

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009;361:1627-38.

Supplementary Appendix

Patient Inclusion Criteria

Patients were eligible for INCLUSION in the study if ALL the following criteria were met:

1. The treating clinician believes that the patient requires CRRT for acute renal failure.
2. The clinician is uncertain about the balance of benefits and risks likely to be conferred by treatment with higher intensity or lower intensity CRRT.
3. The treating clinicians anticipate treating the patient with CRRT for at least 72 hours.
4. Informed consent has been obtained
5. The patient fulfils **ONE** of the following clinical criteria for initiating CRRT:
 - Oliguria (urine output < 100ml/6hr) that has been unresponsive to fluid resuscitation measures.
 - Hyperkalemia ($[K^+] > 6.5$ mmol/L).
 - Severe acidemia (pH < 7.2).
 - Urea > 25 mmol/liter.
 - Creatinine >300 μ mol/L
 - Clinically significant organ oedema in the setting of ARF (eg: lung).

Patient Exclusion Criteria

Patients were EXCLUDED from the study if, in the opinion or knowledge of the responsible clinician ANY of the following criteria were present:

- Patient age is <18 years.
- Death is imminent (<24 hours).
- There is a strong likelihood that the study treatment would not be continued in accordance with the study protocol.
- The patient has been treated with CRRT or other dialysis previously during the same hospital admission.
- The patient was on maintenance dialysis prior to the current hospitalisation.

- The patient's body weight is <60 kg or >100kg.
- Any other major illness that, in the investigator's judgment, will substantially increase the risk associated with the subject's participation in this study.

Termination of Study Treatment

Study treatment (CRRT) was ceased if or when any of the following criteria were met:

- Patient withdraws consent for study treatment **or**
- Patient dies **or**
- Patient leaves the ICU **or**
- Patient urine output is >400ml in the previous 24hrs and the treating clinicians consider renal function has recovered to the point that further RRT is not needed **or**
- The treating clinicians consider it is the patient's best interest to change from CRRT to intermittent dialysis. (Note: where this occurs after less than 72 hours of CRRT the patient will be classified as a screen failure and the screen failure documentation must be completed).

Once the study treatment was ceased, further renal replacement was prescribed at the discretion of the clinical staff managing the patient. Should the patients return to CRRT within 90 days post randomisation, then they had to return to the previously assigned dose if clinically appropriate.

Patients withdrawn from the randomised treatment for any reason were followed up according to the study follow up schedule and analysed according to the intention-to-treat-principle.

DELAYED CONSENT

By group there were 420/747 in the higher intensity group and 425/761 in the lower intensity group who were randomized under the delayed consent procedure. In more details, in 319 patients from the higher intensity group and 317 patients from the lower intensity group delayed consent was followed by subsequent written informed consent by their next of kin. While, in 124 patients in the higher intensity group and 128 patients in the lower intensity group, delayed consent was followed by subsequent written informed consent by the patient.

As previously published (Blood Purif 2008; 27: 199-205) out of 1699 fully eligible patients, 66 (3.9%) refused consent. We now believe the term "consent not obtained" used in our study profile may be misleading. We have changed it to the term "delayed consent rejected". The reasons are summarized below.

Reason for 'consent not obtained' (Now consent rejected)	Total	High	Low
Subject wished to discontinue and requested data withdrawal	8	5	3
Surrogate wished to discontinue and requested data withdrawal	16	12	4
Other	15	6	9
Pt/NOK was not approached for delayed consent due to inappropriate randomisation or inadequate/insufficient data (patient died suddenly or patient did not receive dialysis)	6	4	2
Prior written consent not obtained - EC requested withdrawal of data	2	0	2
Died prior to delayed consent and inappropriate to contact NOK	6	1	5
Verbal consent only - EC requested withdrawal of data	1	1	0
Total	39	23	16

Withdrawal of initial consent by patient or NOK	4	2	2
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Total: withdrawal of data counts = 39 + 4 = 43

As can be seen above, delayed consent was rejected by patients or next of kin on 24 occasions from total of 869 instances (2.8% rejection rate).

Table presenting baseline characteristics using median value with interquartile intervals.

Table 1: Baseline Characteristics of Study Patients

Characteristic	Higher-intensity CRRT	Lower-intensity CRRT
Age --yr	67.3 (57.2 to 76.0)	67.3 (56.4 to 76.4)
Sex –Male	474 (65.7%)	472 (63.5%)
Pre-admission eGFR* (ml/min)	49.3 (30.1 to 72.7)	56.7 (36.7 to 76)
Patients with known eGFR < 60 ml/min	157/408 (34.5%)	185/407(45.4%)
Time in ICU before randomization (hrs)	18 (5 to 48)	20 (6 to 53)
Mechanical ventilation	531 (73.5%)	551 (74.3%)
Severe sepsis	360 (49.9%)	363 (48.9%)

APACHE III score	101 (84 to 118) ± 25.9	100 (86 to 118)
Cardiovascular SOFA score	4 (1 to 4)	4 (2 to 4)
Respiratory SOFA score	3 (2 to 3)	3 (2 to 3)
Coagulation SOFA score	0 (0 to 2)	1 (0 to 2)
Liver SOFA score	0 (0 to 2)	1 (0 to 2)
Weight	80 (70 to 90)	80 (70-90)
Source of admission		
Emergency Department	163/670 (24.3%)	185/700 (26.4%)
Hospital ward	210/670 (31.3%)	177/700 (25.3%)
Transfer from other ICU	51/670 (7.6%)	60/700 (8.6%)
Transfer from other hospital	73/670 (10.9%)	81/700 (11.6%)
From OR after emergency Surgery	93/670 (13.9%)	113/700 (16.1%)
From OR after elective surgery	80/670 (11.9%)	84/700 (12.0%)
Non-operative admission diagnosis		
Cardiovascular	268/533 (50.3%)	266/516 (51.6%)
Genitourinary	120/533 (22.5%)	109/516 (21.0%)
Respiratory	79/533 (14.8%)	67/516 (13.0%)
Gastrointestinal	35/533 (6.6%)	40/516 (7.8%)
Other	31/533 (5.8%)	34/516 (6.6%)
Operative admission diagnosis		
Cardiovascular	122/189 (64.6%)	147/227 (64.8%)
Gastrointestinal	50/189 (26.5%)	48/227 (21.1%)
Trauma	6/189 (3.2%)	15/227 (6.6%)
Other	11/189 (5.8%)	17/227 (7.5%)
Criteria for randomization*		
Oliguria	430/722 (59.6%)	444/743 (59.8%)

Hyperkalemia	68/722 (9.4%)	45/743 (6.1%)
Severe acidemia	257/722 (35.6%)	264/743 (35.5%)
BUN > 70 (Plasma Urea>25mmol/l)	315/722 (43.6%)	286/743 (38.5%)
Creatinine > 3.4 mg/dl (>300 µmol/l)	349/722 (48.3%)	343/743 (38.5%)
Severe organ edema in setting of AKI	323/722 (44.7%)	319/743 (42.9%)
BUN (mg/dl)	58.8 (38.9 to 90.4)	56 (37.5 to 85.1)
Plasma urea (mmol/l)	21 (13.9 to 32.3)	20 (13.4 to 30.4)
Creatinine before randomization (mg/dl)	3.8 ± 2.2	3.8 ± 2.2
Creatinine before randomization (µmol/l)	291 (208 to 390)	279.5 (206 to 410)
pH	7.3 (7.2 to 7.4)	7.3 (7.2 to 7.4)
Bicarbonate (mEq/l)	18 (14 to 22)	18 (14.8 to 22.0)
Base excess (mEq/L)	-8 (-12.9 to -4.0)	-8.0 (-13.0 to -3.0)- 8.2 ± 7

All values presented as median with interquartile range in brackets or as numbers with percentages;

CRRT = continuous renal replacement therapy; e-GFR = estimated GFR (* information on pre-morbid creatinine available in 408 and 407 patients in each group respectively); SOFA= sequential organ failure assessment; APACHE =acute physiology and chronic health evaluation; BUN = blood urea nitrogen; ICU = intensive care unit; OR = operating room; AKI = acute kidney injury; * a given patient may have fulfilled one or more of these criteria

Process characteristics presented as medians and interquartile intervals

Table 2: Characteristics of Study Treatment and Subsequent Use of RRT

	Higher Intensity			Lower Intensity			P value [†]
	Q1	Median	Q3 / n(%)	Q1	Median	Q3 / n(%)	
Days of study treatment	2.00	3.00	7.00	2.00	3.00	7.00	0.35
Daily effluent (ml/kg/hr)	29.83	36.31	39.51	19.72	23.38	24.98	<0.001
Percent of dose delivered	0.75	0.91	0.99	0.79	0.94	1.00	<0.001
Daily BUN (mg/dl)	20.16	28.57	43.41	29.13	40.05	54.62	<0.001
Daily plasma urea(mmol/l)	7.20	10.20	15.50	10.40	14.30	19.50	
Daily serum creatinine (mg/dl)	1.10	1.56	2.30	1.48	2.03	2.76	<0.001
Daily serum creatinine (µmol/l)	98.00	138.00	204.00	131.00	180.00	244.00	
Dialysate and replacement fluid (ml/hr)	2143.00	2619.08	3072.92	1352.71	1659.35	1956.75	<0.001
Daily effluent (ml/hr)	2268.83	2750.00	3197.67	1466.67	1770.31	2065.00	<0.001
Net ultrafiltration (ml/hr)	44.58	99.58	156.58	41.71	95.00	149.75	0.04
Daily fluid balance (ml)	-60.00	0.00	60.00	-60.00	1.00	70.00	0.24
Days of anticoagulation							
- Pre-filter heparin	0.00	0.00	3.00	0.00	0.00	3.00	0.97
- No anticoagulation	0.00	0.00	2.00	0.00	1.00	3.00	0.27
- Heparin and protamine	0.00	0.00	0.00	0.00	0.00	0.00	0.007
- Systemic heparin	0.00	0.00	0.00	0.00	0.00	0.00	0.40
- Other	0.00	0.00	0.00	0.00	0.00	0.00	0.38
Type of anticoagulant received							
- Pre-filter heparin	348/722 48.2%			355/743 47.8%			0.87

- No anticoagulation	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
Daily number of filters used	0.00 1.00 1.00	0.00 1.00 1.00	<0.001
Patients treated with IHD in ICU	55 (7.6%)	52 (7.0%)	0.64

All values presented as medians with interquartile values in brackets ; RRT = renal replacement therapy;

CRRT = continuous renal replacement therapy; BUN = blood urea nitrogen; IHD = intermittent

hemodialysis.

Approach to the reporting of SAE's

Serious adverse events considered to be related to study treatment were reported within 24 hours to the Coordinating Centre. A team (including two medically qualified staff within the management committee) was appointed to review and process these reports in accordance to the protocol and applicable regulatory requirements. An independent data and safety monitoring committee reviewed the safety data (including all adverse events) and interim results.