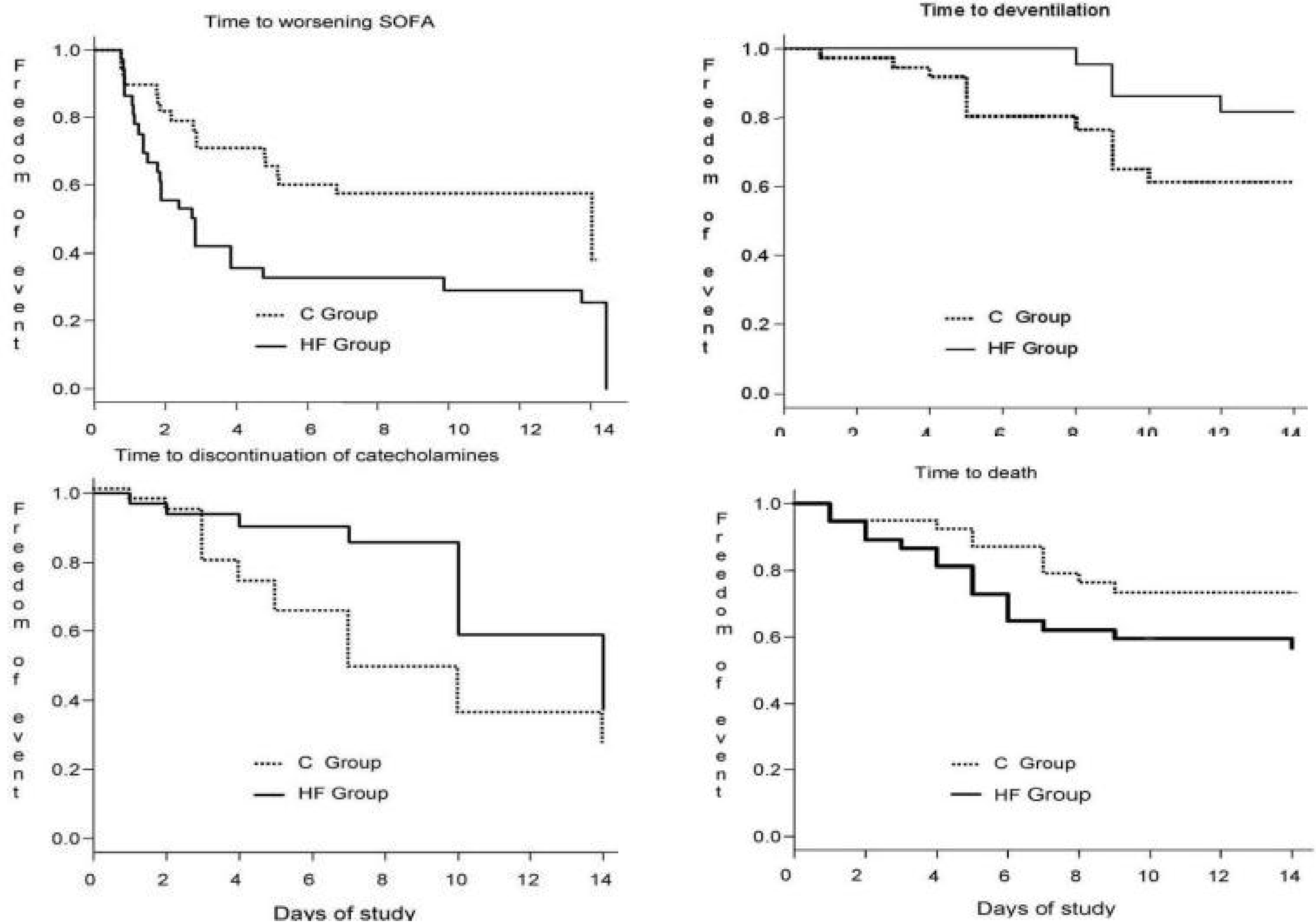
Fluid Balance, Initiation of RRT and Mortality



Fluid Balance, Initiation of RRT and Mortality

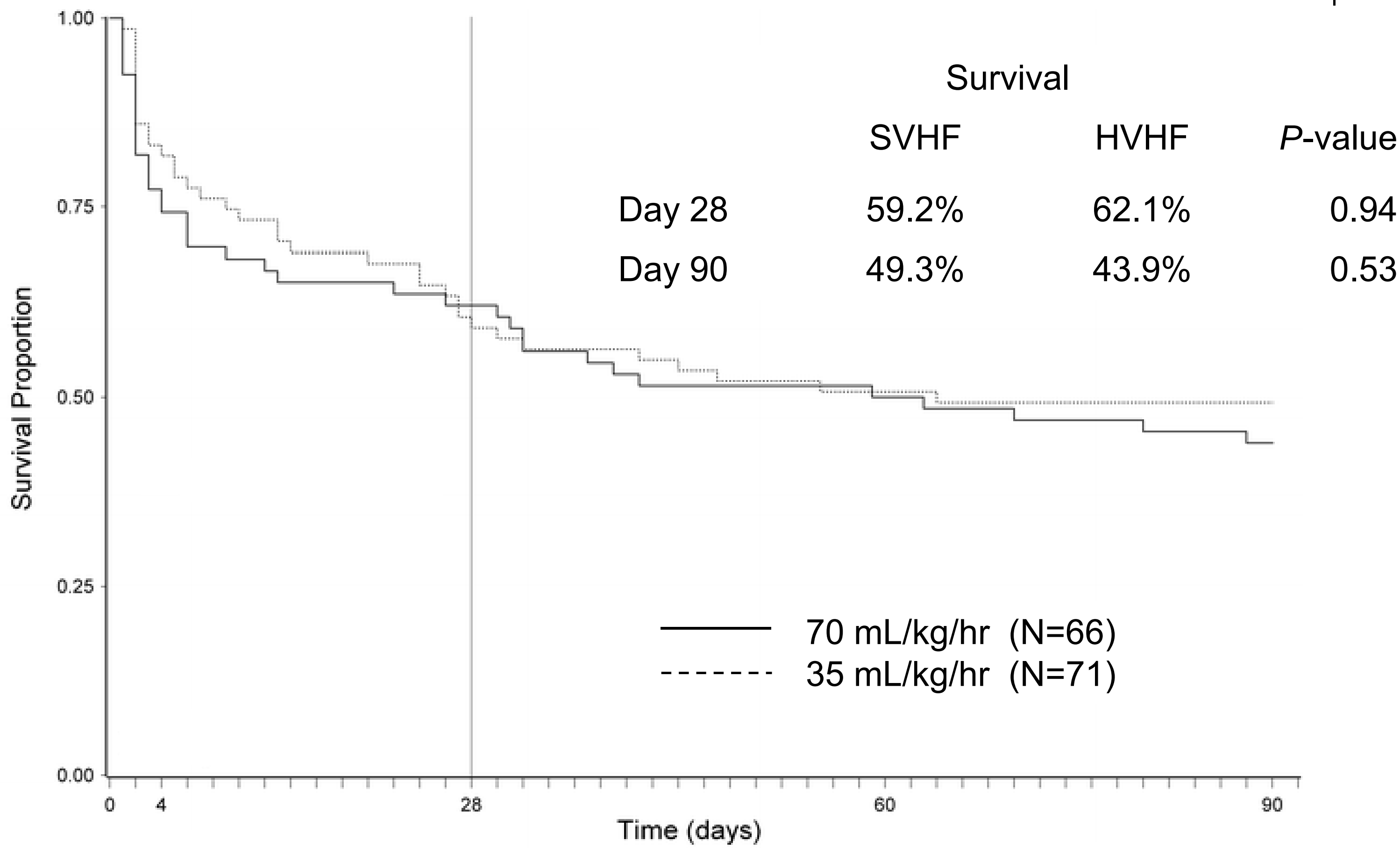


Isovolemic Hemofiltration in Sepsis



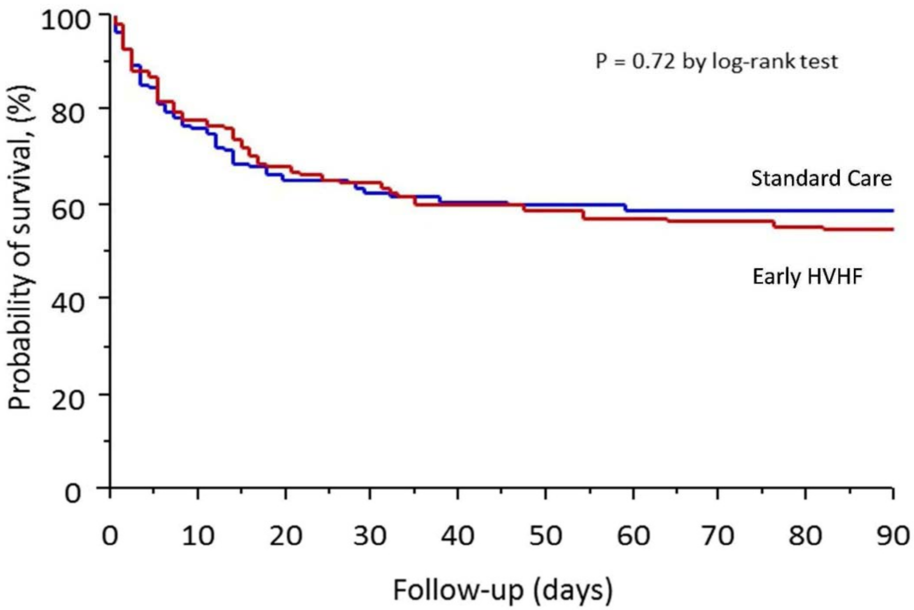
Payen D, et al. Crit Care Med 2009; 37:803-810

High vs. Standard Volume CVVH in Septic Shock: *IVOIRE* Study



Joannes-Boyau O, et al. Intensive Care Med 2013; 39:1535-1546

HVHF post-Cardiac Surgery:
The HEROICS Trial



30 Day Mortality

	HVHF (n=112)	Usual Care (n=112)
All patients	40/112 (36%)	40/112 (36%)
RRT		32/64 (50%)
No RRT		8/48 (17%)

Combes, A et al. Am J Respir Crit Care Med 2015;192: 1179-1190

KDIGO Acute Kidney Injury Clinical Practice Guidelines

- 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 broad 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*)

Clinical Case 1 follow-up

The patient appeared to be improving hemodynamically and his urine output was slowly increasing. We decided to defer placement of the dialysis catheter but performed a “Furosemide Stress Test”

His urine output over the 2 hours after a dose of 1.5 mL/kg furosemide was 350 mL

Over the next three days his urine output progressively increased, his serum creatinine peaked at 4.4 mg/dL (360 μmol/L) and RRT was not initiated

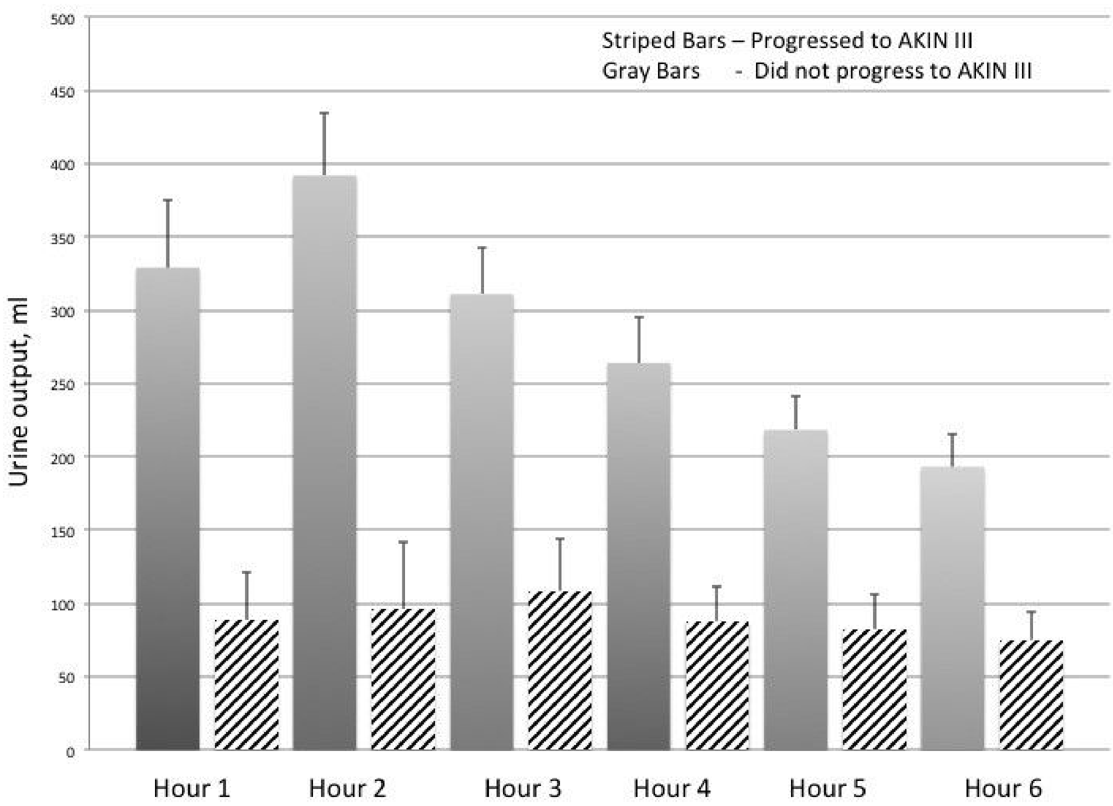
At hospital discharge, on POD 10, his serum creatinine was 1.4 mg/dL (125 μmol/L)

Furosemide Stress Test

- AKIN/KDIGO Stage 1 or 2 AKI
- Administration of dose of IV furosemide
  - 1.0 mg/kg if loop-diuretic naïve
  - 1.5 mg/kg if received loop-diuretic in preceeding week
- A urine output of <200 mL over the ensuring 2 hours predicted progression to Stage 3 AKI

Chawla LS, et al. Critical Care 2013 17:R207

Furosemide Stress Test



Test parameters based on UOP of ≤200 mL over 2 hours		
	AKIN 3	AKIN 3 /Death
Sensitivity	87.1%	90.0%
Specificity	84.1%	74.2%
AUC	0.87	0.81

Chawla LS, et al. Critical Care 2013 17:R207

Furosemide Stress Test and Biomarkers

Biomarker	AUC±SEM	*P* Value for Biomarker Alone	*P* Value Compared With FST alone	AUC of Biomarker and FST±SEM	*P* Value for Biomarker and FST Compared With FST Alone
FST (2-hr UOP)	0.87±0.05	<0.001	NA	NA	NA
Urine NGAL	0.65±0.06	0.04	0.002	0.84±0.05	0.10
Urine IL-18	0.65±0.07	0.04	0.009	0.85±0.05	0.89
Urine KIM-1	0.63±0.06	0.07	0.007	0.86±0.05	0.79
Uromodulin	0.54±0.07	0.54	0.002	0.85±0.05	0.94
Urine IGFBP-7	0.62±0.09	0.20	<0.001	0.88±0.05	0.57
Urine TIMP-2	0.70±0.08	0.03	0.02	0.83±0.06	0.20
Urine IGFBP-7×TIMP-2	0.69±0.08	0.04	0.01	0.90±0.06	0.35
Urine Creatinine	0.48±0.08	0.77	<0.001	0.84±0.06	0.85
Urine ACR	0.56±0.07	0.45	0.002	0.84±0.06	0.32
FeNa	0.51±0.07	0.92	<0.001	0.83±0.06	0.47
Plasma NGAL	0.75±0.08	0.007	0.10	0.86±0.07	0.53

NA, not applicable; ACR, albumin-to-creatinine ratio.

Koyner JL, et al. J Am Soc Nephrol 2015; 26: 2023-2031

Renal Replacement Therapy in Acute Kidney Injury

- When should renal replacement therapy be initiated in AKI?
- Which modality is most appropriate?
- What is the appropriate dose of therapy?

Clinical Case 2

You are asked to evaluate a 53-year-old man with oligoanuric AKI which has developed in the setting of abdominal sepsis and ARDS. The patient was admitted 4 days ago with severe diverticulitis with abdominal soiling. Blood cultures were positive for E. coli and he is on broad spectrum antibiotics. He was initially vasopressor dependent on high-dose norepinephrine, but now has a BP of 100-110/50-60 mmHg on 0.03 mcg/kg/min of norepinephrine. He remains intubated, sedated and mechanically ventilated.

His urine output has been 50-70 mL per day over the past 2 days and his I/O is positive by 9.8 L since admission. His plasma creatinine has increased from 1.1 mg/dL (100 μmol/L) to 4.5 mg/dL (400 μmol/L), his potassium is 5.8 mmol/L and his tCO_2 is 18 mmol/L.

His CXR demonstrates bilateral infiltrates and his ABG has a pH is 7.22, Pco_2 45 mmHg, and Po_2 65 mmHg on an F_iO_2 of 0.7 with PEEP of 12.5 cm H_2O

Audience Response 2

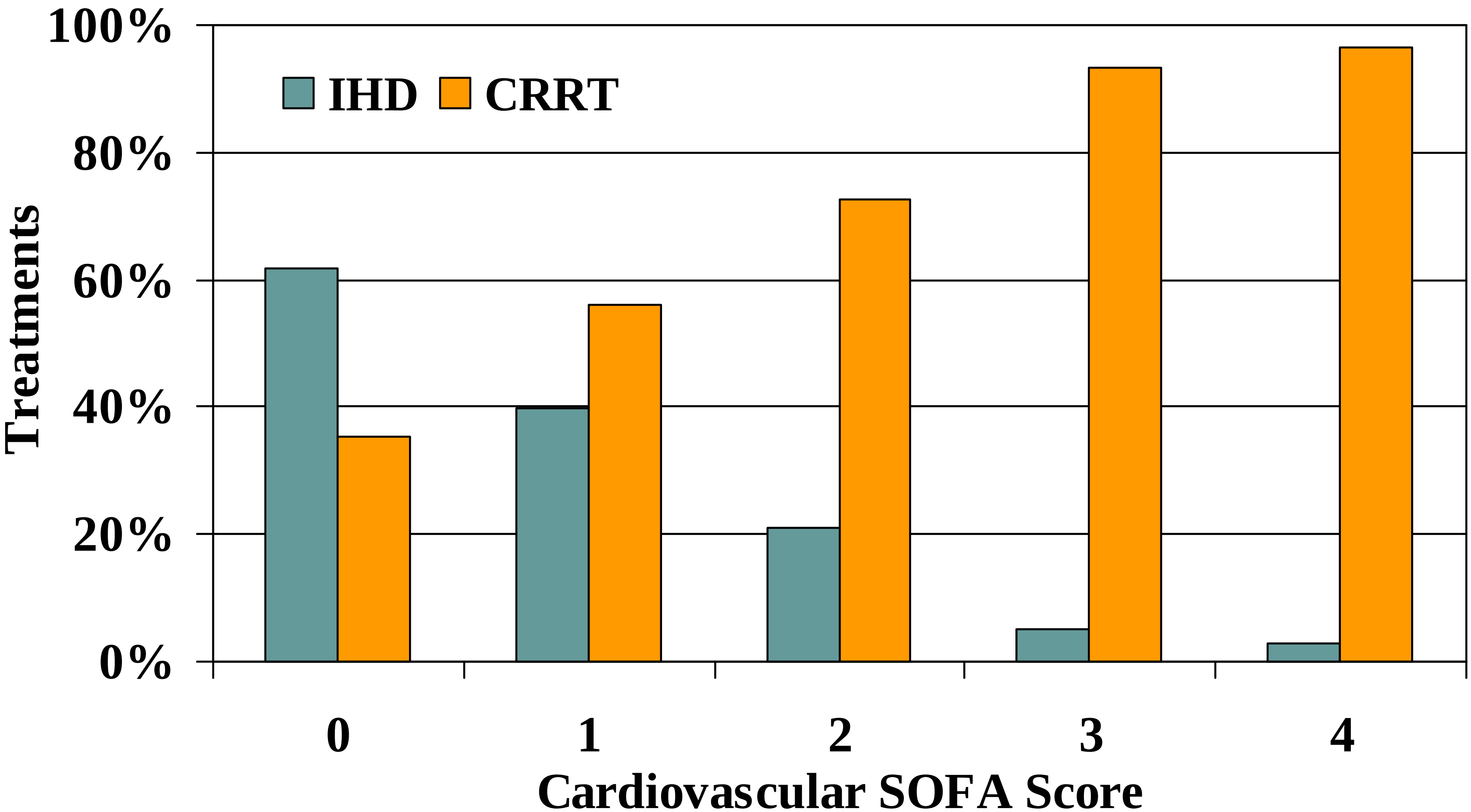
You decide to begin RRT. Which ONE of the following modalities of RRT do you choose to use?

A. Intermittent hemodialysis (IHD)
B. Prolonged intermittent renal replacement therapy (PIRRT)
C. Continuous venovenous hemofiltration (CVVH)
D. Continuous venovenous hemodialysis (CVVHD)
E. Peritoneal dialysis (PD)

Modalities of RRT for AKI

- Intermittent hemodialysis
- Continuous therapies
  - Continuous hemofiltration
  - Continuous hemodialysis
  - Continuous hemodiafiltration
- Prolonged intermittent RRT
- Peritoneal dialysis

ATN Study:
Observational Cohort

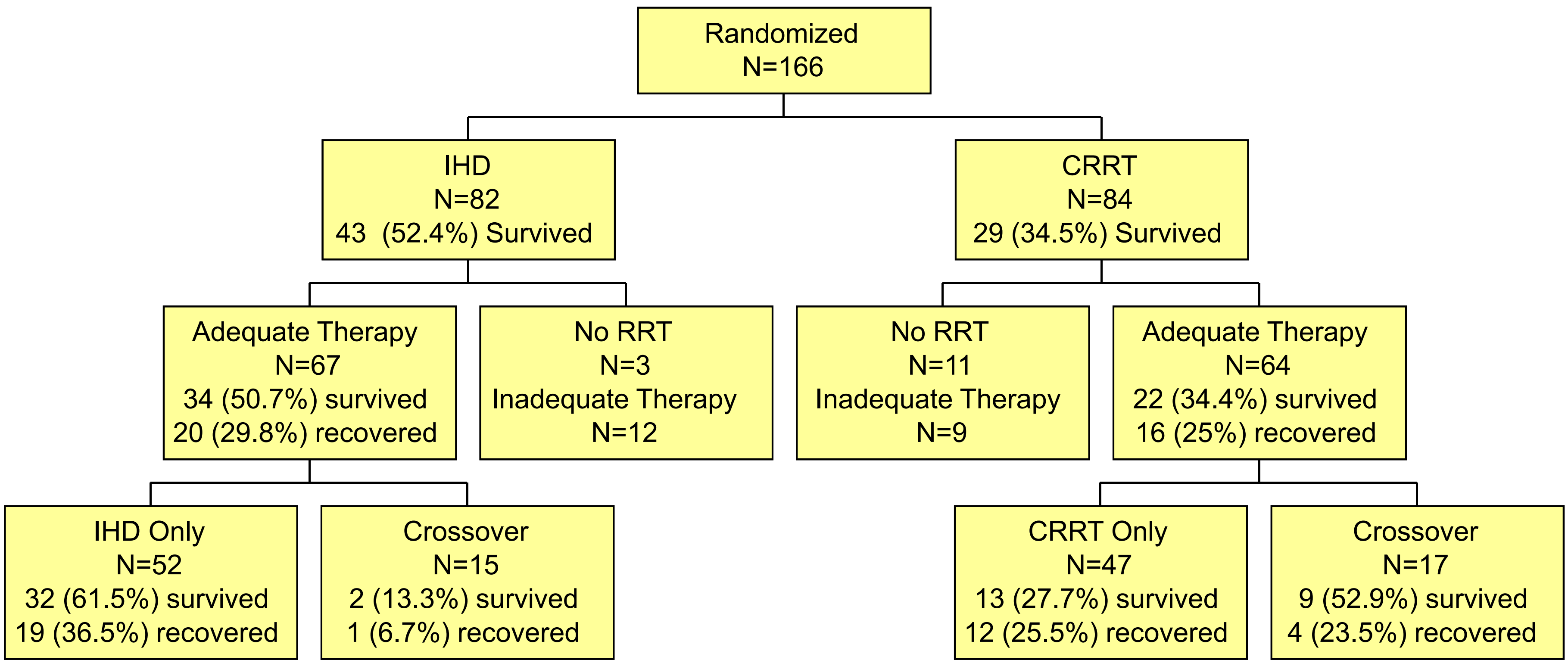


Continuous vs. Intermittent Therapy in Acute Kidney Injury

	CRRT	IHD	p value
N	84	82	
APACHE II Score	23.7	25.5	NS
APACHE III Score	96.4	87.7	0.045
ICU Mortality	59.5%	41.5%	0.02
Hospital Mortality	65.5%	47.6%	0.02
ICU Length of Stay	15.1 days	16.7 days	NS
Renal Recovery	34.9%	33.3%	NS

Mehta R, et al: Kidney Int 2001; 60:1154-1163

Continuous vs. Intermittent Therapy in Acute Kidney Injury



Mehta R, et al: Kidney Int 2001; 60:1154-1163

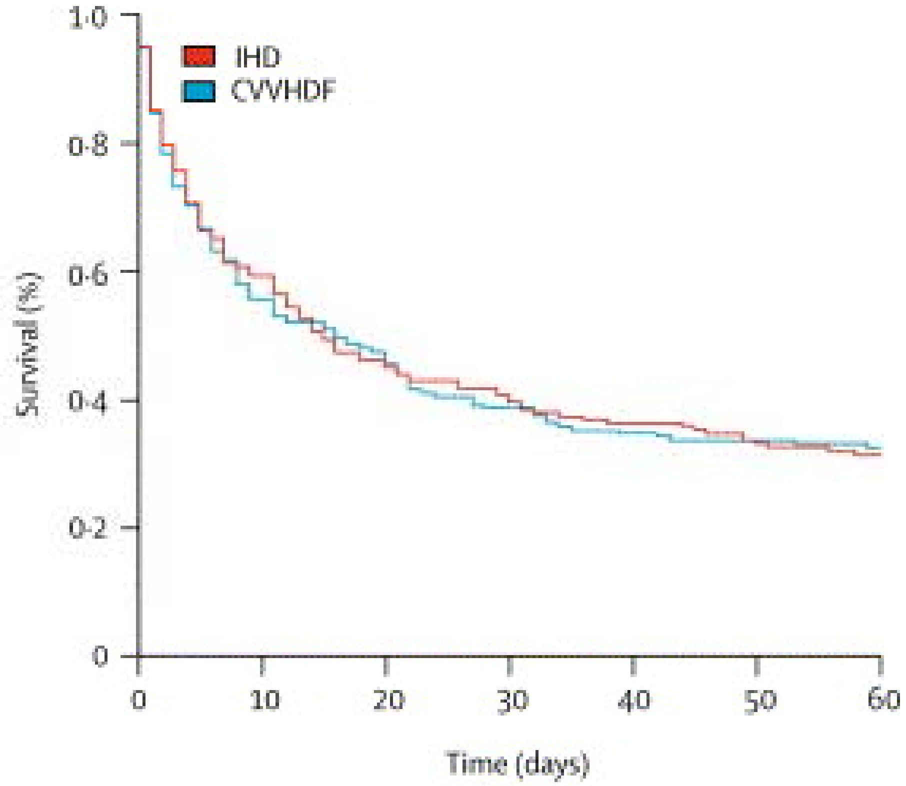
CRRT vs. IHD in Acute Kidney Injury: *Hemodiafe* Study

	IHD (n=184)	CVVHDF (n=175)
Vasopressors	86%	89%
Mechanical Ventilation	95%	98%
Sepsis	69%	56%*
SAPS II	64	65
Crossovers	6	31
Duration of RRT (days)	11	11
60-day survival	31.5%	32.6%#

*p=0.01; #p=0.98

Vinsonneau C, et al: Lancet 2006; 368:379-385

CRRT vs. IHD in Acute Kidney Injury: *Hemodiafe* Study

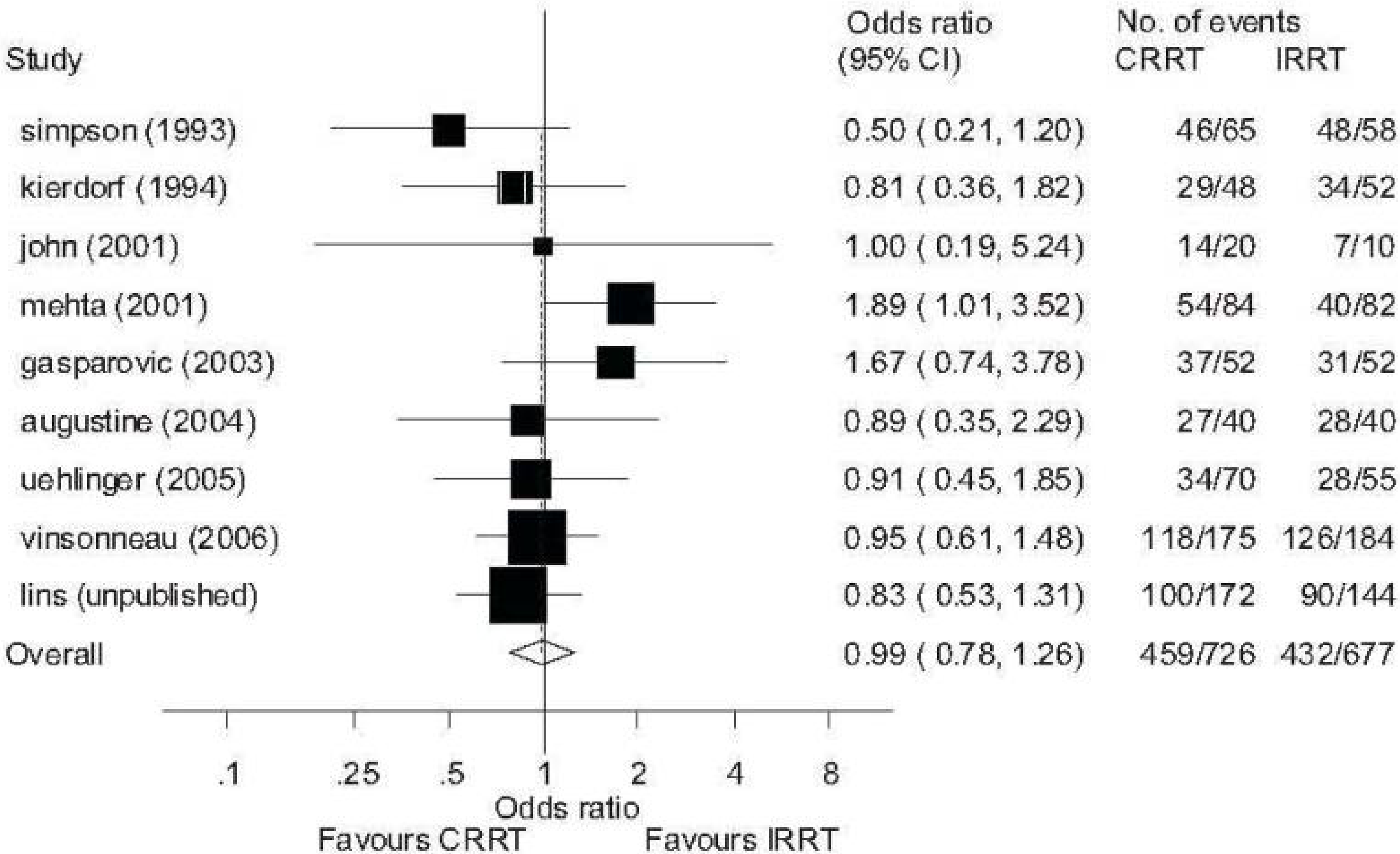


Numbers at risk

IHD	184	85	68	58
CVVHDF	175	83	62	57

Vinsonneau C, et al: Lancet 2006; 368:379-385

Meta-analysis of Studies Comparing IHD to CRRT



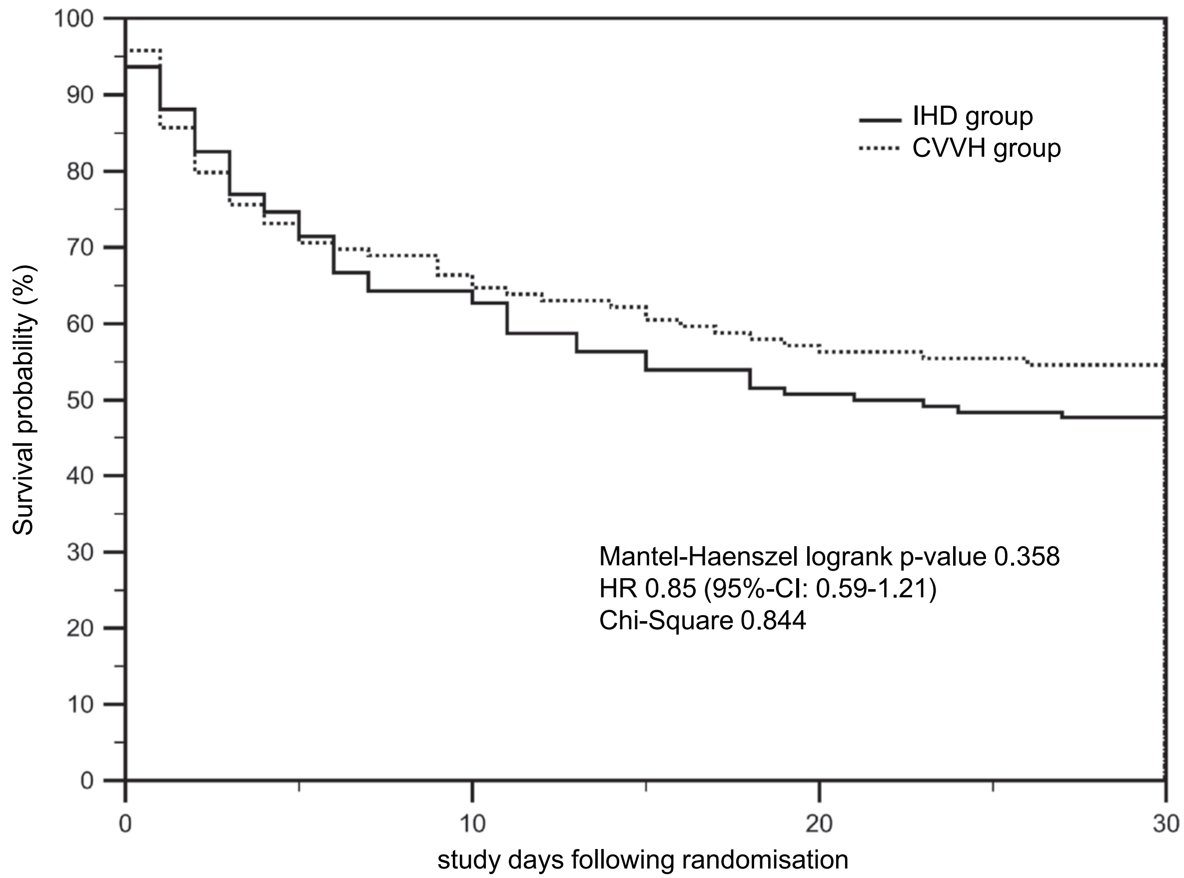
Bagshaw SM, et al. Crit Care Med 2008; 36**:** 610-617

Continuous vs Intermittent RRT: *CONVINT Trial*

	Daily IHD (n=128)	CVVH (n=122)	P-Value
Crossovers	19.5%	45.9%	0.002
Survival 14 days after RRT	39.5%	43.9%	0.81
Mortality 14-day 30-day	 43.6% 52.4%	 37.8% 45.4%	 0.60 0.63
RRT Dependent (among survivors) at day 21 at day 60	 32.3% 26.4%	 29.9% 22.8%	 0.97 0.90
Last serum creatinine (mg/dL)	2.18±1.8	2.12±1.7	0.85

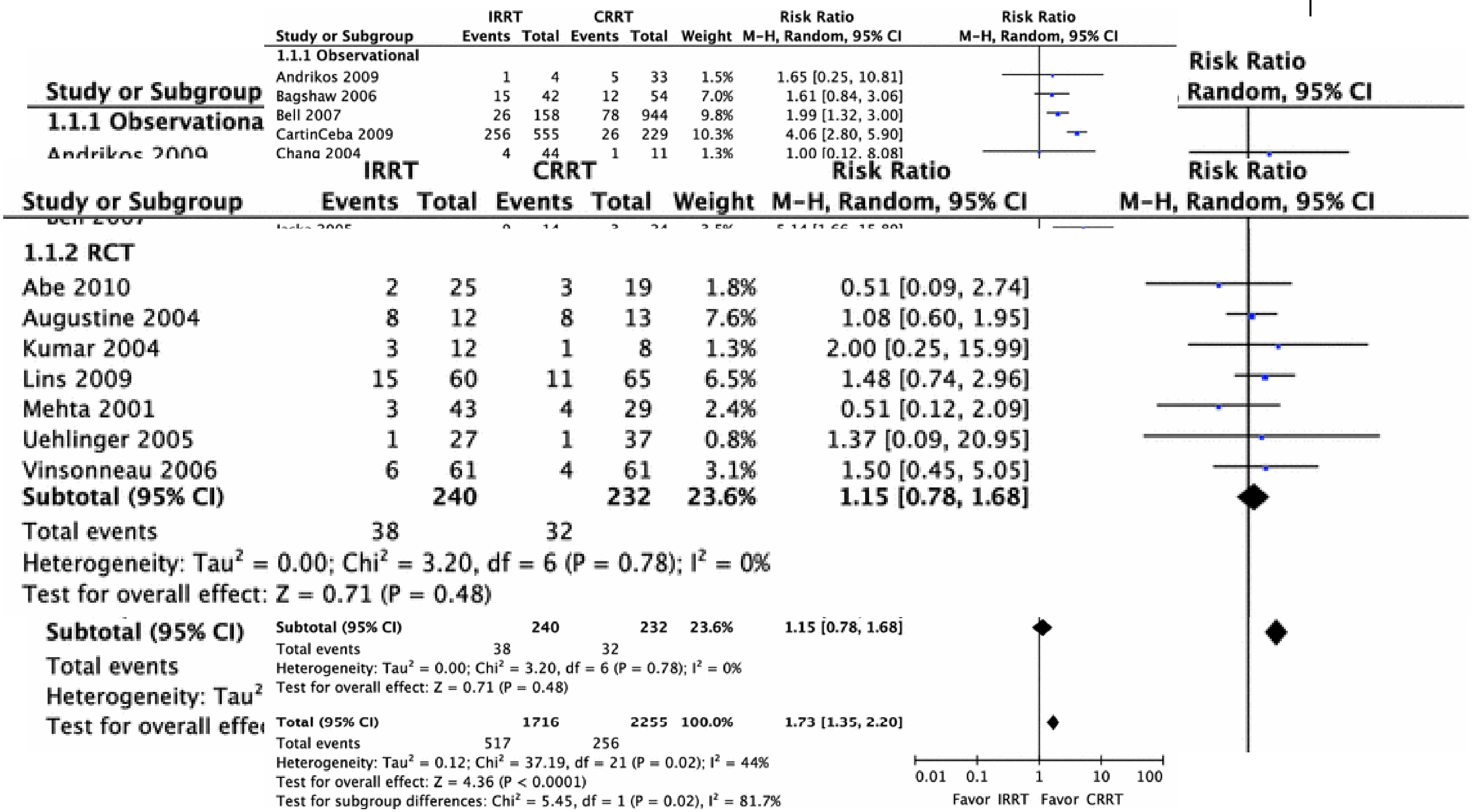
Schefold JC, et al. Critical Care 2014; 18:R11

Continuous vs Intermittent RRT: *CONVINT Trial*



Schefold JC, et al. Critical Care 2014; 18:R11

CRRT vs. IRRT in AKI:
Recovery of Renal Function



Study or Subgroup	IRRT Events	IRRT Total	CRRT Events	CRRT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.2 RCT						
Abe 2010	2	25	3	19	1.8%	0.51 [0.09, 2.74]
Augustine 2004	8	12	8	13	7.6%	1.08 [0.60, 1.95]
Kumar 2004	3	12	1	8	1.3%	2.00 [0.25, 15.99]
Lins 2009	15	60	11	65	6.5%	1.48 [0.74, 2.96]
Mehta 2001	3	43	4	29	2.4%	0.51 [0.12, 2.09]
Uehlinger 2005	1	27	1	37	0.8%	1.37 [0.09, 20.95]
Vinsonneau 2006	6	61	4	61	3.1%	1.50 [0.45, 5.05]
Subtotal (95% CI)		**240**		**232**	**23.6%**	**1.15 [0.78, 1.68]**
Total events	38		32			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.20$, df = 6 (P = 0.78); $I^2 = 0\%$

Test for overall effect: Z = 0.71 (P = 0.48)

Study or Subgroup	IRRT Events	IRRT Total	CRRT Events	CRRT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Observational						
Andrikos 2009	1	4	5	33	1.5%	1.65 [0.25, 10.81]
Bagshaw 2006	15	42	12	54	7.0%	1.61 [0.84, 3.06]
Bell 2007	26	158	78	944	9.8%	1.99 [1.32, 3.00]
CartinCeba 2009	256	555	26	229	10.3%	4.06 [2.80, 5.90]
Chang 2004	4	44	1	11	1.3%	1.00 [0.12, 8.08]
Subtotal (95% CI)		**240**		**232**	**23.6%**	**1.15 [0.78, 1.68]**
Total events	38		32			
Total (95% CI)		**1716**		**2255**	**100.0%**	**1.73 [1.35, 2.20]**
Total events	517		256			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.20$, df = 6 (P = 0.78); $I^2 = 0\%$

Test for overall effect: Z = 0.71 (P = 0.48)

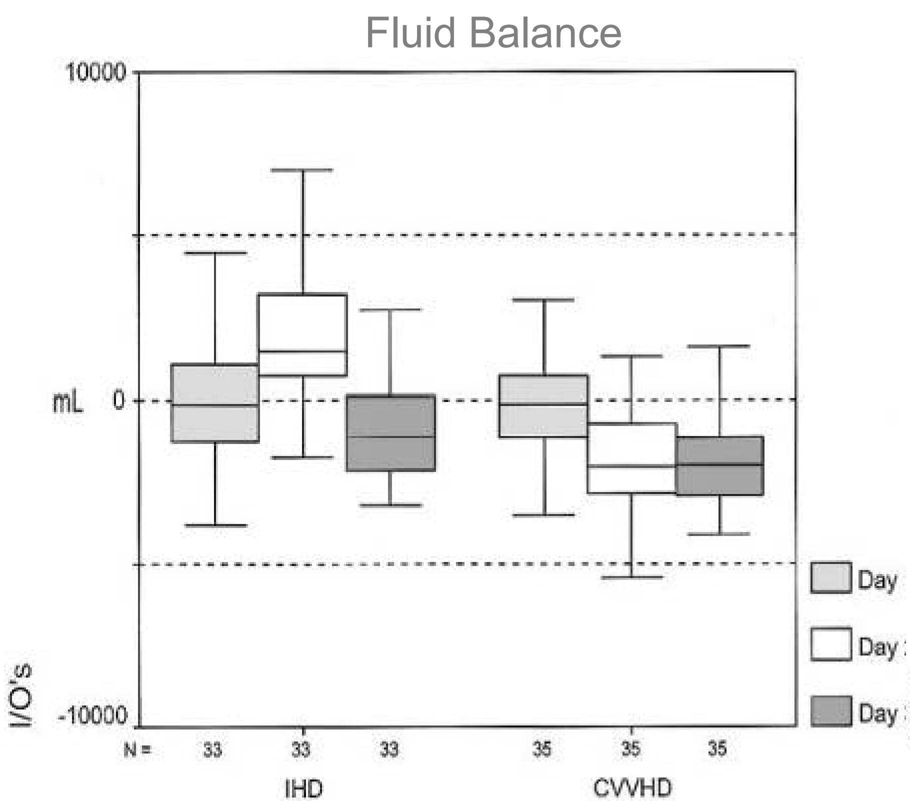
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 37.19$, df = 21 (P = 0.02); $I^2 = 44\%$

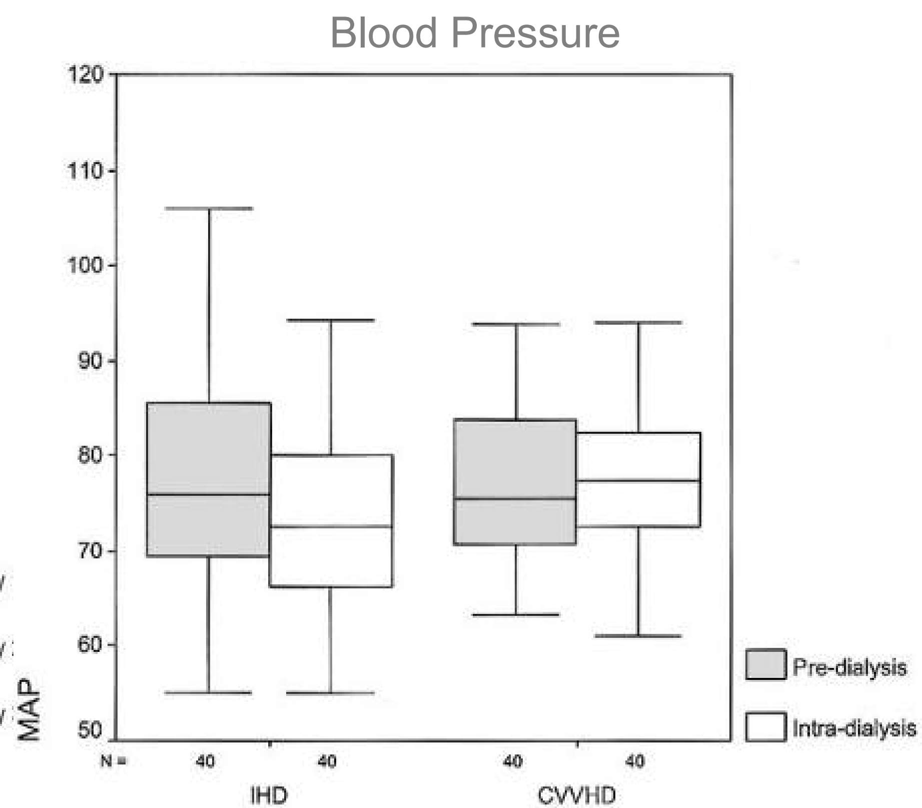
Test for overall effect: Z = 4.36 (P < 0.0001)

Test for subgroup differences: $Chi^2 = 5.45$, df = 1 (P = 0.02), $I^2 = 81.7\%$

Schneider AG, et al. Intensive Care Med 2013; 39:987-997

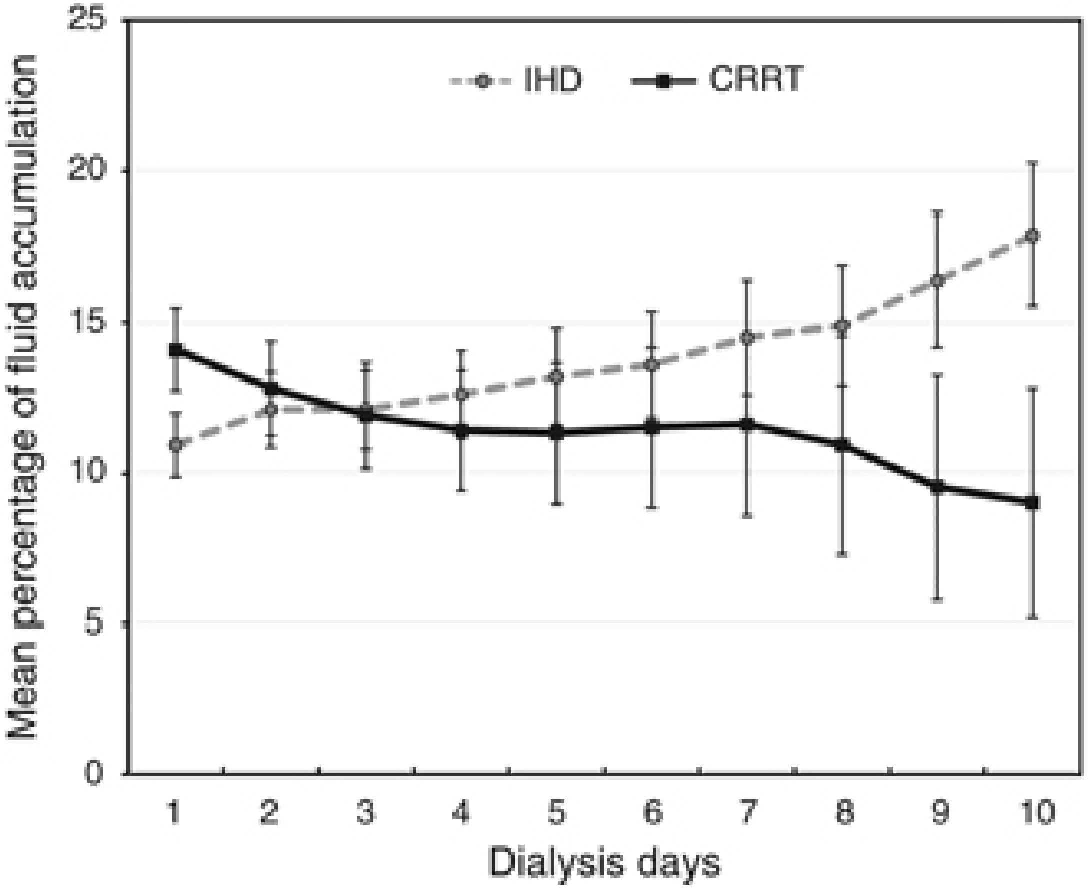
Continuous vs. Intermittent Therapy in Acute Kidney Injury





Augustine JJ, et al. Am J Kidney Dis 2004; 44:1000-1007

PICARD Study: Impact of Fluid Overload at Initiation of RRT

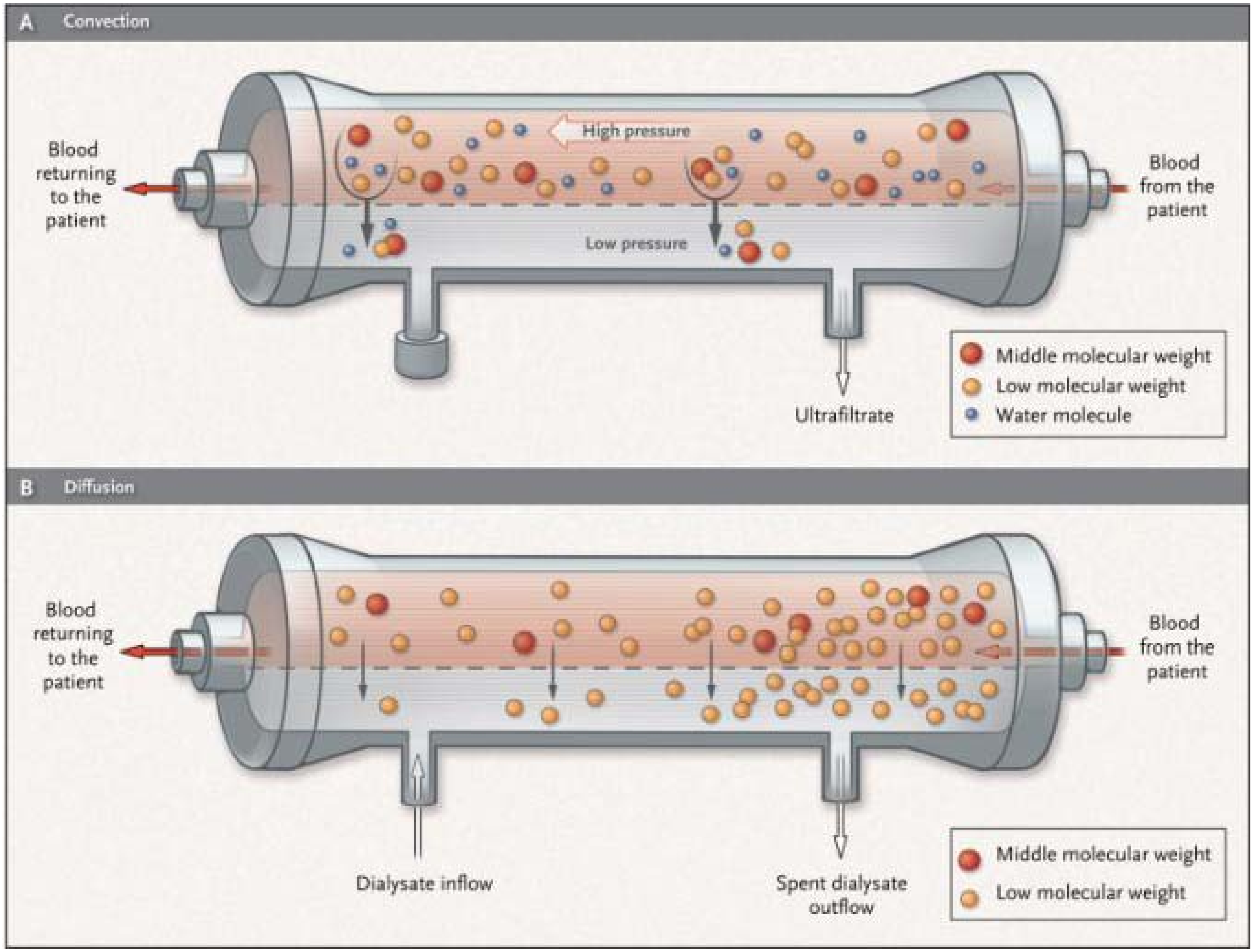


Bouchard J, et al. Kidney Int 2009; 76: 422-427

Issues in Specific Clinical Settings

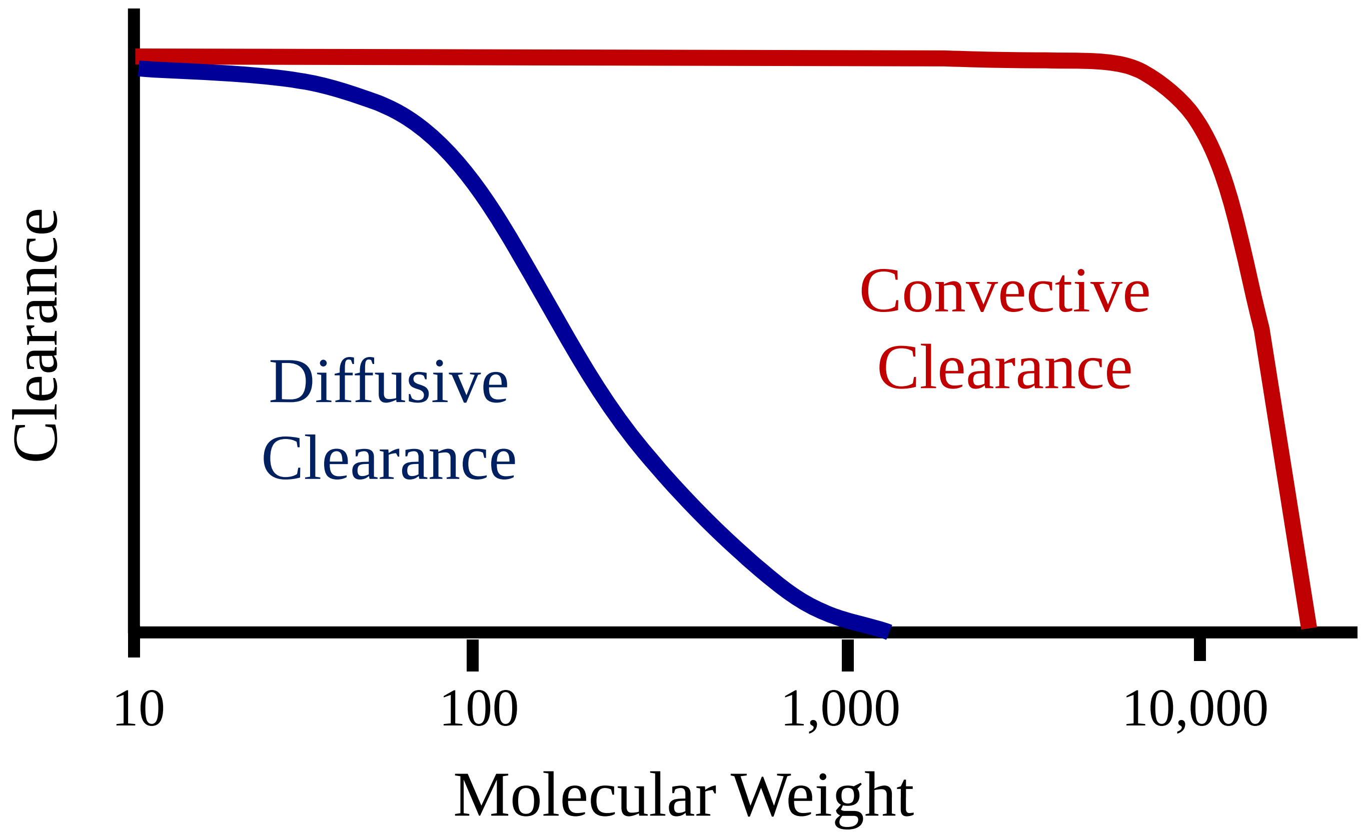
- CRRT may better protect cerebral perfusion in patients with:
  - Fulmanenent hepatic failure
  - Acute brain injury
  - Cerebral edema

Modality of CRRT: Convection versus Diffusion



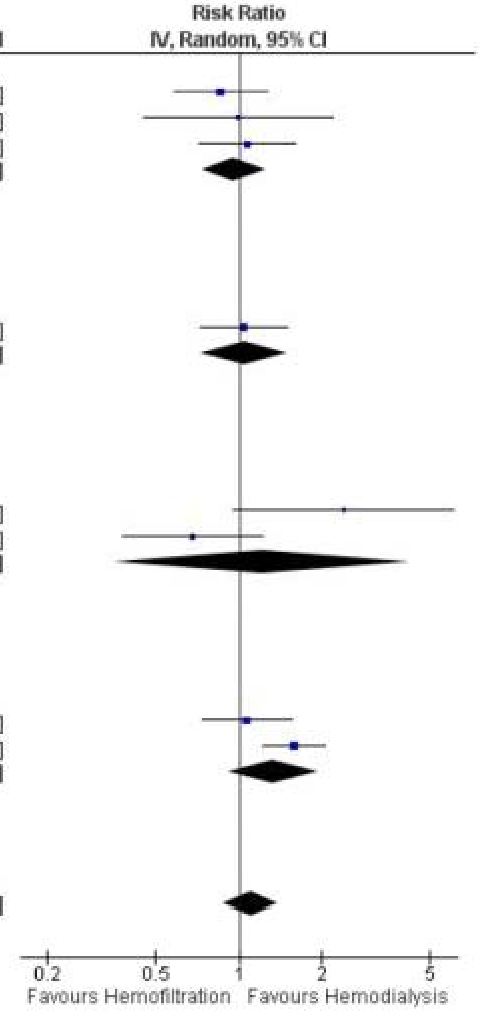
Tolwani A. N Engl J Med 2012; 367: 2505-2514

Convection versus Diffusion



Continuous Hemofiltration versus Continuous Hemodialysis in AKI

Study or Subgroup	Hemofiltration Events	Hemofiltration Total	Hemodialysis Events	Hemodialysis Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Similar Dose Filtration vs Dialysis						
Daud 2006 [25]	7	9	10	11	14.7%	0.86 [0.58, 1.27]
Morgera 2004 [24]	6	12	6	12	6.1%	1.00 [0.45, 2.23]
OMAKI 2012 [30]	22	39	20	38	14.3%	1.07 [0.71, 1.61]
Subtotal (95% CI)		**60**		**61**	**35.1%**	**0.96 [0.73, 1.25]**
Total events	35		36			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
1.1.2 Similar Dose Filtration vs Dialysis-Filtration						
Chang 2009 [27]	26	47	26	49	15.7%	1.04 [0.72, 1.51]
Subtotal (95% CI)		**47**		**49**	**15.7%**	**1.04 [0.72, 1.51]**
Total events	26		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.82)						
1.1.3 Similar Dose (Intermittent) Dialysis-Filtration vs Dialysis						
Pettila 2001 [23]	12	21	4	17	4.8%	2.43 [0.95, 6.18]
Ratanarat 2012 [29]	10	27	18	33	9.6%	0.68 [0.38, 1.22]
Subtotal (95% CI)		**48**		**50**	**14.4%**	**1.22 [0.35, 4.22]**
Total events	22		22			
Heterogeneity: Tau² = 0.65; Chi² = 5.15, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.1.4 Filtration vs Higher-Dose Dailysis-Filtration						
Davenport 1993 [21]	7	8	9	11	15.2%	1.07 [0.73, 1.57]
Saudan 2006 [26]	67	102	43	104	19.6%	1.59 [1.21, 2.08]
Subtotal (95% CI)		**110**		**115**	**34.8%**	**1.34 [0.91, 1.96]**
Total events	74		52			
Heterogeneity: Tau² = 0.05; Chi² = 2.76, df = 1 (P = 0.10); I² = 64%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Total (95% CI)		**265**		**275**	**100.0%**	**1.10 [0.88, 1.38]**
Total events	157		136			
Heterogeneity: Tau² = 0.05; Chi² = 13.96, df = 7 (P = 0.05); I² = 50%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for subgroup differences: Chi² = 1.97, df = 3 (P = 0.58), I² = 0%						



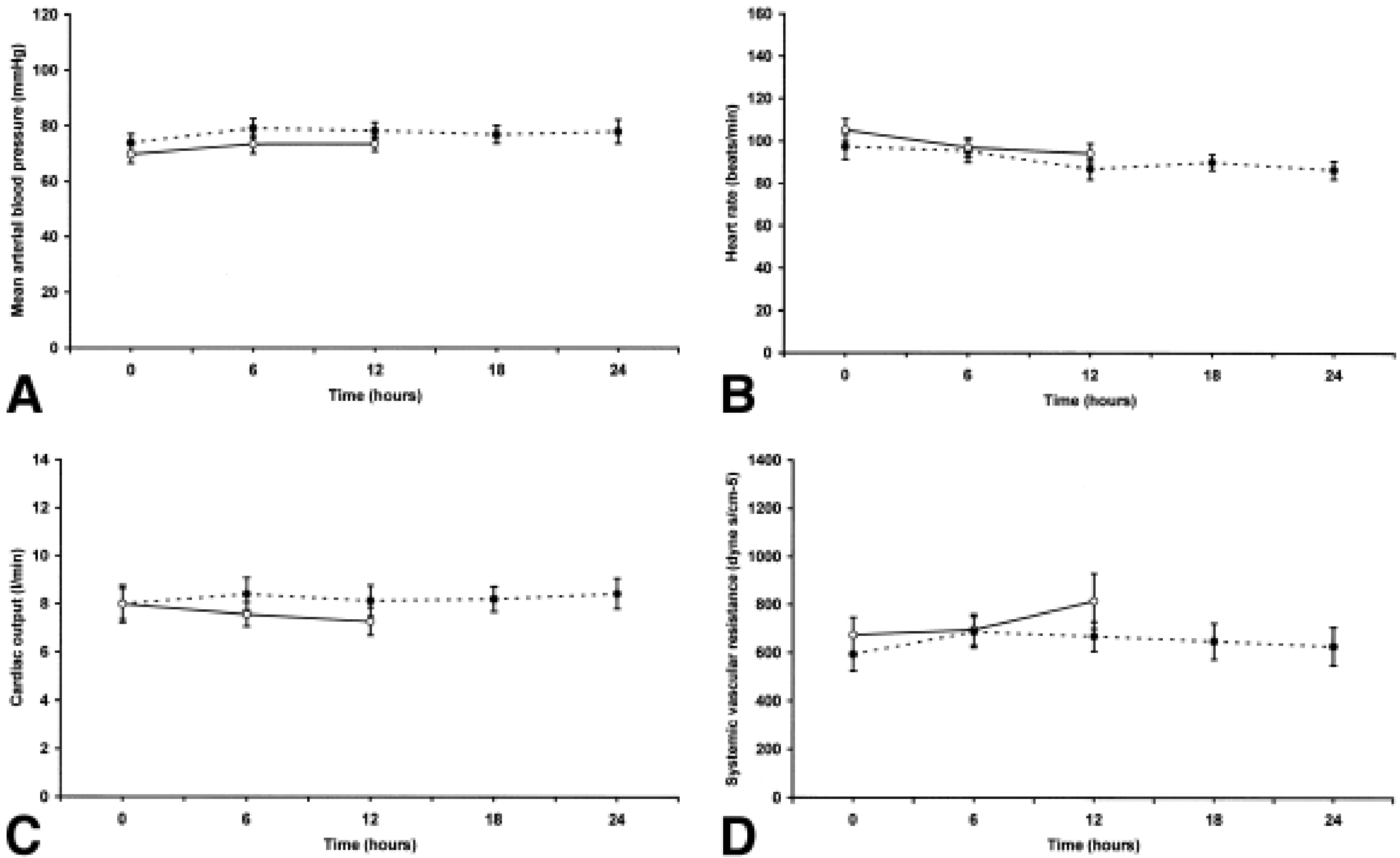
Friedrich JO, et al. Crit Care 2012; 16:R146

Prolonged Intermittent Renal Replacement ("Hybrid") Therapies

- Extended Daily Dialysis (EDD)
- Sustained low-efficiency dialysis (SLED)
- Sustained low-efficiency daily diafiltration (SLEDD-f)
- The Genius® system

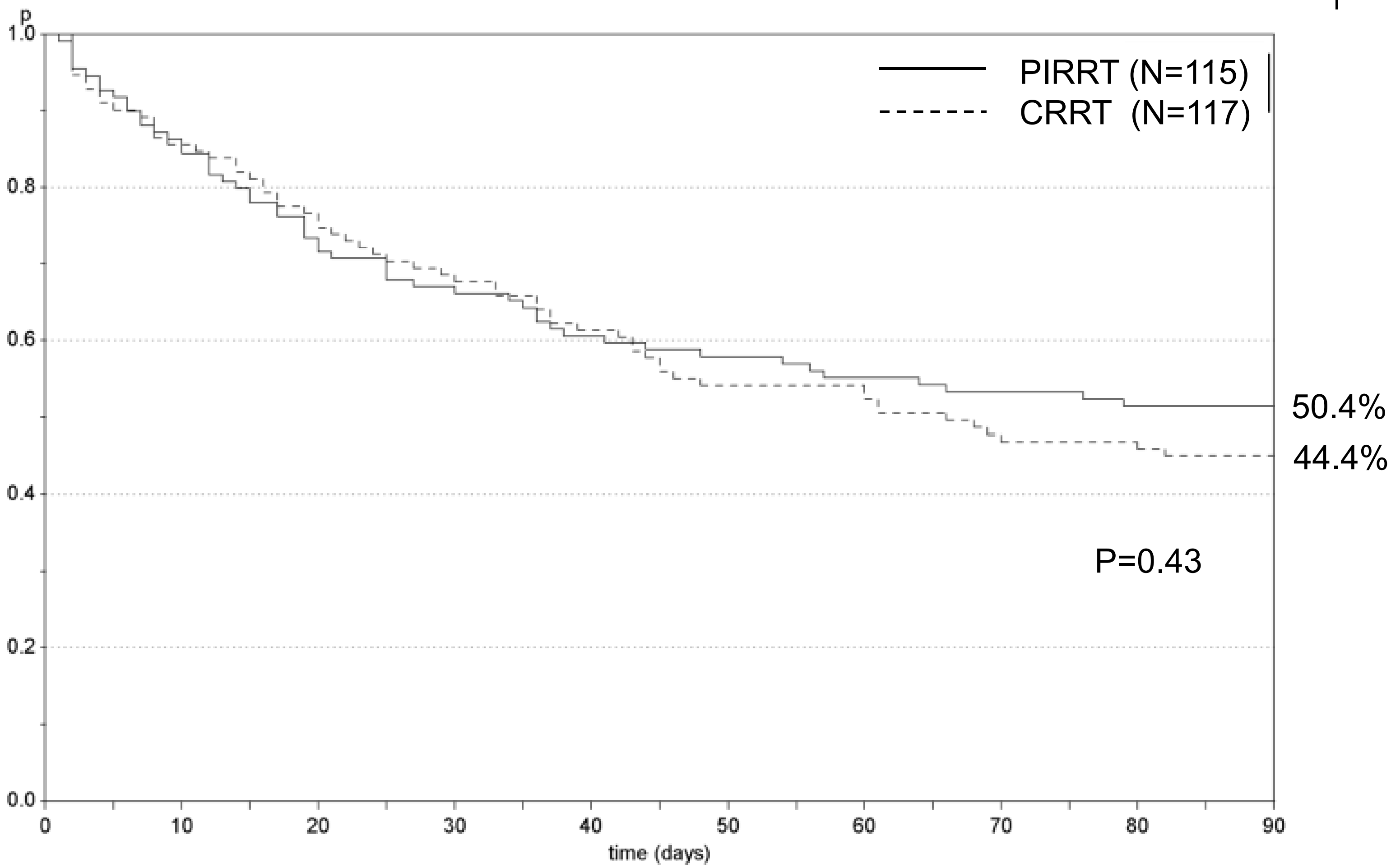
Prolonged Intermittent Renal Replacement Therapy

Comparision of Hemodynamic Parameters with CVVH



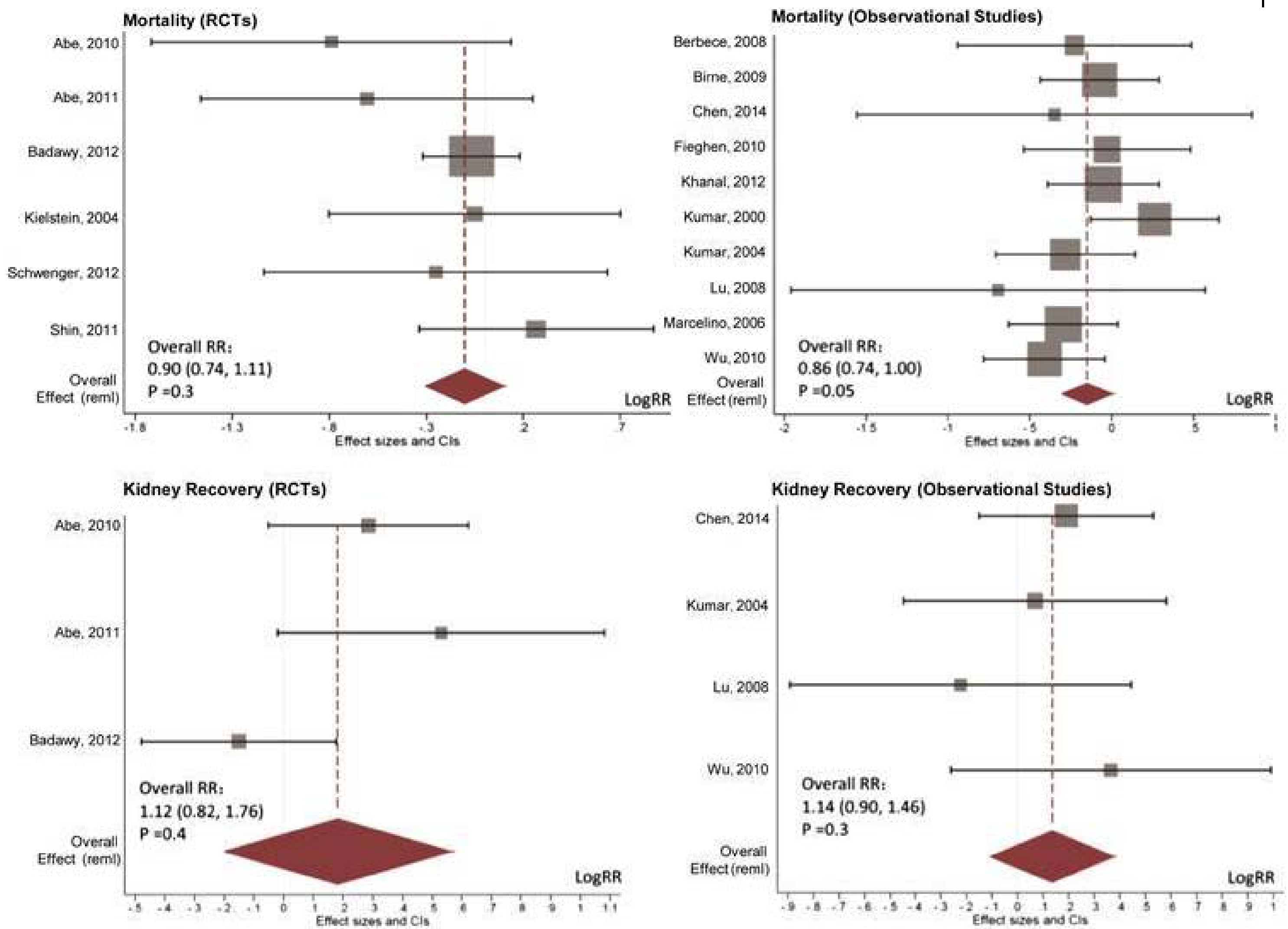
Kielstein JT, et al. Am J Kidney Dis 2004; 43:342-349

PIRRT vs CRRT
RESCUE Trial



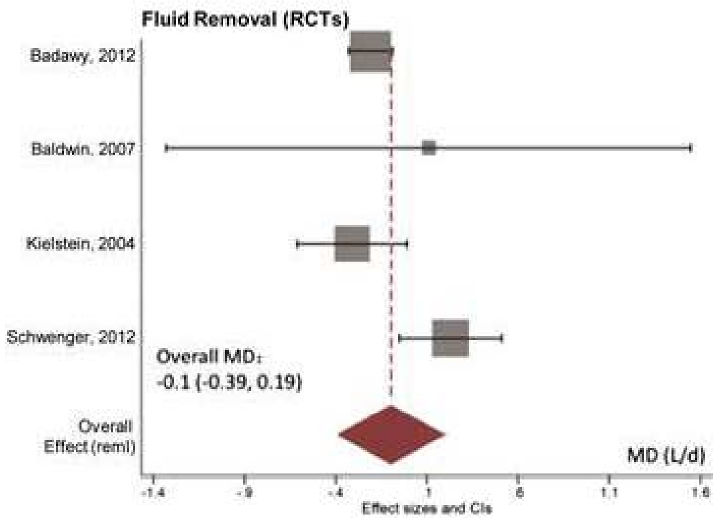
Schwenger V, et al. Crit Care 2012; 16:R140

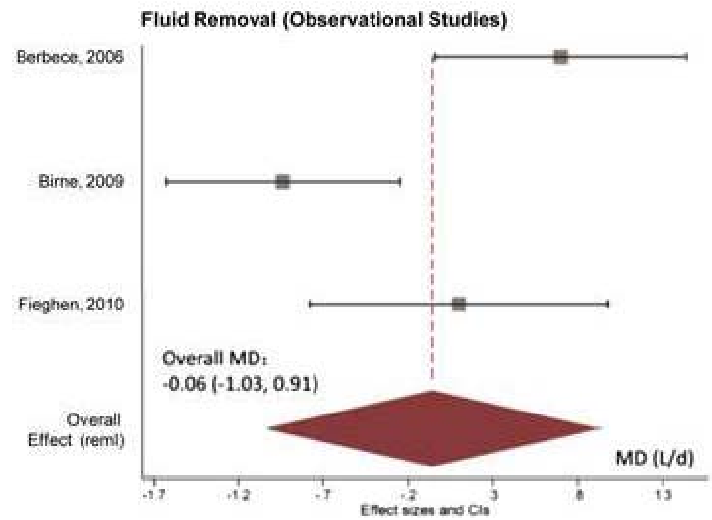
Meta-analysis of Studies Comparing CRRT and PIRRT



Zhang L, et al. Am J Kidney Dis 2015; 66:322-330

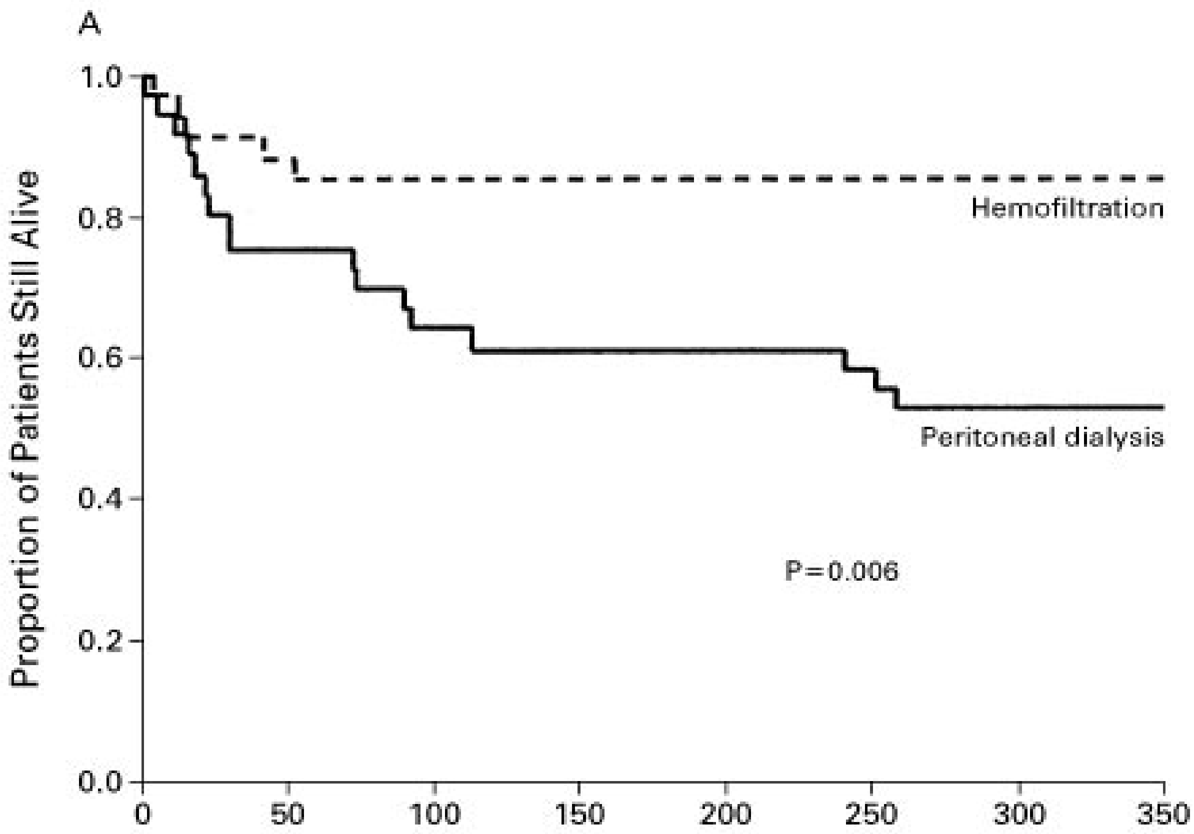
Meta-analysis of Studies Comparing CRRT and PIRRT





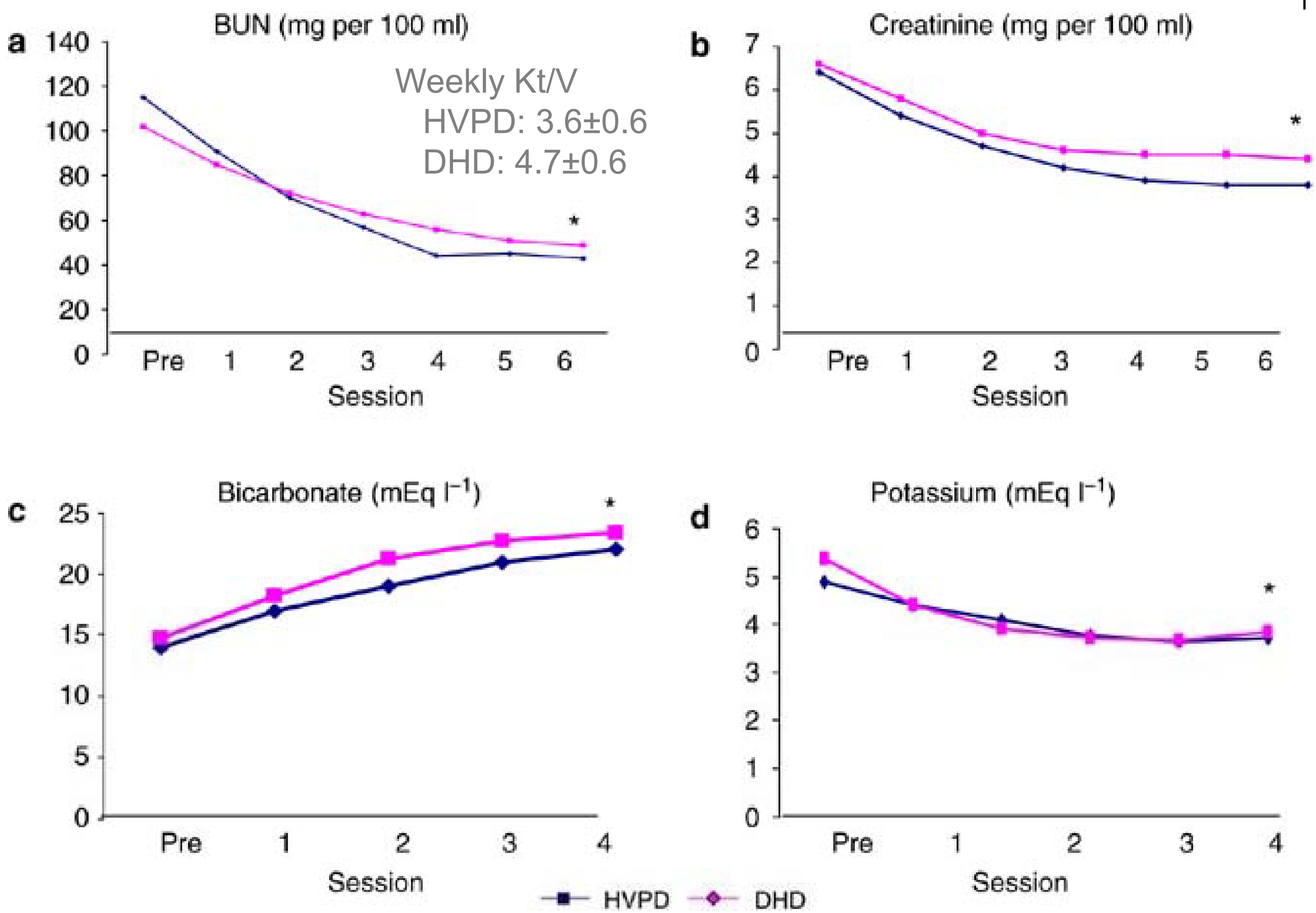
Zhang L, et al. Am J Kidney Dis 2015; 66:322-330

Peritoneal Dialysis vs CVVH in AKI



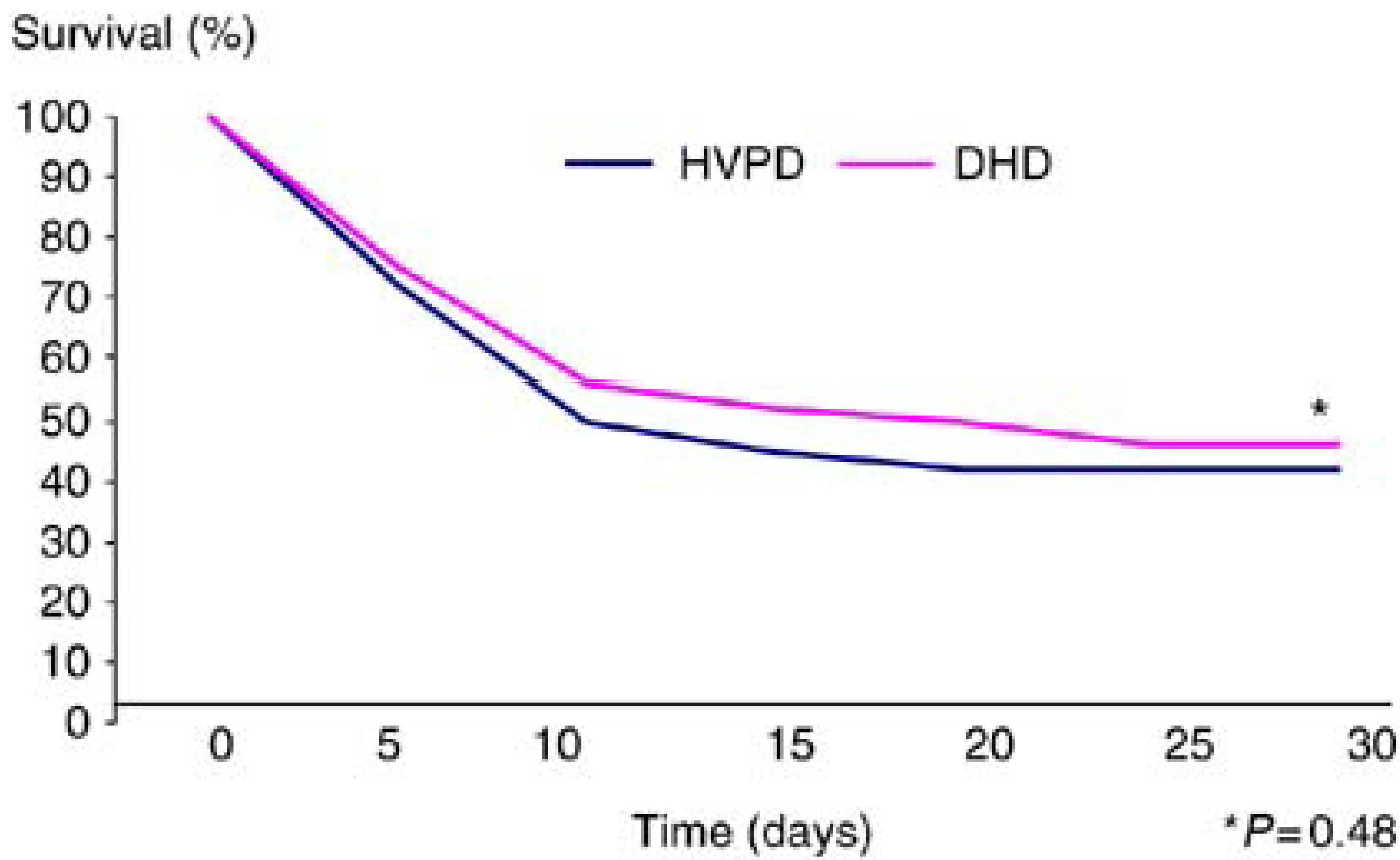
Phu NH, et al: N Engl J Med 2002; 347:895-902

High-Volume PD vs Daily IHD in AKI



Gabriel DP, et al. Kidney Int 2008; 73:S87-S93

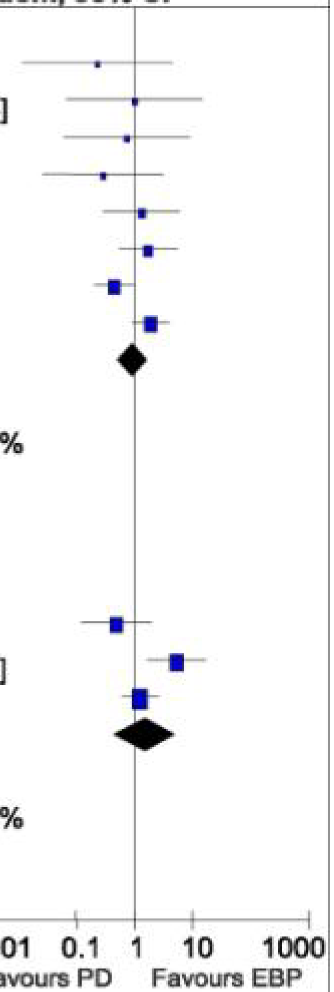
High-Volume PD vs Daily IHD in AKI



Gabriel DP, et al. Kidney Int 2008; 73:S87-S93

Meta-Analysis of PD versus Extracorporeal Blood Purification

	PD Events	PD Total	EBP Events	EBP Total	Odds Ratio M-H, Random, 95% CI
A Cohort Studies					
Hadidy 1989	0	4	25	77	0.23 [0.01, 4.41]
Chow 2007 (A)	8	12	2	3	1.00 [0.07, 14.64]
Kumar 1990	25	42	2	3	0.74 [0.06, 8.77]
Chow 2007 (B)	12	26	3	4	0.29 [0.03, 3.12]
Werb 1979	9	13	12	19	1.31 [0.29, 5.89]
Bellomo 1995	12	16	139	218	1.71 [0.53, 5.47]
Mahajan 2006	46	95	25	37	0.45 [0.20, 1.00]
Watcharotone 2011	47	62	52	83	1.87 [0.90, 3.88]
Subtotal (95% CI)		270		444	0.96 [0.53, 1.71]
Total events	159		260		
Heterogeneity: Tau² = 0.18; Chi² = 9.65, df = 7 (P = 0.21); I² = 27%					
Test for overall effect: Z = 0.15 (P = 0.88)					
B Randomized Studies					
Arogundade 2005	0	4	0	4	Not estimable
George 2011	18	25	21	25	0.49 [0.12, 1.95]
Phu 2002	17	36	5	34	5.19 [1.64, 16.44]
Gabriel 2008	35	60	32	60	1.23 [0.60, 2.52]
Subtotal (95% CI)		125		123	1.50 [0.46, 4.86]
Total events	70		58		
Heterogeneity: Tau² = 0.77; Chi² = 7.29, df = 2 (P = 0.03); I² = 73%					
Test for overall effect: Z = 0.68 (P = 0.50)					



Chionh CY, et al. Clin J Am Soc Nephrol 2013; 8: 1649-1660

Clinical Case 2 follow-up

Based on the clinical setting, there was no one “correct” modality of RRT that should have been used.

Given recent abdominal surgery, I would avoid PD

IHD can safely be performed even in the setting of hemodynamic instability

PIRRT would be a reasonable option

I would probably choose some form of CRRT for more aggressive fljuid removal

Clinical Case 2 follow-up

Based on the clinical setting, there was no one “correct” modality of RRT that should have been used.

- Given recent abdominal surgery, I would avoid PD
- IHD can safely be performed even in the setting of hemodynamic instability
- PIRRT would be a reasonable option
- I opted for CRRT in the hope of achieving more aggressive fluid removal
  - I generally use CVVHD as my modality of CRRT

Summary - 1

- There are insufficient data to determine the optimal timing of RRT in AKI
- Clinical trials to evaluate timing need to include patients who meet criteria for early initiation but recover or die without receiving RRT
- Current evidence suggests that a strategy of delayed RRT may not be inferior to early initiation of RRT, and may reduce the number of patients requiring RRT
- Although severity of fluid overload is strongly associated with adverse outcomes, there are insufficient data to conclude that initiation of therapy based on severity of fluid overload decreases mortality

Summary - 2

- Studies comparing modalities of RRT in AKI have not demonstrated superiority of any individual modality
- Selection of modality should be guided by expertise and resources available at the individual institution