The RENAL Trial: Clinical Outcomes

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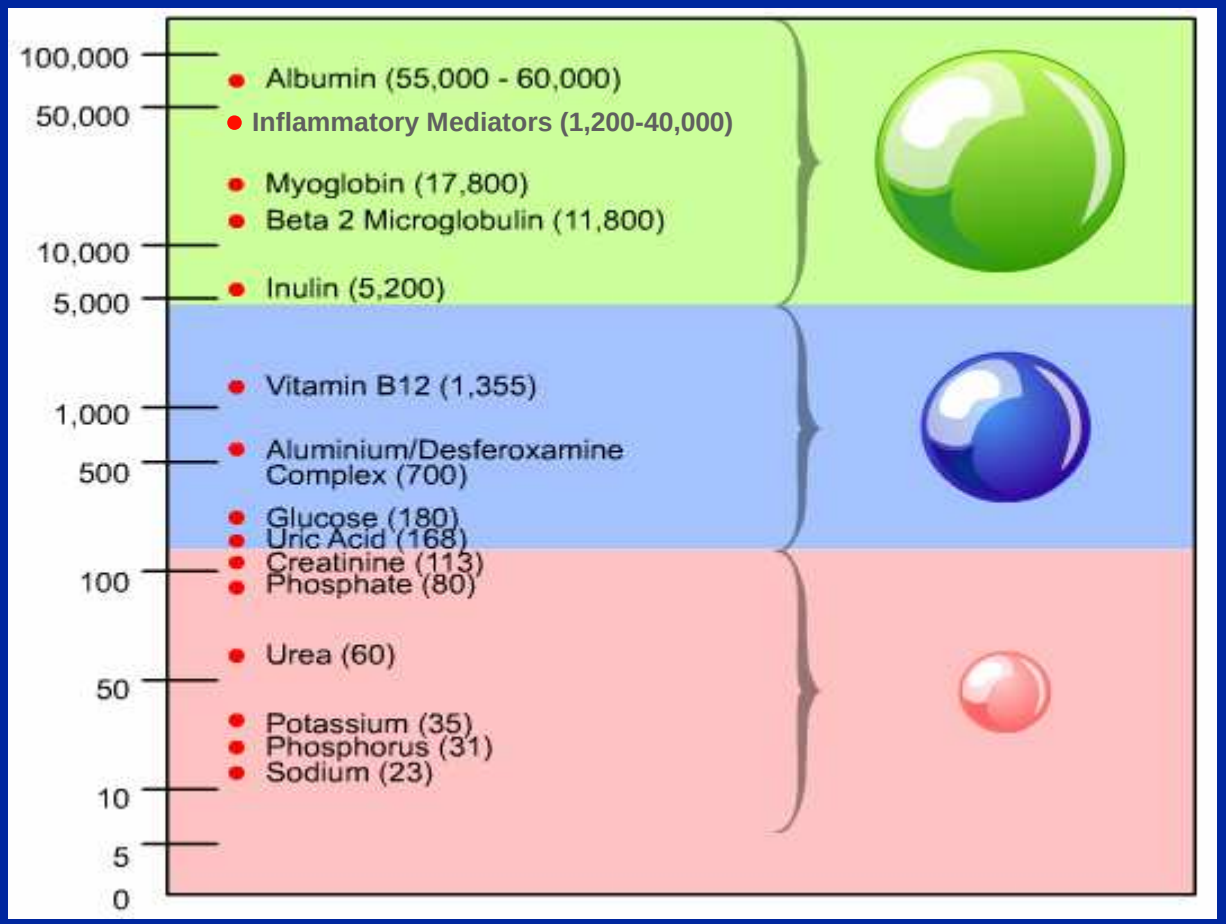
CRRT: Dose Considerations

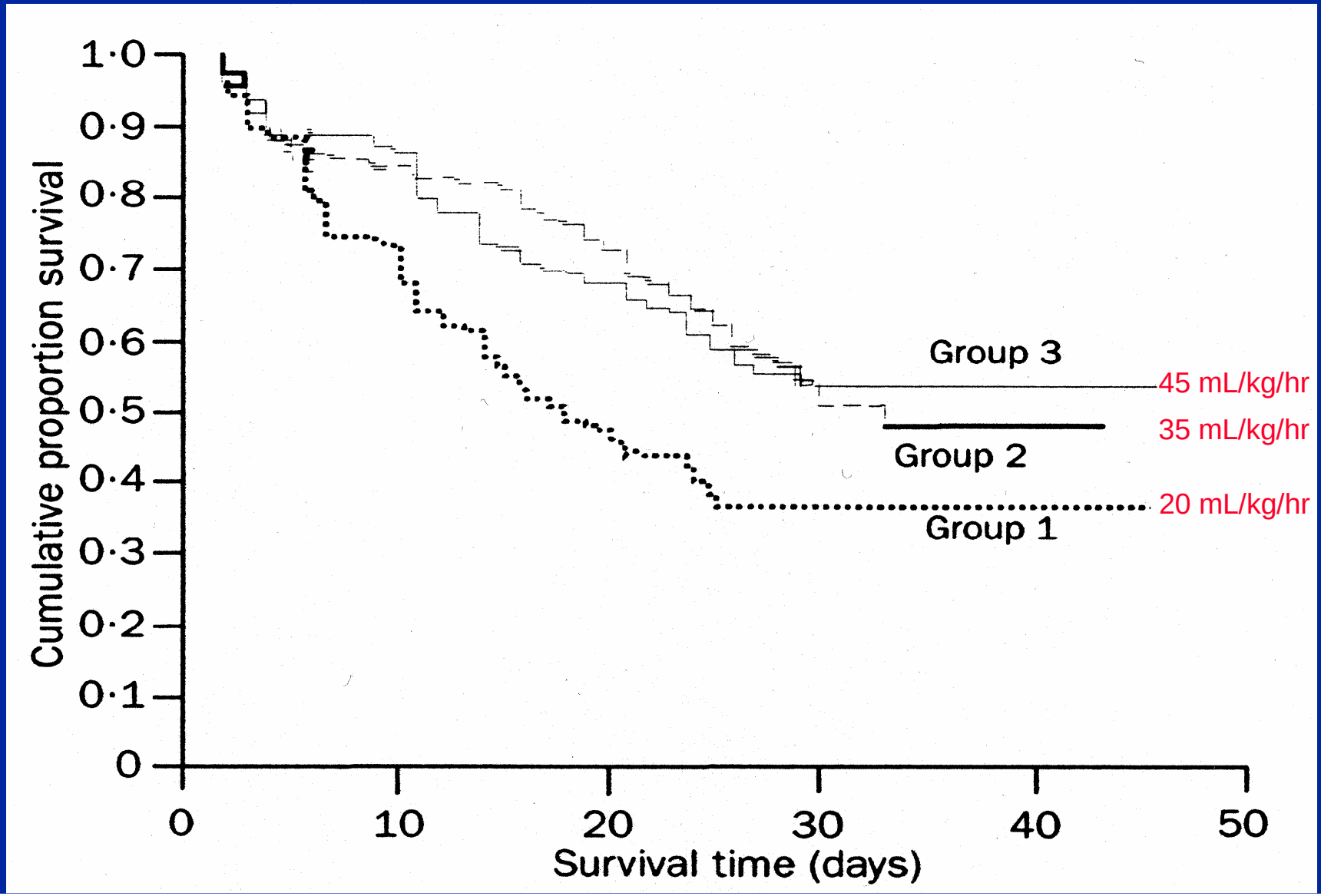
- Modality: spectrum of solutes removed
- Blood flow rate
- Effluent flow rate
- Replacement fluid and/or dialysate: flow rates; type of fluid
- Dilution mode (for convective therapies)
- Filter: membrane type; surface area
- Anti-coagulation delivery
- Access type and location

Solute Classes by Molecular Weight



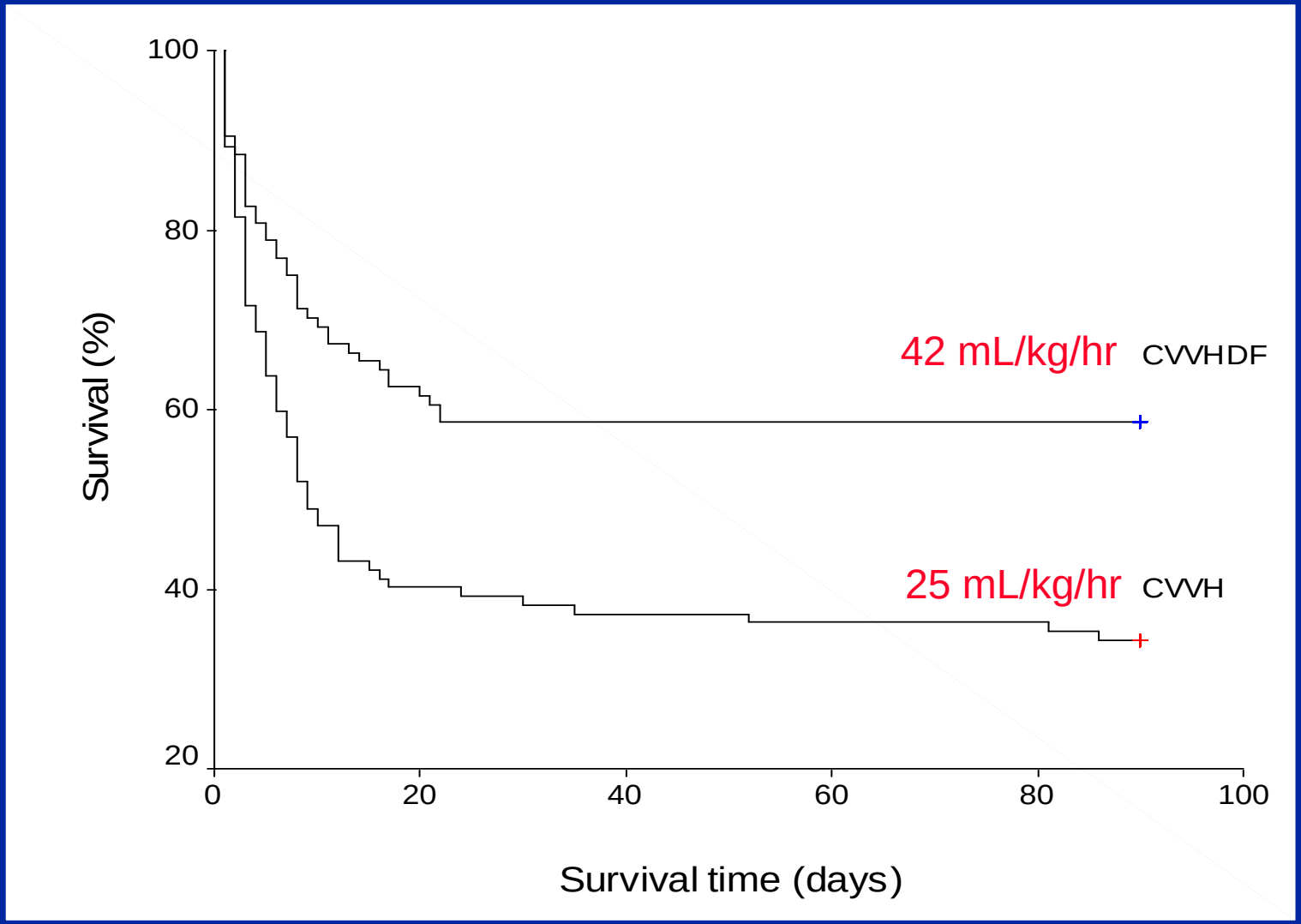
Survival in CVVH Dose Study

Ronco *et al.*, Lancet 2000



Survival in Pre-Dilution CVVH vs CVVHDF

Saudan et al, Kidney Int 2006



VA/NIH Acute Renal Failure Trial Network (ATN) Study

1124 patients
27 sites
3 years

Randomization

	Intensive Management Strategy (561 patients)	**Less Intensive Management Strategy (563 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

Modality Prescription in ATN Study

VA/NIH Trial Group, NEJM 2008

Hemodynamic Status	Modality	Number of Treatments	Percentage of Treatments
Stable*	IHD	5077	100%
Unstable**	CRRT	5967	95.2%
	SLED	299	4.8%

*: SOFA score: 0, 1, or 2

**: SOFA score: 3 or 4

Baseline Patient Characteristics in ATN Study

VA/NIH Trial Group, NEJM 2008

Table 1. **Baseline Characteristics of the Study Patients.***

Characteristic	Intensive Strategy (N=563)	Less-Intensive Strategy (N=561)	P Value†
Age — yr	59.6±15.3	59.7±15.2	0.97
Sex — no./no. with data (%)			
Male	409/563 (72.6)	384/560 (68.6)	0.13
Female	154/563 (27.4)	176/560 (31.4)	
Race or ethnic group — no./no. with data (%)‡			
White	415/563 (73.7)	420/560 (75.0)	0.43
Black	91/563 (16.2)	88/560 (15.7)	
Hispanic	44/563 (7.8)	33/560 (5.9)	
Other	13/563 (2.3)	19/560 (3.4)	
Renal function before onset of acute kidney injury			
Serum creatinine — mg/dl	1.1±0.4	1.1±0.3	0.71
Estimated GFR — no./no. with data (%)			
≥60 ml/min/1.73 m²	342/524 (65.3)	344/523 (65.8)	0.84
45–59 ml/min/1.73 m²	122/524 (23.3)	115/523 (22.0)	
30–44 ml/min/1.73 m²	60/524 (11.5)	64/523 (12.2)	
Cause of acute kidney injury — no./no. with data (%)			
Ischemia	440/536 (82.1)	431/541 (79.7)	0.31
Nephrotoxins	143/514 (27.8)	143/509 (28.1)	0.92
Sepsis	300/531 (56.5)	279/524 (53.2)	0.29
Multifactorial causes	317/534 (59.4)	309/527 (58.6)	0.81

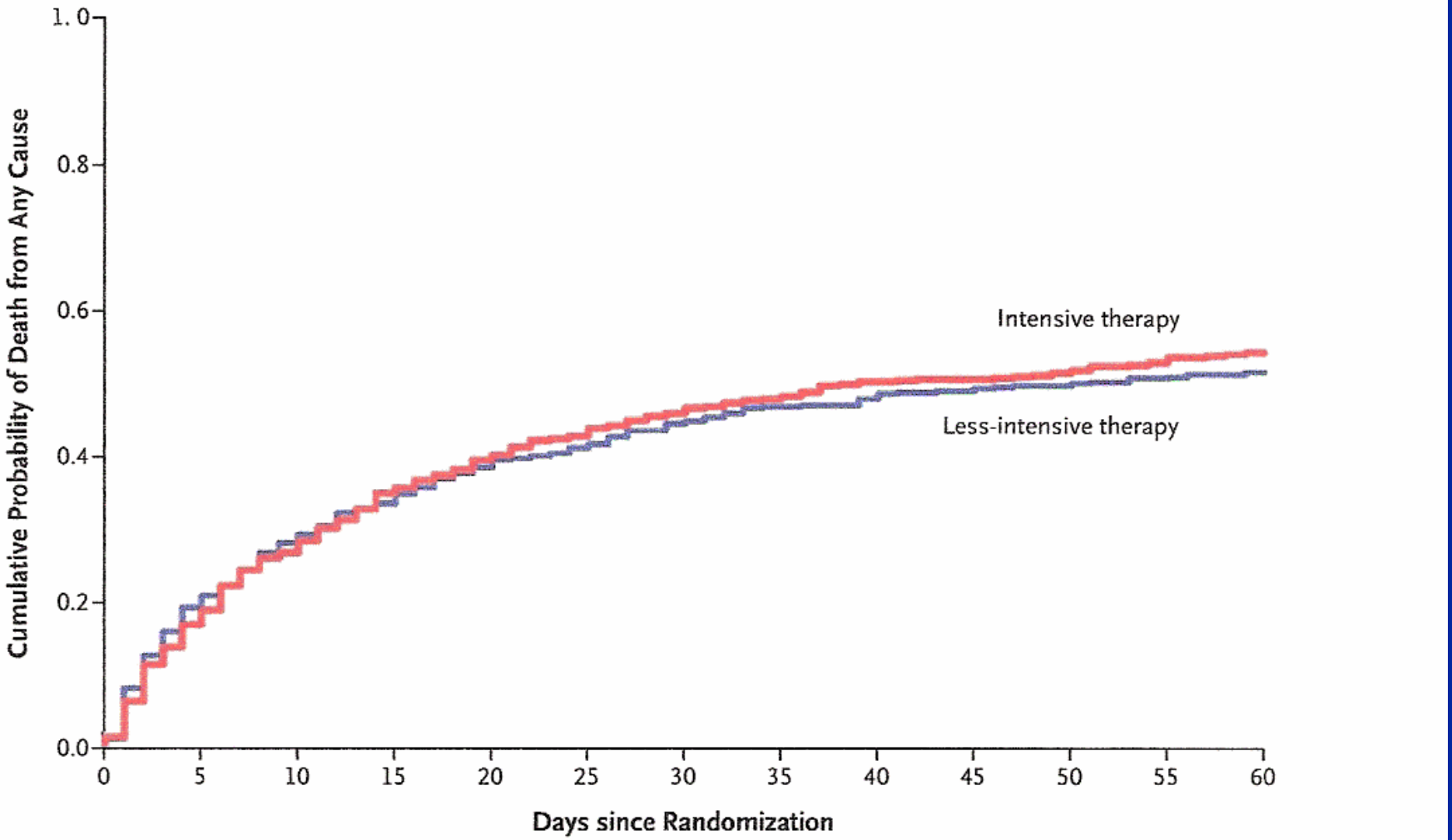
ATN Study: Characteristics of CRRT Group

VA/NIH Trial Group, NEJM 2008

Characteristic of Therapy	Intensive Strategy (N=563)	Less-Intensive Strategy (N=561)
Continuous venovenous hemodiafiltration		
Treatments provided — no.	3178	2789
Days of therapy — no./patient	7.8±6.4	7.3±5.9
Daily duration of therapy/patient — hr		
Median	20.9	21.0
Interquartile range	13.0–23.7	13.0–24.0
Blood flow — ml/min	150±33	140±40
Dialysate flow — ml/hr	1410±346	820±250
Replacement flow — ml/hr	1390±316	830±249
Net ultrafiltration — ml/hr	130±135	130±189
24-hr effluent volume — liters	49.6±22.4	30.5±14.3
Effluent flow — ml/kg/hr		
Prescribed	36.2±3.8	21.5±4.3
Delivered	35.8±6.4	22.0±6.1
Mean daily BUN — mg/dl	33±18	47±23
Anticoagulant — no. of treatments (%)		
None	1736 (54.6)	1666 (59.7)
Heparin	645 (20.3)	530 (19.0)
Citrate	649 (20.4)	495 (17.7)
Other	148 (4.7)	98 (3.5)
Percent of prescribed dose of therapy delivered	89±39	95±35
Isolated ultrafiltration		
No. of treatments	40	219
Net ultrafiltration — liters/treatment	2.1±1.3	2.7±1.0

ATN Study: Primary Outcome

VA/NIH Trial Group, NEJM 2008



Major Criticisms of Study

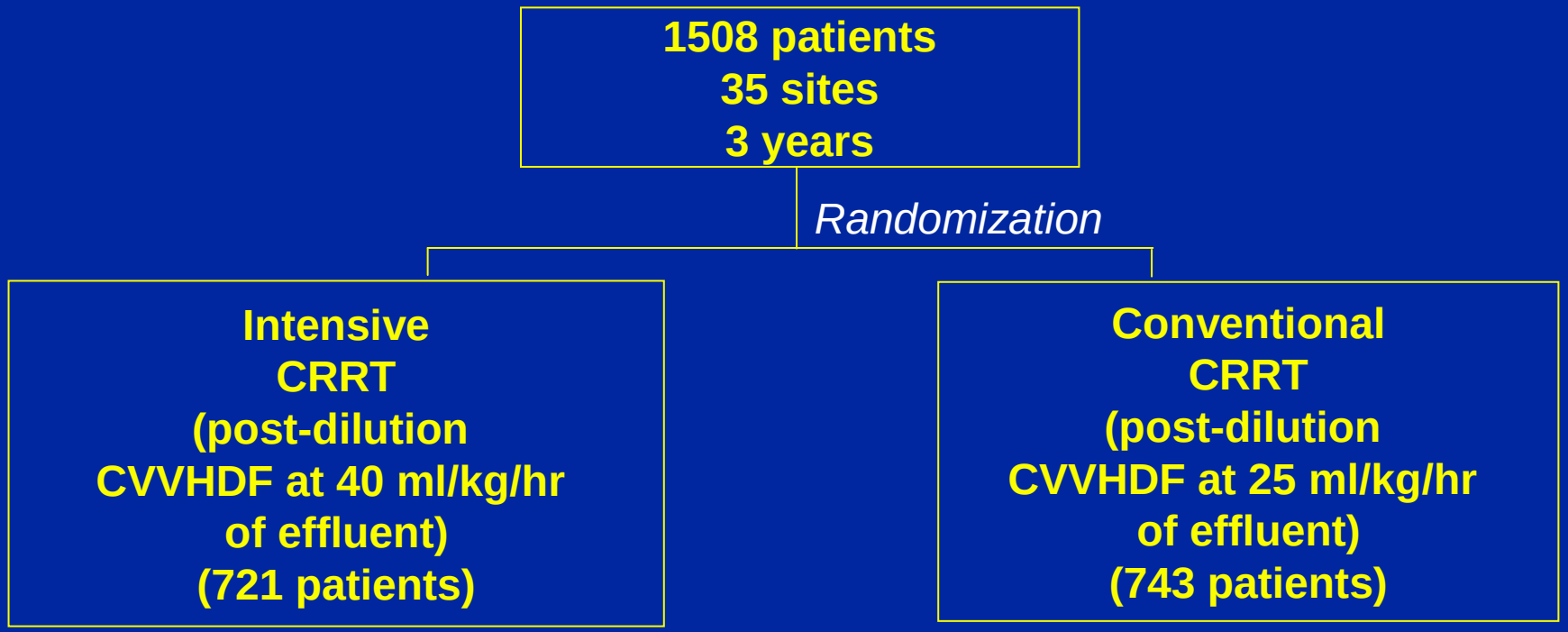
- Effective CRRT dose was significantly lower than Ronco and Saudan studies
- Late initiation of RRT
- Potential independent effect of fluid balance on outcome
- High percentage of patients with RRT “pre-exposure” (when patients were most critically ill)
- Low rate of renal recovery (despite exclusion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

Comparison of Major CRRT Dose Trials

	Ronco[1]	Saudan[2]	Tolwani[3]	ATN[4]
Number of patients	425	206	200	1124
Multi-center RCT	No	No	No	Yes
CKD (%)	NA	33	42	Exclusion
Predominant AKI cause	Surgical	Sepsis	Sepsis	Ischemia
APACHE II	~23	25	26	~29
Initiation BUN (mg/dL)	53	83	75	65
Modality	post CVVH	pre CVVHDF	pre CVVHDF	pre CVVHDF
% Convective	100	~60	43-44	50
Prescribed dose (mL/kg/h)	20/35/45	25/42	20/35	20/35
“Diluted” dose (mL/kg/h)	20/35/45	~20/37	~17/29	~17/27
ICU wait (days)	NA	NA	8	6.9

1: Lancet 2000; 2: Kidney Int 2006; 3: JASN 2008; 4: NEJM 2008

R.E.N.A.L. Trial

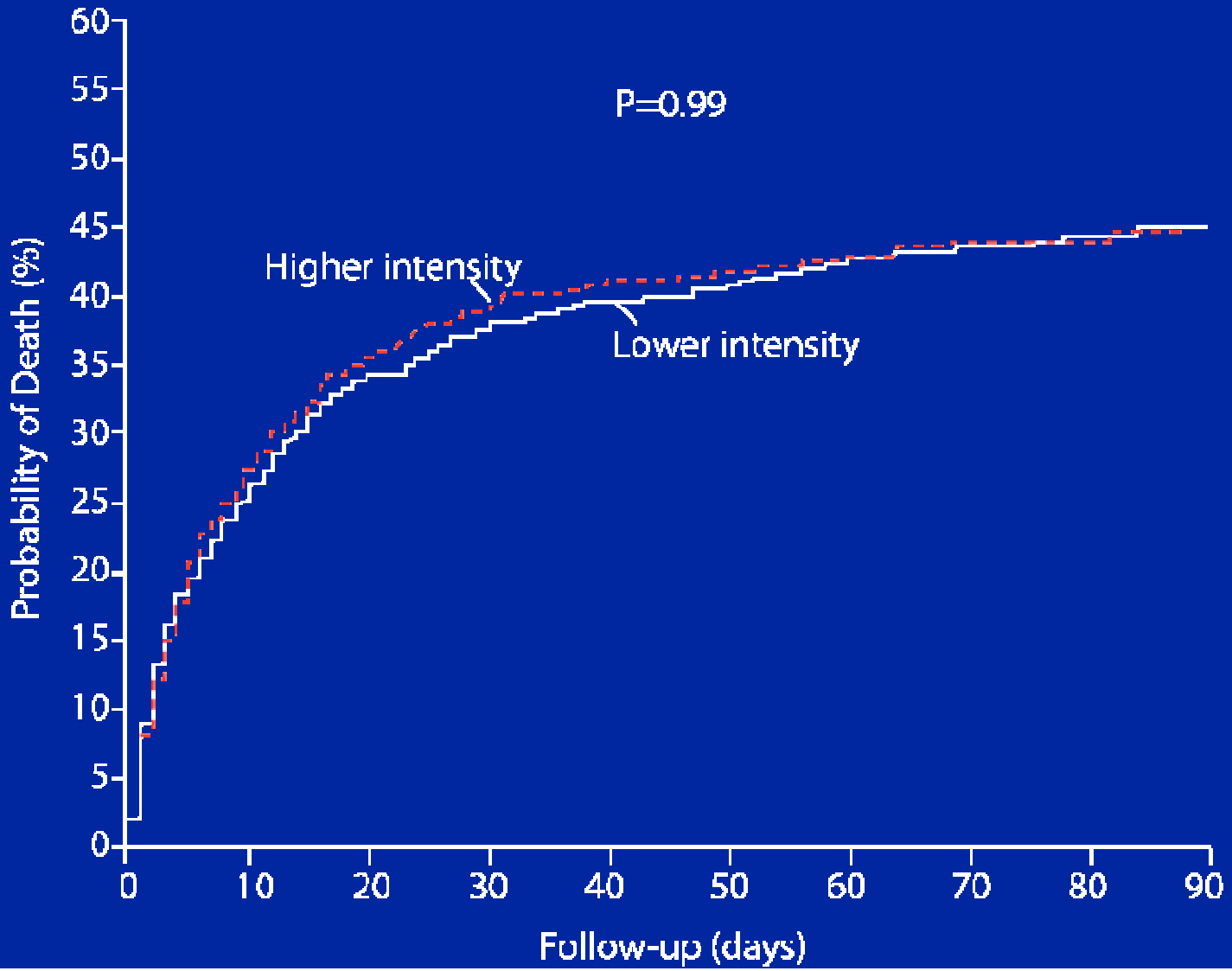

1508 patients
35 sites
3 years
Randomization
Intensive
CRRT
(post-dilution
CVVHDF at 40 ml/kg/hr
of effluent)
(721 patients)
Conventional
CRRT
(post-dilution
CVVHDF at 25 ml/kg/hr
of effluent)
(743 patients)

Process of Care in RENAL

	Low dose	High dose	p
Number of patients	743	722	
Total number of study days	4190	4179	
Mean Days of study treatment/patient	5.9 (7.7)	6.3 (8.7)	0.35
Daily effluent (mL/hr)/patient	1772 (1257)	2698 (1154)	<0.001
Dose delivered mL/kg/hr	22.0 (17.8)	33.4 (12.8)	<0.001
% of prescribed	88	84	<0.001
Filters/day/patient	0.84 (0.81)	0.93 (0.86)	<0.001
Patients treated with IHD in ICU	52 (7.0%)	55 (7.6%)	0.64

Mortality Outcomes in RENAL

Bellomo et al, NEJM 2009



Comparison of RENAL with ATN

Variable	RENAL	ATN
Enrolled	1508	1124
Mean age (yrs)	64.5	59.7
Ventilation	74%	81%
Sepsis (%)	49.5	63
Urea at baseline (mg/dL)	65	66
APACHE II	~26	26.4
Total SOFA score	7.55	7.40
CRRT as initial therapy (%)	100	~50
ICU Days before RRT initiation	2.1	6.7

Comparison of RENAL with ATN

Variable	RENAL	ATN
Mortality day 90	44.7%	
Mortality day 60		52.5%
ICU LOS (at 28 days)	12	?
Hospital LOS (days)	25.2	?
Dialysis dependence @day 28	13.3%	45.2%
Dialysis dependence @day 60		24.6%
Dialysis dependence @day 90	5.6%	

RENAL Trial: Major Points

- Initial response to RENAL has been until recently focused largely on the negative primary outcome result
- HOWEVER, survival and renal recovery outcomes were substantially better in this trial compared to previous AKI studies involving similar patient populations
- The excellent outcomes in RENAL were likely associated with:
  - The nearly exclusive use of CRRT while patients were in the ICU
  - Early initiation of therapy

Effect of AKI and CKD on Progression to ESRD

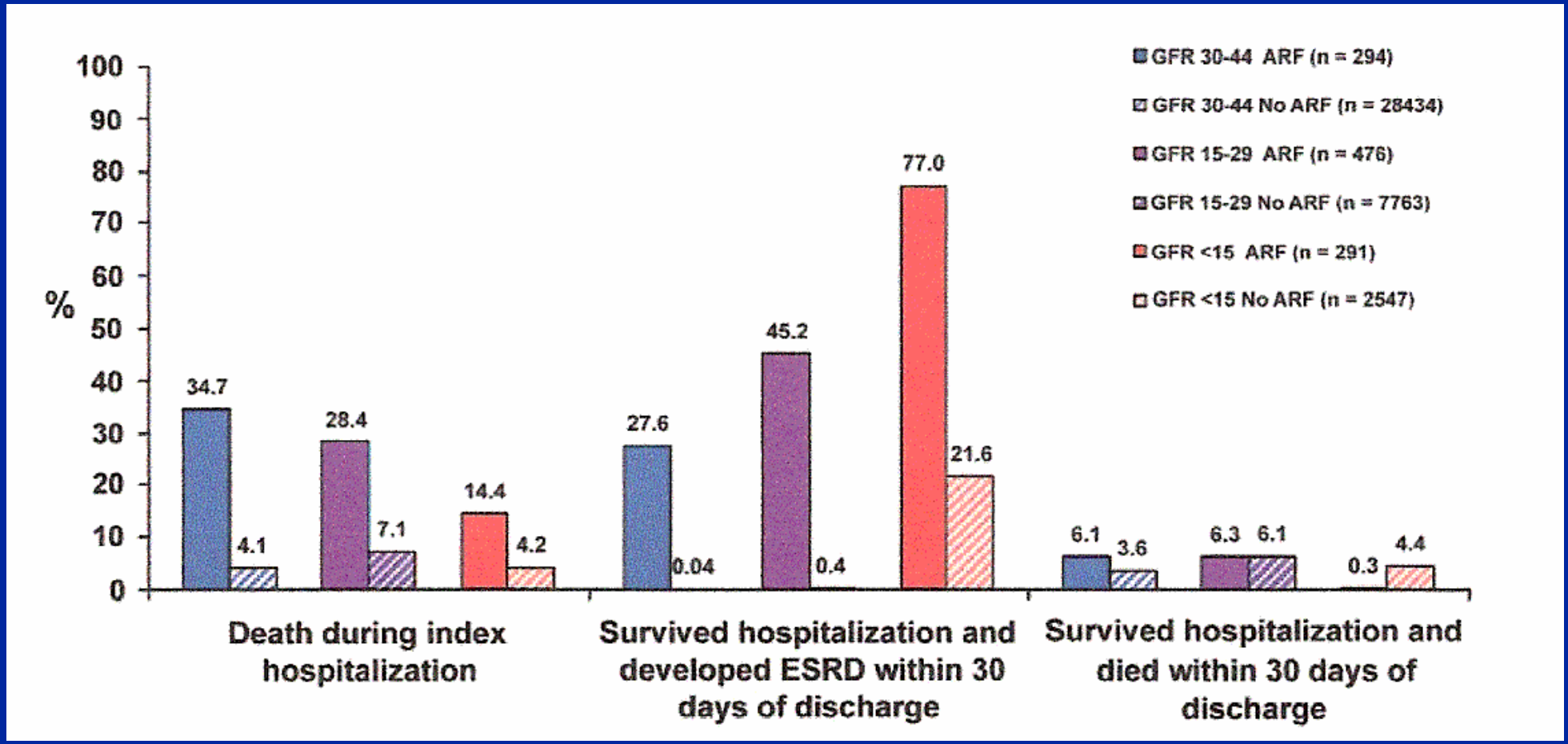
Ishani et al, JASN 2008

Baseline CKD		
yes	25.11	6.82 (6.05 to 7.67)
no	2.60	1.00
AKI		
yes	43.35	6.74 (5.90 to 7.71)
no	4.10	1.00
AKI and CKD		
both AKI and CKD	79.45	41.19 (34.58 to 49.08)
AKI only	24.52	13.00 (10.57 to 15.99)
CKD only	19.88	8.43 (7.39 to 9.61)
no AKI or CKD	2.08	1.00

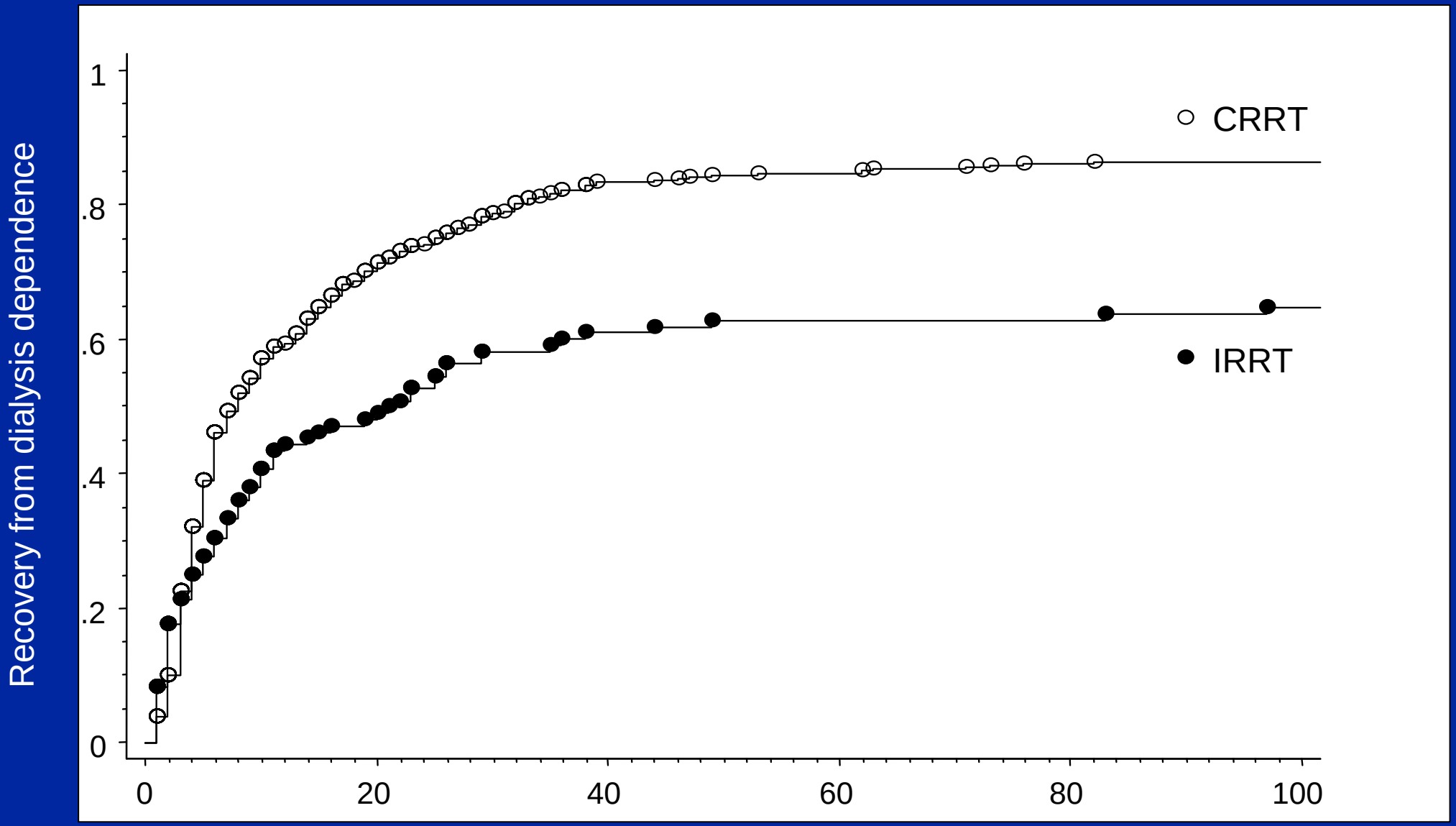
[a]Obtained using Cox proportional models with adjustment for age, gender, race, diabetes, and hypertension.

Acute on Chronic Kidney Failure: Effect on Outcome

Hsu et al, CJASN 2009



Recovery from Dialysis Dependence: BEST Kidney



Uchino *et al.*, Int J Artif Organs 2007

Post-Operative AKI: Predictors of Renal Recovery

Lin et al, Am J Surg 2010

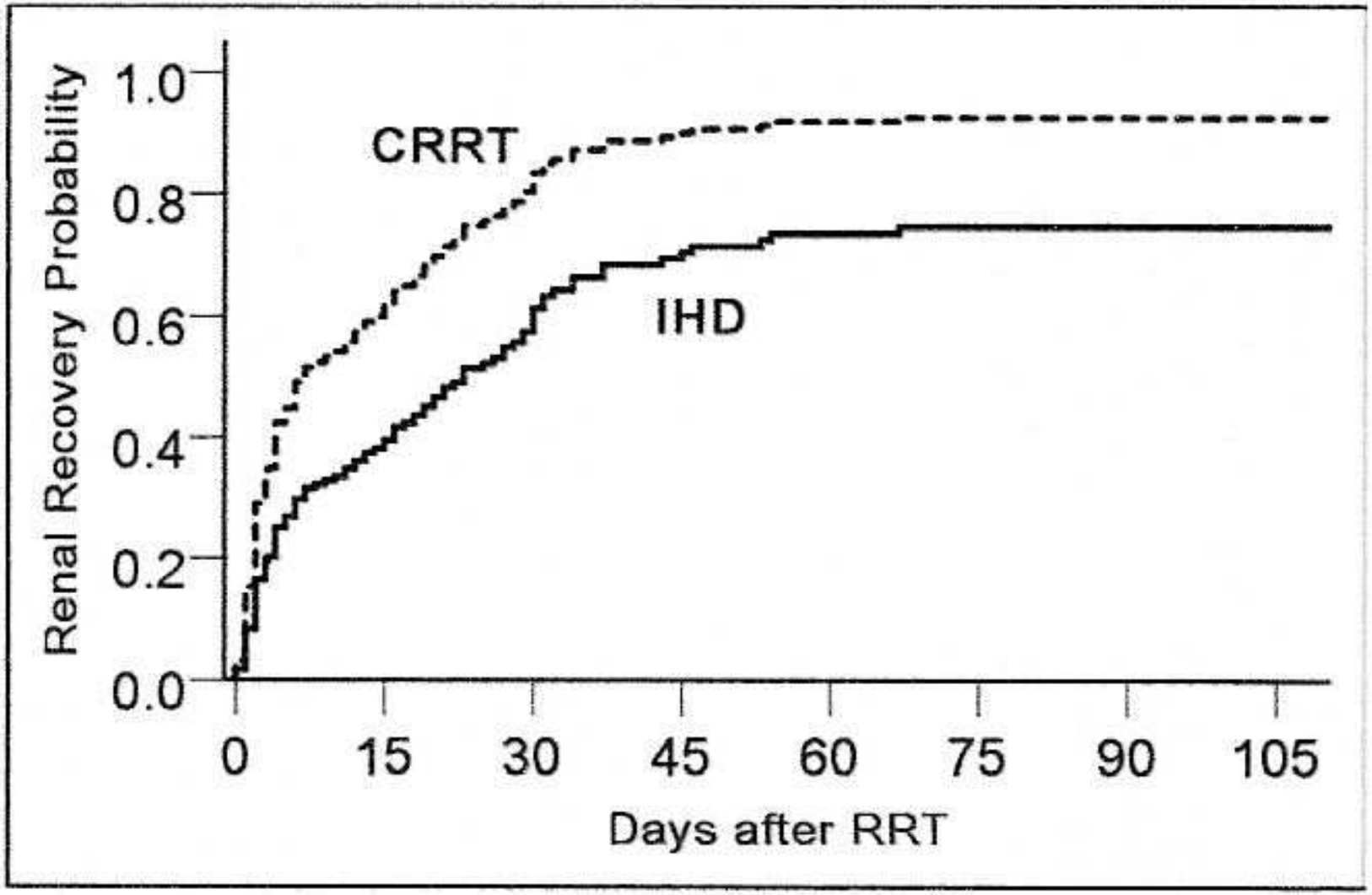
Table 5 Multivariate Cox hazard regression model for the independent factors of subsequent renal recovery up to 90 days after RRT commencement in survivors

Factor	β	χ^2	HR (95% CI)	P
SICU admission				
sCr (mg/dL)	−.166	6.367	.847 (.744–.964)	.012
RRT commencement				
SAPS II score	−.038	14.082	.963 (.944–.982)	<.001
IE score	−.023	8.049	.978 (.963–.993)	.005
RRT modality				
CRRT use	.692	8.806	1.998 (1.265–3.155)	.003

β = β coefficients; HR = hazard ratio; IE = inotropic equivalent; sCr = serum creatinine.

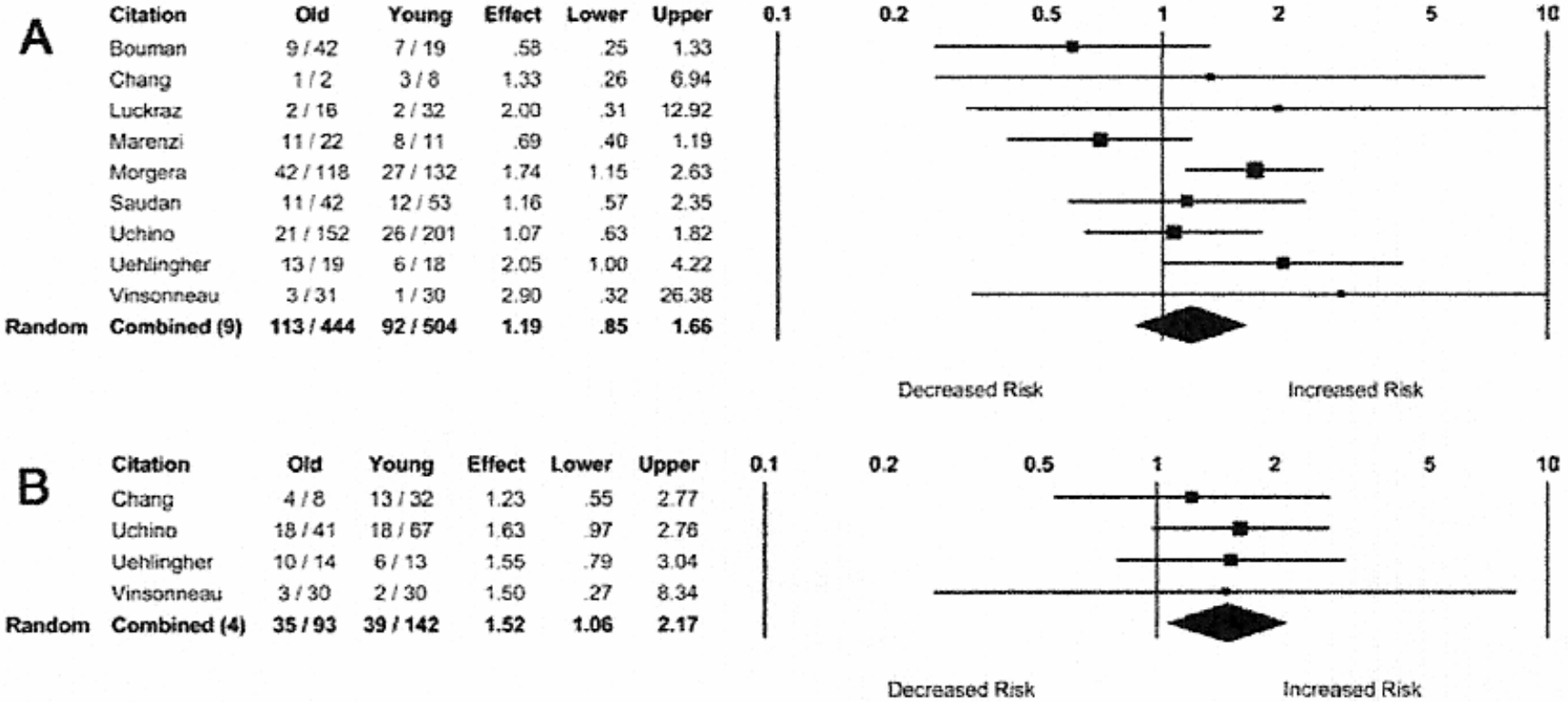
Renal Recovery after Post-Operative AKI

Lin et al, Am J Surg 2010



Effect of RRT Modality on Renal Recovery After AKI in Elderly Patients

Schmitt et al, AJKD 2008



Timing of RRT Initiation: Effect on Outcome

Payen et al, Crit Care 2008

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.

Timing of RRT Initiation: Effect on Outcome

Bagshaw et al, J Crit Care 2008

Timing of Initiation	Crude Mortality (%)	OR for Death
Early (< 2 days)	58.9	1.0
Delayed (2-5 days)	62.1	1.19
Late (> 5 days)	72.8	2.20*

*: Significantly greater than Early group

Early vs Late RRT Initiation According to RIFLE*

Shiao et al, Crit Care 2010

Relative risk (RR) for in-hospital mortality using Cox proportional hazards model

RIFLE categories	Patient number (%)	RR*	95% CI	*P*
RIFLE - R	29 (29.6)	1.000	Reference	
RIFLE - I	27 (27.6)	2.121	0.913-4.927	0.080
RIFLE - F	20 (20.4)	3.194	1.262-8.085	0.014

* Adjusted for age (≧ 65 years vs < 65 years), cardiac failure (with vs without), pre-RRT SOFA scores, and RRT modality (CVVH vs hemodialysis); CVVH = continuous venovenous hemofiltration; 95% CI = 95% confidence interval; RR = relative risk; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment.

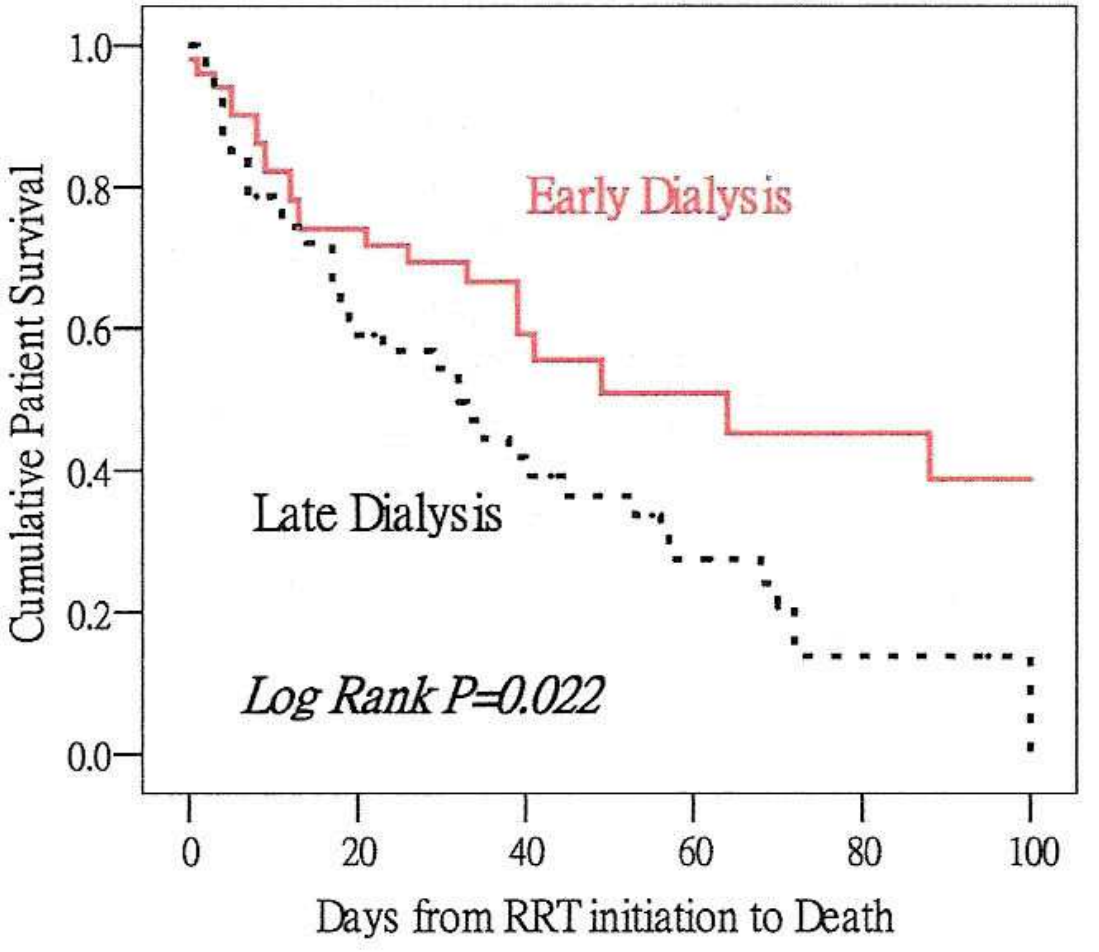
*: Early RRT Initiation: RIFLE “R” stage

*: Late RRT Initiation: RIFLE “I” or “F” stage

Early vs Late RRT Initiation According to RIFLE

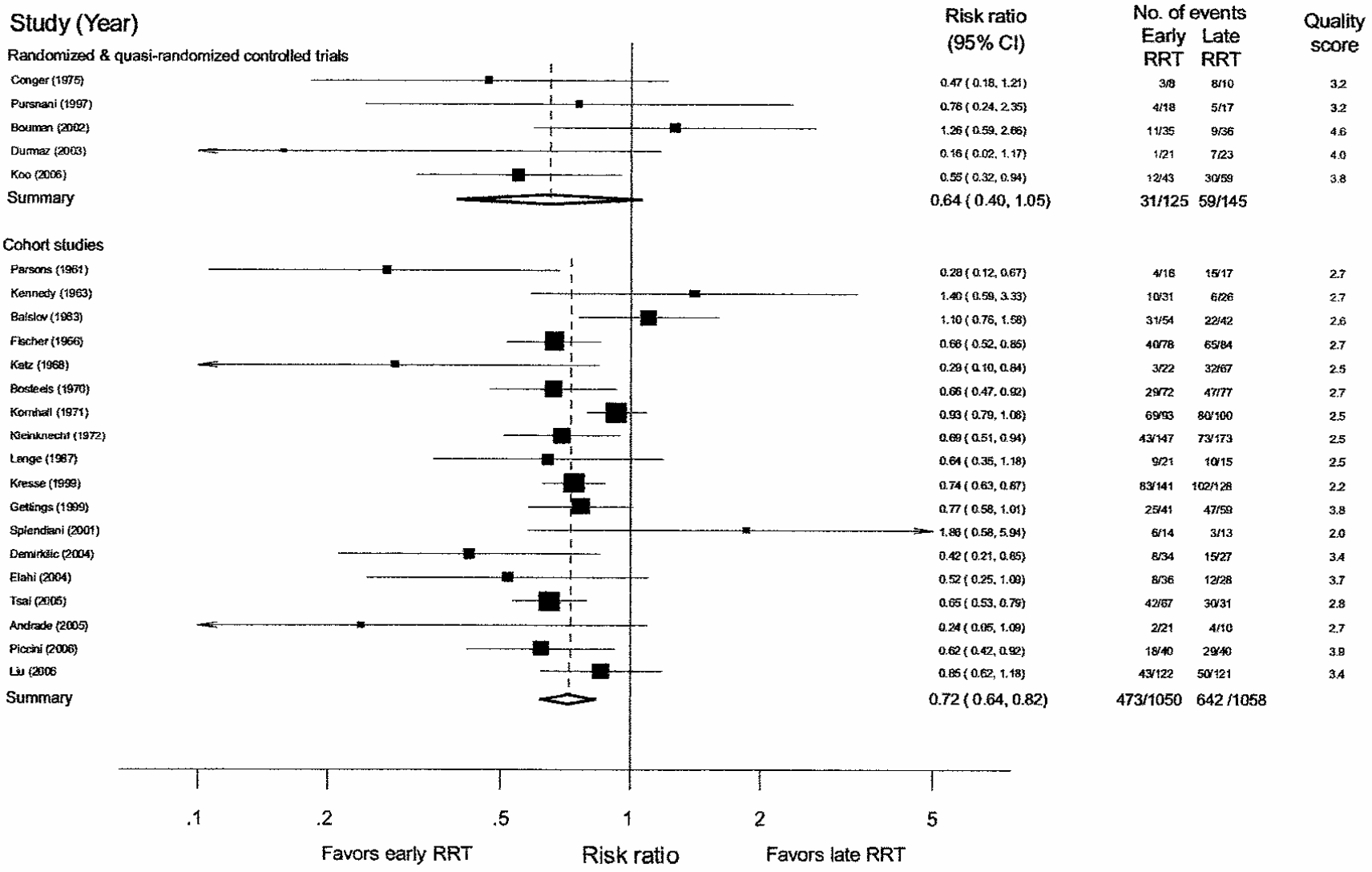
Shiao et al, Crit Care 2010

Figure 2



Timing of RRT Initiation: Meta-Analysis

Seabra et al, AJKD 2008

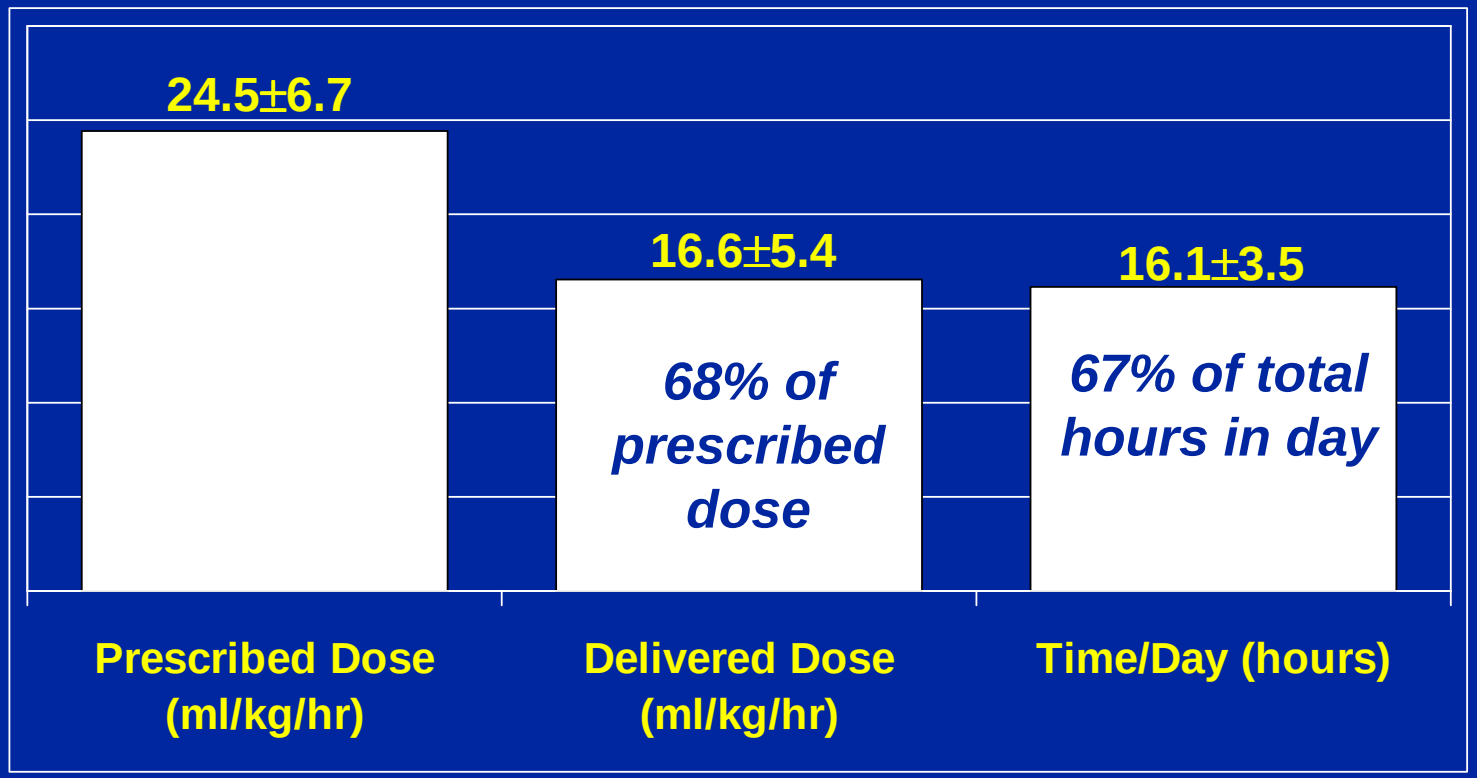


Delivery of Prescribed CRRT Dose

- Ronco (heparin)
  - % delivery ≈ 95% (compensatory UF increases)
  - Filter changed every 24 hrs
- Saudan (heparin)
  - Delivered dose during first 24 hrs = 83%
  - Filter changed every 24 hrs for first two days
- Tolwani (citrate RCA in 91% of patients)
  - Patients achieving >80% of prescribed dose = 79%
- ATN (no anticoagulation in 60% of patients)
  - Average daily CRRT duration = 21 hrs (88%)
- RENAL (heparin): 85% delivery of prescribed dose

CRRT Prescription vs Delivery

Venkataraman et al, J Crit Care, 2002



Research

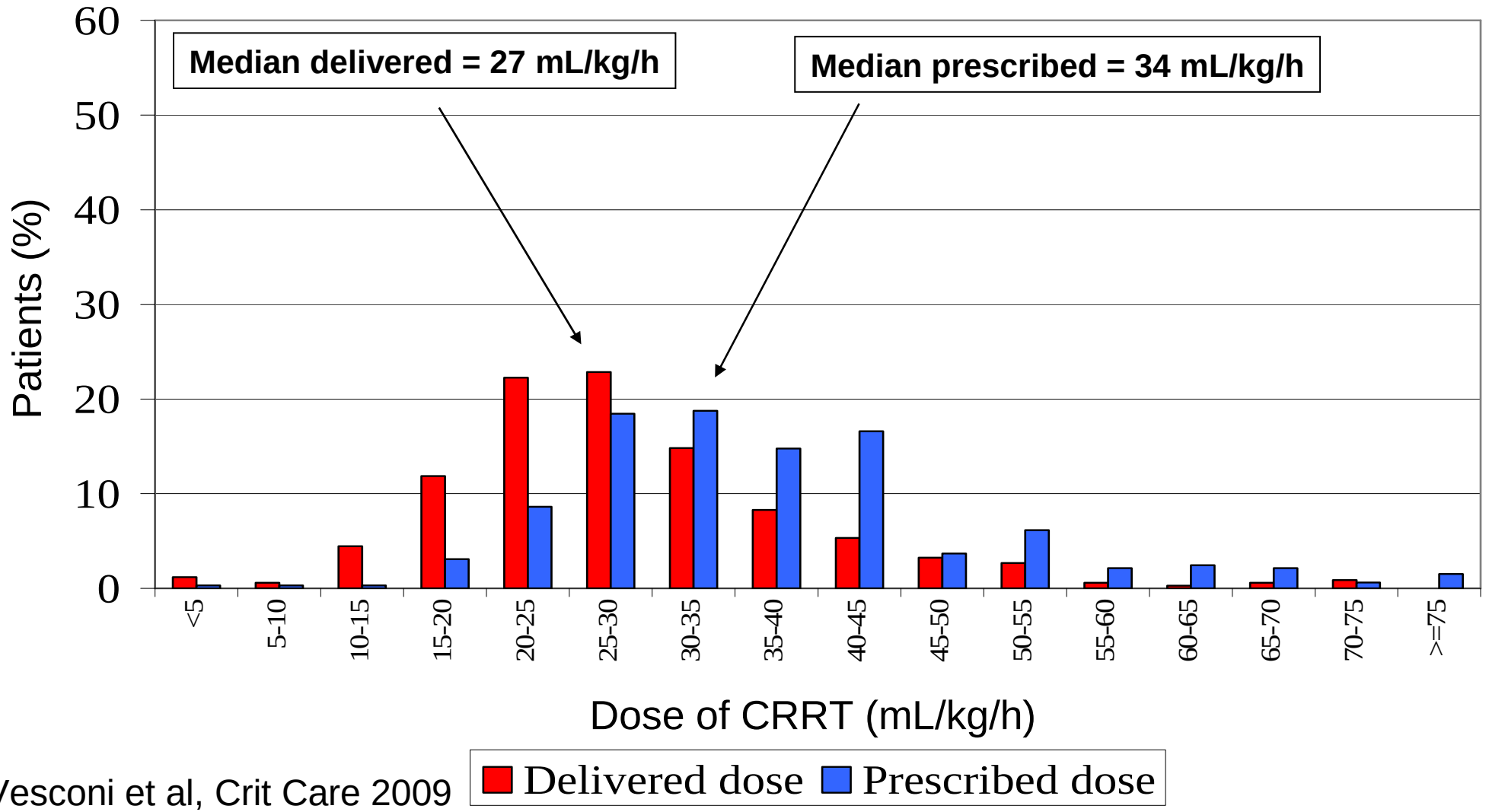
Open Access

Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury

Sergio Vesconi[1*], Dinna N Cruz[2*], Roberto Fumagalli[3], Detlef Kindgen-Milles[4], Gianpaola Monti[1], Anibal Marinho[5], Filippo Mariano[6], Marco Formica[7], Mariano Marchesi[8], Robert René[9], Sergio Livigni[10], Claudio Ronco[2] for the DOse REsponse Multicentre International collaborative Initiative (DO-RE-MI Study Group)

- A prospective multicentre observational study in 30 intensive care units (ICUs) in eight countries from June 2005 to December 2007.
- The observational **DO**se REsponse **M**ulticentre **I**nternational collaborative initiative (DO-RE-MI) analyzes how different modalities of RRT are truly chosen and executed in the field:
- Main Results:
  - CVVHDF remains the most commonly used technique (49%)
  - Clotting and clinical problems represent the most common causes of treatment interruption
  - During RRT, a large variability of administered doses was observed among patients and also within the same patient in different days.
  - In a large proportion of cases, while prescription is around 35ml/kg/h, effective delivery of dose is approximately 20% less

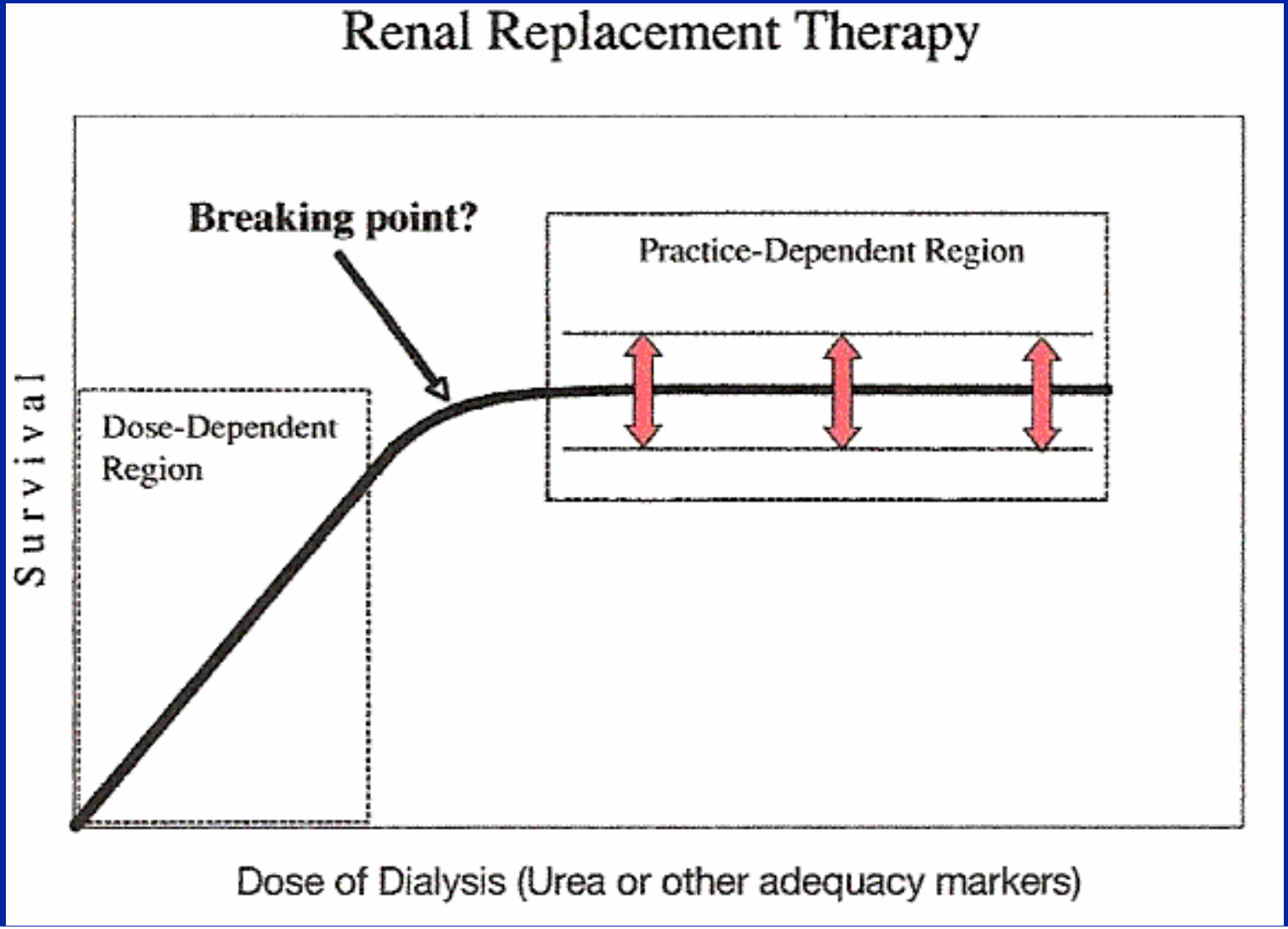
DoReMi Database (N=865)



Vesconi et al, Crit Care 2009

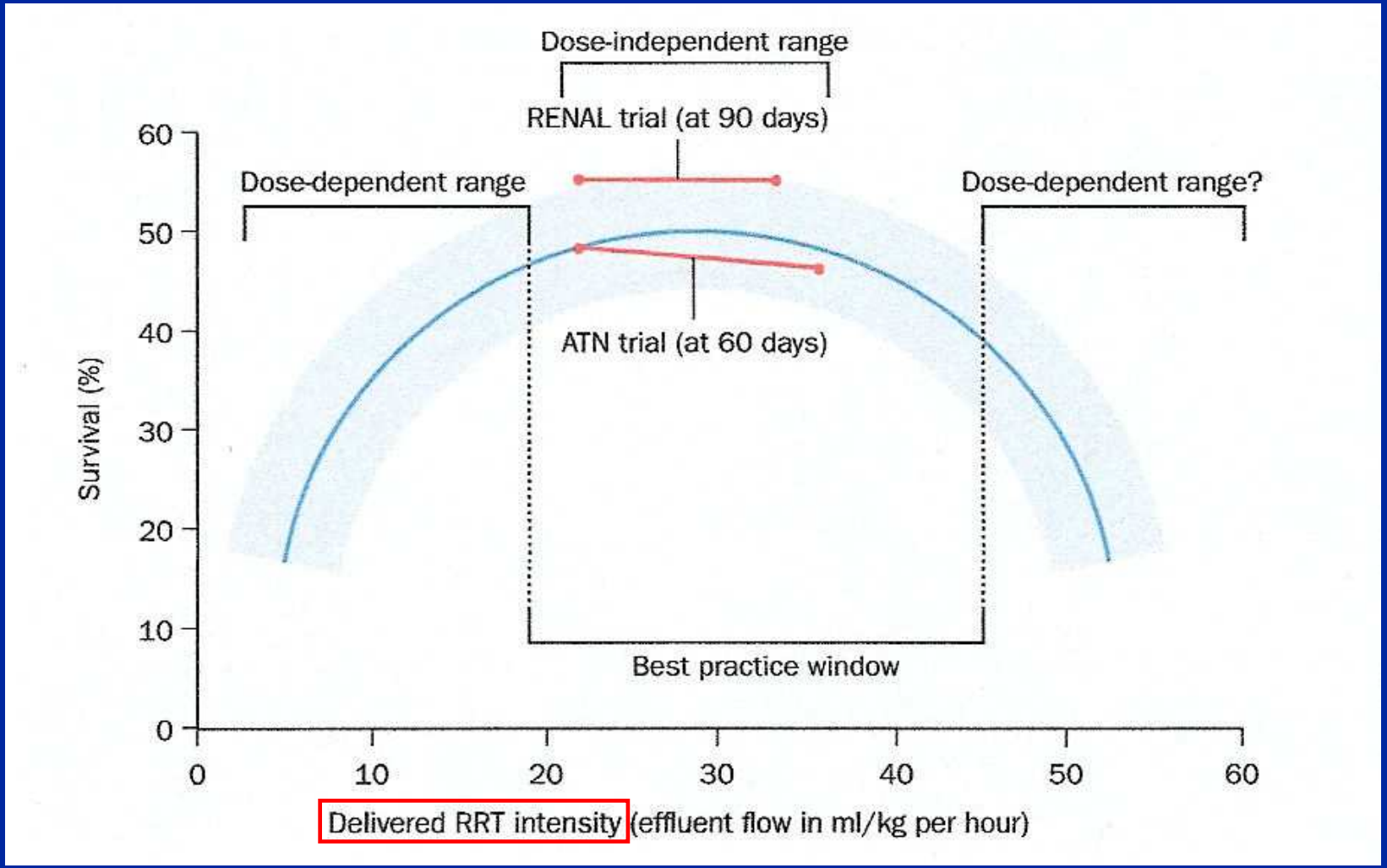
Effect of Dialysis Dose on Patient Outcome

Ronco, Int J Artif Organs 2008



Delivered CRRT Dose: Best Practice Window

Kellum and Ronco, Nature Revs Nephrol 2010



Assessment of Adequate RRT Dose Delivery in AKI

From Palevsky, NEJM 2009

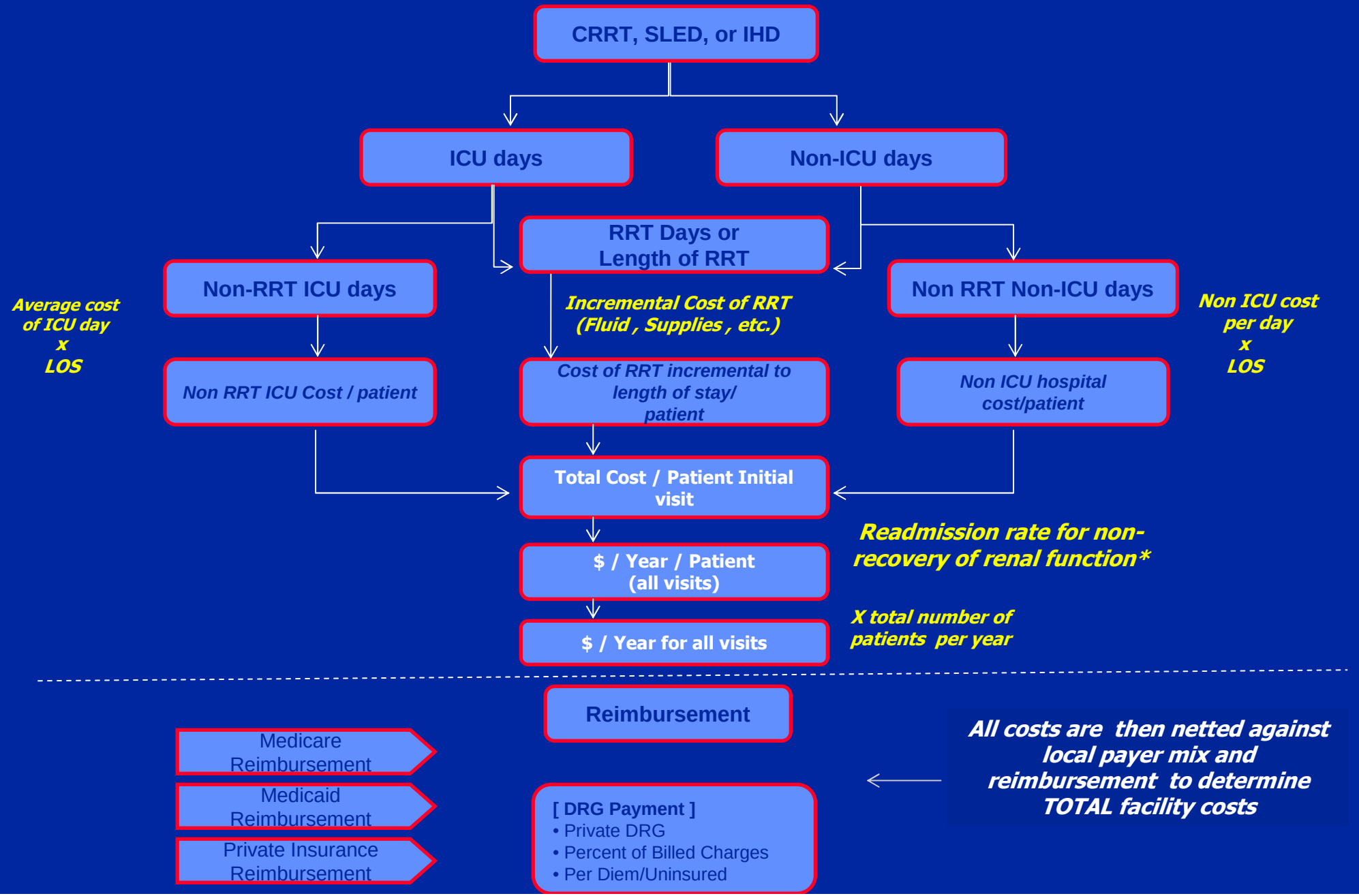
- "In fact, the delivered dose of dialysis for acute kidney injury is frequently not even assessed, highlighting a need to apply the tools of quality assurance and performance improvement that are routine in outpatient dialysis to the practice of renal replacement therapy for acute kidney injury. Adopting such tools will ensure that we provide treatment that is at least as intensive as that provided in the lower-intensity groups in these two studies."

CRRT-Associated Mortality in Major RCTs

Clinical Trial	Comparison	APACHE II	Endpoint	Mortality
Ronco et al (2000)	CRRT Dose	22	15-day[2]	59%[3]
Mehta et al (2001)	IHD vs CRRT	25.5	Hospital	66%
Augustine et al (2004)	IHD vs CRRT	-	Hospital	68%
Saudan et al (2006)	CRRT Dose	25	90-day	66%[3]
Vinsonneau et al (2006)	IHD vs CRRT	25	60-day	68%
Lins et al (2008)	IHD vs CRRT	27	Hospital	58%
Tolwani et al (2008)	CRRT Dose	26	Hospital	60%[3]
ATN Trial (2008)	Dialysis Dose	26.3	60-day	52.5%[4]
RENAL Trial (2009)	CRRT Dose	~26[1]	90-day	45%

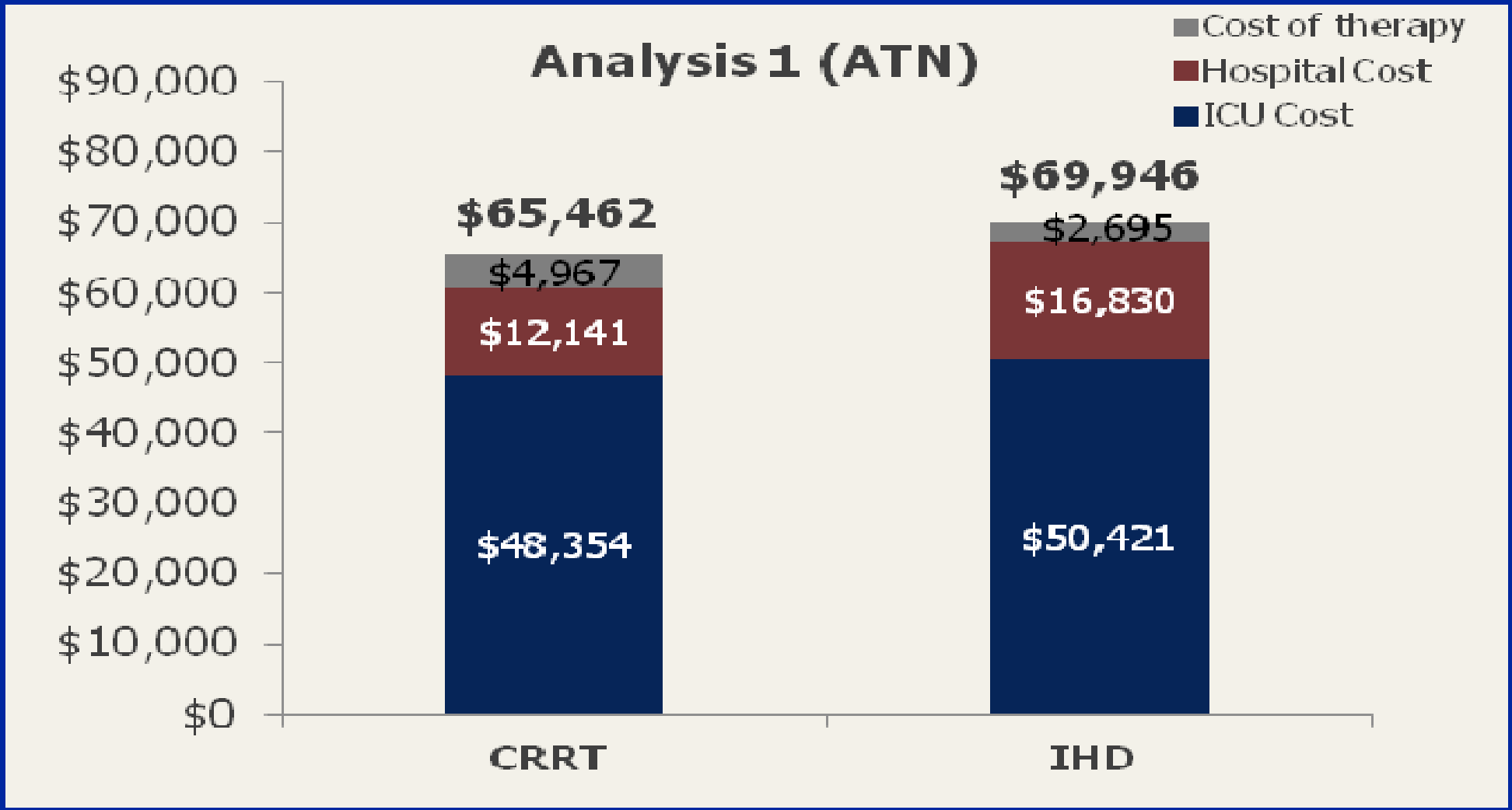
1: APACHE III score 102-103
2: After CRRT cessation
3: Mortality in low-dose group
4: Overall (CRRT + IHD) mortality

AKI Health Economic Model



Facility Specific Cost Outcomes (200 bed ICU)

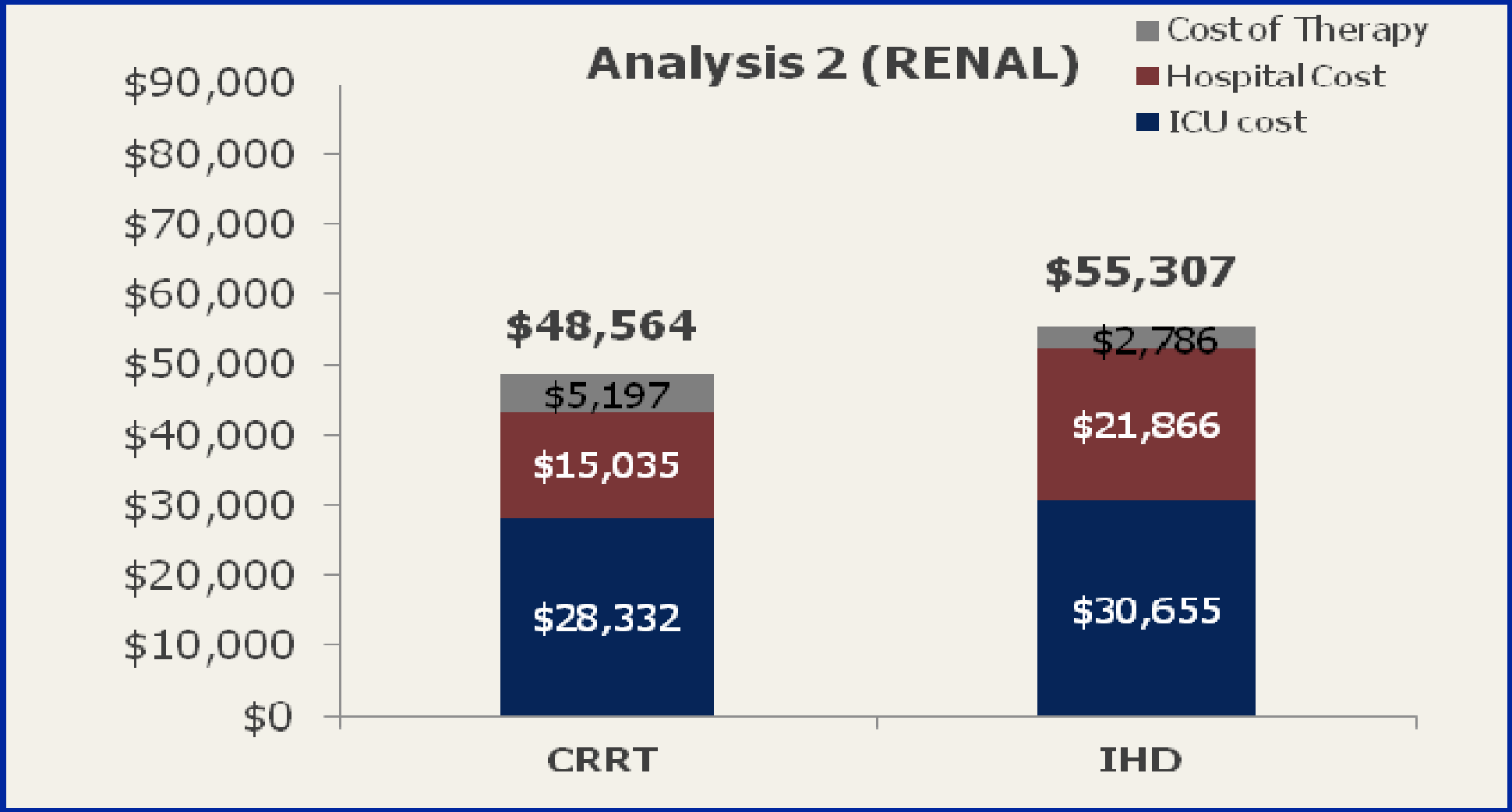
Total Cost per Stay per Patient



Regardless of which trial is used as the model, RRT-specific costs are a small fraction of the total hospital costs for the AKI population

Facility Specific Cost Outcomes (200 bed ICU)

Total Cost per Stay per Patient



Regardless of which trial is used as the model, RRT-specific costs are a small fraction of the total hospital costs for the AKI population

Summary

- Recent multicenter RCTs have failed to confirm earlier trials suggesting a benefit of higher CRRT dose in critically ill patients
- Several differences exist among the various CRRT dose/outcome trials, including total effluent dose, convective contribution, dilution mode, and timing of treatment initiation
- All studies used a “one size fits all” approach and were based on small solute clearance
  - These differences make it very difficult to establish a “standard” CRRT dose in an individual patient
- Routine assessment of delivered CRRT dose should be an integral aspect of patient management in the future

Summary: Health Economics

- Modality choice for AKI in the ICU remains controversial although recent multi-center RCTs confirm that CRRT is standard treatment for hemodynamically unstable patients
- The role of SLED remains unclear and the claim that it is clinically “equivalent“ to CRRT in critically ill AKI patients has **not** been validated
  - SLED and its variants continue to be limited by the absolute lack of clinical outcome data from RCTs
- In light of the small incremental costs related to RRT, AKI modality choice should be driven primarily by the **clinical needs of the patient**
- Future cost analyses should focus not only on short-term costs but also long-term costs, including those related to ESRD “cost avoidance”