

## Original Article

## The Hannover Dialysis Outcome study: comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit

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### Abstract

**Background.** Increasing the dose of renal replacement therapy has been shown to improve survival in critically ill patients with acute kidney injury (AKI) in several smaller European trials. However, a very recent large multicentre trial in the USA could not detect an effect of dose of renal replacement therapy on mortality. Based on those studies, it is not known whether a further increase in dialysis dose above and beyond the currently employed doses would improve survival in patients with AKI. We therefore aimed to assess mortality and renal recovery of patients with AKI receiving either standard (SED) or intensified extended dialysis (IED) therapy in the intensive care unit.

**Methods.** A prospective randomized parallel group study was conducted in seven intensive care units of a tertiary university hospital. Pre-existing chronic kidney disease was an exclusion criterion. A total of 156 patients (570 screened) with AKI requiring renal replacement therapy were randomly assigned to receive standard dialysis [dosed to maintain plasma urea levels between 120 and 150 mg/dL (20–25 mmol/L)] or intensified dialysis [dosed to maintain plasma urea levels <90 mg/dL (<15 mmol/L)]. Outcome measures were survival at Day 14 (primary) and survival and renal recovery at Day 28 (secondary) after initiation of renal replacement therapy.

**Results.** Treatment intensity differed significantly ( $P < 0.01$  for plasma urea and administered dose). No differences between intensified and standard treatment were seen for survival by Day 14 (70.4% versus 70.7%) or Day 28 (55.6% versus 61.3%), or for renal recovery amongst the survivors by Day 28 (60.0% versus 63.0%).

**Conclusions.** Although this study cannot deliver a definitive answer, it suggests that increasing the dose of extended dialysis above the currently recommended dose might neither reduce mortality nor improve renal recovery in critically ill patients, mainly septic patients, with AKI.

**Keywords:** dialysis dose; renal recovery; SLED; survival

### Introduction

Mortality rates of patients with acute kidney injury (AKI) in the intensive care unit (ICU) have changed little over recent decades despite significant advances in supportive care [1]. A recent multinational, multicentre study of 23 000 critically ill patients with AKI revealed that the in-hospital mortality is high, exceeding 60% [2]. A small number of interventions have been shown to improve the in-hospital mortality of these patients, with a dose of renal replacement therapy (RRT) being one of the most important. Patients undergoing continuous venovenous haemofiltration had better outcomes with an ultra-filtration rate of 35 mL/kg/h or 45 mL/kg/h compared to those treated at a rate of 20 mL/kg/h [3]. In a different trial, intermittent haemodialysis on a daily basis resulted in better control of uraemia, fewer hypotensive episodes during dialysis and more rapid resolution of acute renal failure than three times weekly haemodialysis [4]. A very recent large multicentre trial in the USA could not confirm this finding: intensive renal support (intermittent haemodialysis, CVVHDF and extended daily dialysis) in critically ill patients with AKI did not decrease mortality, improve recovery of kidney function or reduce the rate of non-renal organ failure as compared with less-intensive therapy [5]. However, these studies do not exclude the possibility that a further increase in dialysis dose, above and beyond the currently employed doses, would improve survival in patients with AKI, best epitomized by a multidisciplinary stakeholder committee that identified the

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question ‘*What is the optimal “dosage” of RRT to maximize patient and renal survival?*’ as one of the five most important topics of clinical research in this area [6]. Therefore, our study aimed to examine survival and renal recovery in critically ill patients with AKI who were treated with a currently recommended (standard) dose of RRT (= standard extended dialysis ‘SED’) and patients who received intensified RRT (= intensified extended dialysis ‘IED’). All patients were treated with the increasingly used extended dialysis (ED), a hybrid modality of RRT for critically ill patients [7].

## Methods

### Patients

The study protocol was approved by the Hannover Medical School Ethics Committee (project/approval # 2905) and was conducted in accordance with the declaration of Helsinki and German Federal Guidelines. Patients in seven ICUs of our tertiary care centre at the Hannover Medical School suffering from AKI were screened during a total recruitment period of 4 years (from 2003 to 2006); for details of the study protocol please see [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (ID: NCT00529139). In brief, the inclusion criteria were non-post-renal AKI with RRT dependence indicated by the loss of kidney function of >30% calculated eGFR with either the MDRD or Cockcroft–Gault equation or cystatin C GFR within 48 h prior to inclusion and oliguria/anuria (<30 mL/h >6 h prior to inclusion or hyperkalaemia >6.5 mmol/L or severe acidosis with pH<7.15). Exclusion criteria were pre-existing chronic kidney disease (CKD) as defined by an estimated glomerular filtration rate <50 mL/min or a plasma creatinine concentration >1.7 mg/dL (>150 µmol/L) more than 10 days prior to initiation of the first RRT. Additionally, we considered the presence of AV-fistula or dialysis catheter as indicative of CKD. Further exclusion criteria were participation in another study, consent denial or withdrawal and need for extracorporeal membrane oxygenation therapy.

The enrolment was performed by attending nephrologists after obtaining written informed consent from a patient or his/her legal representatives. If the patient was recovering and able to communicate, he/she was informed of the study purpose and consent was required to further maintain his/her status as a study participant. After inclusion, the specific medical condition leading to RRT initiation was documented out of a list of five possible causes requiring immediate RRT. Additionally, up to 12 diagnoses describing the most relevant comorbidities were recorded. Further, blood tests and physiological parameters were obtained for each patient at the time of admission to the intensive care unit after inclusion but before initiation of RRT, and at Days 1, 2, 3, 7, 14, 21 and 28 after initiation of RRT. All patients received a nutritional intake of at least 25–30 kcal/kg/day, preferentially delivered as enteral nutrition. The prescribed protein intake was >1.2 g/kg/day. In the IED (and if necessary in the SED) group, phosphate intravenous supplementation was based on serum phosphorous levels.

### Dialysis equipment

We used the GENIUS™ dialysis system (Fresenius Medical Care, Bad Homburg, Germany), whose technical details are described elsewhere [7]. In brief, the simple single-pass batch dialysis machine provides up to 75 L of an ultra-pure germ- and endotoxin-free pure bicarbonate dialysate per dialysis session. It has only one roller pump in which both blood and dialysate tubing are inserted and that pumps blood and dialysate counter currently with a fixed ratio. Thus, the blood flow determines the duration of the treatment, i.e. the time required to deplete the 75 L dialysate tank. In the present study, we used tubing yielding a fixed flow ratio of 1:1, i.e. blood flow and dialysate flow of ~150 mL/min. Under these conditions, the dialysate dose delivered with one tank was ~9 L/h, and the dialysate was depleted in ~8 h. Furthermore, we used high-flux polysulphone dialysers (F60S, 1.3 m<sup>2</sup>, Fresenius Medical Care, Bad Homburg, Germany) for all treatments. Finally, treatment modality of each single ED was equal, e.g. blood and dialysate flows were similar in patients randomized to the SED and IED groups. Both groups received additional isolated ultra-filtration if needed.

### Interventions, randomization procedure and blinding

After inclusion, patients were randomly assigned 1:1 to one of two different treatment groups. The SED group received one ED in the first 24 h after inclusion, and subsequent treatments were administered on a daily basis in order to maintain a plasma urea level at 120–150 mg/dL (20–25 mmol/L). Patients randomized to IED received at least two ED treatments in the first 24 h; subsequent treatments were dosed to maintain plasma urea levels <90 mg/dL (<15 mmol/L). Dialysis was discontinued in patients meeting the following criteria for renal recovery: urine output >1000 mL/day, increased solute clearance [decline in pre-dialysis plasma urea or serum creatinine concentration and (under stable conditions) serum creatinine with estimated glomerular filtration rate >15 mL/min (by either MDRD, Cockcroft–Gault or cystatin C GFR)].

We used a random number generating software tool to generate the complete allocation sequence prior to inclusion of the first patient. The statistician generating the sequence did not participate in data analysis. After inclusion, patients received their first ED treatment. Only after this treatment were the attending nephrologists unblinded and granted access to the randomization list for group assignment.

### Study outcomes, sample size calculation and statistical analysis

The main objective of the study was to compare the mortality and renal recovery of patients with AKI in the intensive care unit, randomized either to SED or IED. The primary study endpoint was defined as survival at Day 14 after initiation of RRT. Secondary endpoints were survival at Day 28 after initiation of RRT and renal recovery (no RRT requirement) in survivors at Day 28. The null hypothesis was that treatment intensity does not affect primary and secondary endpoints.

According to Schiffli *et al.*, a survival benefit of ~25% can be achieved by daily intermittent haemodialysis with a treatment dose of ~700 mL/kg body weight/day, resulting in plasma urea levels of ~120–150 mg/dL (20–25 mmol/L) as compared to treatments every other day [4]. A similar difference in survival was documented by Ronco *et al.* for a higher treatment dose of continuous haemofiltration [3]. Based on these results, we assumed, a survival benefit of 20% could be achieved by utilizing a dose for the IED group that exceeded the ‘higher’ dose described in the study by Schiffli *et al.* by at least two-fold. Therefore, expecting to reduce mortality from 60% in the SED allocation group to 40% in the IED allocation group, the study design offered a single-sided 80% power with a total of 154 participants and an allocation ratio of 1, as proved by log-rank testing. Hence, we aimed to study 160 patients to allow for some dropouts.

Comparison of the endpoint data was computed by intention-to-treat analysis with the exception of renal recovery as secondary endpoint, which was calculated only amongst survivors. Survival proportions were calculated by the Kaplan–Meier analysis and analysed by log-rank testing (Mantel Cox test). Time frame for censoring the data was the study period (28 days). Numerical data were tested for equal variance using the *F*-test. Independent data with equal variance were tested by two-tailed Student’s *t*-test. Independent data of unequal variance were tested by two-tailed Student’s *t*-test with Welch’s correction. Significance was accepted as  $P < 0.05$ . Data in column graphs are presented as median with interquartile ranges. Data in tables are presented as individually indicated.

## Results

### Study population, follow-up and adherence

Of the 570 patients who were screened for eligibility, 157 patients were randomized to both treatment groups (Figure 1); 413 patients were excluded, mostly due to pre-existing CKD. Seventy-six patients were randomized to the SED group and 81 patients to the IED group. In the SED group, 71 patients received the allocated intervention, whereas in the IED group, 77 patients received the allocated intervention. One participant from the SED group was excluded from final analysis *post hoc* due to not meeting the inclusion criteria. All other randomized participants were included in the final intention-to-treat analysis.

The baseline characteristics are shown in Table 1. Both groups were well matched with respect to important clinical parameters. The duration of ICU treatment prior to inclusion was comparable. The average estimated mortality according to the pre-dialysis APACHE II scores was 56% in the SED group and 61% in the IED group (n.s.). Comorbidity prior to the first RRT was comparable in the treatment groups with systemic inflammatory response syndrome, major surgery and cardiogenic shock being the most frequent. After as few as 24 h following initiation of RRT, the IED treatment resulted in lower mean urea plasma levels of a highly significant difference compared to those in the SED group (data not shown). As evidenced by this clear-cut

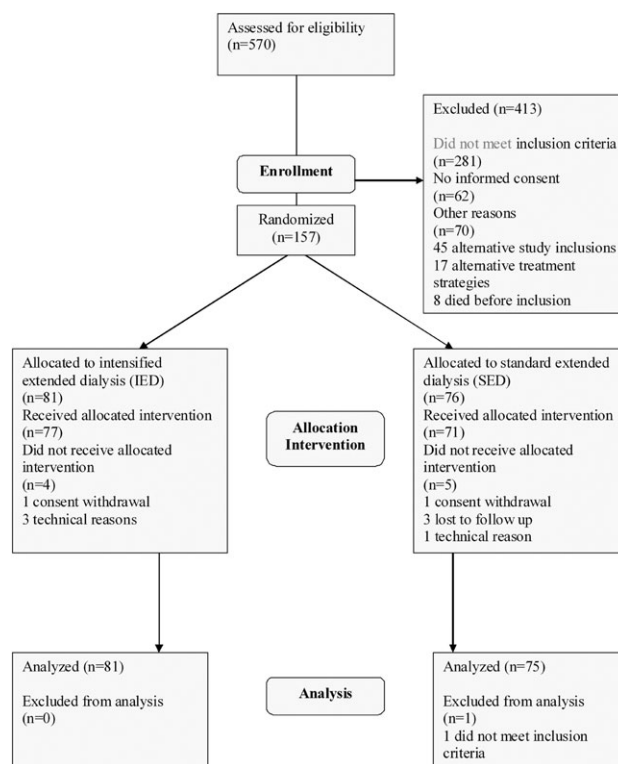


Fig. 1. Design of the trial and flow chart.

difference in treatment intensity, adherence was excellent. Because dialysis dosage prescription was dictated by daily morning plasma urea measurements, this difference was maintained according to the protocol at least until Day 21 ( $P < 0.05$ – $0.001$  when censored for either death or renal recovery), and still showed a strong trend at Day 28 when the study was concluded ( $P = 0.199$ ) (Figure 2). Both groups fit well into the target range of plasma urea, e.g. 48 h after initiation of RRT mean plasma urea level was  $114.1 \pm 36.0$  mg/dL ( $19.1 \pm 6.8$  mmol/L) in the SED group versus  $68.5 \pm 24.0$  mg/dL ( $11.4 \pm 4.1$  mmol/L) in the IED group ( $P < 0.001$ ). In addition, the difference in the total dialysis dose administered during this period was also highly significant (Figure 3), as was treatment intensity, measured as the number of ED treatments and total treatment time—although the single treatments *per se* were equal, as documented by blood flow and dialysate flow as well as red packed cell transfusion frequency during the study period, representing adverse reactions (Table 2).

### Outcome measures

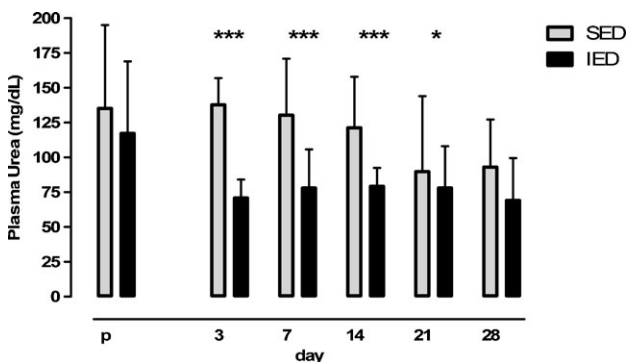
Survival at Day 14 after initiation of RRT was not significantly different between groups, as shown by the Kaplan–Meier curves (Figure 4). All-cause mortality at Day 14 was 29.6% ( $n = 24$ ) in the IED group as compared to 29.3% ( $n = 22$ ) in the SED group ( $P = 0.97$ ). In addition, follow-up clinical characteristics did not show any relevant differences for major variables in either group (Table 3). The SOFA score, as a measure for the severity of illness, was identical in both groups as were indices of kidney function. Survival at Day 28 after initiation of RRT was also not

**Table 1.** Baseline characteristics of patients randomized on an intention to treat basis

|   | SED <sup>a</sup> (n = 75) | IED <sup>b</sup> (n = 81) | P-value |
|---|---------------------------|---------------------------|---------|
| Age, mean (SD) (years)  | 51.5 (15.3)               | 50.0 (14.9)               | 0.55    |
| Male gender, no. (%)  | 46 (61.3)                 | 53 (65.4)                 | 0.59    |
| Body weight (SD) (kg)   | 74.2 (15.0)               | 78.8 (19.8)               | 0.11    |
| Days in ICU <sup>c</sup> before the start of RRT <sup>d</sup> , mean (SD) (day)         | 5.5 (8.2)                 | 6.2 (9.6)                 | 0.60    |
| Last known creatinine >10 days before the start of RRT <sup>d</sup> , mean (SD) (mg/dL) | 1.01 (0.36)               | 0.96 (0.30)               | 0.33    |
| Creatinine at inclusion, mean (SD) (mg/dL)  | 3.09 (1.65)               | 3.08 (1.67)               | 0.99    |
| BUN <sup>e</sup> at inclusion, mean (SD) (mg/dL)  | 65.4 (30.2)               | 60.3 (28.1)               | 0.28    |
| Urine volume at RRT <sup>d</sup> initiation, mean (SD) (mL/day)                         | 982 (1244)                | 1070 (1339)               | 0.68    |
| APACHE II score at RRT <sup>d</sup> initiation (SD)                                     | 30.3 (7.6)                | 32.8 (7.4)                | 0.03    |
| SOFA <sup>g</sup> score at RRT <sup>d</sup> initiation, mean (SD)                       | 13.7 (3.6)                | 14.4 (3.7)                | 0.32    |
| Patients receiving catecholamine support at RRT <sup>d</sup> initiation, no. (%)        | 53 (70.7)                 | 60 (74.1)                 | 0.64    |
| Comorbidity at RRT <sup>d</sup> initiation <sup>i</sup>                                 |                           |                           |         |
| SIRS <sup>h</sup> /sepsis, no. (%)  | 51 (68.0)                 | 62 (76.5)                 | 0.11    |
| Major surgery, no. (%)  | 38 (50.7)                 | 52 (64.2)                 | 0.08    |
| Cardiogenic shock, no. (%)  | 24 (32.0)                 | 26 (32.1)                 | 0.99    |
| Cause for initiation of RRT <sup>d,i</sup>  |                           |                           |         |
| Anuria/oliguria, no. (%)  | 52 (69.3)                 | 62 (76.5)                 | 0.31    |
| Hyperkalaemia >6.5 mmol/L, no. (%)  | 5 (6.8)                   | 5 (6.2)                   | 0.90    |
| Acidosis with pH <7.15, no. (%)   | 7 (9.3)                   | 11 (13.6)                 | 0.41    |
| Loss of CrCl <sup>h</sup> ≥ 70% of a last known value in <48 h, no. (%)                 | 66 (88.0)                 | 74 (91.4)                 | 0.49    |
| Azotaemia, hypervolaemia, no. (%)   | 3 (4.0)                   | 2 (2.5)                   | 0.59    |

<sup>a</sup>SED, standard extended dialysis; <sup>b</sup>IED, intensified extended dialysis; <sup>c</sup>ICU, intensive care unit; <sup>d</sup>RRT, renal replacement therapy; <sup>e</sup>blood urea nitrogen; <sup>f</sup>SOFA, sepsis-related organ failure assessment; <sup>g</sup>SIRS, systemic inflammatory response syndrome; <sup>h</sup>CrCl, creatinine clearance; <sup>i</sup>Values >100% attributes to multiple nominations.

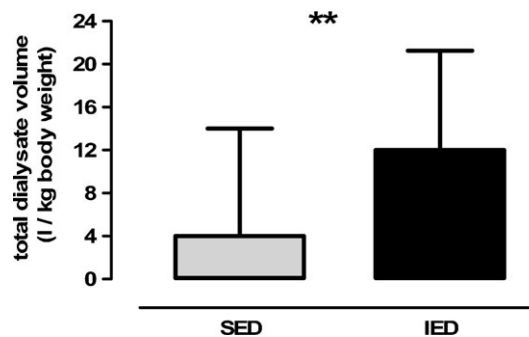
Creatinine: mg/dL × 88.4 = μmol/L; BUN: Plasma Urea × 0.467 (mg/dL).



**Fig. 2.** Course of plasma urea levels during the study period. Values are presented pre-dialysis (P) and on follow-up Days 3, 7, 14, 21 and 28 after initiation of renal replacement therapy. IED—intensified extended dialysis; SED—standard extended dialysis; \*\*\* $P < 0.001$ ; \* $P < 0.05$ . Data are censored for patients with recovered kidney function and death, depicting only values from patients with ongoing dialysis therapy. Highly significant lower plasma urea levels in the IED group were reached already at Day 1 (after two dialysis treatments within the first 24 h) and maintained throughout the study period. Median with interquartile range.

significantly different: all-cause mortality was 44.4% ( $n = 36$ ) in the IED group compared to 38.7% ( $n = 29$ ) in the SED group ( $P = 0.47$ ). Renal recovery among the survivors, defined as no need for dialysis at the end of the study period, also did not differ significantly with 63% in the SED versus 60% in the IED-allocation group ( $P = 0.77$ ) (Table 3).

We also examined the effect of treatment dose on respiratory support requirement in those critically ill patients who presented with multi-organ failure and needed mechanical ventilation: intensified ED did not have an effect



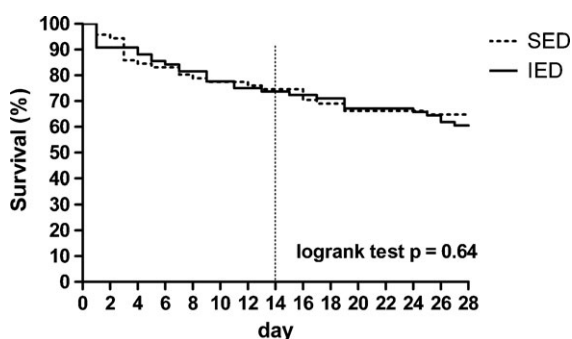
**Fig. 3.** Total administered dialysate volume. Data are normalized to body weight. Median dialysate volume applied was 12.0 L/kg in the intensified extended dialysis (IED) group versus 4.0 L/kg in the standard extended dialysis (SED) group. \*\* $P < 0.01$ . Median with interquartile range.

**Table 2.** Treatment analysis

|   | SED <sup>a</sup> (n = 75) | IED <sup>b</sup> (n = 81) | P-value |
|---|---------------------------|---------------------------|---------|
| Treatments, mean (SD), no.                        | 7.7 (8.1)                 | 13.3 (10.2)               | <0.001  |
| Total treatment time, mean (SD) (min)             | 4152 (4702)               | 7279 (5660)               | <0.001  |
| Blood flow, mean (SD), (mL/min)                   | 151 (31)                  | 152 (24)                  | 0.62    |
| Transfusions of RPC <sup>c</sup> , mean (SD), no. | 18.4 (21.5)               | 21.5 (22.0)               | 0.41    |

<sup>a</sup>SED, standard extended dialysis; <sup>b</sup>IED, intensified extended dialysis; <sup>c</sup>RPC, red packed cells.

on the duration of mechanical ventilation compared to SED (Figure 5A). The same was true for the total ICU treatment time (Figure 5B).



**Fig. 4.** Survival at Days 14 and 28 after initiation of renal replacement therapy shown by Kaplan–Meier curves. No significant differences were detected in the survival proportions. Survival at Day 14 was 70.4% in the intensified extended dialysis (IED) group versus 70.7% in the standard extended dialysis (SED) group ( $P = 0.97$ ). Survival at Day 28 was 61.3% in the SED group versus 55.6% in the IED group ( $P = 0.47$ ).

**Table 3.** Follow-up characteristics of survivors at Day 14 and Day 28

|   | SED <sup>a</sup> ( $n = 75$ ) | IED <sup>b</sup> ( $n = 81$ ) | $P$ -value |
|---|-------------------------------|-------------------------------|------------|
| Survivors at Day 14, no. (%)  | 53 (70.7)                     | 57 (70.4)                     | 0.97       |
| SOFA <sup>c</sup> score at Day 14, mean (SD)                          | 9.7 (4.1)                     | 9.7 (5.4)                     | 0.98       |
| Catecholamine therapy at Day 14, no. (%)                              | 10 (13.3)                     | 12 (14.8)                     | 0.79       |
| eGFR <sup>d</sup> at Day 14, mean (SD) (mL/min)                       | 52 (51)                       | 59 (53)                       | 0.55       |
| Urine volume at Day 14, mean (SD) (mL/day)                            | 1844 (1692)                   | 1422 (1439)                   | 0.21       |
| Survivors at Day 28, no. (%)  | 46 (61.3)                     | 45 (55.6)                     | 0.47       |
| SOFA <sup>c</sup> score at Day 28, mean (SD)                          | 10.0 (3.9)                    | 8.8 (5.4)                     | 0.43       |
| Catecholamine therapy at Day 28, no. (%)                              | 5 (6.7)                       | 4 (4.9)                       | 0.41       |
| eGFR <sup>d</sup> at Day 28, mean (SD) (mL/min)                       | 61 (53)                       | 74 (76)                       | 0.43       |
| Urine volume at Day 28, mean (SD) (mL/day)                            | 1609 (1446)                   | 1874 (1369)                   | 0.49       |
| Renal recovery <sup>f</sup> (no RRT <sup>e</sup> ) at Day 28, no. (%) | 29 (63.0)                     | 27 (60.0)                     | 0.77       |

<sup>a</sup>SED, standard extended dialysis; <sup>b</sup>IED, intensified extended dialysis; <sup>c</sup>SOFA, sepsis-related organ failure assessment; <sup>d</sup>eGFR, estimated glomerular filtration rate [Cockcroft–Gault]; <sup>e</sup>RRT, renal replacement therapy; <sup>f</sup>Only survivors.

## Discussion

This is the first prospective randomized study investigating the effect of two different doses of ED on mortality and renal recovery in critically ill patients with AKI. The pertinent findings of our study are (1) a high treatment dose of RRT can be safely delivered with ED, (2) intensified RRT improves the control of uraemia, but (3) this better control of uraemia has no effect on mortality or renal recovery.

### Dose of RRT and survival

Several studies have shown that increasing the dose of RRT improves survival in patients with AKI. This is true for both intermittent and continuous modes of RRT [3,4,8,9]. How-

ever, the relationship between the dose of RRT and survival does not seem to be a linear one, and especially in critically ill patients, this dose/survival relationship could not be confirmed by all authors [10]. Moreover, a very recent large multicentre trial in the USA showed that intensive renal support (intermittent haemodialysis, CVVH and extended daily dialysis) in critically ill patients with AKI did not decrease mortality, improve recovery of kidney function or reduce the rate of non-renal organ failure as compared with less-intensive therapy [5]. Based on those studies, it is not known whether a further increase in dialysis dose above and beyond the currently employed doses would improve survival in patients with AKI. Ronco *et al.* already hypothesized that the positive effect of increasing the dose of RRT seems to plateau and further improvements cannot be obtained by increasing treatment intensity [3]. They did not detect a difference in survival of patients receiving 35 versus 45 mL/kg/h substitution fluid during continuous venovenous haemofiltration. It is important to point out that our SED group was treated with a dialysis dose that was comparable with the high-dose treatment groups of previously published trials, e.g. the daily dialysis group from Schiff *et al.* or the 35 mL/kg/h group from Ronco *et al.* [3,4]. The IED group in the present study represented a further increase in dialysis dose not yet investigated in randomized controlled trials. Hence, our study provides evidence that intensified RRT aiming for near-normal urea levels does not affect mortality or renal recovery. Potential factors that could have confounded the results with IED, such as elimination of phosphate or removal of antibiotics, were actively managed during the study [11–13]. It is of interest, however, that in controlled studies of RRT in patients with CKD, an increase in the treatment dose of haemodialysis [14] or continuous ambulatory peritoneal dialysis [15] also did not result in better survival. The results of the present study indicate that this also holds true for intensified RRT in critically ill patients, and thus have several important implications for the growing numbers of centres performing ED worldwide. First, the potential risk of bleeding in the setting of prolonged anticoagulation due to an intensified (e.g. twice daily) treatment time does not seem justified, as we were able to confirm in our study once again (Table 2). Secondly, increasing treatment intensity, which results in higher costs due to additional nursing time and equipment operating time, should not be employed on a routine basis. Although our study does not eliminate the possibility that a high-dose RRT leads to a survival advantage in critically ill patients with AKI, it shows that the magnitude of such a benefit, if present at all, would be exceedingly small.

We cannot rule out that the lack of benefit of a higher dialysis dose is due to the fact that we solely studied a mainly diffusive mode of RRT. Indeed, ED has been shown to be inferior in removal of beta-2 microglobulin [12] indicating an inferior clearance of middle molecules. The same could hold true for mediators and cytokines, which, however, had not been studied in our population. Hence, it is possible that a higher removal of mediators and cytokines from the blood compartment in the proinflammatory phase of sepsis using convective modes of RRT might provide a benefit for selected patients.

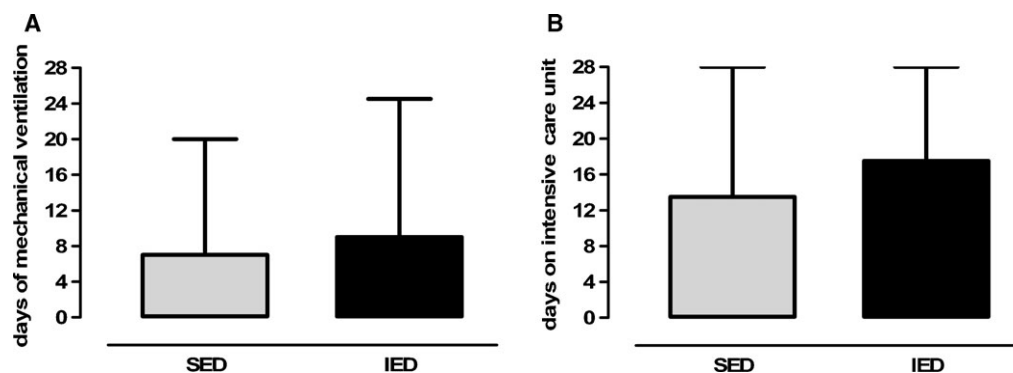


Fig. 5. Requirement of mechanical ventilation (A) and total treatment time (B) on the intensive care unit. Observational period was of 28 days. There were no significant differences between treatment groups for either of the observations. Median with interquartile range.

### Dose of RRT and renal recovery

Of patients who survive an episode of AKI in the intensive care unit, 5–30% will remain on chronic RRT without renal recovery [16]. In our study, renal survival on Day 28 was ~60% in both groups. This is important as even a slight difference in renal recovery between different treatment doses might significantly influence the overall cost-effectiveness of each treatment dose. Results of several studies suggested that the mode of RRT influences renal recovery. However, a meta-analysis by Tonelli *et al.* showed that in comparison to intermittent haemodialysis, continuous RRT does not improve survival or renal recovery in unselected critically ill patients with AKI [17]. Interestingly, Augustine *et al.* recently showed that renal recovery was influenced by blood pressure changes during RRT, with lower recovery rates correlating with a greater decrease in mean arterial pressure during the initial treatment [18]. This is in line with data showing that a decline in renal perfusion during intermittent haemodialysis might delay tubular regeneration in post-ischaemic AKI [19]. Treatment with ED has been repetitively shown to grant excellent cardiovascular stability independently of the type of dialysis machine used [12,20–22].

### Limitations of the study

We wish to point out potential limitations of our study. First, this study compares two doses of ED, i.e. an RRT that mainly operates on diffusive transport mechanisms and the results cannot necessarily be extrapolated to mostly convective therapies. Nevertheless, Ronco *et al.* earlier described that for the latter, the positive effect on survival of increasing the dose seems to plateau [3]. Moreover, Saudan *et al.* recently reported their findings in severely ill patients with AKI that adding a dialysis dose conferred better survival, especially with low-molecular-weight solutes during continuous venovenous haemofiltration [8]. However, it must be pointed out that these authors achieved a combined dose of continuous haemodialysis and haemofiltration that was ~43 mL/kg/h, i.e. comparable to those in the higher dose treatment group by Ronco *et al.* [3]. Secondly, although the key features of ED, i.e. long dialysis time and slow

dialysate and blood flow rates, are available to programmes worldwide, the GENIUS machine has some different features that theoretically might have influenced the results. If these different features would play a role, this could be regarded as a systematic error, with no influence on dose-related issues. Thirdly, our definition of AKI differed from the recently proposed definition by the Acute Kidney Injury Network [1], which is relevant for comparison of our results to recent and future studies. Fourthly, as there is ongoing uncertainty about the utility of small solute clearance as a determinant of dialysis efficacy in extended dialysis, we used surrogate markers of dialysis dose, i.e. cumulative treatment time and cumulative treatment volume [23]. Our scepticism to use Kt/V as a appropriate model for the description of urea kinetics in ED is supported by a recent study of Eloot *et al.* [24], who showed that despite a comparable Kt/V the total solute removal for creatinine and urea increased with dialysis time from 4 over 6–8 h, i.e. better solute removal despite identical Kt/V. Fifthly, the APACHE II scores of more than 30 for both groups at the time of RRT initiation indicated that the study population was more critically ill than those described by Ronco *et al.*, Schifffl *et al.* and the VA-Network study [3–5]. Hence, we cannot exclude that increasing the dose of ED beyond a certain point might be beneficial for patients with less severe critical illness. However, with respect to the distribution of comorbid conditions, our mono-centric spectrum of AKI-related comorbidity compares well to the data published by Uchino *et al.* derived from a large multicentre study [2]. Sixthly, the study was not powered to rule out the possibility that a higher dialysis dose might be beneficial; however, if a benefit exists our data suggest that it might be a marginal one whose clinical significance might be negligible. Lastly, urea, the main blood marker of uraemia that was adjusted to and controlled by our therapy, might not adequately reflect the complex problem of uraemic retention/dialytic clearance [25].

In summary, although this study cannot deliver a definitive answer, it suggests that increasing the dose of extended dialysis above the currently recommended dose might neither reduce mortality nor improve renal recovery in critically ill patients, mainly septic patients, with AKI.

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**Conflict of interest statement.** D.F. planned the study, wrote the protocol, applied for Ethics Committee approval and approval by official institutions and participated in the execution of the study and in the writing of the draft and the final version of the manuscript. He has seen and approved the final version of the manuscript, and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He received an unrestricted research grant from Fresenius Medical Care (FMC) Germany (see Acknowledgements), speaker's honoraria from Fresenius Medical Care (FMC) Germany. R.F.-W. participated in planning the study, wrote the computer file required to store and analyse the data, participated in the execution of the study and contributed in analysing the data, participated in the writing of the draft and the final version of the manuscript. He has seen and approved the final version of the manuscript and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He has no conflicts of interest/financial disclosures. C.H. has participated in planning and execution of the study, and in the writing of the draft and the final version of the manuscript. He has seen and approved the final version of the manuscript, and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She has no conflicts of interest/financial disclosures. N.J. participated in the execution of the study. She has seen and approved the final version of the manuscript and had full access to the data. She has no conflicts of interest/financial disclosures. J.V. participated in the execution of the study. She has seen and approved the final version of the manuscript, and had full access to the data. She has no conflicts of interest/financial disclosures. L.H. participated in planning of the statistical analysis of the study. He has seen and approved the final version of the manuscript, and had full access to the data. He has no conflicts of interest/financial disclosures. H.H. participated in the planning of the study. He has seen and approved the final version of the manuscript and had full access to the data. He has no conflicts of interest/financial disclosures. J.T.K. participated in the planning of the study design, writing the protocol and the application for Ethics Committee approval and participated in the execution of the study. He participated in the writing of the draft and the final version of the manuscript. He has seen and approved the final version of the manuscript, and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He received speaker's honoraria from Fresenius Medical Care (FMC) Germany. The results of the HANDOUT study were presented at the following meetings: (1) 44th Congress of the European Dialysis and Transplant Association, Barcelona, Spain, 23 June 2007 (Best Abstract Award to R. Faulhaber-Walter), (2) Annual Meeting of the American Society of Nephrology—Renal Week 2007, San Francisco, USA, 2 November 2007.

## References

1. Mehta RL, Kellum JA, Shah SV *et al.* Acute Kidney Injury Network (AKIN): report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11: R31
2. Uchino S, Kellum JA, Bellomo R *et al.* Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005; 294: 813–818
3. Ronco C, Bellomo R, Homel P *et al.* Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* 2000; 356: 26–30
4. Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002; 346: 305–310
5. VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; 359(1): 7–12
6. Davenport A, Bouman C, Kirpalani A *et al.* Delivery of renal replacement therapy in acute kidney injury: what are the key issues? *Clin J Am Soc Nephrol* 2008.
7. Fliser D, Kielstein JT. Technology Insight: treatment of renal failure in the intensive care unit with extended dialysis. *Nat Clin Pract Nephrol* 2006; 2: 32–39
8. Saudan P, Niederberger M, De Seigneux S *et al.* Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 2006; 70: 1312–1317
9. Storck M, Hartl WH, Zimmerer E *et al.* Comparison of pump-driven and spontaneous continuous haemofiltration in postoperative acute renal failure. *Lancet* 1991; 337: 452–455
10. Bouman CS, Oudemans-van Straaten HM, Tjissen JG *et al.* Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med* 2002; 30: 2205–2211
11. Czock D, Husig-Linde C, Langhoff A *et al.* Pharmacokinetics of moxifloxacin and levofloxacin in intensive care unit patients who have acute renal failure and undergo extended daily dialysis. *Clin J Am Soc Nephrol* 2006; 1: 1263–1268
12. Kielstein JT, Kretschmer U, Ernst T *et al.* Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. *Am J Kidney Dis* 2004; 43: 342–349
13. Burkhardt O, Hafer C, Langhoff A *et al.* Pharmacokinetics of eraptenem in critically ill patients with acute renal failure undergoing extended daily dialysis. *Nephrol Dial Transplant* 2009; 24(1): 267–271
14. Eknoyan G, Beck GJ, Cheung AK *et al.* Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; 347: 2010–2019
15. Paniagua R, Amato D, Vonesh E *et al.* Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 2002; 13: 1307–1320
16. Silvester W. Outcome studies of continuous renal replacement therapy in the intensive care unit. *Kidney Int Suppl* 1998; 66: S138–S141
17. Tonelli M, Manns B, Feller-Kopman D. Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. *Am J Kidney Dis* 2002; 40: 875–885
18. Augustine JJ, Sandy D, Seifert TH *et al.* A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis* 2004; 44: 1000–1007
19. Manns M, Sigler MH, Teehan BP. Intradialytic renal haemodynamics—potential consequences for the management of the patient with acute renal failure. *Nephrol Dial Transplant* 1997; 12: 870–872
20. Kumar VA, Yeun JY, Depner TA *et al.* Extended daily dialysis versus continuous hemodialysis for ICU patients with acute renal failure: a two-year single center report. *Int J Artif Organs* 2004; 27: 371–379
21. Lonnemann G, Floege J, Kliem V *et al.* Extended daily venovenous high-flux haemodialysis in patients with acute renal failure and multiple organ dysfunction syndrome using a single path batch dialysis system. *Nephrol Dial Transplant* 2000; 15: 1189–1193
22. Marshall MR, Golper TA, Shaver MJ *et al.* Sustained low-efficiency dialysis for critically ill patients requiring renal replacement therapy. *Kidney Int* 2001; 60: 777–785
23. Marshall MR, Golper TA, Shaver MJ *et al.* Urea kinetics during sustained low-efficiency dialysis in critically ill patients requiring renal replacement therapy. *Am J Kidney Dis* 2002; 39: 556–570
24. Eloot S, Van Biesen W, Dhondt A *et al.* Impact of hemodialysis duration on the removal of uremic retention solutes. *Kidney Int* 2008; 73: 765–770
25. Vanholder R, De SR, Glorieux G *et al.* Review on uremic toxins: classification, concentration, and interindividual variability. *Kidney Int* 2003; 63: 1934–1943

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