ORIGINAL RESEARCH ARTICLE

Treatment patterns of patients with acute heart failure who develop acute kidney injury

Jubran Boulos[1], Wisam Darawsha[1], Zaid A. Abassi[2,4], Zaher S. Azzam[3,4] and Doron Aronson[1,4]*

[1]Department of Cardiology, Rambam Medical Center, Bat Galim, Haifa, Israel; [2]Department of Physiology and Biophysics, Rambam Medical Center, Haifa, Israel; [3]Department of Internal Medicine B, Rambam Medical Center, Haifa, Israel; [4]Ruth and Bruce Rappaport Faculty of Medicine, Technion—Israel Institute of Technology, Haifa, Israel

Abstract

Aims   In the present study, we aimed to determine the relationship between therapeutic decisions during the treatment of acute heart failure (AHF) patients who develop acute kidney injury (AKI) and subsequent renal and clinical outcomes.
Methods and results   We studied 277 patients with AHF and AKI, defined as an increase of >0.3 mg/dL in serum creatinine. The physician response to AKI was determined through a treatment composite score that captured changes in medical management in response to AKI, including a reduction (≥50%) or discontinuation of selected medication classes [angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-Is/ARBs), beta-blockers, and diuretics] and fluids administration. ACE-Is/ARBs, beta-blockers, and diuretics were reduced or discontinued in 103 (55.4%), 84 (38.9%), and 166 (61.5%), respectively. Fluids were administered to 130 (46.9%) patients. Discontinuation rates of ACE-Is/ARBs, beta-blockers, diuretics, and fluids administration were higher in patients with hypotension (systolic blood pressure < 90 mm Hg; $P = 0.001$). In a logistic regression model, a composite score > 1 was associated with greater likelihood of renal function recovery (odds ratio 3.47, 95% confidence interval 2.06–5.83; $P < 0.0001$) but with a smaller reduction in congestion index ($P = 0.021$). Unadjusted 6 months mortality was higher in patients with a composite treatment score > 1 (hazard ratio 1.71, 95% confidence interval 1.12–2.61; $P = 0.01$). After adjustments, the treatment composite score was no longer associated with mortality.
Conclusions   Discontinuation or dose reduction of diuretics or neurohormonal blockers may improve renal outcome at the price of less efficient decongestion. Our results emphasize the need for randomized clinical trials that address the treatment of AHF patients with AKI.

Introduction

The great majority of acute heart failure (AHF) hospitalizations are due to congestion.[1–3] Acute kidney injury (AKI) complicating decongestive AHF therapy is currently defined as the acute (Type 1) cardio-renal syndrome and is often clinically recognized as worsening renal function after initiation of acute therapies.[4] Acute kidney injury, often defined as an increase in creatinine of >0.3 mg/dL from baseline, occurs in 20–30% of patients with AHF and is associated with greater length of stay (LOS), hospital readmission, and increased mortality.[5–8]

There are no proven treatments or guidelines for patients who develop AKI in the setting of AHF. In a recent clinical trial, investigators were encouraged to decrease the doses of angiotensin-converting enzyme inhibitors (ACE-Is) and beta-blockers if cardio-renal syndrome developed in temporal association with diuretic dose escalations.[9] However, depending on the haemodynamic status and degree of congestion, potential interventions for patients with AKI can include both intensification or de-escalation of loop diuretics and neurohormonal blockers or the use of vasodilators, positive inotropes, or ultrafiltration.

Temporary interruptions of diuretics or neurohormonal blockers may address potential concerns of transient intravascular volume depletion and represent standard clinical practice.[9] However, interruption of neurohormonal blockade

and intravenous fluids administration may potentially lead to clinical deterioration. In the present report, we studied physician responses to AKI occurring during AHF therapy, in its relationship to renal and clinical outcomes.

Methods

Acute heart failure cohort

Between January 2008 and April 2014, patients admitted to the Rambam Medical Center, Haifa, Israel, with the primary diagnosis of AHF entered a prospective registry.[10,11] Eligible patients were those hospitalized as with new-onset or worsening pre-existing heart failure (HF) as primary cause of admission.[12] In addition, patients were required to have a brain natriuretic peptide (BNP) level > 400 pg/mL at admission, using the AxSYM BNP microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). The study was approved by the institutional review committee on human research (RBM-12-0477).

Definitions

Acute kidney injury was defined based on the maximal increase of >0.3 mg/dL in serum creatinine from admission value at any time during hospital stay,[11] as used in the majority of prior studies.[13,14] Transient AKI was defined when by the time of discharge, serum creatinine decreased to a level that was 50% lower than the peak increase in serum creatinine.

Estimated glomerular filtration rate (eGFR) was derived using the Chronic Kidney Disease Epidemiology Collaboration formula.[15] Hypotension during hospital stay was defined as systolic blood pressure (SBP) of <90 mm Hg.[16]

Assessment of congestion

The degree of congestion at admission was evaluated based on a combination of several signs and symptoms. A 10-point scale ranging from 0 to 9 was constructed as follows[17–19]: orthopnoea (1 point), raised jugular venous pressure (*n* = 1), hepatomegaly (*n* = 1), chest radiograph showing pulmonary venous congestion, interstitial oedema or alveolar oedema (*n* = 1), chest radiograph showing pleural effusion (*n* = 1), and presence of peripheral oedema (absent/trace, 0 point; slight, 1 point; moderate, 2 points; marked, 3 points; and anasarca, 4 points). A composite congestion index was calculated by summing the individual components. Assessment of the degree of congestion was performed at admission and prior to discharge.

Categorization of the physician response to acute kidney injury

Our primary goal was to determine the physician response to AKI through changes in medical management and use of selected classes of medications during the AKI event with respect to renal and clinical outcomes. Medications were categorized into classes of interest including (i) ACE-Is/ angiotensin receptor blockers (ACE-Is/ARBs), (ii) beta-blockers, and (iii) spironolactone and loop diuretics.

For each medication, patients were classified as 'reduced or discontinued' as temporary or permanent reduction of the dose by ≥50% or discontinuation of the medication. In addition, because dose reduction or discontinuation of >1 medication may impact renal and overall clinical outcome, a composite treatment score was defined based on 'reduced or discontinued' classification of any of the three selected medication classes (ACE-I/ARB, beta-blockers, and diuretics). In addition, intravenous fluids administration was also considered as an intervention that may affect renal outcome and was therefore included as a component of the composite treatment score. The study population was subsequently divided into two groups using the cut-off of ≥1 for the composite treatment score.

Events data collection

Following hospital discharge, mortality data was acquired by reviewing the national death registry and by contacting each patient individually and independently reviewing the hospital course for major clinical events if the patient had been rehospitalized.

Statistical analysis

The baseline characteristics of the groups were compared using unpaired *t*-tests or the non-parametric Mann–Whitney *U* test for continuous variables and by the χ^2 statistic for categorical variables.

Multivariable logistic regression model with backward stepwise selection was used to determine the relationship between clinical variables and the likelihood of the AKI being transient. To minimize false-positive variable selection, we constructed 1000 bootstrap samples. For each sample, we used a logistic regression model with the backward elimination. Variables consistently chosen in >75% of bootstrap samples were included in the final model.

Length of stay was treated as count variable and was modelled using zero-truncated negative binomial regression, with estimates reported as incident rates ratios. Six months event-free survival was estimated by the Kaplan–Meier method, and curves were compared with the log-rank test.

Stepwise Cox proportional hazards models with backward selection were used to determine which variables were significantly related to all-cause mortality or the combined endpoint of mortality and rehospitalization. Each variable was tested univariately and then retested after adjustments for other possible cofounders in the Cox model. Variables with $P < 0.1$ in the univariate Cox regression analysis were used in the multivariable Cox model. The following baseline clinical characteristics were considered in the multivariate procedure: composite treatment score, age, gender, discharge eGFR, discharge blood urea nitrogen (BUN), discharge haemoglobin, BNP levels, history of diabetes mellitus and hypertension, atrial fibrillation, elevated troponin level at admission, ejection fraction (dichotomized as above or below 50%), use of inotropes, renal function recovery during hospital course, and the composite index. Differences were considered statistically significant at the two-sided $P < 0.05$ level. Statistical analyses were performed using the STATA version 15.1 (College Station, TX, USA).

Results

During the study period, 1314 were admitted with acute decompensated HF, with 277 patients who met the inclusion criteria (21.1%). Of the patients meeting all inclusion criteria, 186 (67.1%) were being treated with ACE-Is/ARBs, 216 (78.0%) with beta-blockers, 37 (13.5%) with spironolactone, and 270 with diuretics (98.2%).

During hospitalization as AKI developed, ACE-Is/ARBs, beta-blockers, and diuretics were reduced or discontinued in 103 (55.4%), 84 (38.9%), and 166 (61.5%), respectively. Fluids were administered to 130 (46.9%) patients (mean volume of 700 ± 400 mL). In 92 patients (33.2%), fluids were administered without discontinuation of diuretics, and in 37 patients (13.4%), fluids were administered without dose reduction of diuretics.

Demographic and clinical characteristics of the patients according to the composite score are shown in *Table 1*. Patients with higher composite score were older, had lower congestion index, and had higher baseline use of ACE-Is and ARBs.

The median increase in serum creatinine (baseline to peak) was 0.60 mg/dL [interquartile range (IQR) 0.55–0.67 mg/dL]. *Figure 1* shows that discontinuation rates of ACE-Is/ARBs, beta-blockers, diuretics, and fluids administration were higher in patients in whom the magnitude of creatinine increase was greater than the median creatinine increase. However, discontinuation of medical therapy and fluids administration was also frequent (32–53%) with smaller increases in creatinine.

**Table 1** Clinical characteristics according to the composite treatment score

	Composite treatment score		
Characteristic	≤1 (*n* = 121)	>1 (*n* = 156)	*P*-value
Age (years)	76 ± 11	79 ± 11	0.04
Female	54 (45%)	85 (54%)	0.10
Hypertension	101 (83%)	134 (86%)	0.58
Diabetes mellitus	71 (59%)	75 (48%)	0.08
Chronic lung disease	30 (25%)	29 (19%)	0.21
Coronary artery disease	87 (72%)	97 (72%)	0.09
Systolic blood pressure (mm Hg)	144 ± 27	139 ± 31	0.15
Baseline creatinine (mg/dL)	1.63 (1.13–2.30)	1.45 (1.13–1.98)	0.15
Baseline eGFR (mL·min^{-1}/1.73 m^{-2})	35 (23–53)	37 (27–53)	0.48
Baseline BUN (mg/dL)	36 (21–49)	32 (22–44)	0.44
Serum sodium (mmol/L)	137 ± 5	137 ± 8	0.25
Baseline haemoglobin (g/dL)	11.5 ± 1.8	11.3 ± 1.7	0.61
BNP (ng/mL)	958 (703–745)	1011 (620–1713)	0.99
Cardiac troponin I elevation	25 (21%)	35 (22%)	0.72
Atrial fibrillation	46 (38%)	66 (42%)	0.47
LVEF < 50%	46 (44%)	52 (42%)	0.73
Baseline congestion index	3 (2–4)	2 (1–3)	0.004
Baseline medical therapy			
Beta-blockers	84 (69)	110 (72)	0.84
ACE-Is/ARBs	60 (50)	111 (71)	<0.0001
Spironolactone	5 (4)	7 (4)	0.87
Digoxin	14 (12)	19 (12)	0.88
Clinical events			
Six months mortality	33 (27)	63 (40)	0.01[a]
Six months mortality or readmission	50 (41)	87 (56)	0.005[a]
Renal function recovery	43 (36)	97 (62)	<0.0001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LVEF, left ventricular systolic function.
Values are expressed as number (%) of patients, mean value ± standard deviation, or median (interquartile range).
[a]Log-rank test.

Figure 1 Proportion of dose reduction or discontinuation of medications or fluids administration according to the magnitude of creatinine increase (above or below median value) during the acute kidney injury event. ACE-Is/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.
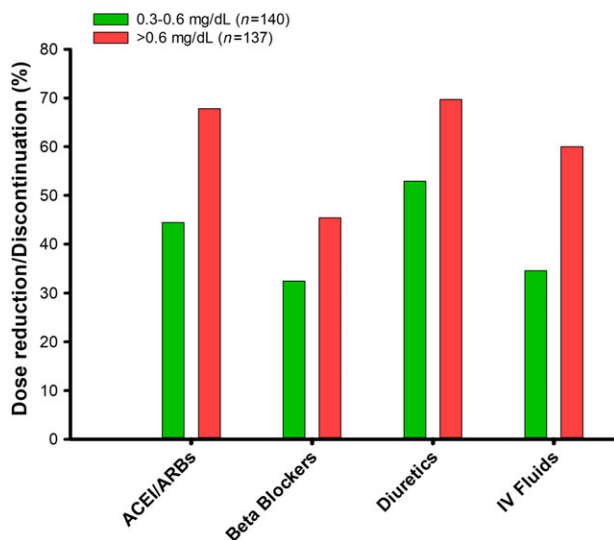
Impact of blood pressure

Of the 277 study patients, 94 (33.9%) had an episode of hypotension. The median time from admission to hypotension was 2 days (IQR 1–5 days). The median nadir SBP for patients with hypotension was 80 mm Hg (IQR 72–85 mm Hg). Thirty-four of these patients (31.2%) were treated with inotropes. Nadir SBP was significantly lower in patients with composite score above 1 [85 mm Hg (IQR 75–91) vs. 90 mm Hg (IQR 85–96); $P = 0.009$]. *Figure 2* shows that hypotension was associated

Figure 2 Impact of hypotension on the proportion of patients with dose reduction or discontinuation of evidence-based therapies or fluids administration.
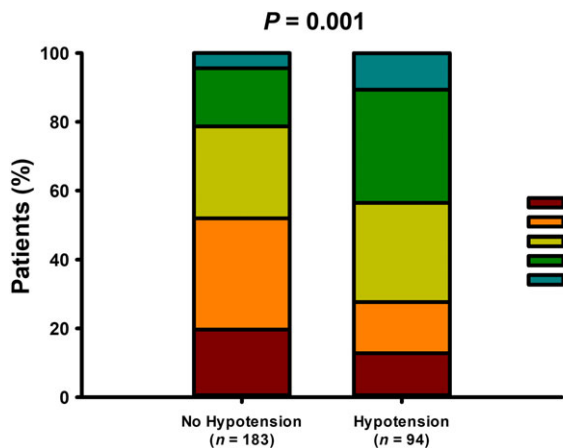

with higher rates of discontinuation/dose reduction of evidence-based therapies or fluids administration. However, there was no difference between the two groups in the magnitude of SBP drop from baseline to nadir values [49 mm Hg (IQR 30–65) vs. 41 mm Hg (IQR 31–59); $P = 0.26$].

Renal outcome

Figure 3 shows the changes in serum creatinine and BUN in the two study groups. The reduction in serum creatinine from peak level to discharge was significantly larger in patients with a composite score > 1 [0.56 mg/dL (IQR 0.13–1.10 mg/dL) vs. 0.15 mg/dL (IQR 0–0.50 mg/dL) compared with patients with composite score ≤ 1; $P < 0.0001$]. Overall, improvement in renal function occurred in 97 (63%) and 43 (36%) patients with and without treatment composite score above 1, respectively ($P < 0.0001$). In a multivariable logistic

Figure 3 Box-and-whisker plot of (A) creatinine and (B) blood urea nitrogen (BUN) values at three time points: admission, peak during hospital stay, and discharge. The line within the box denotes the median, and the box spans the interquartile range (25th to 75th percentiles). Whiskers extend from the 5th to 95th percentiles.
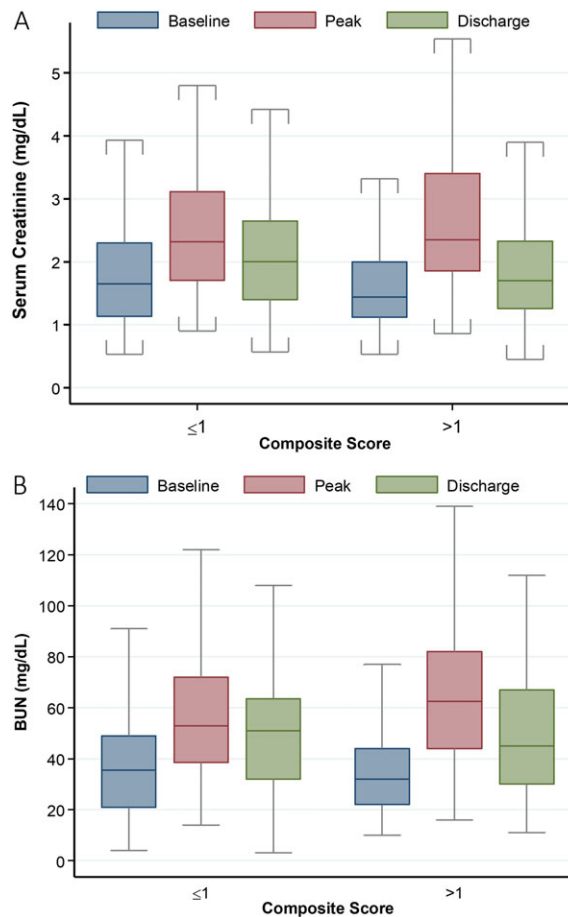
regression model, the composite score was associated with a greater likelihood of renal function recovery, whereas the use of inotropes was negatively associated with renal function recovery (*Table 2*).

Congestion

During hospital stay, the reduction in the congestion index was larger in patients with a composite score of ≤1 [median −2 points (IQR −1 to −3)] as compared with patients with a composite score above 1 [median −1 point (IQR 0 to −2); *P* = 0.021].

Length of hospital stay

The median hospital LOS was 7 days (IQR 6–8 days) in patients with composite score ≤ 1 and 12 days (IQR 10–13 days) in patients with composite score > 1. A composite score above 1 was an independent predictor of longer hospital LOS (*Table 3*).

Mortality and rehospitalization after hospital discharge

During the 6 months after hospital discharge, 96 patients (34.7%) died and 54 (19.5%) were readmitted for HF decompensation. *Figure 4*A shows that the unadjusted mortality rates were higher in patients with a composite score above 1. The unadjusted hazard ration for mortality was 1.71 (95% confidence interval 1.12–2.61; *P* = 0.01). Similar results were obtained for the combined endpoint of mortality and rehospitalization for HF (*Figure 4*B).

Figure 4 Kaplan–Meier survival plot of (A) mortality and (B) mortality and rehospitalizations for heart failure (HF) in subgroups defined by the composite treatment score. *P*-values are for the overall comparison among the groups using the log-rank test.
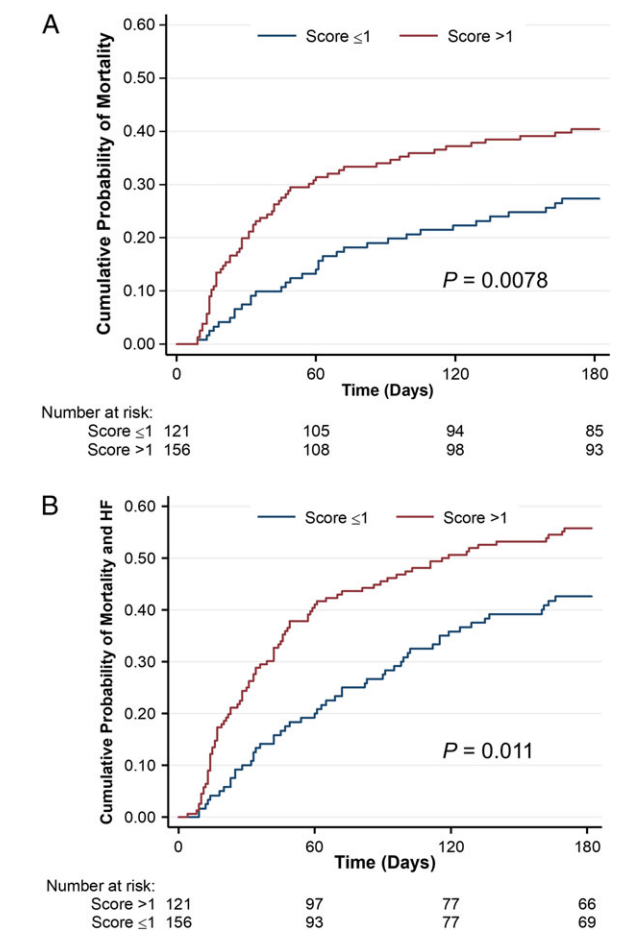

Table 2 Logistic regression model for renal function recovery

Variable	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Use of inotropes	0.69 (0.36–1.32)	0.47	0.46 (0.23–0.92)	0.03
Composite treatment score > 1[a]	3.00 (1.83–4.91)	<0.0001	3.47 (2.06–5.83)	<0.0001

CI, confidence interval; OR, odds ratio.
[a]Increasing score indicates discontinuation of more medications or fluids administration.

Table 3 Unadjusted and adjusted zero-truncated negative binomial regression for length of stay

Variable	Unadjusted IRR (95% CI)	*P*-value	Adjusted IRR (95% CI)	*P*-value
Use of inotropes	1.51 (1.20–1.93)	0.001	1.30 (1.03–1.64)	0.025
Anaemia[a]	1.39 (1.11–1.74)	0.004	1.31 (1.07–1.61)	0.01
Ln BNP	1.29 (1.13–1.48)	<0.0001	1.28 (1.12–1.46)	<0.0001
Composite treatment score > 1	1.65 (1.32–2.06)	<0.0001	1.59 (1.30–1.96)	<0.0001

BNP, brain natriuretic peptide; CI, confidence interval; IRR, incidence rate ratio.
[a]World Health Organization definition.

Table 4 shows the results of a multivariable Cox model for all-cause mortality. After adjustments, the composite score was no longer associated with mortality. Independent predictors of post-discharge mortality included hypotension (SBP < 90) during hospital course, elevated BUN at hospital discharge, and use of inotropes during hospital course (*Table 4*).

Discussion

In the present study, we conducted a survey of how physicians respond to an acute decline in renal function occurring during therapy of AHF. Discontinuation or dose reduction of evidence-based therapies was frequent, as well as fluids administration. Although part of the medical management appeared to be related to key clinical variables such as hypotension and severity of creatinine elevations, the changes in the medical management of patients with worsening renal function were only partly explained by these factors. Withdrawal of neurohormonal blockade and fluids administration was associated with improved renal outcome but with lesser degree of decongestion.

Hospitalization for HF occurs 1 million times per year in the USA alone and represents one of the strongest predictors of poor prognosis.[20,21] The most common reason for hospitalization in these patients is worsening chronic HF with pulmonary or systemic congestion.[1,22] Thus, the primary therapeutic objective in the majority of patients hospitalized with AHF is to optimize volume status.[2]

Acute kidney injury, currently defined as acute (Type 1) cardio-renal syndrome,[23] is common in hospitalized patients with AHF and defines a higher-risk population because of its association with hospital readmissions and post-discharge mortality.[5,24–26] How to manage worsening renal function in the setting of decongestive therapy and what targets to use when adjusting diuretic and other medical therapies are frequent questions that arise in patients with AHF. Temporary interruptions of diuretics or neurohormonal blockers can address potential concerns regarding transient intravascular volume depletion or intrarenal haemodynamics and appear to represent standard clinical practice.[9] However, when AKI complicates the management of AHF, there are no clinical trial data to guide therapy.

Aggressive diuresis can be associated with worsening renal function,[27] especially in the presence of ACE inhibition.[28] Diuretics can impair renal function by activating the renin–angiotensin–aldosterone system[29] and by producing intravascular volume depletion. Angiotensin-converting enzyme inhibitors can lower glomerular hydrostatic pressure and decrease GFR by inhibiting of efferent renal arteriolar resistance, and these effects are more evident after diuresis.[30] In the present study, the attempts to correct hypotension or improve renal haemodynamics by changes in the medical regimen and fluids administration were associated with greater likelihood renal functional recovery. However, these patients also had less efficient decongestion, which may lead to early post-discharge readmission.

Fluids administration

Because fluid overload is a major contributor to acute decompensation in patients with HF,[2,31] and ineffective decongestion predicts adverse clinical outcomes,[32] the administration of intravenous fluids in the setting of AHF requires a clear indication. There are several possible explanations for intravenous fluids administration in acutely decompensated inpatients. First, some patients may have received fluids because of haemodynamic instability. Second, fluids may have been administered to counter the detrimental effects of excessive loop diuretic therapy. Although fluids administration may have been clinically justified in some patients, a third of the patients in the present study were treated with fluids while continuing to receive diuretics. This practice is not easily justified on clinical grounds in AHF with worsening renal function.

Table 4 Unadjusted and adjusted Cox proportional hazard model for mortality

Variable	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Age (per 10 years increase)	1.45 (1.18–1.79)	0.001	—	—
Discharge eGFR (per 10 mL·min^{-1}/1.73 m^2 increase)	0.79 (0.70–0.90)	<0.0001	—	—
Discharge BUN (per 10 mg/dL increase)	1.16 (1.10–1.22)	<0.0001	1.13 (1.03–1.23)	0.03
Discharge Hb (per 1 g/dL increase)	0.85 (0.76–0.95)	0.006	—	—
Serum sodium < 136 mmol/L	1.57 (1.03–2.40)	0.04	—	—
BNP > median value	1.53 (1.02–2.30)	0.04	—	—
Hypotension during hospitalization	3.26 (2.18–4.89)	<0.0001	2.28 (1.33–3.91)	0.005
Composite treatment score > 1	1.71 (1.12–2.61)	0.01	—	—
Use of inotropes	4.31 (2.77–6.69)	<0.0001	2.28 (1.33–3.91)	0.003

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio.

Clinical outcomes

In unadjusted analyses, we observed higher rates of post-discharge mortality and readmission for HF in patients in whom discontinuation of evidence-based therapies and/or fluids administration was more common. One possibility is that the management of AKI may directly worsen the clinical outcomes. However, it is also possible that discontinuation of evidence-based therapies and administration of fluids is a marker of greater clinical severity rather than a cause of worse outcomes. Given the observational nature of our data, our findings should not be considered causal at this stage. Indeed, after adjustments for other risk variables, the composite score was no longer an independent predictor of mortality.

Study limitations

Several limitations of our study should be acknowledged. First, this was a post hoc analysis of our registry data, and thus, the results must be regarded as hypothesis generating and exploratory and require validation in other studies. Our analysis used information based on medical record abstraction, which is dependent on the accuracy and completeness of physician documentation. However, undocumented change in medical regimen is unlikely in our institution because a computerized physician order is required for any change. The management of AHF in our institution may not be representative of other hospitals. Finally, our study was underpowered to detect an impact of decongestion on clinical outcomes.

Conclusions

Current understanding of the mechanisms that underlie the development of the cardio-renal syndrome is insufficient to make effective and informed therapeutic decisions. Discontinuation or dose reduction of diuretics or neurohormonal blockers may improve renal outcome at the price of less efficient decongestion, with potential implications for the risk of readmissions. Our results emphasize the need for randomized clinical trials that address the treatment of AHF patients who develop AKI.

Conflict of interest

None declared.

Funding

None.

References

1. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP, ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; **149**: 209–216.
2. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen D, Zannad F, Anker SD, Rhodes A, McMurray J, Filippatos G, European Society of Cardiology, European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010; **12**: 423–433.
3. Mentz RJ, Kjeldsen K, Rossi GP, Voors AA, Cleland JG, Anker SD, Gheorghiade M, Fiuzat M, Rossignol P, Zannad F, Pitt B, O'Connor C, Felker GM. Decongestion in acute heart failure. *Eur J Heart Fail* 2014; **16**: 471–482.
4. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol* 2012; **60**: 1031–1042.
5. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014; **35**: 455–469.
6. Goldberg A, Hammerman H, Petcherski S, Zdorovyak A, Yalonetsky S, Kapeliovich M, Agmon Y, Markiewicz W, Aronson D. Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. *Am Heart J* 2005; **150**: 330–337.
7. Goldberg A, Kogan E, Hammerman H, Markiewicz W, Aronson D. The impact of transient and persistent acute kidney injury on long-term outcomes after acute myocardial infarction. *Kidney Int* 2009; **76**: 900–906.
8. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail* 2002; **8**: 136–141.
9. Bart BA, Goldsmith SR, Lee KL, Redfield MM, Felker GM, O'Connor CM, Chen HH, Rouleau JL, Givertz MM, Semigran MJ, Mann D, Deswal A, Bull DA, Lewinter MM, Braunwald E. Cardiorenal rescue study in acute decompensated

heart failure: rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. *J Card Fail* 2012; **18**: 176–182.

10. Makhoul BF, Khourieh A, Kaplan M, Bahouth F, Aronson D, Azzam ZS. Relation between changes in red cell distribution width and clinical outcomes in acute decompensated heart failure. *Int J Cardiol* 2013; **167**: 1412–1416.

11. Aronson D, Darawsha W, Promyslovsky M, Kaplan M, Abassi Z, Makhoul BF, Goldberg A, Azzam ZS. Hyponatraemia predicts the acute (type 1) cardio-renal syndrome. *Eur J Heart Fail* 2014; **16**: 49–55.

12. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB, OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol* 2007; **50**: 768–777.

13. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Cas LD. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. *Eur J Heart Fail* 2008; **10**: 188–195.

14. Voors AA, Davison BA, Felker GM, Ponikowski P, Unemori E, Cotter G, Teerlink JR, Greenberg BH, Filippatos G, Teichman SL, Metra M, on behalf of the Pre-RELAX-AHF study group. Early drop in systolic blood pressure and worsening renal function in acute heart failure: renal results of Pre-RELAX-AHF. *Eur J Heart Fail* 2011; **13**: 961–967.

15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612.

16. Patel PA, Heizer G, O'Connor CM, Schulte PJ, Dickstein K, Ezekowitz JA, Armstrong PW, Hasselblad V, Mills RM, McMurray JJV, Starling RC, Tang WHW, Califf RM, Hernandez AF. Hypotension during hospitalization for acute heart failure is independently associated with 30-day mortality: findings from ASCEND-HF. *Circ Heart Fail* 2014; **7**: 918–925.

17. Aronson D, Darawsha W, Atamna A, Kaplan M, Makhoul BF, Mutlak D, Lessick J, Carasso S, Reisner S, Agmon Y, Dragu R, Azzam ZS. Pulmonary hypertension, right ventricular function, and clinical outcome in acute decompensated heart failure. *J Card Fail* 2013; **19**: 665–671.

18. Aronson D, Burger AJ. Diuretic response: clinical and hemodynamic predictors and relation to clinical outcome. *J Card Fail* 2016; **22**: 193–200.

19. Wattad M, Darawsha W, Solomonica A, Hijazi M, Kaplan M, Makhoul BF, Abassi ZA, Azzam ZS, Aronson D. Interaction between worsening renal function and persistent congestion in acute decompensated heart failure. *Am J Cardiol* 2015; **115**: 932–937.

20. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation* 2012; **125**: 188–197.

21. Ahmed A, Allman RM, Fonarow GC, Love TE, Zannad F, Dell'italia LJ, White M, Gheorghiade M. Incident heart failure hospitalization and subsequent mortality in chronic heart failure: a propensity-matched study. *J Card Fail* 2008; **14**: 211–218.

22. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003; **41**: 1797–1804.

23. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P, for the Acute Dialysis Quality Initiative (ADQI) consensus group. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J* 2010; **31**: 703–711.

24. Aronson D. Cardiorenal syndrome in acute decompensated heart failure. *Expert Rev Cardiovasc Ther* 2012; **10**: 177–189.

25. Aronson D, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med* 2004; **116**: 466–473.

26. Akhter MW, Aronson D, Bitar F, Khan S, Singh H, Singh RP, Burger AJ, Elkayam U. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with decompensated heart failure. *Am J Cardiol* 2004; **94**: 957–960.

27. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter M, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty S, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM, NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011; **364**: 797–805.

28. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999; **138**: 285–290.

29. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 1985; **103**: 1–6.

30. Dzau VJ, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984; **100**: 777–782.

31. Weintraub NL, Collins SP, Pang PS, Levy PD, Anderson AS, Arslanian-Engoren C, Gibler WB, McCord JK, Parshall MB, Francis GS, Gheorghiade M, American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims. A scientific statement from the American Heart Association. *Circulation* 2010; **122**: 1975–1976.

32. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M, on behalf of the EVEREST trial investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013; **34**: 835–843.