

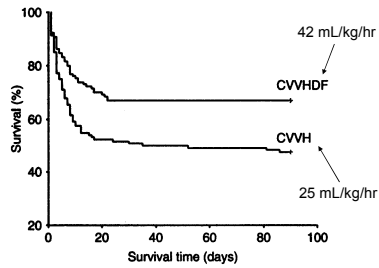
Treatment Parameters in Comparative Study
of CVVH and CVVHDF
Saudan et al, Kidney Int 2006

Table 2 | Intervention data

	CVVH group (n=102)	CVVHDF group (n=104)
Mean prescribed ultrafiltration dose (ml/kg/h)	25 ± 5	24 ± 6
Mean prescribed dialysis dose (ml/kg/h)	—	18 ± 5
Bicarbonate replacement fluid (%)	58	52
Delivered dose during first 24 h (%)	87 ± 11	83 ± 16
T ^o after 24 h CRRT	36.6 ± 0.7	36.7 ± 0.7
CRRT-free days at day 28 (days)	22 (9)	23 (7)
Mechanical ventilation-free days at day 28 (days)	19 (10)	21 (9)
Cumulative NA dose (mg)	35 (1-172)	11 (0-107)
Duration of ICU stay (days)	6 (2-10)	8 (4-16)

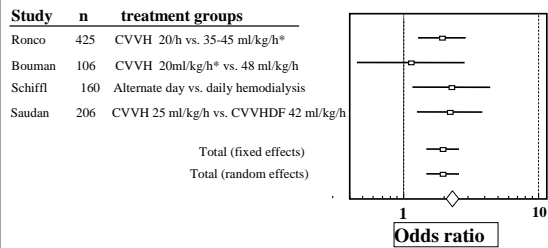
CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; ICU, intensive care unit; NA, noradrenaline; T^o, temperature.

Survival Comparison: CVVH vs CVVHDF
Saudan et al, Kidney Int 2006



More RRT is Better
Odds Ratio: 1.95 (95% CI 1.48 - 2.58, p < 0.001)

Forest plot pooling trials of RRT dose



Kellum, Nat Clin Pract Nephrol 2007

Therapy Dose in ARF: Recent Expert Recommendation

- “Patients with ARF should be treated with at least 35 mL/kg/h of hemofiltration/hemodiafiltration or daily hemodialysis until or unless ongoing multi-center clinical trials show otherwise.”

Kellum JA, Nature Clinical Practice Nephrology 2007

Why Did We Do This Study?

Concerns regarding:

- Different technique
- Different patient population
- Outcome measures
- The presumed increase in cost in high dose groups
- Adverse events due to increased effluent losses
- **Single centre study should not be translated to changes in practice**

• We believed our survival using current practice appeared better than in Ronco's low dose group

Power

- Ronco's study decreased mortality from 59% to 42%
- RENAL: 90% power to detect half this decrease (8%)
- Number required =1500 patients

Inclusion Criteria

- Critically-ill ICU patients
- 18 years or older
- In addition, must have at least one of the following criteria:
 - Oliguria (< 100ml/6hr) unresponsive to fluid
 - Hyperkalaemia (> 6.5 mmol/L)
 - Severe acidaemia (pH < 7.2)
 - Urea > 25 mmol/L (70 mg/dl)
 - Creatinine >300 µmol/L (3.4 mg/dL)
 - Clinically significant organ edema (e.g. pulmonary edema)

Exclusion Criteria

- Any previous renal replacement therapy during the index admission; or
- Maintenance dialysis for end stage kidney disease

Randomisation

- Via a randomly generated number
- Via a secure, password protected, encrypted, web-based interface

Setting up the Study

- Control arm “dose” = current practice
- Treatment arm = a “dose” between the 2 higher Lancet doses
- Adequate dose separation between the 2 arms
- *Post-dilution rather than pre-dilution*
- CRRT technique had to be feasible for the available machines
- Standardise membranes and fluid replacement

Intervention

CVVHDF for all patients

- Post-dilution fluid replacement
- Dialysate to replacement fluid ratio of 1:1
- Effluent flow of **25 ml/kg/hour (low dose)**
- Effluent flow of **40 ml/kg/hour (high dose)**
- Blood flow >150 mls/min
- AN 69 membrane filters
- Haemosol (bicarbonate based) dialysate & replacement fluid

End Points

1^o endpoint

- 90-day all cause mortality

2^o endpoint

- 28-day all cause mortality
- Death before discharge

3^o endpoint

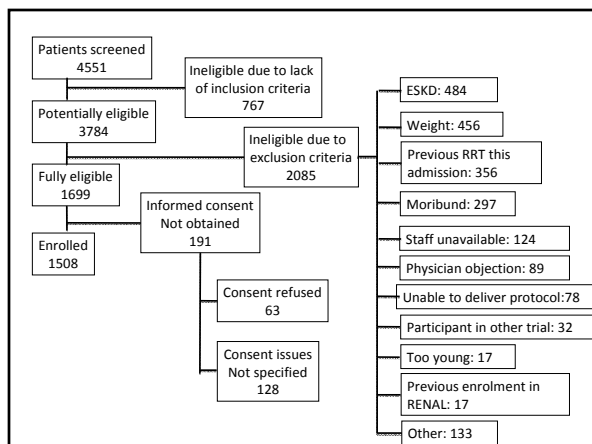
- Length of ICU stay
- Length of hospital stay
- Duration of renal & other organ support
- Dialysis-independent survival

Statistics

- Two interim efficacy and safety analyses
- Performed by an independent statistician
- After 500 and 1000 patients had completed 90 days
- Interim analyses reviewed by an independent Data Monitoring Committee (Oxford - Colin Baigent chair)
- All analyses were performed by intention-to-treat with no imputation for missing values
- Pre-determined statistical analysis plan prior to knowledge of trial findings
- Pre-specified subgroup analyses

Study

- 1/12/2005 -31/8/2008
- 1508 critically ill patients with acute kidney injury
- 35 ICUs in Australia and New Zealand



Enrolment Rate

- 1508 enrolled
- = 33% of patients screened
- = 89% of fully eligible patients



Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

ABSTRACT

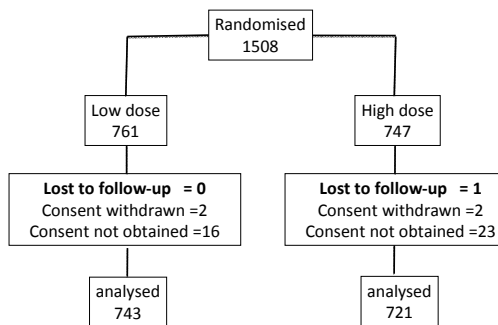
BACKGROUND

The optimal intensity of continuous renal-replacement therapy remains unclear. We conducted a multicenter, randomized trial to compare the effect of this therapy, delivered at two different levels of intensity, on 90-day mortality among critically ill patients with acute kidney injury.

METHODS

We randomly assigned critically ill adults with acute kidney injury to continuous renal-replacement therapy in the form of postdilution continuous venovenous hemodiafiltration with an effluent flow of either 40 ml per kilogram of body weight per hour (higher intensity) or 25 ml per kilogram per hour (lower intensity). The primary outcome measure was death within 90 days after randomization.

The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group and the George Institute for International Health. The members of the Writing Committee for the RENAL Replacement Therapy Study (Frank Bellomo, M.D., Alan Cassa, M.G., Ph.D., Lorenz Gella, M.D., Ph.D., Simon Finfer, M.D., Martin Gallagher, M.D., Sengul Lee, Ph.D., Colin McArdle, M.D., Shee McGarrahan, M.D., John McHugh, M.D., Ph.D., Ralph Nunn, M.D., Ph.D., M.F.H., Carlos Schwab, M.D., and Steve So, Ph.D.) take re-



Baseline Characteristics: 1

Baseline variable	Low intensity	High intensity
Randomised & data	743	721
Sex (%male)	63.5	65.7
Age (mean)	64.4	64.7
Weight (kg, mean)	80.5	80.8
Time: ICU adm-rand (hrs)	54.5	48.4

Baseline Characteristics: 2

Baseline variable	Low intensity	High intensity
Sepsis at baseline (%)	48.9	49.9
APACHE III score (mean)	102.3	102.5
Pts with >=1 non-renal	87.5	87.1
Mechanical ventilation (%)	74.3	73.5

Baseline Characteristics: 3

Baseline variable	Low intensity	High intensity
SOFA Resp (mean)	2.7	2.8
SOFA Coag (mean)	1.0	0.9
SOFA Liver (mean)	1.0	0.9
SOFA Cardiovasc (mean)	2.9	2.9
SOFA Renal (mean)	2.7	2.7

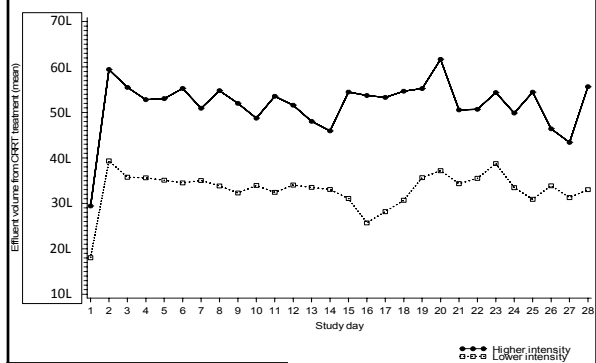
Baseline Biochemistry

Baseline variable	Low intensity	High intensity
Na ⁺ (mmol/L)	138	138
K ⁺ (mmol/L)	4.8	4.9
Cl ⁻ (mmol/L)	105	105
HCO ₃ ⁻ (mmol/L)	18.5	18.1
Urea (mmol/L)	22.8	24.2
Cr (mcmol/L)	330	338

Process of Care

	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 (mls/hr)/patient	1772 (1257)	2698 (1154)	<0.001
Dose delivered mls/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

Mean daily effluent during study treatment



Renal

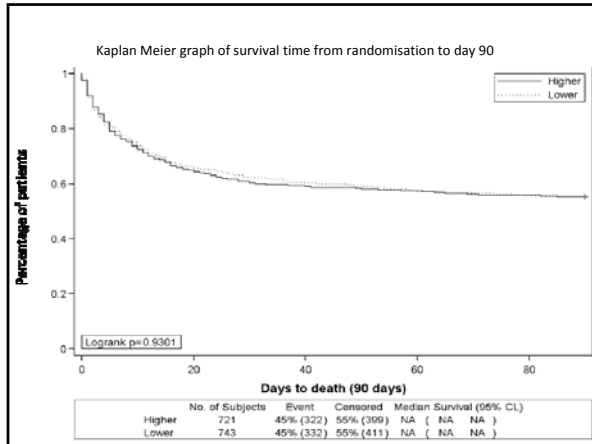
	Low dose	High dose	p
Morning urea (mmol/L)	15.9 (7.9)	12.7 (8.5)	<0.001
Morning creatinine (mcmol/L)	203.9 (114.6)	170.3 (120.8)	<0.001

Biochemistry

	Low dose	High dose	p
Sodium	136.7 (4.1)	136.8 (3.7)	0.122
Chloride	103.3 (4.5)	103.8 (4.0)	<0.001
Potassium	4.35 (0.55)	4.33 (0.54)	0.136
Phosphate	1.24 (0.54)	1.12 (0.57)	<0.001
Magnesium	1.03 (0.26)	0.97 (0.22)	<0.001
Ionized calcium	1.20 (0.20)	1.23 (0.19)	<0.001
Albumin	24.96 (5.97)	24.40 (6.15)	<0.001

Outcomes

	Low dose	High dose	P
Death at day 90	44.7%	44.7%	0.99
Death at day 28	36.9%	38.5%	0.52
Died in ICU	34.2%	34.8%	0.81
Died in hospital outside ICU	10.2%	9.4%	0.60
Died after hospital discharge	0.3%	0.4%	0.63



Secondary Outcomes

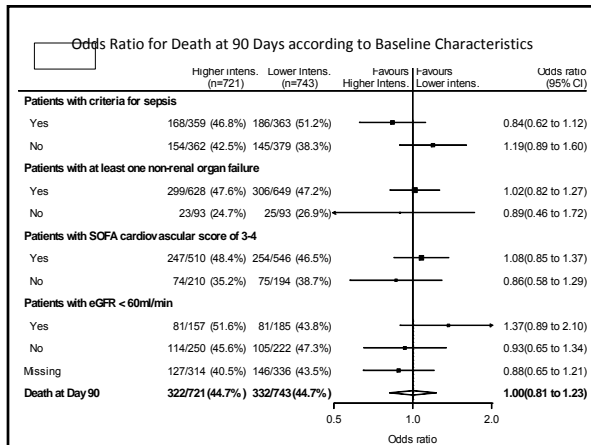
	Low dose	High dose	P
Mechanical ventilation to day 28	7.4 (7.5)	7.3 (7.5)	0.79
ICU stay from randomization to day 90	11.8 (14.2)	11.8 (14.1)	0.95
Hospital stay from randomization to day 90	25.7 (24.7)	26.0 (25.8)	0.79

Renal Outcomes

	Low dose	High dose	P
Renal dependence at day 28	12.2%	14.5%	0.31
Renal dependence at day 90	4.4%	6.8%	0.14
RRT days to day 90	11.5 (18.0)	13.0 (20.8)	0.14

Tertiary Outcomes

New Organ failures to 90 days	Low dose	High dose	P
0	46.2	47.7	0.57
1	35.4	35.2	0.93
2	14.7	13.9	0.65
3	3.4	3.2	0.85
4	0.4	0.1	0.33



Serious Adverse Effects

	Low dose	High dose	p
N	743	722	
Patients with hypophosphatemia (<0.8 mmol/L)	396 (54.0%)	461 (65.1%)	<0.001
Patients with hypokalemia (<3.5)	180 (24%)	168 (23%)	0.34
Patients with Arrhythmia (%)	337 (45.5%)	303 (42.0%)	0.18
Patients with Arrhythmia requiring Rx (%)	267 (36.0%)	240 (33.2%)	0.26
Patients with Arrhythmia causing Haemodynamic instability (%)	181 (24.4%)	200 (27.7%)	0.15
Patients with Disequilibrium (%)	0 (0%)	3 (0.4%)	0.08
Other	5 (0.7%)	4 (0.6%)	0.77

Conclusions

- RENAL is the largest multi-centre RCT of intensity of CRRT in ICU patients with acute kidney injury
- It successfully achieved balanced randomisation as shown by baseline features
- It successfully delivered two different intensities of CRRT as shown by process of care data with excellent group separation

Conclusions

- Higher intensity CRRT did not affect survival
- Higher CRRT intensity did not affect secondary outcome measures
- There was no evidence of different effects in different subgroups

Comparisons with VA/NIH Acute Renal Failure Trial Network

- 1124 patients
- VA used a mix of IHD and CRRT
- Concurrence of findings:
“Intensive renal support in critically ill patients with acute kidney injury did not decrease mortality, improve recovery of kidney function or reduce rate of non-renal organ failures.”

N. Engl. J. Med 208:359

Comparison with VA/NIH Study

Variable	RENAL	VA/NIH
Enrolled	1508	1124
Mean age	64.5	59.7
Male (%)	64.6	70.6
Weight	80.6	84.1
Sepsis (%)	49.5	63
Pre-rand Rx (%)	0	64.3
ICU Days before random	2.1	6.7
Urea at baseline	23.3	24.2
Total SOFA score (resp, CVS, liver, coag)	7.55	7.40
Ventilation	73.9%	80.6%

Comparison with VA/NIH Study

Variable	RENAL	VA/NIH
Mortality day 90	44.7%	
Mortality day 60		52.5%
Duration RRT days	12.2	unclear
Hospital LOS days	25.2	unclear
Renal dependence @day 28	13.3%	45.2%
Renal dependence @day 60		24.6%
Renal dependence @day 90	5.6%	

So... we looked at the data at day 28 the same way the ATN folks did....

RRT free days:

ATN RRT free days at 28 days = 6 days in one group and 7 days in the other....with overall average **6.5 days**

RENAL = overall average = **17 days !!**

ATN = a 61.7% relative decrease in RRT-free days at 28 days compared to RENAL

Where to from here?

- Pooling Individual Patient Data (IPD) RENAL and VA/NIH
 - Funded
- Long-term (5 year) follow-up of RENAL survivors to determine
 - Mortality, development of CKD, QOL
- Need to explore **timing of initiation** of RRT for AKI and **effect of choice of modality on renal recovery**.

- **RENAL = lowest mortality and better recovery**
- **Is CRRT at 25 ml/kg/hr the standard of care?**
- **The journey to improve outcomes in critically ill patients with acute kidney injury continues**

Acknowledgements

- Supported by grants from the National Health and Medical Research Council (NHMRC) of Australia (Grant No 352550) and Health Research Council (HRC) of New Zealand (Grant No 06-357)
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- We acknowledge the nurses in our intensive care units, our physician colleagues and our patients and their families for the support of this trial
