

Original Article

## Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial

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### Abstract

**Background.** There is uncertainty on the effect of different dialysis modalities for the treatment of patients with acute kidney injury (AKI), admitted to the intensive care unit (ICU). This controlled clinical trial performed in the framework of the multicentre SHARF 4 study (Stuivenberg Hospital Acute Renal Failure) aimed to investigate the outcome in patients with AKI, stratified according to severity of disease and randomized to different treatment options.

**Methods.** This was a multicentre prospective randomized controlled trial with stratification according to severity of disease expressed by the SHARF score. ICU patients were eligible for inclusion when serum creatinine was >2 mg/dL, and RRT was initiated. The selected patients were randomized to intermittent (IRRT) or continuous renal replacement therapy (CRRT).

**Results.** A total of 316 AKI patients were randomly assigned to IRRT ( $n = 144$ ) or CRRT ( $n = 172$ ). The mean age was 66 (range 18–96); 59% were male. Intention-to-treat analysis revealed a mortality of 62.5% in IRRT compared to 58.1% in CRRT ( $P = 0.430$ ). No difference between IRRT and CRRT could be observed in the duration of ICU stay or hospital stay. In survivors, renal recovery at hospital discharge was comparable between both groups. Multivariate analysis, including the SHARF score, APACHE II and SOFA scores for correction of disease severity, showed no difference in mortality between both treatment modalities. This result was confirmed in pre-specified subgroup analysis (elderly, patients with sepsis, heart failure, ventilation) and after exclusion of possible confounders (early mortality, delayed ICU admission).

**Conclusions.** Modality of RRT, either CRRT or IRRT, had no impact on the outcome in ICU patients with AKI. Both modalities need to be considered as complementary in the

treatment of AKI (Clinical Trial: SHARF 4, NCT00322933, <http://ClinicalTrials.gov>).

**Keywords:** acute kidney injury; continuous renal replacement therapy; intermittent renal replacement therapy; mortality; randomized clinical trial

### Introduction

Acute kidney injury (AKI) is frequently part of a multiple-organ dysfunction syndrome in critically ill patients admitted to an intensive care unit (ICU). Patients have a high mortality rate despite renal replacement therapy (RRT) [1,2]. Insight into incidence and prognosis of AKI is mandatory in view of its therapeutic, ethical and economic implications [3–6].

The influence of different types of RRT on the outcome of AKI is a controversial issue. Opposing results have been published. Most of the observational studies, however, were neither randomized nor prospective and suffer from selection bias [7–11]. Randomized clinical trials of continuous versus intermittent dialysis provide no evidence for a survival benefit of one of the treatment options [12–15].

Systematic reviews of the available studies supported the conclusion that dialytic modality used in AKI does not affect rates of death or renal recovery [16–18]. According to the authors, the design of new clinical trials would need to account for, among others, a higher sample size and particularly a better control of the severity of illness of the included population.

In previous parts of the Stuivenberg Hospital Acute Renal Failure (SHARF) project, we developed a predictive model for hospital mortality in 197 patients admitted to a single ICU (SHARF 1 and 2) [19]. This SHARF score was validated in a multicentre, prospective study in 293 patients in 8 ICUs (SHARF 3) [20] (see supplementary data

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online). The SHARF score was tested in several subpopulations and compared between centres. Subsequently, it was used for comparative studies between treatments and between centres [20].

In the SHARF 4 study, we compared prospectively the outcome of different modes of therapy [daily intermittent renal replacement therapy (IRRT) versus continuous renal replacement therapy (CRRT)]. The SHARF score was used to control for disease severity. This article will focus on the comparison between both treatment options in a randomized clinical trial with the short-term outcome on hospital mortality and renal recovery at hospital discharge used as end-points.

## Subjects and methods

### *Participating hospitals*

In order to include a sufficient number of AKI patients per centre in the trial, hospitals qualified for participation if they had at least 600 beds, a centre for the treatment of end-stage kidney disease (ESKD) patients, a multipurpose ICU with at least 12 beds, at least 30 patients with AKI treated with RRT during the past year and regular use of both intermittent and continuous techniques. A centre questionnaire was sent to candidate centres in order to check qualifying criteria.

### *Patients*

All adult (age  $\geq 18$  years old) AKI patients with a serum creatinine  $>2$  mg/dL that were consecutively admitted in the participating centres were registered. Patients were excluded if they had pre-existing chronic renal disease, defined as a serum creatinine  $>1.5$  mg/dL or with the clearly reduced kidney size on ultrasound. Severity of illness was defined in all these patients by calculating the SHARF score [20] (see supplementary data online). When the attending physician decided, based on his experience and the rules of good clinical practice in this field, that there was a need for RRT, patients became eligible for the randomized study and were stratified in three classes of disease severity according to the SHARF score (SHARF  $<30$ , 30–60,  $>60$ ). Within each stratum, patients were randomized to daily IRRT (intermittent haemodialysis during 4–6 h daily) or CRRT (continuous veno-venous haemofiltration).

### *Data collection*

The following data were collected: demographic data (age, sex, weight and height), course of hospitalization (date of admission to the hospital and ICU, date of discharge from the ICU and hospital or date of death), date of AKI diagnosis, type of AKI (prerenal, renal, postrenal, acute on chronic disease), cause of AKI (acute tubular necrosis, acute glomerulonephritis, acute interstitial nephritis, systemic disease), setting of AKI (medical, surgical) and serum creatinine at different time points during hospitalization. Parameters of the SHARF score were collected at the first day when the criteria of AKI were met. For patients referred to the ICU later in the course of their AKI, the day

of admission to the ICU was the starting day. Overall severity was evaluated with the APACHE II score [21] and the SOFA score [22] at admission to the ICU.

The following short-term outcome parameters were measured: hospital mortality, length of stay at ICU and hospital and an estimated glomerular filtration rate (eGFR) at hospital discharge according to the Cockcroft and Gault formula.

### *Allocation of treatment*

Separately for each participating centre, the choice of RRT treatment modality was randomized within each stratum of the SHARF score. Stratified block randomization was achieved within the electronic case report form (CRF) using a computer-generated sequence of random numbers. If the investigator decided not to randomize, the program was electronically blocked until he completed the reason for non-randomization.

### *Renal replacement therapy*

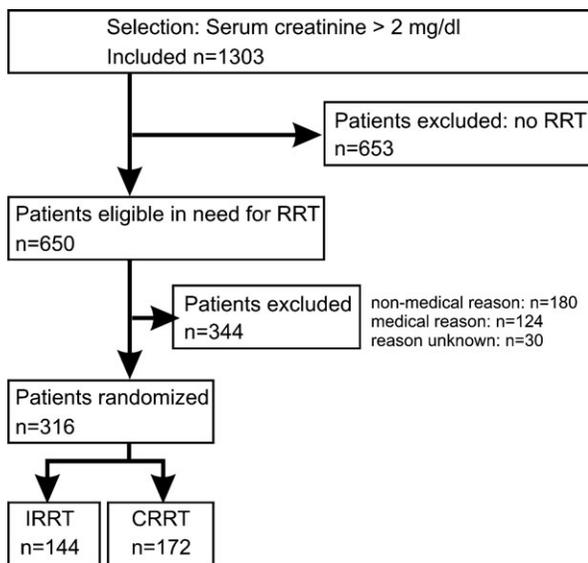
The techniques used to perform RRT were in agreement with the standard procedures of the participating centres. The strategy chosen in the protocol was the result of a questionnaire on current practice on RRT in the participating hospitals. For IRRT, a central venous access, a biocompatible membrane (polysulfone or AN 69) and bicarbonate dialysate were used. Daily dialysis was performed during 4–6 h per session with a blood flow of 100–300 mL/min and a dialysate flow of 300–500 mL/min. For CRRT, a central venous access, a biocompatible membrane (polysulfone or AN 69) and post-dilution continuous veno-venous haemofiltration (CVVH) were used. It was continued during 24 h/day with a blood flow rate of 100–250 mL/min, an ultrafiltration rate of 1–2 L/h and either lactate or bicarbonate solutions were used. For both modalities, anticoagulation was performed according to the centre practice, either with unfractionated heparin, low molecular weight heparin or citrate. The randomly assigned treatment modality of IRRT or CRRT had to be continued daily during at least 3 consecutive days. Thereafter treatment could be continued according to the needs of the patients. The motivation for any change in the randomized treatment was recorded in the electronic CRF. Data of all RRT treatments were recorded, including date, type of treatment, effective duration, ultrafiltration rate and artificial kidney.

### *Sample size calculation*

The sample size calculation was based on the assumption that the overall mortality would be 50% as in the former SHARF studies [19,20] and that a difference of 10% in mortality between IRRT and CRRT had to be detected to be clinically relevant. With a first-order error of 5% and a power of 80% a sample size of 407 patients was needed in each treatment group.

### *Statistical analysis*

The data analysis of this randomized clinical trial was performed according to the intention-to-treat principle. Outcome variables used were hospital mortality, mortality at



**Fig. 1.** Flow chart of the SHARF 4 study. RRT = renal replacement therapy; IRRT = intermittent renal replacement therapy; CRRT = continuous renal replacement therapy.

10 and 30 days after diagnosis of AKI, length of stay in ICU and hospital and renal function at hospital discharge. Univariate analysis was performed on all parameters in order to find significant differences between groups using Student's *t*-test and the chi-square test. Life table analysis was used to compare hospital survival in both treatment groups with Cox proportional hazards regression to control for covariates. Multivariate analysis was performed using logistic regression with mortality as dependant outcome variable. For pre-specified subgroup analysis, selection was based on reported evidence that these subgroups included the most complicated patients showing the highest comorbidity and mortality. Confounding factors were selected if they showed a significant difference in the comparison between both treatment options and contributed effectively and independently to the observed outcome. Statistical significance was set at the 0.05 level (two-sided). All analyses were performed using SPSS, version 12.0.

#### *Institutional review board*

The protocol has been approved initially by the Ethics Committee of the Public Hospital Sector of Antwerp and by the Ethics Committee of each participating centre. A written informed consent has been asked from each patient or his representative in the case that the patient was unconscious or intubated.

## Results

In a period of 3 years (April 2001–March 2004), nine Belgian participating centres selected 316 patients for inclusion in the clinical trial. Calculation of the SHARF score revealed that 42 patients belonged to SHARF class 1, 70 to class 2 and 204 to class 3 with SHARF scores below 30, between 30 and 60 and above 60, respectively. After

**Table 1.** Baseline characteristics and clinical parameters of patients randomized to intermittent or continuous renal replacement therapy

	IRRT	CRRT	<i>P</i> -value of difference
Number of AKI patients	<i>n</i> = 144	<i>n</i> = 172	
Age: mean (range)	67 (20–96)	65 (18–89)	0.120
Male	58.3%	60.0%	
Female	41.7%	40.0%	0.765
Type of AKI			
Pre-renal	28.6%	36.3%	
Renal	71.4%	63.7%	0.150
Specified renal causes of AKI			
Acute tubular necrosis	88.5%	87.5%	
Other	11.5%	12.5%	0.821
Setting of AKI			
Medical	71.0%	72.9%	
Surgical	29.0%	27.1%	0.717
Delayed admission to ICU	58.7%	51.8%	0.217
Severity parameters [mean (SD)]			
SHARF 0 (baseline)	65.3 (32.5)	67.7 (26.9)	0.488
APACHE II (baseline)	27.1 (11.5)	26.3 (11.2)	0.584
SOFA 0 (baseline)	10.8 (3.4)	10.7 (3.4)	0.839

AKI = acute kidney injury; ICU = intensive care unit; RRT = renal replacement therapy; IRRT = intermittent renal replacement therapy; CRRT = continuous renal replacement therapy.

stratification in these SHARF classes, IRRT was randomly assigned in 144 patients, CRRT in 172 patients (Figure 1).

The eligible population consisted of 650 patients. Exclusion from randomization was for a non-medical reason in 54% of patients (lack of time to complete computer entries, technical computer problems, dialysis modality not available and SHARF parameters not available at randomization), based on a clinical reason in 37% of patients (mainly coagulation disturbances and haemodynamic instability) and the reason was unknown in 9% of cases.

The mean age of the randomized population was 66 years (range 18–96); 59% were male. Basic characteristics as well as severity scores (SHARF, APACHE II and SOFA) were comparable between both treatment groups (Table 1). At diagnosis of AKI, mean serum creatinine was 3.6 mg/dL (SD 2.3) in IRRT and 3.4 mg/dL (SD 2.3) in CRRT patients ( $P = .305$ ). Patients randomized to IRRT were treated for a median of four sessions (range 1–35) with a mean duration of 4 h (SD 0.9); patients randomized to CRRT were treated for a median of 4 days (range 1–32) with a mean substitution of 1.8 L (SD 0.8) or 21.0 mL/kg (SD 9.5). Cross-over of treatment within the first 3 days of RRT treatment was noted from IRRT to CRRT in 11 patients and from CRRT to IRRT in 12 patients. The main reason for conversion from IRRT to CRRT was haemodynamic instability, and for conversion from CRRT to IRRT coagulation problems.

An overall mortality of 60.1% was observed. Within the three SHARF score classes, mortality was 19%, 59% and 69%, respectively. Intention-to-treat analysis revealed a mortality of 62.5% in patients treated with IRRT

compared to 58.1% in patients treated with CCRT ( $P = 0.430$ ) (Table 2). No difference in mortality between both treatment options could be observed within each of the three SHARF classes. Also after exclusion of patients treated for <3 days, mortality did not differ significantly, with 56%

in IRRT and 61% in CRRT, respectively ( $P = 0.567$ ). Additionally, no difference between IRRT and CRRT could be noted in the duration of ICU stay or hospital stay. In survivors, at hospital discharge, an eGFR of <15 mL/min (stage 5) was observed in 25% of IRRT and 17% of CRRT patients (Table 2).

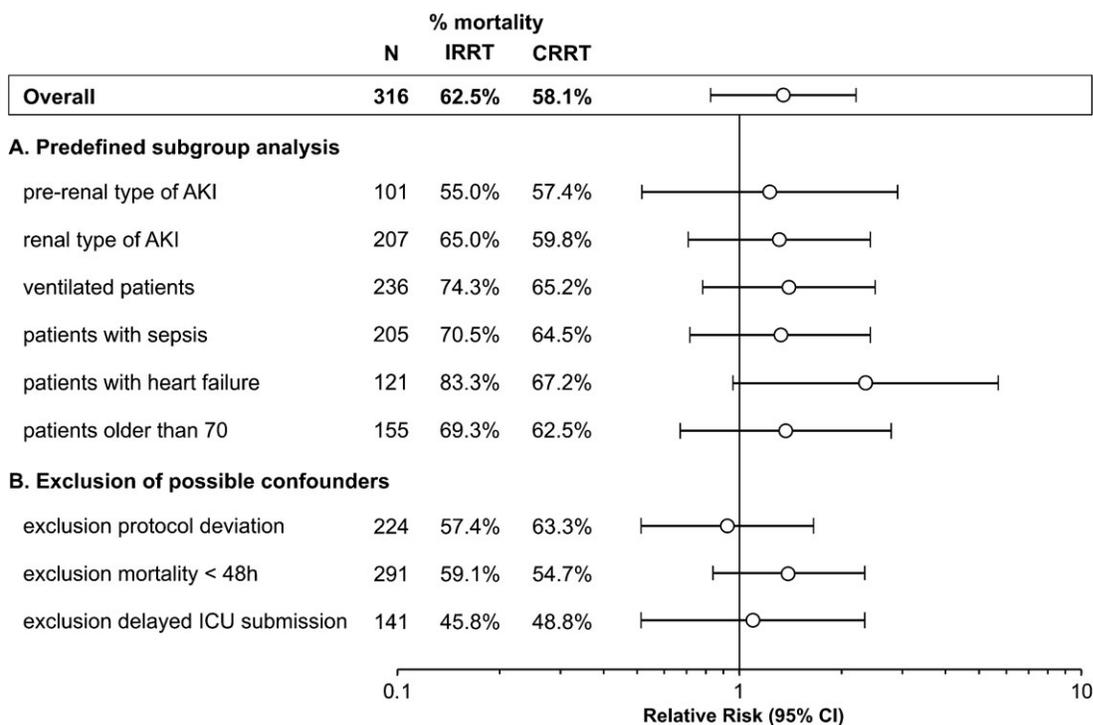
A separate analysis of the non-randomized population yielded the same outcome results comparing both treatment options, confirming the results of the clinical trial. The non-randomized patients were significantly younger, and had comparable SHARF scores and a lower APACHE II score ( $P = 0.001$ ).

Multivariate analysis using the SHARF score for correction of disease severity revealed that there was no difference in mortality between both treatment modalities. Subgroup analysis, including only older patients, ventilated patients, patients with sepsis or heart failure and patients with pre-renal or renal type of AKI, confirmed the overall result showing no increased risk of mortality for the use of CRRT compared to IRRT (Figure 2). The result was also confirmed after excluding possible confounders such as patients who died within 48 h after ICU admission, patients with delayed admission to the ICU or patients with protocol deviation (Figure 2). Additionally, life table analysis with Cox regression for correction of disease severity using the SHARF, APACHE II and SOFA scores did not show any difference for ICU survival between both treatment groups (Figure 3). Ten days after the diagnosis of AKI, hospital mortality in the IRRT and CRRT groups was 19% and 14%, respectively. After 30 days, mortality increased to 45% and 36%, respectively.

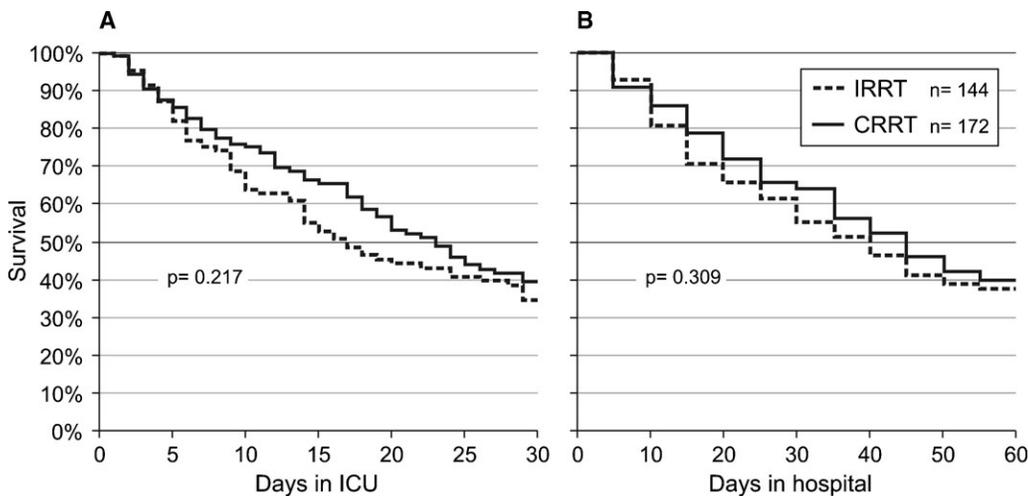
**Table 2.** Outcome in patients randomized to intermittent or continuous renal replacement therapy

	IRRT	CRRT	<i>P</i> -value of difference
Number of AKI patients	<i>n</i> = 144	<i>n</i> = 172	
Hospital mortality	62.5%	58.1%	0.430
ICU and hospital stay			
Days in ICU: mean (SD)	17.2 (18.7)	18.7 (19.0)	0.510
Days in hospital: mean (SD)	31.4 (29.7)	36.8 (31.0)	0.345
Renal outcome in survivors			
CKD stage 1–2 (GFR ≥60 ml/min)	29.8%	28.8%	
CKD stage 3 (GFR 30–59 ml/min)	29.8%	28.8%	
CKD stage 4 (GFR 15–29 ml/min)	14.9%	25.5%	
CKD stage 5 (GFR <15 ml/min or ESKD)	25.5%	16.9%	0.474

AKI = acute kidney injury; ICU = intensive care unit; GFR = glomerular filtration rate; RRT = renal replacement therapy; IRRT = intermittent renal replacement therapy; CRRT = continuous renal replacement therapy; ESKD = end-stage kidney disease; CKD = chronic kidney disease.



**Fig. 2.** Outcome in patients randomized to intermittent (IRRT) or continuous (CRRT) renal replacement therapy. Relative risk calculation based on binary logistic regression analysis with IRRT as reference category, controlled for disease severity using the SHARF score.



**Fig. 3.** Survival curves in patients randomized to intermittent (IRRT) or continuous (CRRT) renal replacement therapy investigating ICU mortality and hospital mortality. Life table analysis was performed with Cox regression for correction of disease severity using the SHARF, APACHE II and SOFA scores.

## Discussion

In this controlled randomized trial with stratification according to disease severity, comparable mortality rates were observed in AKI patients treated with intermittent or continuous techniques of RRT. Also the length of stay in the ICU and the hospital, as well as renal function at hospital discharge, was comparable for both treatment options. The robustness of the results was supported by different pre-planned subgroup analysis. Among them, sepsis and ventilated groups that suffer from the most complicated forms of AKI confirm the lack of difference between both modalities. Exclusion of possible confounders, such as patients with protocol violations, patients dying within 48 h after ICU admission or patients with delayed admission to the ICU, did not influence the results.

Recruitment of patients ended before the required sample size was reached. Despite our experience, derived from a previous multi-centre study [20], we were confronted with the problem that many centres made a final decision to choose either CRRT or IRRT in the mean time. For this study, however, centres with routine practice in both RRT modalities were required. Working with a limited number of centres, we were obliged to end recruitment too early since motivation declined and policy in the different centres changed considerably within this 3-year period.

From the eligible population, only ~50% were effectively randomized. This limited proportion of included patients is an important limitation of this study. However, most patients were excluded for a non-medical reason, limiting the chance for bias in the selection. All non-randomized patients had complete data collection, enabling us to perform the same analysis in the non-randomized population. In the non-randomized patients, who were younger and scored lower on the disease severity parameters, exactly the same results were obtained. These observations pointed to the fact that there was no selection bias in

view of disease severity with selection failure in more severe patients.

In the 1990s, the superiority of CRRT as first choice treatment in AKI patients was frequently claimed on the base of a better prognosis in retrospective and non-randomized observational trials [23–27]. Many observational studies, however, found that CRRT was associated with increased mortality [8–11]. These studies pointed to the problem of residual confounding by severity of illness, arguing that the observed results may have been because CRRT was applied to the more severely ill patients. Particularly in critically ill patients, a survival benefit of CRRT has been claimed by the advocates of CRRT [7,17,26–27]. A randomized controlled study and a prospective cohort study focussing on critically ill patients, however, provided no evidence for a better survival [15,28] or a better clinical outcome [29] in severe patients treated with CRRT. Recently, two retrospective cohort studies focussing on renal function confirmed the equal outcome for mortality but showed that CRRT was an independent predictor of renal recovery among hospital survivors [30,31]. Although we observed the same trend in our cohort, this observation could not be statistically corroborated (see Table 2).

Until now, randomized controlled trials failed to demonstrate a survival benefit for CRRT [12–15]. Most of these clinical trials, however, were underpowered and did not take into account severity of disease. Among them, only the Cleveland group stratified their patients according to a severity of illness score, the Cleveland Clinic Foundation severity score. They also found no difference in hospital mortality in their small prospective randomized study [13]. The finding of comparable outcomes for both treatment options was confirmed in two meta-analysis [16,17] and a recently published comprehensive review of options for renal replacement in AKI [18].

From the published results it was clear that further studies should need a randomized approach taking into account

severity of illness in order to solve the actual controversy between both treatment options.

Moreover, outcome could be influenced by the dose of RRT administered [18,32]. Within the SHARF project, data on delivered dose were collected and a comparison between both treatment options in respect to delivered dose was performed, showing no effect on outcome [33]. The recent findings of the VA/NIH Acute Renal Failure Trial Network [34] confirmed that the low doses used in this study did not bias the obtained results. Additionally, it was suggested that outcomes over a prolonged period of time should be addressed [16,18]. This SHARF 4 cohort has been followed prospectively during 2 years to address questions of long-term outcome and economical issues [35,36].

In the study presented here, we compared, prospectively and randomized, IRRT and CRRT in 314 AKI patients admitted to the ICU and found no difference in hospital mortality, hospital length of stay and renal recovery at discharge between both patient groups. The use of the SHARF score for correction of disease severity enabled the confirmation that CRRT showed no survival benefit, even in critically ill patients. Since evidence is growing about the comparable outcome for both modalities, consensus is also growing to merely consider the different treatment options as complementary. Probably in the future, a combination of CRRT for early correction of haemodynamic instability, intensive, daily IRRT (SLEDD) as long as multiple organ failure exists and classic intermittent haemodialysis for long-lasting and isolated AKI, have to be used as complementary Extra Corporeal Treatment Modalities.

## Supplementary data

Supplementary data is available online at <http://ndt.oxfordjournals.org>.

**Acknowledgements.** Participating centres of the SHARF 4 study were the University Hospital of Brussels (P. Van der Niepen, D. Verbeelen, I. Hubloue), ZNA Stuivenberg Hospital (R. Daelemans, M. Malbrain, J. Leijts, R. L. Lins), University Hospital Gent (E. Hoste, R. Lameire, W. Van Biesen), University Hospital Liège (P. Damas, B. Dubois, J. M. Krzesinski), Brugmann University Hospital, Brussels (J. Devriendt, M. Dratwa, R. Wens), AZ St. Augustinus, Antwerpen (L. Van Looy), AZ St. Elisabeth, Brussels (M. Malbrain), AZ St. Jan, Genk (R. De Jongh) and AZ Saint Jean, Bruxelles (G. Van Roost, B. Denis, P. Weyers, F. Zeghiche). Data collection was performed by L. Buyst, T. De Keyser, J. W. De Neve, V. Lins, T. Mellaerts, S. Van Bastelaere and A. Van Berendonckx. Secretarial help of S. Van Bastelaere was highly appreciated.

**Conflict of interest Statement.** None declared.

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*Received for publication: 4.4.08*

*Accepted in revised form: 15.9.08*

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