Conflicts of Interest

Research support: NIH, Fresenius Medical Services

Member: FDA Advisory Panel, Gastroenterology and Urology Devices

Consultant : Kai Pharmaceuticals, Genzyme, Thrasos, Nephrion

Renal Replacement Therapy in AKI : the Prescription makes little difference

Jonathan Himmelfarb, M.D.

Professor of Medicine

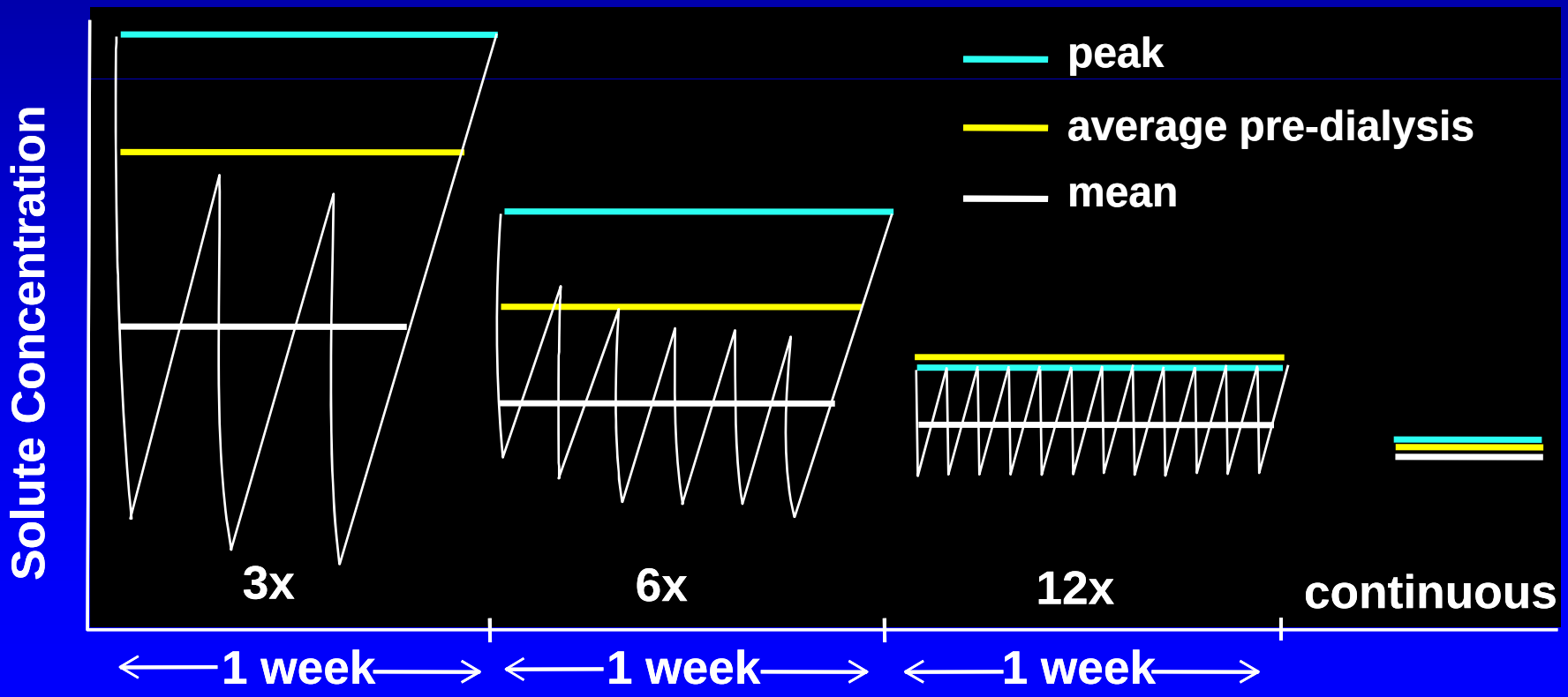
Joseph W. Eschbach Endowed Chair for Kidney Research

Director Kidney Research Institute

University of Washington

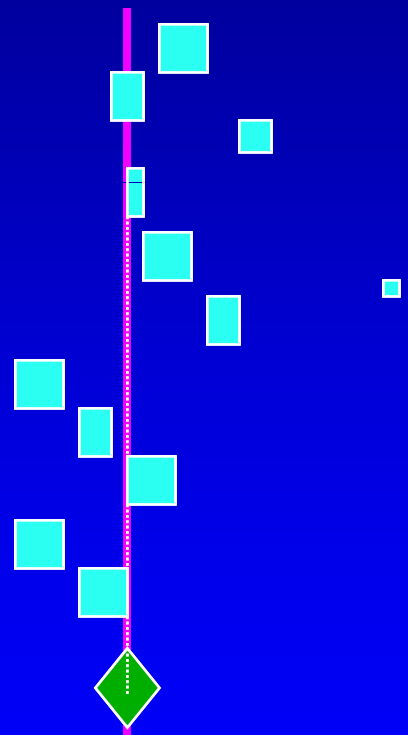
Dialysis Frequency and Solute Levels

The Case for CRRT vs IHD



Courtesy T. Depner

RR for Death: Non-Randomized Studies



	RISK RATIO	%	WEIGHT
Mauritz	1.21 [0.96-1.53]	22	5.2
Paganini	0.99 [0.70-1.25]	47	7.1
Bastien	1.50 [1.01-2.22]	32	4.2
McDonald	1.03 [0.63-1.69]	10	2.4
Kierdorf	1.19 [1.04-1.37]	73	14.4
Kruczynski	3.30 [1.22-8.96]	23	1.0
Van Bommel	1.36 [0.91-3.03]	34	4.8
Neveu	0.65 [0.54-0.79]	141	10.5
Rialp	0.87 [0.62-1.23]	21	5.5
Bellomo	1.15 [0.95-1.39]	47	16.6
Swartz	0.60 [0.43-0.77]	137	18.6
Ji	0.88 [0.62-1.27]	92	9.9
OVERALL	1.00 [0.92-1.08]		

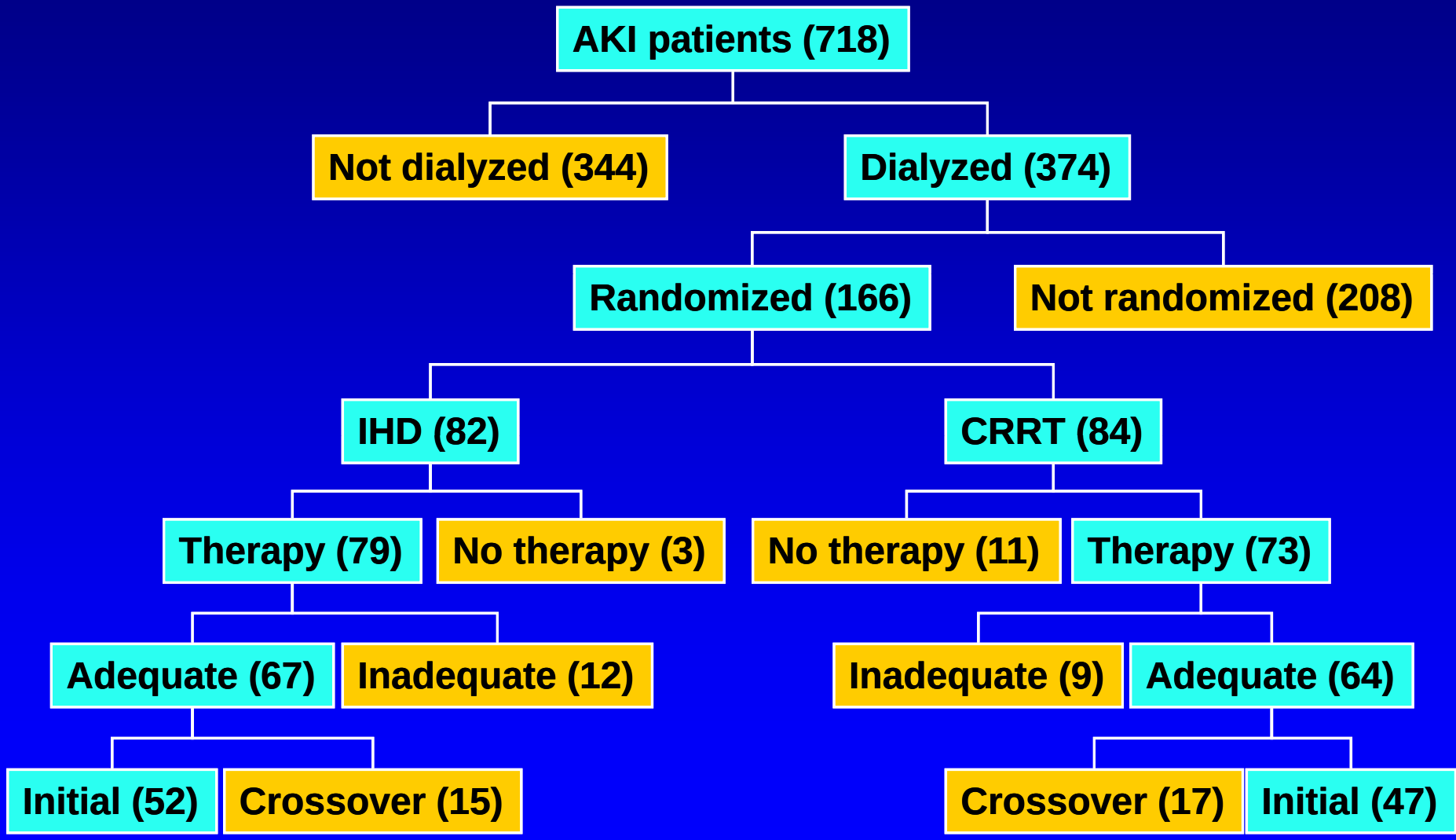
Favors IHD

Favors CRRT

0.2 0.5 1 2 10

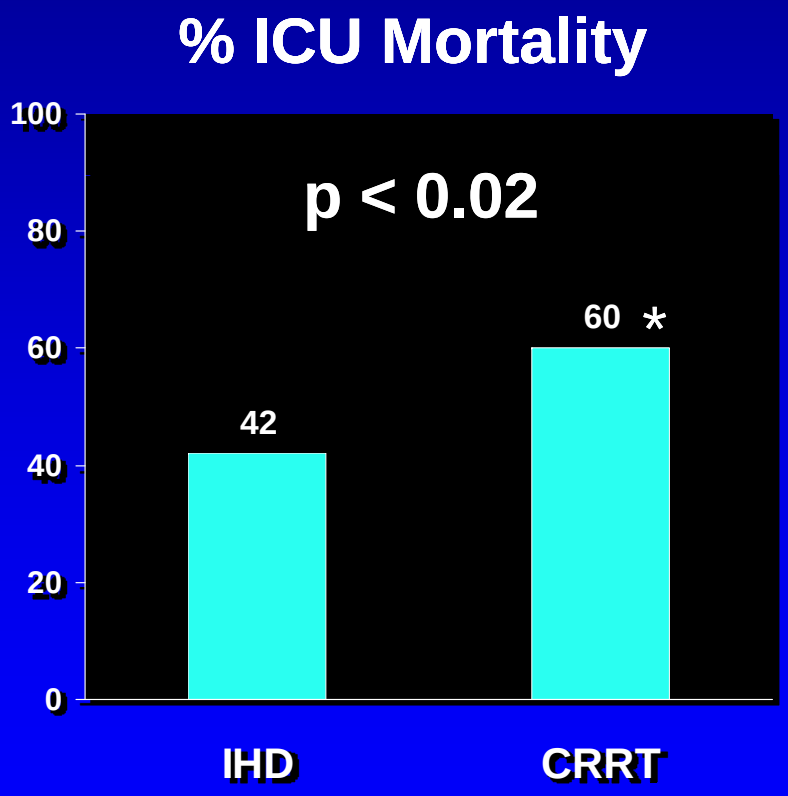
Tonelli et al, AJKD 40:875-885, 2002

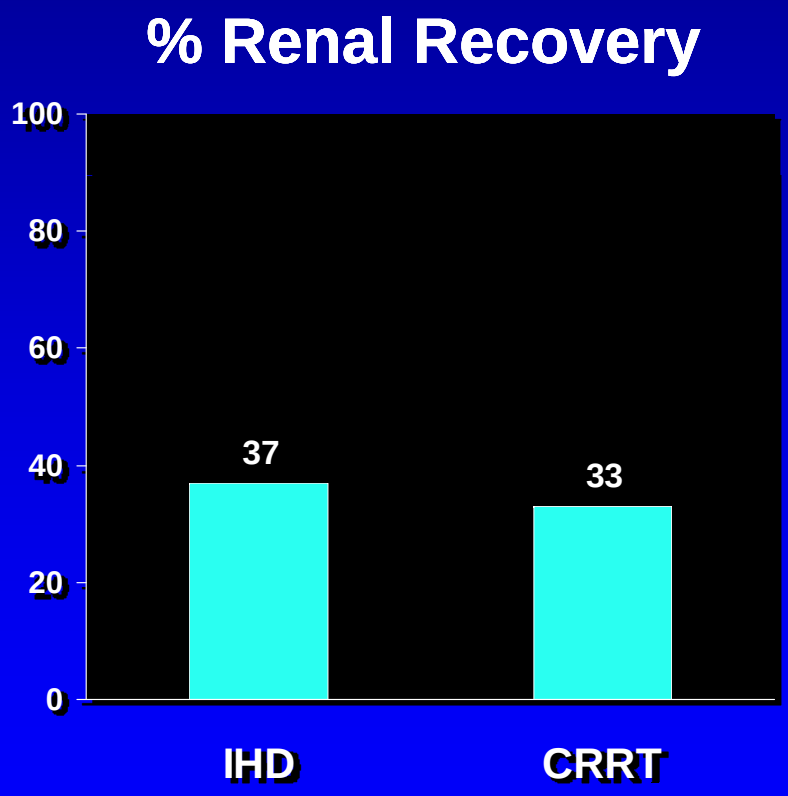
UCSD: CRRT vs. IHD Randomized Trial



Mehta et al, KI 60: 1154-1163, 2001

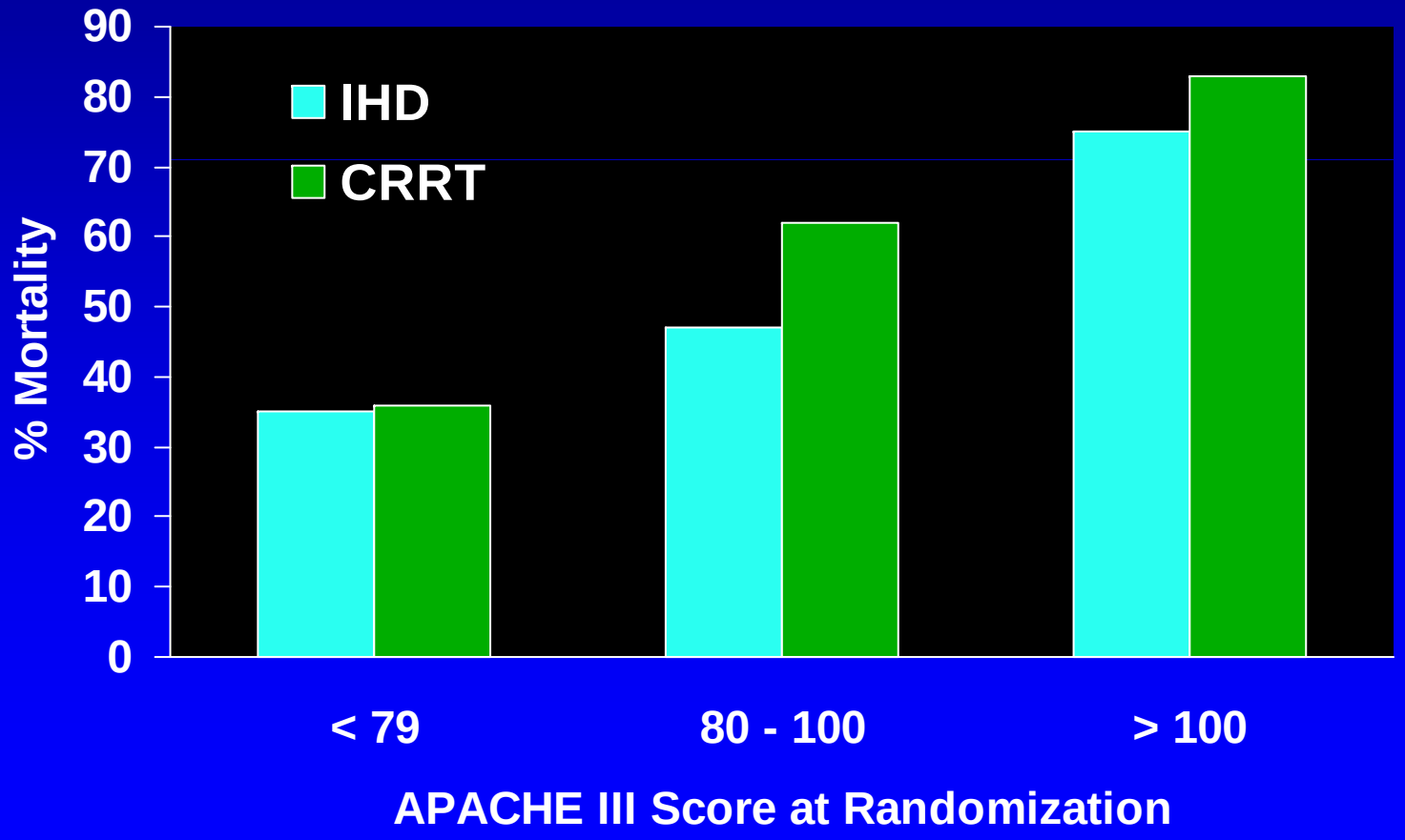
UCSD: CRRT vs. IHD Randomized Trial





Adapted from Mehta et al, KI 60: 1154-1163, 2001

UCSD: CRRT vs. IHD Randomized Trial



Mehta et al, KI 60: 1154-1163, 2001

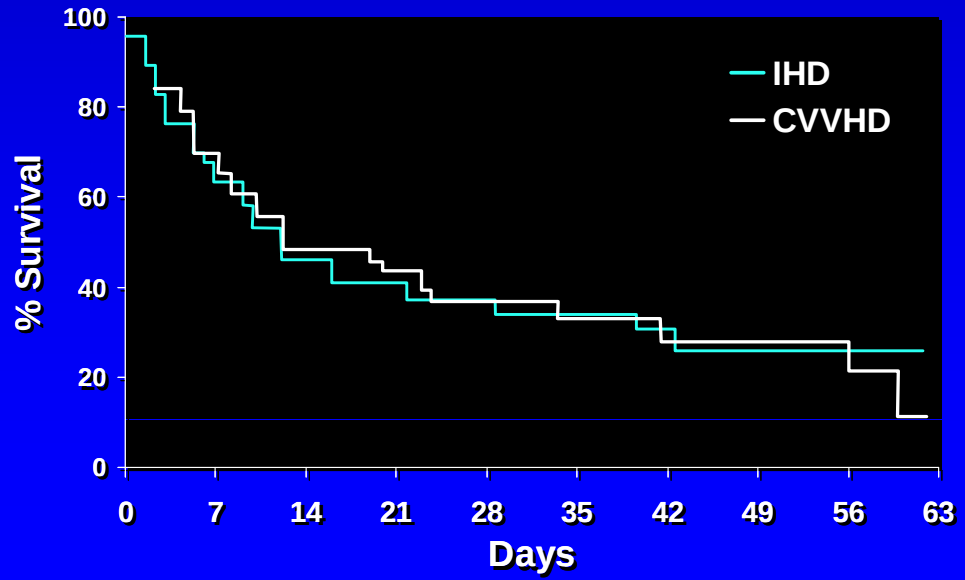
Cleveland Clinic: CRRT vs. IHD Randomized Trial

- Single center RCT (1995 - 1999)
- 80 critically ill patients
- CVVHD vs. IHD
- Stratified on CCF severity score
- All treatments polysulfone, low flux, HCO_3^-, heparin

Augustine et al, AJKD 44(6): 1000-1007, 2004

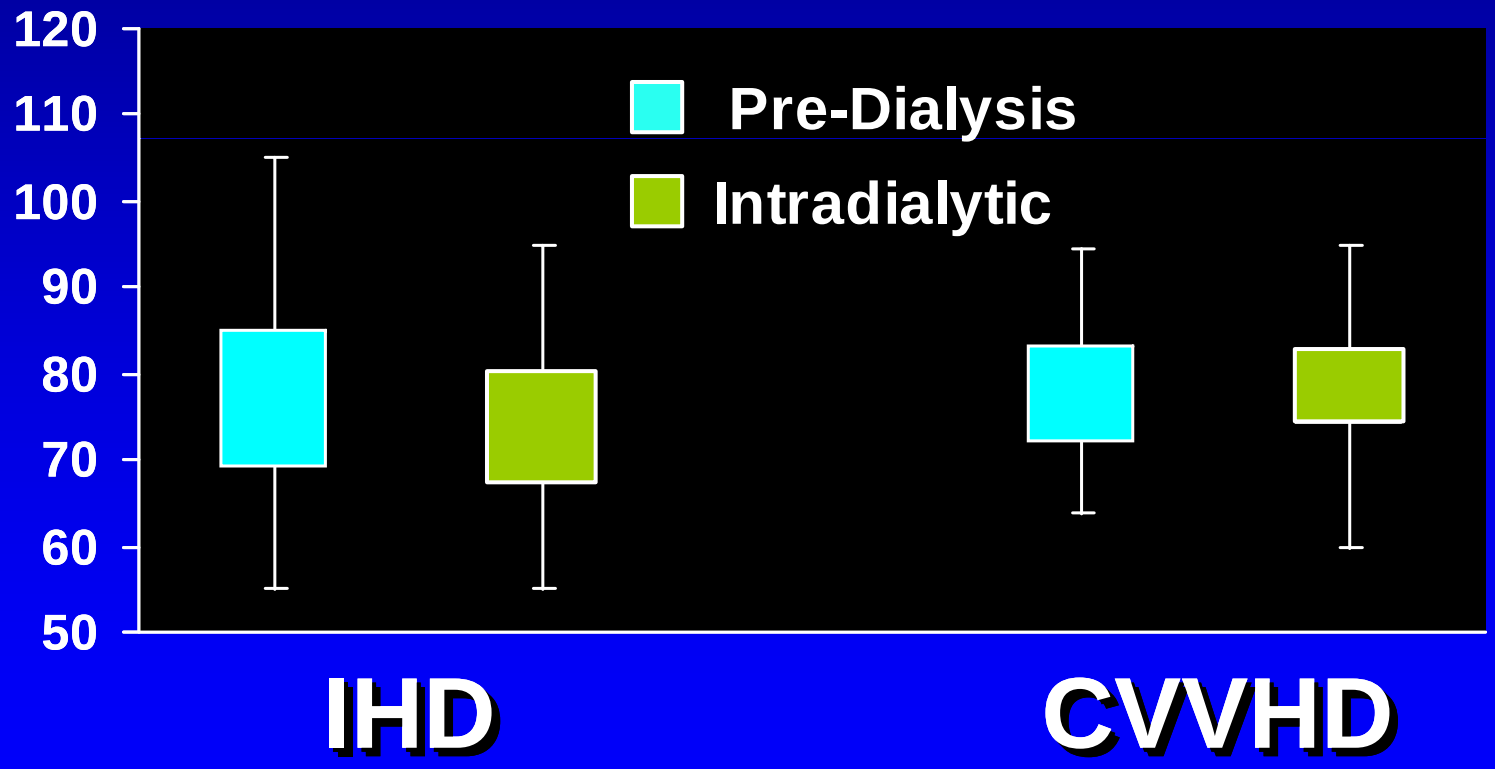
Cleveland Clinic: CRRT vs. IHD Randomized Trial

	CVVHD n = 40	IHD n = 40	*p*
In-Hospital Mortality	27 (68%)	28 (70%)	NS
Mean Survival, *days*	14.3	10.7	NS
Renal Functional Recovery	5 (13%)	4 (10%)	NS



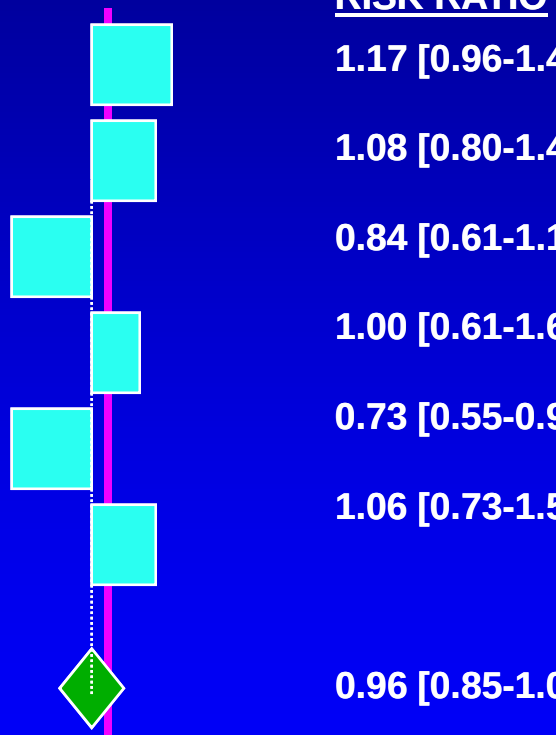
Augustine et al, AJKD 44(6): 1000-1007, 2004

Cleveland Clinic Trial: Mean Arterial Pressure



Augustine et al, AJKD 44(6): 1000-1007, 2004

Relative Risk for Death: RCTs



	RISK RATIO	n IHD	%WEIGHT
Simpson	1.17 [0.96-1.42]	58	22.3
Kierdorf RCT	1.08 [0.80-1.46]	52	15.5
Sandy	0.84 [0.61-1.15]	40	14.6
Johns	1.00 [0.61-1.64]	20	4.8
Mehta	0.73 [0.55-0.96]	82	28.0
Uehlinger	1.06 [0.73-1.52]	55	14.8
OVERALL	0.96 [0.85-1.08]	p=0.50	

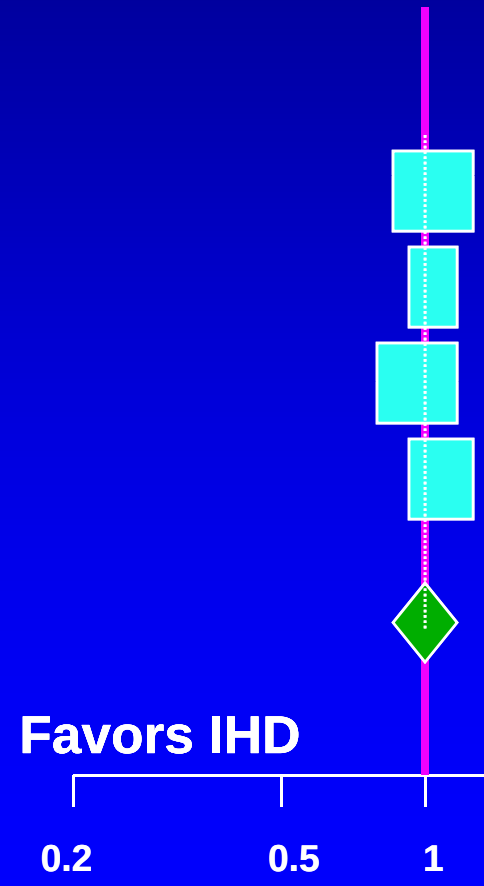
Favors IHD

Favors CRRT

0.2 0.5 1 2 10

Tonelli et al, AJKD 40:875-885, 2002

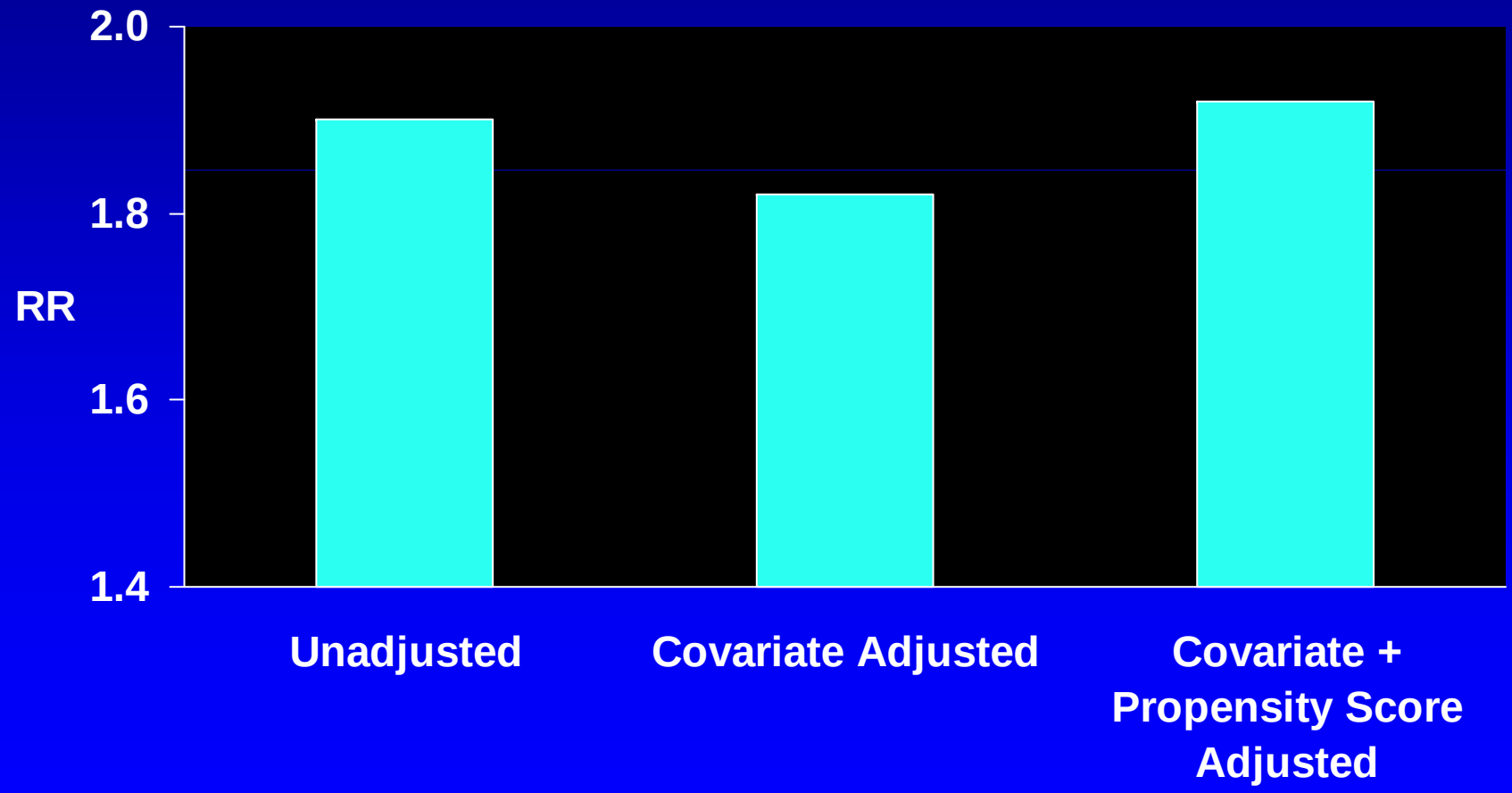
RR for Renal Death: Randomized Trials



	RISK RATIO	% WEIGHT
Sandy	1.07 [0.88-1.29]	25.3
Johns	1.00 [0.68-1.46]	8.3
Mehta	0.95 [0.76-1.19]	43.2
Uehlinger	1.10 [0.78-1.56]	23.2
OVERALL	1.02 [0.89-1.17]	

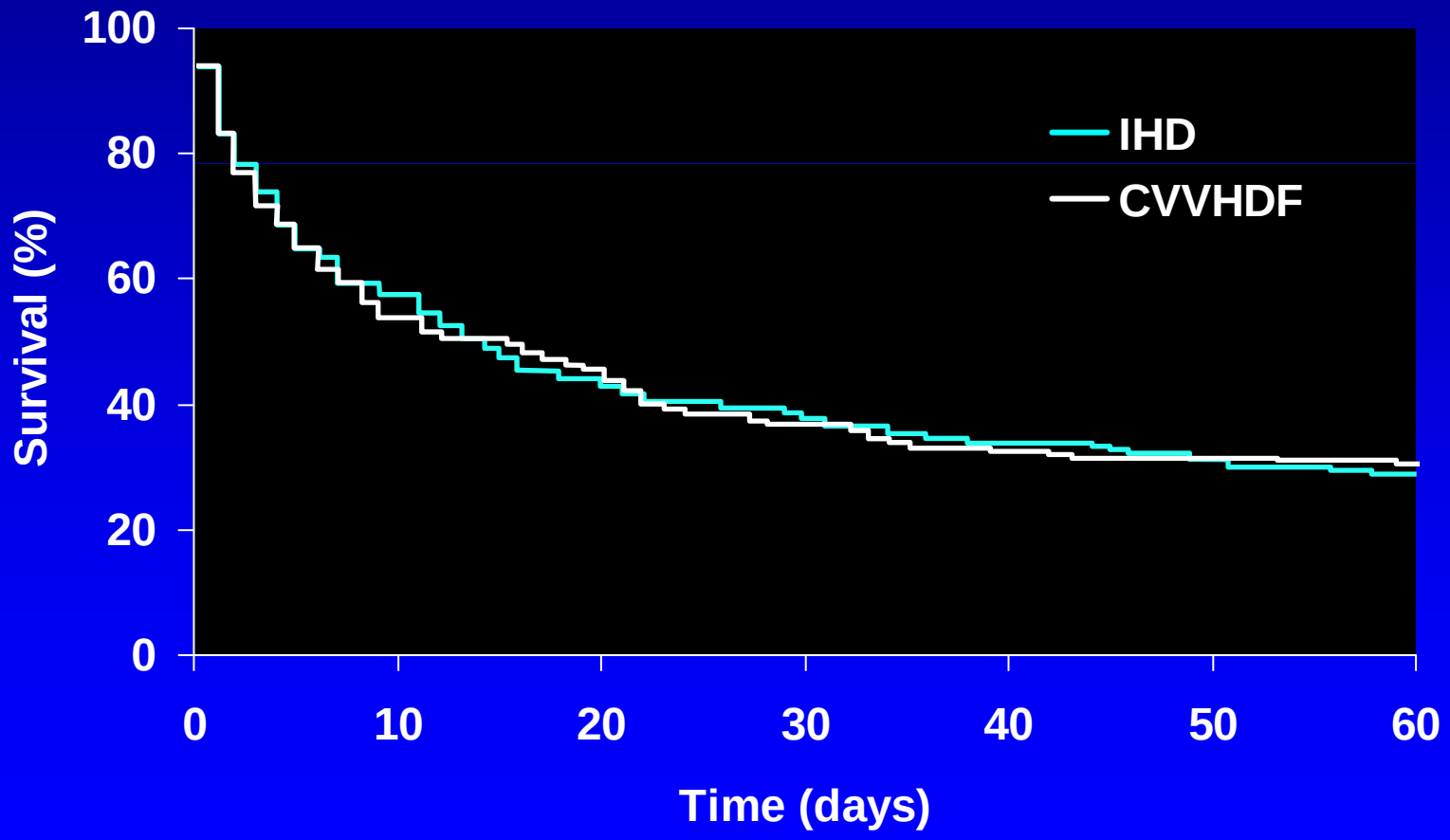
Tonelli et al, AJKD 40:875-885, 2002

PICARD: Modality and Mortality Risk



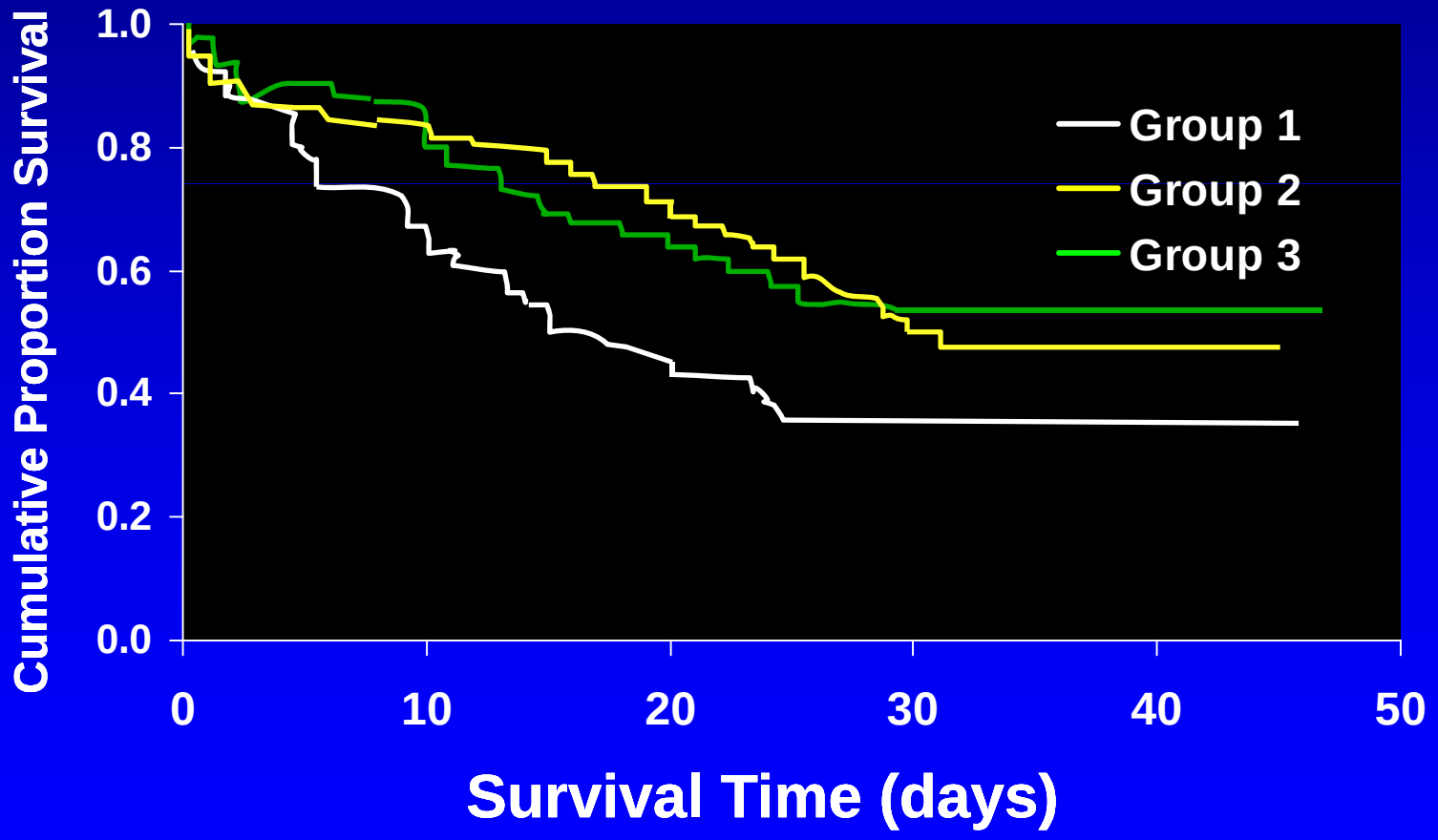
Cho et al, JASN 2006

Hemodiaf Study



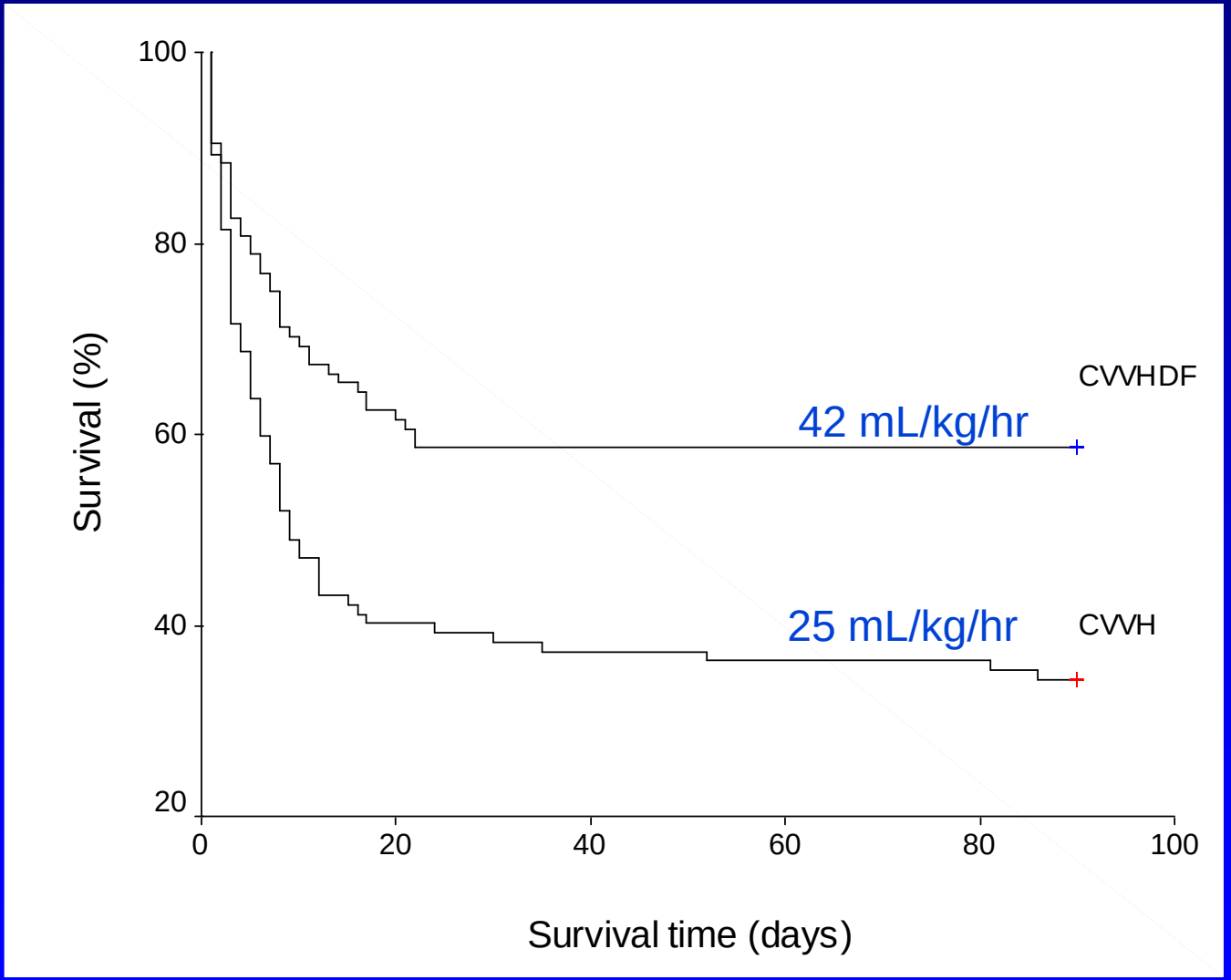
Vinsonneau et al, Lancet 368: 379-385, 2006

CVVH Dose and Mortality



Ronco et al, Lancet 356, 2000

CVVH vs CVVHDF



Saudan et al, Kidney Int 2006

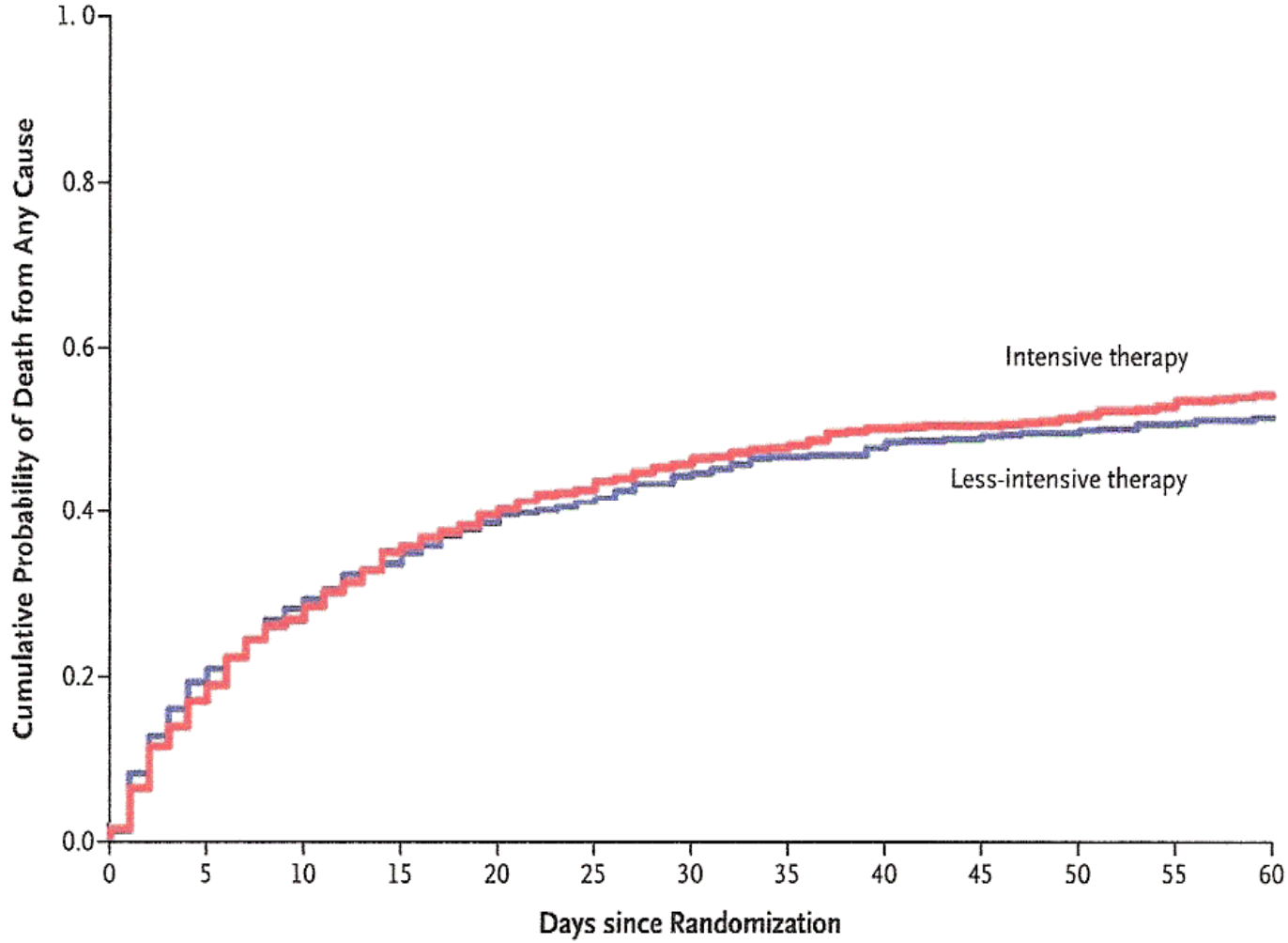
ATN Trial

1164 patients
31 sites (24 VA, 7 other)
3 years

Randomization

	Intensive Management Strategy (582 patients)	**Conventional Management Strategy (582 patients)**
Stable hemodynamics ***(SOFA 0-2)***	• **IHD 6x/week @ Kt/V of ~1.2/session**	• **IHD 3x/week @ Kt/V of ~1.2/session**
Unstable hemodynamics ***(SOFA 3-4)***	• **CVVHDF @ 35 mL/kg/hr, or** • **SLED/EDD 6x/week**	• **CVVHDF @ 20 mL/kg/hr, or** • **SLED/EDD 3x/week**

ATN Study: Primary Outcome

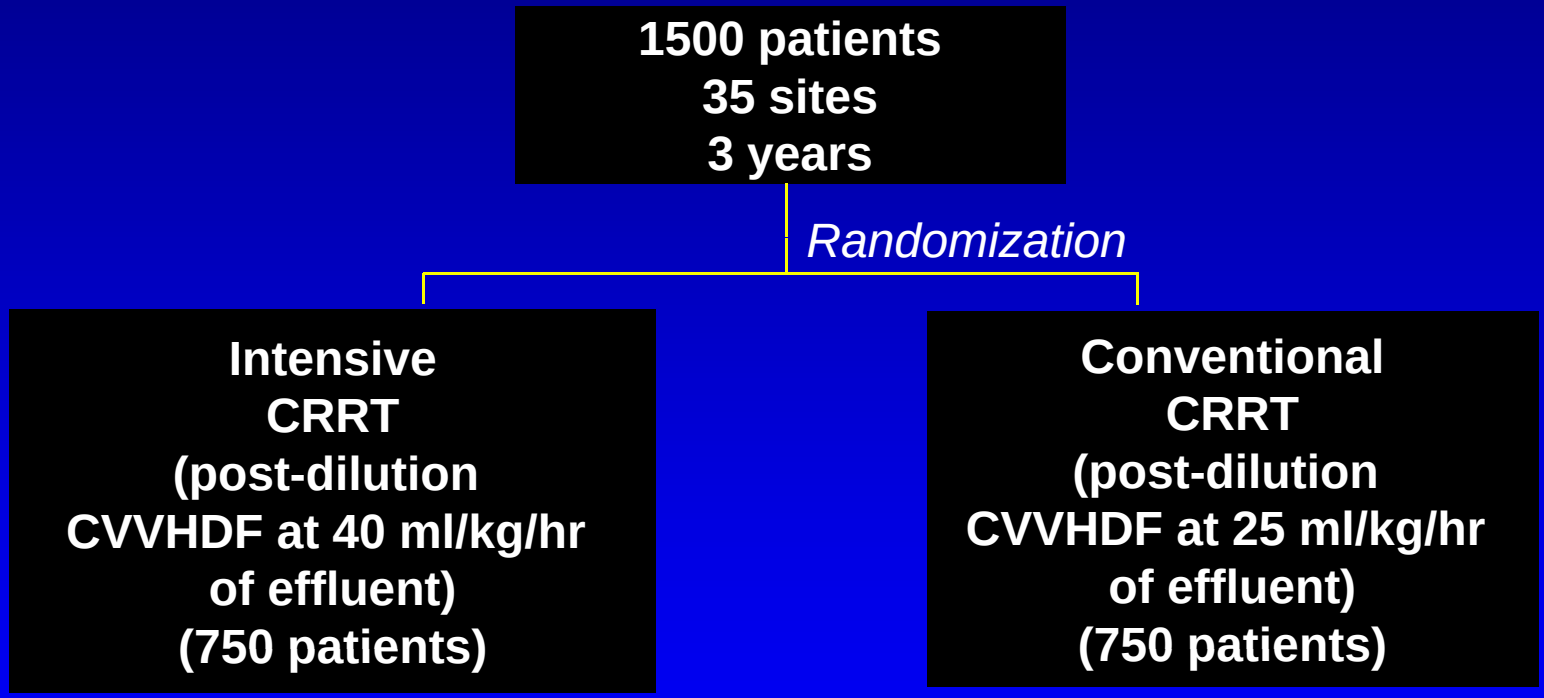


N Engl J Med. 2008;359:7-20

Major Criticisms of ATN Study

- Effective CRRT dose was significantly lower than Ronco and Saudan studies
- Late initiation of RRT
- Potential independent effect of fluid balance on outcome
- High percentage of patients with RRT “pre-exposure” (when patients were most critically ill)
- Low rate of renal recovery (despite exclusion of patients with moderate/advanced CKD)

R.E.N.A.L. Trial


1500 patients
35 sites
3 years
Randomization
Intensive
CRRT
(post-dilution
CVVHDF at 40 ml/kg/hr
of effluent)
(750 patients)
Conventional
CRRT
(post-dilution
CVVHDF at 25 ml/kg/hr
of effluent)
(750 patients)

RENAL Trial: Study Design

- 1508 patients (35 centers) in Australia/New Zealand
- Conducted from December 2005 to September 2008
- Two groups treated with post-dilution CVVHDF
  - Group 1: 40 mL/kg/hr
  - Group 2 (SOC in AUS/NZ): 25 mL/kg/hr (both groups: BFR = 150 mL/min; D:R=1:1)
  - Exclusively with AN69 filters
- CRRT was initial treatment in all patients and applied almost exclusively while patients in ICU
- Primary outcome: 90-day mortality
- Major secondary outcomes
  - 28-day mortality
  - ICU and hospital length of stay (LOS)
  - Renal recovery rate

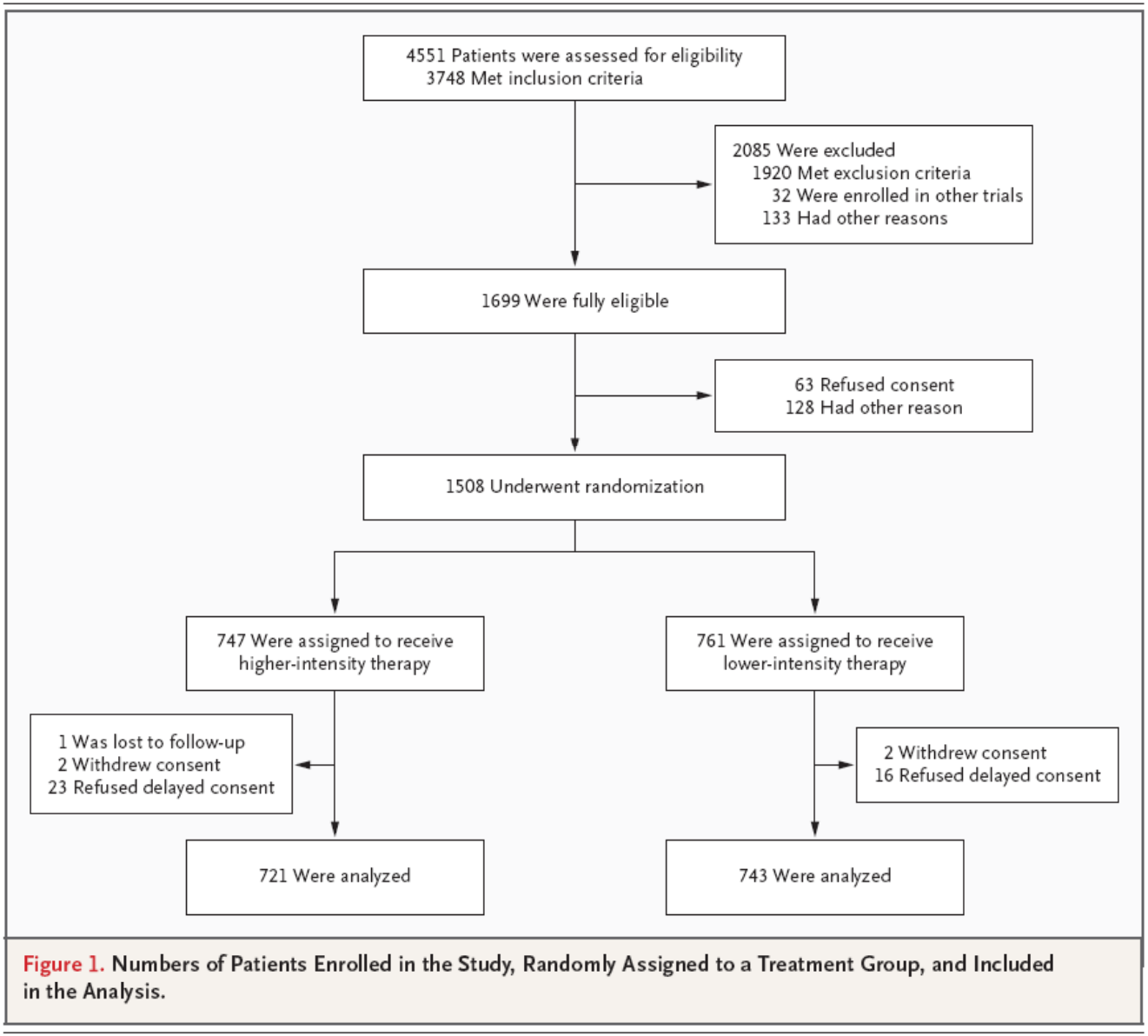


Figure 1. Numbers of Patients Enrolled in the Study, Randomly Assigned to a Treatment Group, and Included in the Analysis.

RENAL Replacement Therapy Study Investigators. *N Engl J Med* **1629**, 1627-1638 (2009)

Table 2. Characteristics of Study Treatments and Subsequent Use of Renal-Replacement Therapy.*

Characteristic	Higher-Intensity CRRT	Lower-Intensity CRRT	P Value†
Duration of study treatment — days	6.3±8.7	5.9±7.7	0.35
Flow rate of effluent — ml/kg/hr	33.4±12.8	22±17.8	<0.001
Dose delivered — %	0.84±0.27	0.88±0.34	<0.001
BUN — mmol/liter/day‡	12.7±8.5	15.9±7.9	<0.001
Serum creatinine — μmol/liter/day§	170±121	204±115	<0.001
Dialysate and replacement fluid — ml/hr	2588±1122	1666±1204	<0.001
Dose of effluent — ml/hr/day	2698±1154	1771±1257	<0.001
Net ultrafiltration — ml/hr	110±100	106±108	0.04
Fluid balance — ml/day	−20±29	−20±26	0.24
Duration of anticoagulation — days			
Prefilter heparin	2.2±3.3	2.2±3.3	0.97
No anticoagulation	1.6±2.9	1.8±2.9	0.27
Heparin and protamine	1.1±3.0	0.7±2.0	0.007
Systemic heparin	0.7±1.9	0.7±2.10	0.40
Other	0.3±1.5	0.2±1.2	0.38
Type of anticoagulant received — no./total no. (%)¶			
Prefilter heparin	348/722 (48.2)	355/743 (47.8)	0.87
No anticoagulant	332/722 (46.0)	379/743 (51.0)	0.05
Heparin and protamine	145/722 (20.1)	132/743 (17.8)	0.25
Systemic heparin	125/722 (17.3)	138/743 (18.6)	0.52
Other	48/722 (6.6)	42/743 (5.7)	0.42
Filters used daily — no.	0.93±0.86	0.84±0.81	<0.001
Patients treated with IHD in ICU — no. (%)	55/722 (7.6)	52/743 (7.0)	0.64

* Plus–minus values are means ±SD. BUN denotes blood urea nitrogen, CRRT continuous renal-replacement therapy, ICU intensive care unit, and IHD intermittent hemodialysis.
† P values were calculated with the use of Student's t-test or the chi-square test, as appropriate.
‡ To convert the values for blood urea nitrogen to milligrams per deciliter, divide by 0.357.
§ To convert the values for creatinine to milligrams per deciliter, divide by 88.4.
¶ Some patients received more than one type of anticoagulant.

RENAL Replacement Therapy Study Investigators. *N Engl J Med* **1632**, 1627-1638 (2009)

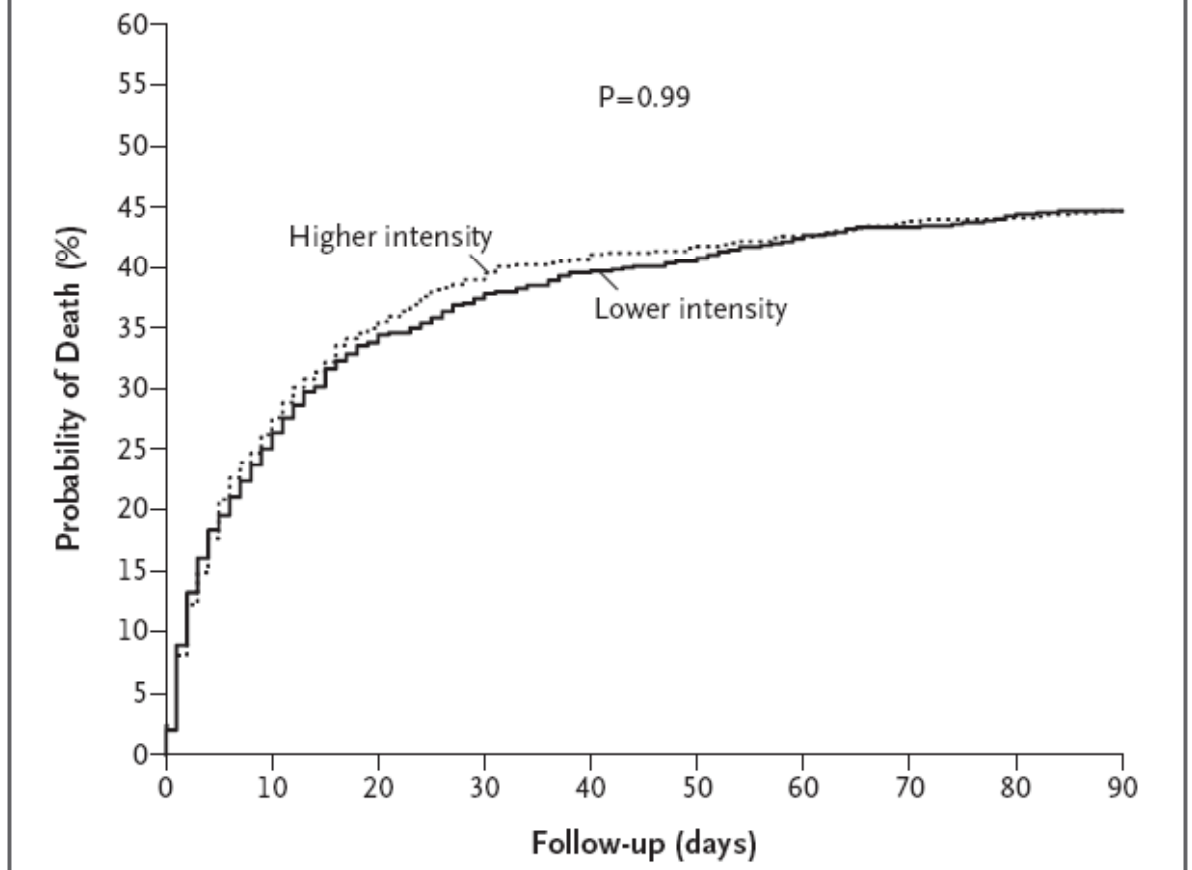


Figure 2. Kaplan–Meier Estimates of the Probability of Death.

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.

RENAL Replacement Therapy Study Investigators. *N Engl J Med* **1634**, 1627-1638 (2009)

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
No. of days of RRT, from randomization to day 90	13.0±20.8	11.5±18.0	—	0.14
No. of days in ICU	11.8±14.1	11.8±14.2	—	0.95
No. of days in hospital	26±25.8	25.7±24.7	—	0.79
No. of days of mechanical ventilation	7.3±5	7.4±5	—	0.79
No. of nonrenal organ failures — no./total no. (%)‡				
0	344/722 (47.6)	343/743 (46.2)	—	0.57
1	254/722 (35.2)	263/743 (35.4)	—	0.93
2	100/722 (13.9)	109/743 (14.7)	—	0.65
3	23/722 (3.2)	25/743 (3.4)	—	0.85
4	1/722 (0.1)	3/743 (0.4)		0.33

* Plus–minus values are means ±SD.
† P values were calculated with Student's t-test or the chi-square test, as appropriate.
‡ Data on nonrenal organ failures are for the 90-day study period.

RENAL Replacement Therapy Study Investigators. *N Engl J Med* **1633**, 1627-1638 (2009)

RENAL Trial: Major Results

- Two groups well matched for illness severity and all measured clinical parameters
- 90-day mortality identical (45%) in both groups
- Renal recovery rate at 90 days was 93% in both groups. No significant differences in any of secondary outcomes
- Other significant factors
  - CRRT was initiated early in both groups (average ~50 hrs after ICU admission)
  - Average delivered dose ~85% of prescribed dose

Weighing the Evidence

Why doesn't the Renal Replacement Therapy Prescription Make a Difference?

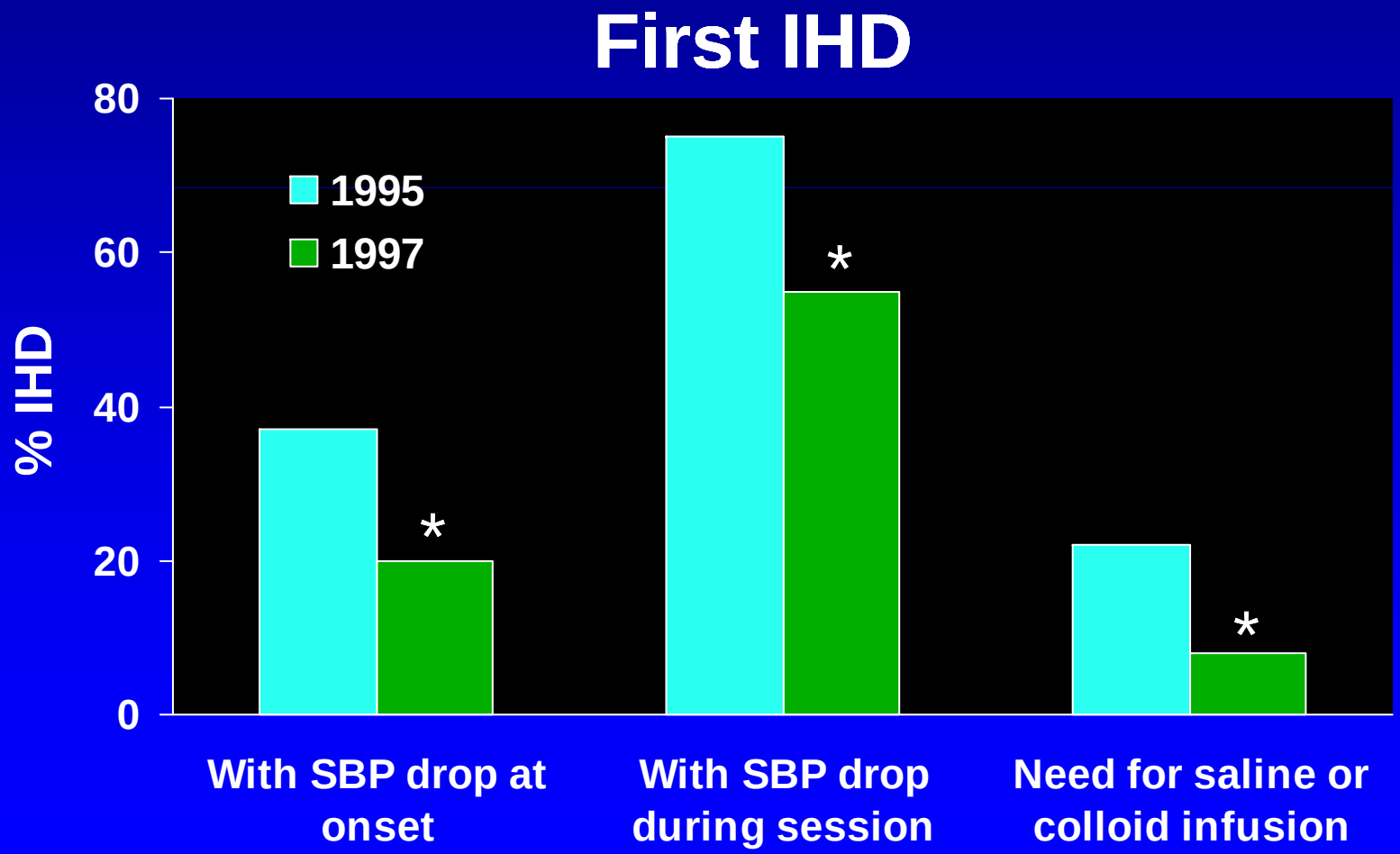
- Intermittent dialysis is better than we give it credit for (safety, avoidance of complications)
- More intensive therapy may be less safe or more complicated than we think
- Outcomes are primarily determined by underlying illness

Intermittent Hemodialysis Practice Guidelines

- Biocompatible membranes
- Primed circuit
- High dialysate sodium
- Cool dialysate
- Hold vasodilator therapy
- Sequential dialysis/ UF
- 4 hour sessions

Schortgen et al, Am J Respir Crit Care Med 162: 197-202, 2000

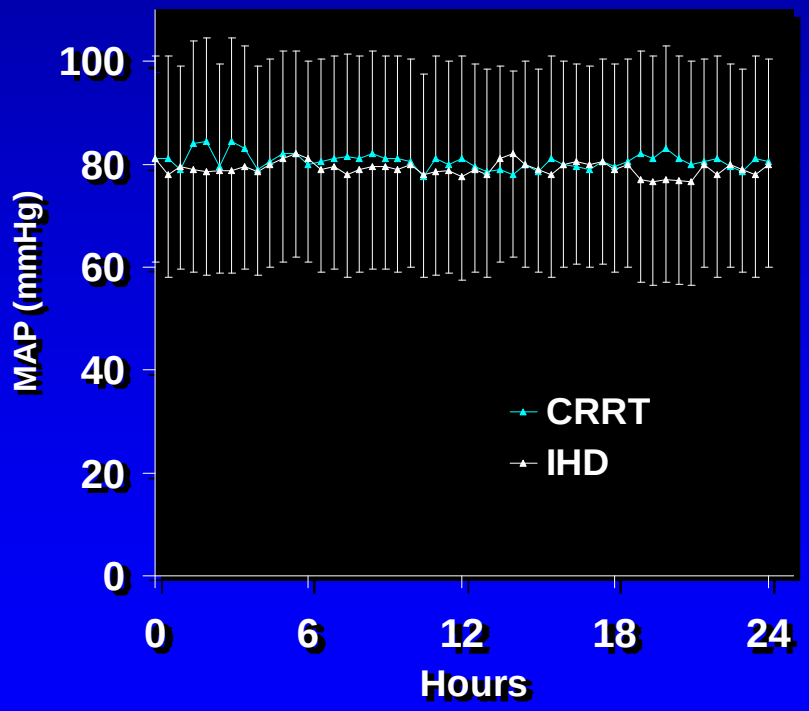
Hemodynamic Tolerance of IHD



Schortgen et al, Am J Respir Crit Care Med 162: 197-202, 2000

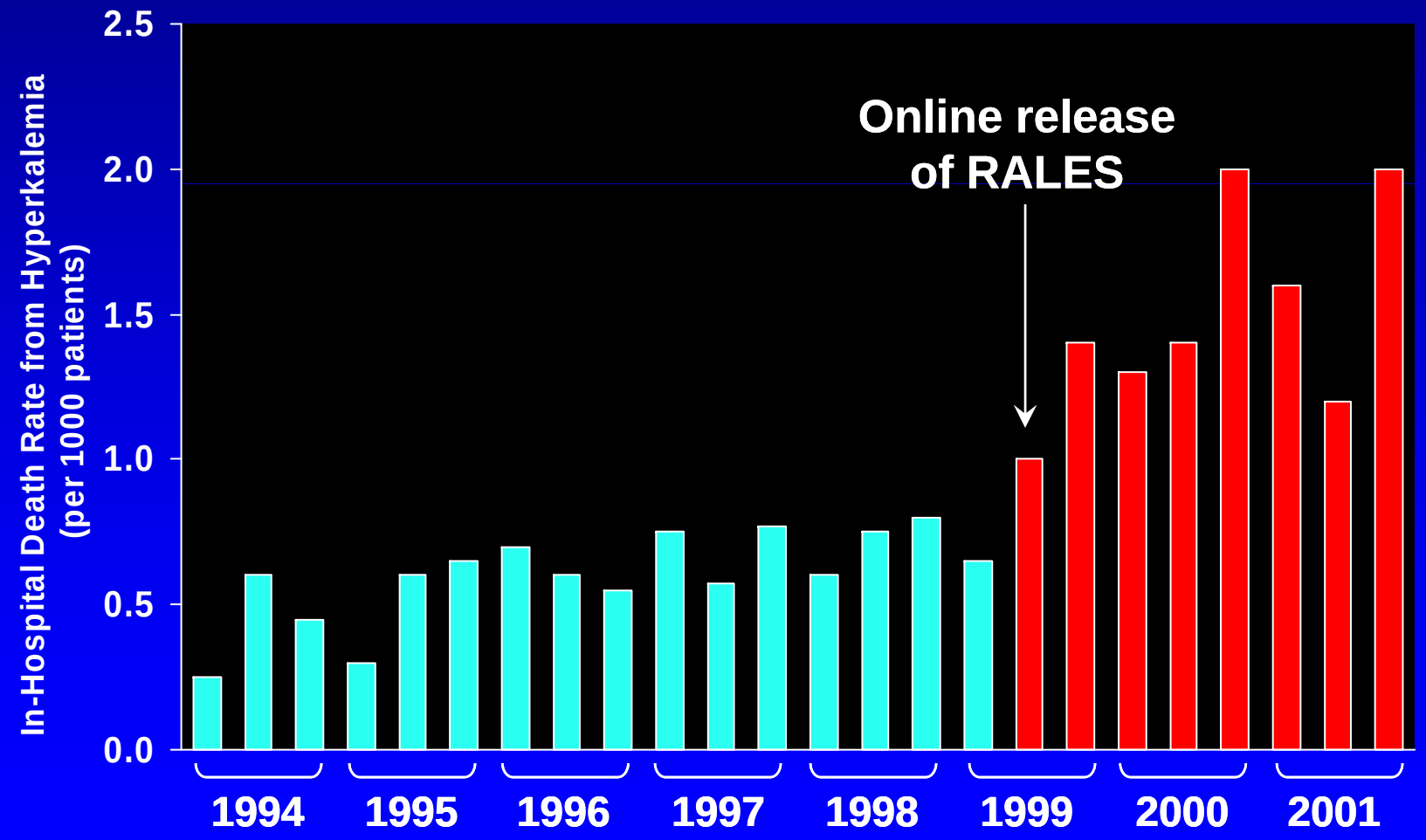
IHD vs. CRRT: Hemodynamics

- Randomized crossover trial CAVH vs IHD
- No difference in MAP
- No difference in UF
- No difference in pressors



Misset et al, Intensive Care Med 22: 742-746, 1996

Lethal Hyperkalemia After RALES Study Publication



Juurlink et al, NEJM 351: 543-551, 2004

FDA Preliminary Public Health Notification: Gambro Prisma® Continuous Renal Replacement System

Issued: August 23, 2005

Dear Renal Dialysis Caregivers:

This is to alert you to the danger of not responding adequately to any of the "Incorrect Weight Change Detected" alarms of the Gambro Prisma® Continuous Renal Replacement System, and to recommend specific actions to prevent injuring patients. Gambro Renal Products, Inc. and FDA have determined that several serious injuries and deaths have occurred when users did not respond appropriately to one or more of the *"Incorrect Weight Change Detected"* alarms (Effluent Weight, Replacement Solution Weight, or Dialysate Weight). These alarms are designed to alert the user when a potential fluid imbalance has occurred during the course of Continuous Renal Replacement Therapy (CRRT). If these alarms are ignored, an excessive amount of fluid can be removed from or administered to the patient.

The injuries and deaths have resulted because of excessive ultrafiltration (fluid being removed from the patient's body). The exact number of serious injuries and deaths are not known at this time because the firm and FDA are currently reviewing the data.

Reflections on the Ideal and the Real

- **Love is an ideal thing, marriage a real thing, a confusion of the real with the ideal never goes unpunished.**
  Johann Wolfgang von Goethe
- **New medicines and new methods of cure always work miracles for a while.**
  William Heberden (1710-1801)

Goals of Renal Replacement Therapy

Chronic Kidney Disease

- Renal replacement
- Improve organ function
- Ameliorate uremic syndrome
- Long term survival
- Quality of life

Acute Kidney Injury

- Renal support
- Improve organ function
- Do no harm
- Short term survival
- Recovery of kidney function

Renal Replacement Therapy in AKI

Theoretical Limitations

- Secluded solutes
- Concentration independent toxicity
- Non-fractional removal
- Intravascular access only
- Safety concerns

Knowledge Gaps

- When to initiate
- Identification toxic solutes
- Best indicator solutes
- Difficulty kinetics/mass balance
- When to stop