Comparison of Urine Output among Patients Treated with More Intensive Versus Less Intensive RRT: Results from the Acute Renal Failure Trial Network Study

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Abstract

Background and objectives Intensive RRT may have adverse effects that account for the absence of benefit observed in randomized trials of more intensive versus less intensive RRT. We wished to determine the association of more intensive RRT with changes in urine output as a marker of worsening residual renal function in critically ill patients with severe AKI.

Design, setting, participants, & measurements The Acute Renal Failure Trial Network Study (n=1124) was a multicenter trial that randomized critically ill patients requiring initiation of RRT to more intensive (hemodialysis or sustained low–efficiency dialysis six times per week or continuous venovenous hemodiafiltration at 35 ml/kg per hour) versus less intensive (hemodialysis or sustained low–efficiency dialysis three times per week or continuous venovenous hemodiafiltration at 20 ml/kg per hour) RRT. Mixed linear regression models were fit to estimate the association of RRT intensity with change in daily urine output in survivors through day 7 (n=871); Cox regression models were fit to determine the association of RRT intensity with time to ≥50% decline in urine output in all patients through day 28.

Results Mean age of participants was 60±15 years old, 72% were men, and 30% were diabetic. In unadjusted models, among patients who survived ≥7 days, mean urine output was, on average, 31.7 ml/d higher (95% confidence interval, 8.2 to 55.2 ml/d) for the less intensive group compared with the more intensive group (P=0.01). More intensive RRT was associated with 29% greater unadjusted risk of decline in urine output of ≥50% (hazard ratio, 1.29; 95% confidence interval, 1.10 to 1.51).

Conclusions More intensive versus less intensive RRT is associated with a greater reduction in urine output during the first 7 days of therapy and a greater risk of developing a decline in urine output of ≥50% in critically ill patients with severe AKI.

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Introduction

Critically ill patients who develop AKI requiring RRT have a high estimated mortality of approximately 50%–60% (1–3). The use of RRT in this clinical setting is designed to optimize acid-base balance, small solute clearance, and volume control. Providing more intensive RRT (*via* greater solute clearance as measured by urea kinetic modeling) was, therefore, hypothesized to be beneficial (4–6). However, when tested in subsequent larger randomized, controlled trials, higher-intensity RRT in AKI has failed to improve outcomes compared with standard intensity therapy (7–9). A potential explanation for the absence of benefit may be an increased risk of adverse events associated with more intensive therapy. Enhanced clearance of small solutes may result in electrolyte depletion (8,10), and enhanced removal of antibiotics may result in decreased efficacy in the treatment of infections (11,12). In addition, untoward hemodynamic effects, such as greater frequency of intradialytic hypotension (IDH; *e.g.*, precipitated by rapid changes in plasma osmolality) (8), may exacerbate organ ischemia, including hypoperfusion of the already injured kidney parenchyma.

Preservation of urine output is an important prognostic indicator in the setting of AKI. Patients with AKI who develop reduced urine output have substantially greater risk of death (13–16), longer duration of dialysis dependence (16), and longer hospital stay (13) compared with those who do not. Reduced urine output in patients with AKI requiring RRT may indicate a greater severity of kidney injury with less likelihood of renal recovery (17), greater associated mortality (14), and predisposition to complications related to volume management (18,19). No study to our knowledge has tested whether more intensive RRT in AKI leads to a reduction in urine output, a potential surrogate marker of residual renal function.

To test the hypothesis that more intensive RRT may cause adverse effects on urine output, we performed a

post hoc analysis of the Acute Renal Failure Trial Network (ATN) Study to determine the association of more intensive versus less intensive RRT with postrandomization changes in urine volume.

Materials and Methods

Study Design and Population

The ATN Study was a prospective, multicenter, randomized clinical trial of more intensive (hemodialysis [HD] or sustained low–efficiency dialysis six times per week or continuous venovenous hemodiafiltration at 35 ml/kg per hour) versus less intensive (HD or sustained low–efficiency dialysis three times per week or continuous venovenous hemodiafiltration at 20 ml/kg per hour) RRT in critically ill patients with a clinical diagnosis consistent with acute tubular necrosis (n=1124). Details of the study design have been previously reported (8,20). Notable exclusion criteria included a baseline serum creatinine >2 mg/dl for men and >1.5 mg/dl for women, AKI felt to not be caused by acute tubular necrosis, more than one HD treatment or >24 hours of continuous RRT before randomization, and expected survival <28 days because of an underlying terminal chronic condition. Survival to day 7 (n=871) was a prespecified requirement for our primary *post hoc* analyses because of the competing risk of mortality in critically ill patients with AKI. The study protocol pertaining to these *post hoc* analyses was deemed exempt under 42 CFR §46.101(b)(4) by the Partners Healthcare Institutional Review Board.

Exposures and Outcomes

The exposure of interest was the randomized treatment assignment of more intensive versus less intensive RRT. The primary outcome of interest was the rate of change in daily urine output in patients who survived from randomization through (and including) day 7 (n=871). Additional analyses were performed to determine the association of more intensive versus less intensive RRT with the need for continued RRT at days 28 and 60. The secondary outcome was the time to ≥50% decline in daily urine output in the complete cohort from randomization through day 28 (n=1103). The majority of urine outputs (95.7%) were recorded as timed 24-hour collections during each study day. For those with collection periods other than 24 hours (median =12 hours; interquartile range [IQR], 7–16 hours), the estimated daily output was extrapolated according to the following equation: daily urine output = (urine volume/hours of collection) ×24.

Study Data

All study data in the ATN Study were recorded on case report forms and submitted to a central data coordinating center. Demographic data (sex, race, and age), comorbid data (ischemic heart disease, congestive heart failure, peripheral vascular disease, hypertension, stroke, liver disease, diabetes, malignancy, baseline cardiovascular [CV] sequential organ failure assessment [SOFA] score, and 24-hour urine volume), and anthropometric data (weight and height) were recorded at baseline for all participants. The original ATN Study defined baseline oliguria as an average urine output <20 ml/h over a 24-hour period. However, in light of the observed distribution of the baseline 24-hour urine volumes, we defined baseline oliguria as a 24-hour urine volume <110 ml/d (the 25th percentile). Postrandomization physiologic data, including urine volume, BUN, the CV component of the SOFA score, and net fluid balance (total intake − [total output + ultrafiltration]), were recorded on days 1–14, 21, and 28.

Statistical Analyses

Continuous variables were examined graphically and recorded as means (±SDs) for normally distributed data or medians (with IQRs) for non–normally distributed data. Comparisons were made using t tests or Wilcoxon rank sum tests as appropriate. Categorical variables were examined by frequency distribution and recorded as proportions, and comparisons were made using the chi-squared test. To model the daily urine output for the primary analyses, the following unadjusted linear mixed model was fit (model 1), where Y_{ijk} denotes the urine output for patient k in treatment group i (i=1 → less intensive RRT; i=2 → more intensive RRT) on day j: $E[Y_{ijk}]=\mu\ldots+\tau_i+\alpha\times j+\gamma_i\times j+d_{j(k)}+\varepsilon_{ijk}$. In this model, μ represents the intercept, τ_i represents a fixed effect for treatment i, α represents a fixed effect for day j, γ_i represents an interaction effect for treatment i and day j, $d_{j(k)}$ represents a random effect of day j nested within patient k (to account for correlation among urine output levels within each patient across time), and ε_{ijk} represents an error term for Y_{ijk}, which is normally distributed with mean =0 and variance of σ^2_ε. We also fit separate unadjusted models to assess each of the following effects on daily urine output: (*1*) the interaction between treatment assignment and treatment modality and (*2*) the interaction between treatment assignment and baseline urine output. Subsequently, a multivariable model was fit (model 2) that adjusted for the following baseline variables: sex, race (black versus nonblack), age, ischemic heart disease, congestive heart failure, peripheral vascular disease, hypertension, stroke, liver disease, diabetes, malignancy, CV component of the SOFA score (0, 1, 2, 3, or 4), oliguria, weight, and height. All models were implemented in SAS (SAS Institute Inc., Cary, NC) using PROC GLIMMIX, where the Kenward–Roger denominator degrees of freedom method was used. Analogous models were fit for those who survived through day 28.

Exploratory models examining the daily rate of change were fit by adjusting for the same covariates as model 2 in addition to individual adjustment for time–varying covariates of interest (for survivors through day 7). These prespecified covariates included daily measurement of BUN, CV SOFA score, and net fluid balance. Logistic regression models were subsequently fit to determine the unadjusted and adjusted (model 2) associations of RRT intensity with the need for continued RRT at days 28 and 60.

For analysis of the secondary outcome, unadjusted and adjusted (model 2) Cox proportional hazards models were fit to estimate the association of more intensive versus less intensive RRT with time to decline in urine output of ≥50%. Fixed effects with nominal two–sided P values of <0.05 were considered statistically significant. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc.) and Stata MP13.1 (StataCorp., College Station, TX).

Results

Of the 1124 individuals in the ATN Study, 871 survived through day 7 and were included in our primary analyses. Mean age was 59.6±15.3 years old, 14.9% were black, and 30.4% were diabetic. The demographic and comorbid characteristics of individuals according to randomized treatment arms were comparable at baseline (Table 1). During the first 7 days of the study, the average CV SOFA score and ultrafiltration volume achieved by RRT were similar between the treatment arms. BUN was lower in the more intensive arm, whereas net fluid balance was more negative in the less intensive arm (Table 2).

Rate of Change in Daily Urine Output from Randomization through Day 7

Urine volume at the time of randomization was similar in both groups (median =264 ml/d; IQR, 106–473 in the less intensive group and median =274 ml/d; IQR, 110–489 in the more intensive group; *P* difference =0.49). During the initial 7-day period, the unadjusted mean urine output increased by 23.2 (95% confidence interval [95% CI], 6.6 to 39.8) ml/d with less intensive therapy and decreased by 8.5 (95% CI, −25.2 to 8.1) ml/d with more intensive therapy (Figure 1). The difference in the daily rate of change in urine output was 31.7 (95% CI, 8.2 to 55.2) ml/d higher, favoring the less intensive therapy arm. When adjusted for baseline covariates (model 2), the mean urine output increased by 26.6 (95% CI, 9.4 to 43.7) ml/d with less intensive therapy and decreased by 9.7 (95% CI, −27.0 to 7.6) ml/d with more intensive therapy. The difference was 36.3 (95% CI, 11.9 to 60.7) ml/d, favoring the less intensive therapy arm. In exploratory analyses aimed at uncovering potential pathway intermediaries, three prespecified time–varying covariates (net daily fluid balance, BUN, and CV component of the SOFA score) were added individually to model 2. Each resulted in a modest attenuation of the effect estimate for the difference in daily rate of change compared with model 2 alone (Table 3).

When the analyses were restricted to those who survived through day 28, the unadjusted mean urine output increased by 3.5 (95% CI, −2.9 to 9.8) ml/d with less intensive therapy and decreased by 2.7 (95% CI, −8.8 to 3.4) ml/d with more intensive therapy. The difference was 6.2 (95% CI, −2.6 to 15.0) ml/d higher with less intensive therapy. When adjusted for baseline covariates (model 2), the mean urine output increased by 4.6 (95% CI, −2.0 to 11.2) ml/d with less intensive therapy and decreased by 1.6 (95% CI, −7.9 to 4.8) ml/d with more intensive therapy. The difference was 6.1 (95% CI, −3.0 to 15.3) ml/d higher with less intensive therapy.

There was no evidence for effect modification on the basis of modality of RRT (*P* interaction >0.90). When baseline urine output was considered as a continuous variable, there was marginal evidence for the presence of effect modification (*P* interaction =0.08). Therefore, exploratory analyses were performed to assess the association of treatment assignment in the subgroups of patients who were oliguric and patients who were not oliguric. For those who were oliguric at baseline, the adjusted difference (model 2) in the daily rate of change in urine output was 11.4 ml/d (95% CI, −17.0 to 39.8), in favor of the less intensive arm; for those

Table 1. Baseline characteristics of individuals who survive through day 7 according to RRT intensity randomized groups

Characteristic	RRT Intensity		*P* Value[a]
	Less Intensive, *n*=436	More Intensive, *n*=435	
Men, %	70.2	73.6	0.27
Age, yr	59.7±15.4	59.5±15.3	0.83
Black, %	14.7	15.2	0.84
Ischemic heart disease, %	24.1	22.0	0.48
Heart failure, %	26.5	24.5	0.51
Peripheral vascular disease, %	15.8	18.7	0.28
Hypertension, %	2.9	4.6	0.18
Diabetes, %	29.2	31.6	0.45
Stroke, %	9.0	10.8	0.39
Liver disease, %	17.1	14.2	0.24
Malignancy, %	15.6	18.0	0.36
Weight, kg	85.0±18.7	84.1±19.7	0.48
Height, in	68.0±3.9	68.1±3.8	0.70
CV SOFA score	2 (0–4)	2 (0–4)	0.19
Total SOFA score	14 (11–16)	14 (11–17)	0.26
Baseline 24-h urine volume, ml	264 (106–473)	274 (110–489)	0.49
Nonoliguric,[b] %	74.9	75.4	0.86

CV SOFA, cardiovascular component of the sequential organ failure assessment score at baseline; SOFA, sequential organ failure assessment score.

[a]*P* value for difference; significance testing was by *t* test or Wilcoxon rank sum test for continuous variables or chi-squared test for categorical variables. Continuous variables are presented as means±SDs if normally distributed and medians (25th to 75th percentiles) if non-normally distributed.

[b]Oliguria was defined as baseline prerandomization 24-hour urine output <110 ml/d.

Table 2. Differences in physiologic parameters of interest in individuals who survived through day 7

Characteristic	RRT Intensity		*P* Value
	Less Intensive	More Intensive	
No. of treatments	5 (3–7)	6 (6–7)	<0.001
CV SOFA score	2 (0–4)	1 (0–4)	0.07
BUN, mg/dl	48 (34–67)	35 (24–51)	<0.001
Ins	2500 (1530–3980)	2830 (1770–4397)	<0.001
Outs	722 (262–1600)	614 (200–1420)	<0.001
Urine	159 (35–530)	106 (20–365)	<0.001
UF volume, ml	1850 (524–3000)	1700 (500–3000)	0.22
Net balance, ml	−220 (−1500–1301)	4 (−1304–1712)	<0.001

Summary statistics were calculated by averaging the daily measurement of parameters of interest for each individual over the 7 study days and are presented as medians (25th to 75th percentiles). Differences were assessed by Wilcoxon rank sum tests. Ins indicate daily fluid intake in milliliters. Outs indicate daily fluid loss (excluding urine and UF) in milliliters. UF volume indicates daily fluid loss removed by RRT modalities in milliliters. Net balance indicates total intake − (total output + UF volume). CV SOFA, cardiovascular component of the sequential organ failure assessment score; UF, ultrafiltration.

who were nonoliguric at baseline, the adjusted difference in the daily rate of change was 45.7 ml/d (95% CI, 14.2 to 77.2), in favor of the less intensive arm (Table 4).

Consistent with the results of the primary study (8), there was no association of more intensive RRT with a greater odds for continued RRT requirement at either day 28 (unadjusted odds ratio [OR], 1.26; 95% CI, 0.96 to 1.64 and adjusted OR, 1.32; 95% CI, 0.98 to 1.77) or day 60 (unadjusted OR, 1.20; 95% CI, 0.87 to 1.65 and adjusted OR, 1.26; 95% CI, 0.88 to 1.79).

Time to ≥50% Decline in Urine Output from Randomization through Day 28

In unadjusted analyses, there was a 29% greater risk of ≥50% decline in daily urine output (hazard ratio, 1.29; 95% CI, 1.10 to 1.51; *P*=0.001) in patients randomized to more intensive versus less intensive therapy (Figure 2). When adjusted for baseline covariates (model 2), the effect estimate was accentuated (hazard ratio, 1.37; 95% CI, 1.15 to 1.63). The results were qualitatively similar when the composite outcome of time to death or ≥50% decline of urine output was considered (data not shown).

Discussion

In this *post hoc* analysis of the ATN Trial Study, we report that more intensive RRT in critically ill patients with AKI resulted in a greater reduction in the daily rate of change in urine output than less intensive dosing of RRT

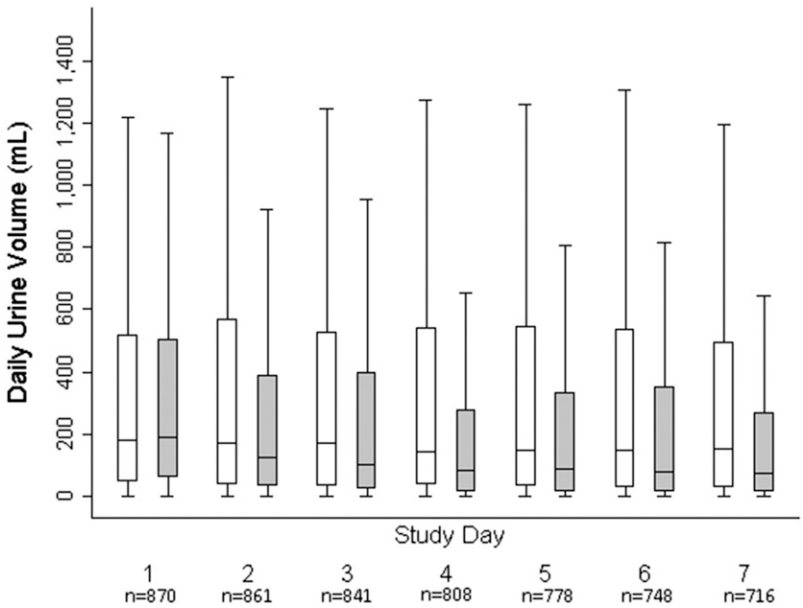

Figure 1. | Box plots of daily urine output according to RRT intensity. Less intensive is shown in white, and more intensive is shown in gray. The top line of each box represents the 75th percentile, the middle line represents the 50th percentile, and the bottom line represents the 25th percentile.

Table 3. Differences (less intensive RRT − more intensive RRT) in rate of change in daily urine output with individual additional adjustment for prespecified time–varying covariates in individuals who survived through day 7

Model	Daily Rate of Change in Urine Output		
	Less Intensive RRT	More Intensive RRT	Difference (Less Intensive − More Intensive)
Unadjusted, *n*=871			
Rate, ml/d (95% confidence interval)	23.2 (6.6 to 39.8)	−8.5 (−25.2 to 8.1)	31.7 (8.2 to 55.2)
P value	0.01	0.31	0.01
Model 2, *n*=783			
Rate, ml/d (95% confidence interval)	26.6 (9.4 to 43.7)	−9.7 (−27.0 to 7.6)	36.3 (11.9 to 60.7)
P value	0.002	0.27	0.004
Model 2 and daily net fluid balance, *n*=775			
Rate, ml/d (95% confidence interval)	14.8 (1.2 to 28.4)	−18.2 (−31.3 to −5.1)	33.0 (14.2 to 51.7)
P value	0.03	0.01	<0.001
Model 2 and daily CV SOFA score, *n*=776			
Rate, ml/d (95% confidence interval)	2.2 (−13.9 to 18.2)	−27.3 (−42.7 to −11.9)	29.5 (7.5 to 51.5)
P value	0.79	<0.001	0.01
Model 2 and daily BUN, *n*=783			
Rate, ml/d (95% confidence interval)	26.8 (9.5 to 44.1)	−4.3 (−22.1 to 13.4)	31.2 (6.6 to 55.7)
P value	0.002	0.63	0.01

Model 2 was adjusted for baseline sex, race (black versus nonblack), age, ischemic heart disease, congestive heart failure, peripheral vascular disease, hypertension, stroke, liver disease, diabetes, malignancy, cardiovascular component of the sequential organ failure assessment score (CV SOFA) score (0, 1, 2, 3 or 4), oliguria, weight, and height.

during the first week of therapy but did not result in differences in dialysis dependence at day 28 or 60. We also report that patients randomized to more intensive therapy had a greater risk of decline in urine output of ≥50%. These results suggest that lower urine output is a potential early adverse effect of more intensive RRT.

Before the availability of routine biochemical analyses, urine output was the major parameter by which changes in

Table 4. Analyses of the daily rate of change in urine output according to the presence or absence of baseline oliguria in individuals who survived through day 7

Sub-Group	Daily Rate of Change in Urine Output		
	Less Intensive RRT	More Intensive RRT	Difference (Less Intensive − More Intensive)
Oliguria (model 2), *n*=198			
Rate, ml/d (95% CI)	29.9 (9.9 to 49.9)	18.5 (−1.6 to 38.6)	11.4 (−17.0 to 39.8)
P value	0.003	0.07	0.43
Nonoliguria (model 2), *n*=585			
Rate, ml/d (95% CI)	25.5 (3.3 to 47.6)	−20.2 (−42.6 to 2.2)	45.7 (14.2 to 77.2)
P Value	0.02	0.08	0.004

Estimates were adjusted for baseline sex, race (black versus nonblack), age, ischemic heart disease, congestive heart failure, peripheral vascular disease, hypertension, stroke, liver disease, diabetes, malignancy, cardiovascular component of the sequential organ failure assessment score (CV SOFA) score (0, 1, 2, 3 or 4), weight, and height. Oliguria was defined as baseline prerandomization 24-hour urine output <110 ml/d. 95% CI, 95% confidence interval.

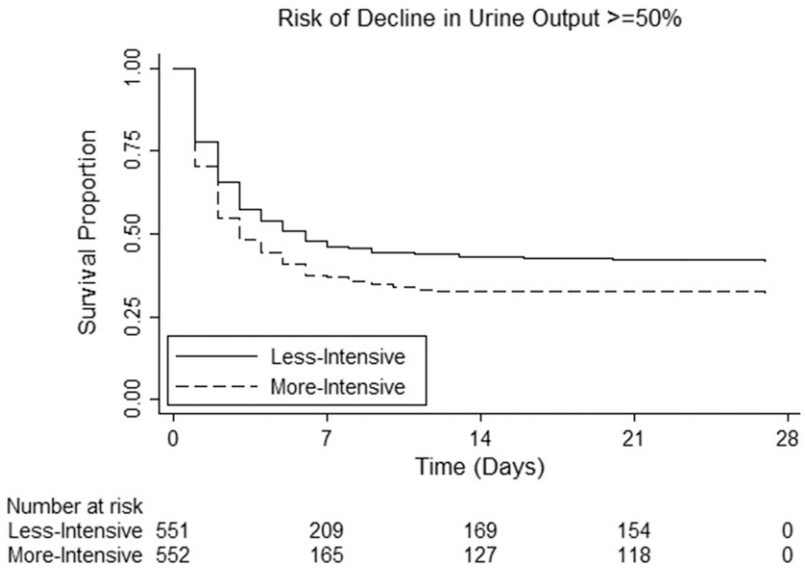

Figure 2. | Kaplan–Meier survival estimates for the association of more intensive versus less intensive RRT with the decline in urine output to ≥50% from baseline.

kidney function could be assessed; it remains an important clinical parameter in everyday practice. Several consensus panels have incorporated lower thresholds of urine output in the definition of AKI (*e.g.*, RIFLE [21], AKI Network [AKIN] [22], and Kidney Disease Improving Global Outcomes [23]) in recognition of the association of decreased urine output in critically ill patients with adverse outcomes. For example, in 1977, Anderson *et al.* (13) studied 90 patients with AKI (defined as persistent rise in serum creatinine >2 mg/dl despite corrective measures) and reported that patients who were not oliguric had a significantly shorter hospital stay, required RRT less frequently, and had lower mortality than those with oliguria. More recently, Oh *et al.* (16) examined urine output measurements over the 6-hour period before the initiation of continuous RRT in 361 critically ill Korean patients. They found that those with predialysis 6-hour urine outputs above the median (≥107 ml) had lower mortality in both unadjusted and case mix–adjusted analyses. Similar patterns of association with mortality have been reported in studies from South America (15) and Canada (14).

Greater degrees of volume overload have been associated with a higher risk of adverse outcomes, including greater risk of 60-day mortality (24,25), longer duration of ventilator dependence (18,26), and slower recovery of renal function in those with AKI requiring RRT (19). Of note, although no randomized studies have been implemented to test if earlier initiation of RRT for volume control is beneficial (because volume removal by RRT may be offset by decreases in urine output), there is biologic plausibility to suggest that preservation of urine output may be a reasonable clinical management goal. In our study, we found that the intensity of RRT associated with modest but significant differences in the rate of change in urine output, with greater increases in the daily rate of change in urine output reported in the less intensive arm. Although the less intensive arm had a slightly more negative average net fluid balance during the first 7 study days, in exploratory models, additional adjustment for time–varying net fluid balance actually resulted in modest attenuation of the effect estimates. This suggests that fluid status may partly mediate the association of RRT intensity with changes in urine volume but is not the major explanatory variable.

An important factor that may contribute to differences in urine output according to RRT intensity could be the presence of more hemodynamic instability associated with greater intensity or frequency of dialytic therapy. Indeed, the ATN Study reported that IDH events requiring vasopressor support or other interventions were more frequent in the intensive RRT arm (8), largely as a result of the greater absolute number of intermittent HD treatments in this arm. In exploratory models, we noted that additional adjustment for time–varying CV SOFA scores (a measure of hemodynamic stability) resulted in a modest attenuation of the effect estimates for daily rate of change in urine output. These observations raise the possibility that IDH could confound or lie on the causal pathway for the association of lower urine output with more intensive dialytic therapy. Analogous evidence exists in a *post hoc* analysis of patients on chronic HD from the Hemodialysis Study, in whom we previously reported that higher versus lower target Kt/V was associated with a greater risk of IDH (27), which, has been associated with greater decline in residual urine output by others (28).

The minimum daily urine output in humans with normal kidney function is determined by (*1*) the obligate solute excretion from byproducts of metabolism and (2) the maximum concentrating ability of the kidney. This equates to a minimum urine output of approximately 400 ml/d, with measurements below this having traditionally been defined as oliguria, and measurements <100 ml/d being defined as anuria. (29,30) Thus, higher clearance of small solutes (particularly urea) by more intensive versus less intensive RRT in

the ATN Study (8) may have partially contributed to a lower obligate urine volume (31,32). In our exploratory analyses, we noted that adjustment for time-updated measurements of BUN resulted in attenuation of the effect estimate for the difference in daily rate of change in urine output, supporting the notion that adjustment for BUN as a marker of solute load resulted in a smaller difference in changes in urine output between the less intensive and more intensive arms. Again, analogous evidence exists in patients on chronic HD, in whom more frequent HD (resulting in lower time–averaged urea concentrations) has been reported to be associated with a more rapid decline in urine output (33,34).

To assess if the association of RRT intensity with changes in urine volume persists over time, the data were analyzed in those who survived through day 28. In this case, there were no notable differences, suggesting that RRT intensity may have a greater influence on changes in urine output earlier in the course of AKI in critically ill patients. Supportive evidence for this assertion is provided by the fact that the favorable associations with less intensive therapy were more pronounced in those who were non-oliguric at baseline (which we defined as baseline 24-hour urine ≥110 ml/d) compared with those who were oliguric. However, we found no association of more intensive therapy with risk of persistent RRT requirement at day 28 or 60. Indeed, prior studies of strategies to augment urine output with diuretics in patients with AKI have not been shown to improve mortality or reduce the need for RRT (35,36). However, we are cognizant of the fact that the primary study was not powered for these *post hoc* subgroup analyses, which should be interpreted as hypothesis generating. Similarly, the analyses in the survivors through day 28 and later may be subject to selection and survivor biases.

The ATN Study afforded a unique opportunity to test the effect of RRT intensity on changes in urine output, a biologically plausible adverse effect of intensive RRT. The major strength of our report is that the primary analyses were performed according to the randomized treatment assignments from the ATN Study, which limits confounding by disease severity. Adjustment for potential confounding variables did not result in qualitative changes to the patterns of association that we observed, which might be expected from the balance in baseline covariates in participants included in this analysis. Furthermore, our results were consistent across the primary analysis (change in urine output in survivors through day 7) and in the secondary analysis (time to decline in urine output of ≥50%). Limitations of this analysis include the *post hoc* nature of the study, because the trial was not designed to examine urine output as the outcome of interest, and limitations in generalizability from a randomized, controlled trial. Because of data limitations, we were not able to adjust for dialysate sodium, temperature, or changes in serum osmolality in relation to the timing of dialytic therapies or dosage or duration of diuretic therapy.

In conclusion, we report that the use of more intensive RRT is associated with a decline in the daily rate of change in urine output during the first week of therapy among critically ill patients requiring RRT initiation, consistent with a potentially early adverse effect of more intensive RRT on residual renal function. Additional studies should identify the mechanistic basis for our findings. Identifying the optimal RRT strategy in AKI has the potential to improve the outcomes of hundreds of thousands of patients annually and should be a major focus of investigative efforts in critical care nephrology.

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Disclosures

None.

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