EDITORIAL

Reconsidering Ultrafiltration in the Acute Cardiorenal Syndrome

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Aggressive diuretic therapy in a patient who is hospitalized for acute decompensated heart failure often leads to progressive renal dysfunction despite persistent congestion. The underlying mechanisms of this so-called acute cardiorenal syndrome are complex and not fully understood.[1,2] As initial therapy in this setting, ultrafiltration as compared with diuretic therapy may result in a higher rate of sodium and volume removal, with greater weight loss and less frequent rehospitalizations.[3,4] These findings have suggested that ultrafiltration can provide more effective relief of congestion than pharmacologic therapy can, particularly in the setting of cardiorenal compromise. Ultrafiltration may also reduce diuretic-induced neurohormonal activation, restore responsiveness to diuretics, and improve outcomes.

As now reported in the *Journal*, the results of the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) directly challenge our understanding of the effectiveness of ultrafiltration. In this well-designed and well-executed study, ultrafiltration did not result in greater weight loss or improved renal function as compared with pharmacologic therapy and was associated with a similar rate of death or rehospitalization for acute decompensated heart failure.[5] The use of an elaborate drug algorithm (involving continuous infusion of diuretics with the addition of metolazone, vasoactive therapy, or both) to overcome resistance to diuretics may have made it unnecessary for clinicians to lower diuresis targets in response to the acute cardiorenal syndrome, thus eliminating the potential confounder of inadequate pharmacologic management. Furthermore, there was an unexpected overall decrease in serum creatinine level in the pharmacologic-therapy group, rather than the anticipated increase, thus refuting the claim that ultrafiltration is less harmful to renal function. It is difficult to argue that ultrafiltration provides "diuretic sparing" benefits in patients with acute cardiorenal syndrome when a well-managed pharmacologic approach provided equivalent clinical outcomes with fewer serious adverse effects.

How do we reconcile the promising results from previous ultrafiltration studies with the somewhat unanticipated findings from CARRESS-HF? CARRESS-HF investigated a patient population that had persistent congestion with a rising serum creatinine level. This population may have an attenuated response to standard pharmacologic therapy as compared with patients receiving ultrafiltration as initial therapy. There has been recent appreciation that worsening renal function during treatment of acute decompensated heart failure may reflect underlying diminished renal reserve rather than treatment effects.[6] In fact, CARRESS-HF illustrates the overall dismal outcomes in patients in whom the acute cardiorenal syndrome develops. Regardless of treatment strategy, only approximately one tenth of the patients had adequate decongestion at 96 hours, and more than a third of the patients died or were readmitted to the hospital for acute decompensated heart failure within 60 days, despite substantial overall weight loss. Hence, the results of CARRESS-HF may be consistent with the findings of single-center studies of ultrafiltration in patients with the acute cardiorenal syndrome, which have shown a low rate of renal recovery despite effective volume removal and favorable hemodynamic effects.[7,8]

We simply do not know whether a rise in serum creatinine level during treatment represents desired effects of hemoconcentration (when ther-

apy is efficacious) or undesired deterioration of renal function (when therapy is ineffective). In fact, transient changes in serum creatinine levels during therapy for acute decompensated heart failure may not necessarily reflect substantial underlying renal injury or adverse long-term consequences if congestion is adequately relieved.[9,10]

The effect of therapy on the bivariate primary end point of change in weight and change in serum creatinine level may be dependent on the rate at which congestion is being relieved. Previous studies have used similar ultrafiltration rates with shorter treatment durations.[3,4] It is conceivable that a slower but steady ultrafiltration rate may help maintain an adequate plasma refill rate. This may result in longer duration of ultrafiltration and greater volume removal without inducing azotemia. It is important to remember that the ultimate goal is to relieve congestion safely and not to show how promptly the excess volume can be removed. Therefore, future studies are needed to determine the safest and most effective rate, duration, and amount of sodium and volume removal with ultrafiltration to achieve the best possible clinical outcomes in patients with the acute cardiorenal syndrome.

There is a pressing need to continue the search for better strategies to manage the acute cardiorenal syndrome, and we may have to challenge our preconceptions. Once touted as a promising option for cardiorenal rescue therapy, ultrafiltration as performed in CARRESS-HF can no longer be considered to be a favorable choice for routine therapy in patients with the acute cardiorenal syndrome. CARRESS-HF reminds us that we need to refine the use of ultrafiltration in treatment for acute decompensated heart failure and also to devote much effort to determining how best to prevent the acute cardiorenal syndrome in the first place. We may even have to confront the possibility that the pressure to reduce hospital length of stay with a strategy of initial aggressive diuresis in patients with acute decompensated heart failure may actually result in an increased incidence of the acute cardiorenal syndrome and cause unwanted consequences. Perhaps slow and steady may ultimately win the race after all.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

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ABSTRACT

BACKGROUND

Ultrafiltration is an alternative strategy to diuretic therapy for the treatment of patients with acute decompensated heart failure. Little is known about the efficacy and safety of ultrafiltration in patients with acute decompensated heart failure complicated by persistent congestion and worsened renal function.

METHODS

We randomly assigned a total of 188 patients with acute decompensated heart failure, worsened renal function, and persistent congestion to a strategy of stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients). The primary end point was the bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 hours after random assignment. Patients were followed for 60 days.

RESULTS

Ultrafiltration was inferior to pharmacologic therapy with respect to the bivariate end point of the change in the serum creatinine level and body weight 96 hours after enrollment (P=0.003), owing primarily to an increase in the creatinine level in the ultrafiltration group. At 96 hours, the mean change in the creatinine level was −0.04±0.53 mg per deciliter (−3.5±46.9 μmol per liter) in the pharmacologic-therapy group, as compared with +0.23±0.70 mg per deciliter (20.3±61.9 μmol per liter) in the ultrafiltration group (P=0.003). There was no significant difference in weight loss 96 hours after enrollment between patients in the pharmacologic-therapy group and those in the ultrafiltration group (a loss of 5.5±5.1 kg [12.1±11.3 lb] and 5.7±3.9 kg [12.6±8.5 lb], respectively; P=0.58). A higher percentage of patients in the ultrafiltration group than in the pharmacologic-therapy group had a serious adverse event (72% vs. 57%, P=0.03).

CONCLUSIONS

In a randomized trial involving patients hospitalized for acute decompensated heart failure, worsened renal function, and persistent congestion, the use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 hours, with a similar amount of weight loss with the two approaches. Ultrafiltration was associated with a higher rate of adverse events. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00608491.)

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The acute cardiorenal syndrome (type 1) is defined as worsening renal function in patients with acute decompensated heart failure.[1] It occurs in 25 to 33% of patients with acute decompensated heart failure and is associated with poor outcomes.[1,2] Multiple processes contribute to the development of the acute cardiorenal syndrome, including extrarenal hemodynamic changes, neurohormonal activation, intrarenal microvascular and cellular dysregulation, and oxidative stress.[1] In some cases, intravenous diuretics, which are often administered in patients with acute decompensated heart failure,[3] may directly contribute to worsening renal function.[1,4,5] The use of diuretics to treat persistent congestion after the onset of worsening renal function may lead to further kidney injury.

Venovenous ultrafiltration is an alternative therapy in this setting. Potential advantages of ultrafiltration include greater control over the rate and volume of fluid removal, greater net loss of sodium, and less neurohormonal activation.[6] Current treatment guidelines state that ultrafiltration is a reasonable approach in patients with congestion that is not responding to medical therapy (class IIa, level of evidence B).[3] However, little is known about the safety and efficacy of ultrafiltration as compared with pharmacologic therapy in patients with acute decompensated heart failure complicated by acute cardiorenal syndrome and persistent congestion.[4] Therefore, we designed the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) to compare the effect of ultrafiltration with that of stepped pharmacologic therapy on renal function and weight loss in patients with heart failure who have worsening renal function and persistent congestion.[7]

Methods

Study Oversight

The National Heart, Lung, and Blood Institute (NHLBI)–sponsored Heart Failure Network conceived, designed, and conducted the CARRESS-HF. The trial protocol was approved by a protocol review committee and a data and safety monitoring board, both appointed by the NHLBI, and by the institutional review board at each participating site. All study-related activities, including the collection and analysis of the data, were coordinated by the data coordinating center at the Duke Clinical Research Institute. The first draft of the manuscript was written by the first author, and the final draft was revised, reviewed, and approved by all the authors. All the authors assume responsibility for the overall content and integrity of the article. The authors, steering committee, and executive committee of the Heart Failure Network made the decision to submit the manuscript for publication and vouch for the data and analysis and for the fidelity of this report to the study protocol (which is available with the full text of this article at NEJM.org). CHF Solutions (Brooklyn Park, MN) provided limited financial support for the purchase of ultrafiltration filters but had no role in the conduct of the trial, analysis of the data, or interpretation of the results. No data or draft of the manuscript was shared with CHF Solutions before publication.

Study Design

The design of and rationale for the trial have been described previously.[7] The CARRESS-HF was a randomized trial that compared ultrafiltration with a strategy of diuretic-based stepped pharmacologic therapy. Patients who were hospitalized with acute decompensated heart failure as the primary diagnosis were eligible for enrollment. There was no exclusion criterion that was based on ejection fraction. All patients had worsened renal function (defined as an increase in the serum creatinine level of at least 0.3 mg per deciliter [26.5 μmol per liter]) within 12 weeks before or 10 days after the index admission for heart failure. All patients were required to have at least two of the following conditions at the time of randomization: at least 2+ peripheral edema, jugular venous pressure greater than 10 cm of water, or pulmonary edema or pleural effusion on chest radiography. Patients with a serum creatinine level of more than 3.5 mg per deciliter (309.4 μmol per liter) at the time of admission and those receiving intravenous vasodilators or inotropic agents were excluded from the study. A complete list of the trial inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

All study participants provided written informed consent before randomization. With the use of an automated Web-based system, patients were randomly assigned, in a 1:1 ratio, to either ultrafiltration therapy or pharmacologic therapy. A permuted-block randomization scheme was used, with stratification according to clinical site.

For patients assigned to ultrafiltration therapy, loop diuretics were to be discontinued for the

duration of the ultrafiltration intervention. Fluid status was managed by means of ultrafiltration with the use of the Aquadex System 100 (CHF Solutions) according to the manufacturer's specifications. Ultrafiltration was performed at a fluid-removal rate of 200 ml per hour. The addition of intravenous vasodilators or positive inotropic agents after randomization was prohibited unless they were deemed to be necessary as rescue therapy.

For patients assigned to stepped pharmacologic therapy, intravenous diuretics were used to manage signs and symptoms of congestion. Investigators were encouraged to decrease doses, increase doses, or continue current doses of diuretics as necessary to maintain a urine output of 3 to 5 liters per day. Recommendations regarding the use of intravenous vasodilators and inotropic agents for patients in whom the target urine output could not be attained were based on the individual patient's blood pressure, ejection fraction, and the presence or absence of right ventricular failure at 48 hours. The details of the stepped pharmacologic-therapy algorithm are provided in the Supplementary Appendix.

In both groups, the assigned treatment strategy was to be continued until the signs and symptoms of congestion in the patient were reduced to the best extent possible. Crossover was discouraged. Diuresis or ultrafiltration could be slowed or temporarily discontinued to address technical problems or clinical care requirements, as determined by the treating physician.

TRIAL END POINTS

The primary end point was the change in the serum creatinine level and the change in weight, considered as a bivariate response, between the time of randomization and 96 hours after randomization.[7] The use of a bivariate primary end point (in which the change in serum creatinine level and the change in weight are considered simultaneously, with the results displayed on a two-dimensional grid) was intended to allow for the integration of two clinically important outcomes.[8] Secondary end points included the rate of clinical decongestion and measures of global well-being and dyspnea. Clinical decongestion was defined as jugular venous pressure of less than 8 cm of water, no more than trace peripheral edema, and the absence of orthopnea. Global well-being and dyspnea were assessed with the use of a visual-analogue scale that ranged from 0 to 100, with higher scores indicating greater well-being and less severity of dyspnea, respectively.[9] A complete listing of secondary end points is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

On the basis of data from the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial,[10] the standard deviation of the change in weight at 96 hours was estimated to be 3.1 to 3.5 kg (6.8 to 7.7 lb), and the standard deviation of the change in the creatinine level at 96 hours was estimated to be 0.55 to 0.75 mg per deciliter (48.6 to 66.3 μmol per liter). We estimated that with enrollment of 200 participants, the study would have more than 90% power to detect a difference of 0.5 SD between the treatment groups for each component of the bivariate primary end point.

The primary analyses were based on the intention-to-treat principle. Baseline characteristics are presented as means and standard deviations or medians and interquartile ranges. The response of each patient with respect to the bivariate primary end point was displayed on a two-dimensional grid representing changes in the creatinine level and changes in weight 96 hours after randomization. For the comparison of treatment groups in the primary analysis, we used a multivariate linear-regression model, adjusting for baseline weight and creatinine level.[7] A 95% confidence region (an ellipse) for the mean bivariate response (change in creatinine level and change in weight) in each treatment group and for the average between-group difference in the bivariate response was identified with the use of the multivariate linear-regression model framework.[8,11]

The primary analysis was based on results of creatinine testing performed at the core laboratory, when those were available; otherwise, the results of testing performed at local laboratories were used. Body weight was measured by research personnel with the use of a locally available scale. Site personnel were encouraged to use the same scale for all patients whenever possible (and otherwise, the same scale for all weight assessments of a particular patient) and to weigh patients in the morning before breakfast, with patients wearing hospital gowns and no shoes. In the case of patients for whom 96-hour data were missing owing to death or early discharge from the hospital (13 patients in each treatment

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Pharmacologic Therapy (N=94)	Ultrafiltration (N=94)
Age — yr		
Median	66	69
Interquartile range	57–78	61–78
Male sex — no. (%)	68 (72)	73 (78)
White race — no. (%)†	67 (71)	72 (77)
Weight — lb		
Median	234	207
Interquartile range	190–292	172–265
Ejection fraction — %		
Median	35	30
Interquartile range	25–55	20–52
Hospitalization for heart failure in previous yr — no./total no. (%)	73/92 (79)	70/93 (75)
Ischemia as cause of heart failure — no. (%)	48 (51)	66 (70)
History of atrial fibrillation or flutter — no. (%)	48 (51)	54 (57)
Diabetes mellitus — no. (%)	63 (67)	61 (65)
Medications received before hospitalization		
ACE inhibitor or ARB — no. (%)	49 (52)	52 (55)
Beta-blocker — no. (%)	73 (78)	74 (79)
Aldosterone antagonist — no. (%)	17 (18)	21 (22)
Furosemide-equivalent diuretic		
Patients receiving medication — no. (%)	90 (96)	86 (91)
Furosemide-equivalent dose — mg/day		
Median	120	120
Interquartile range	80–160	80–240
Blood urea nitrogen — mg/dl		
Median	50.5	48.7
Interquartile range	39.0–64.0	39.5–66.0
Creatinine — mg/dl‡		
Median	2.09	1.90
Interquartile range	1.71–2.65	1.57–2.37
Qualifying increase in creatinine — mg/dl§		
Median	0.46	0.43
Interquartile range	0.37–0.70	0.35–0.60
NT-proBNP — pg/ml¶		
Median	4007	5013
Interquartile range	1128–8534	2310–10381

* There were no significant differences between the groups in the baseline characteristics listed here, with the exception of ischemia as the cause of heart failure (P=0.007). ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and NT-proBNP N-terminal pro–brain natriuretic peptide. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for blood urea nitrogen to micromoles per liter, multiply by 0.357. To convert the values for weight to kilograms, multiply by 0.45.
† Race was self-reported.
‡ The creatinine values reflect the results of testing performed at the core laboratory only.
§ The qualifying increases in creatinine level reflect the results of testing performed at local laboratories.
¶ The reference range for NT-proBNP is 5 to 70,000 pg/ml.

group), the last-observation-carried-forward method was used for imputation of data on creatinine level and weight. Two patients who were randomly assigned to ultrafiltration were not included in the primary end-point analysis owing to missing baseline data on creatinine level (1 patient) or lack of all post-baseline data on creatinine level (1 patient). Cumulative event rates for secondary end points involving time-to-event data were estimated with the use of the Kaplan–Meier method.[12] Hazard ratios, their 95% confidence intervals, and P values for the comparison of the two treatment groups were determined with the use of the Cox regression model.[13] A two-sided alpha level of 0.05 was considered to indicate statistical significance. All data analyses were conducted with the use of SAS software, version 9.2.

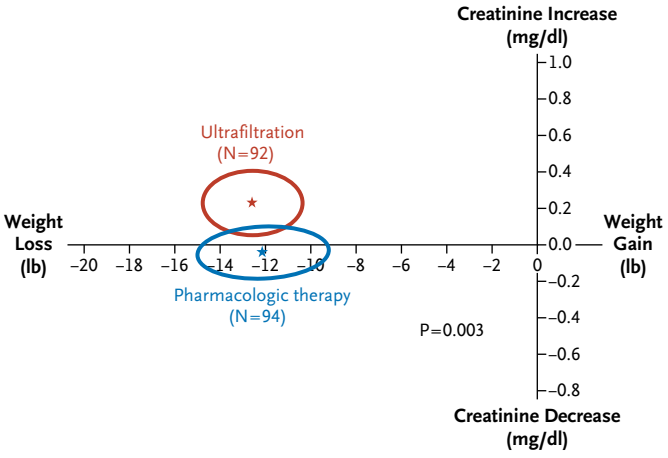

Figure 1. Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).

The ellipses represent the 95% confidence regions and the stars the exact values for the mean changes in the serum creatinine level and weight at 96 hours in the ultrafiltration group and the pharmacologic-therapy group. Data from two patients who had been randomly assigned to the ultrafiltration group were excluded from the analysis: baseline creatinine measurements were missing for one patient, and all post-baseline creatinine measurements were missing for the other patient. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for weight to kilograms, multiply by 0.45.

RESULTS

PATIENTS

Patients were enrolled in the trial between June 22, 2008, and January 27, 2012, at 22 sites in the United States and Canada. Enrollment ended on February 3, 2012, on the recommendation of the data and safety monitoring board, after 188 of the planned 200 patients had been enrolled, because of a lack of evidence of benefit, as well as an excess of adverse events, with ultrafiltration.

A total of 94 patients were enrolled in each treatment group. The baseline demographic and clinical characteristics are shown in Table 1. The median age of the population was 68 years, 75% of the patients were men, 85% had hypertension, and 66% had diabetes mellitus. The median ejection fraction was 33%. A total of 77% of the patients had been hospitalized for heart failure during the previous year. The median time from the index hospital admission (the admission qualifying the patient for enrollment in the study) to random assignment to a treatment group was 34 hours. The qualifying serum creatinine value was obtained after admission to the hospital in 95% of the participants. The median qualifying increase in the creatinine level was 0.45 mg per deciliter (39.8 μmol per liter).

STUDY TREATMENTS

All 94 patients in the pharmacologic-therapy group received intravenous diuretics. The median duration of the stepped pharmacologic-therapy intervention was 92 hours (interquartile range, 56 to 138). The primary reasons that stepped pharmacologic therapy was discontinued were the following: the best possible fluid volume was reached (72% of the patients), the creatinine level was increased (12%), there was evidence of intravascular volume depletion (3%), and blood pressure dropped or clinical instability developed (2%). Six participants (6%) in the pharmacologic-therapy group underwent ultrafiltration during the first 7 days (two of whom underwent ultrafiltration before the primary end-point assessment on day 4). In addition to receiving loop diuretics, 46% of the participants in the pharmacologic-therapy group received treatment with metolazone within the first 7 days, 5% were treated with intravenous vasodilators, and 12% were treated with intravenous inotropic agents before the day 4 assessment.

Ultrafiltration was started a median of 8 hours after random assignment, and the median duration of the treatment was 40 hours (interquartile range, 28 to 67). The primary reasons that ultrafiltration was stopped were the following: the best possible fluid volume was reached (50% of the patients), the creatinine level was increased

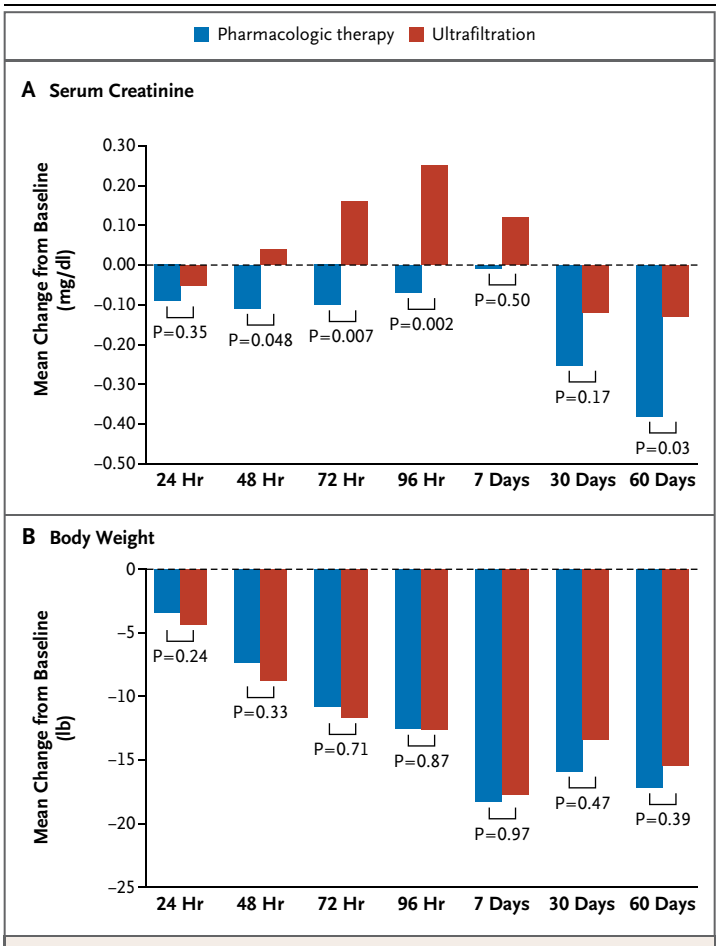

Figure 2. Changes from Baseline in Serum Creatinine and Body Weight at Various Time Points, According to Treatment Group.

The P values were calculated with the use of a Wilcoxon test. The data on creatinine levels reflect results from testing in local laboratories only.

(16%), difficulties developed with vascular access (9%), and thrombosis of the ultrafiltration circuit developed (9%). Eight patients (9%) in the ultrafiltration group received intravenous diuretics instead of ultrafiltration, and an additional 28 (30%) received intravenous diuretics after ultrafiltration was stopped and before the 96-hour assessment. A total of 3% of the patients received vasodilators and 3% received intravenous inotropic agents before the day 4 assessment. Randomization, treatment, and follow-up of the patients are shown in Figure S1 in the Supplementary Appendix.

PRIMARY END POINT

There was a significant difference between the treatment groups in the bivariate end point of change in weight and change in serum creatinine level 96 hours after enrollment (P=0.003) (Fig. 1, and Fig. S2 in the Supplementary Appendix). This difference was due primarily to an increase in the serum creatinine level in the ultrafiltration group. At 96 hours, the mean change in the serum creatinine level from the level measured at the time of randomization was a decrease of 0.04±0.53 mg per deciliter (3.5±46.9 μmol per liter) in the pharmacologic-therapy group, as compared with an increase of 0.23±0.70 mg per deciliter (20.3±61.9 μmol per liter) in the ultrafiltration group (P=0.003). There was no significant difference between pharmacologic therapy and ultrafiltration with respect to the mean weight loss 96 hours after enrollment (5.5±5.1 kg [12.1±11.3 lb] and 5.7±3.9 kg [12.6±8.5 lb] in the two groups, respectively; P=0.58).

SECONDARY END POINTS

The changes from baseline in the creatinine level at 48, 72, and 96 hours and at 60 days differed significantly between the patients in the pharmacologic-therapy group and those in the ultrafiltration group (Fig. 2A). However, there were no significant differences between the treatment groups at the time of discharge or on day 7, whichever occurred first, or at the 30-day assessment. There were no significant between-group differences in weight at any of the time points (Fig. 2B).

The rate of clinical decongestion at 96 hours was low in the two treatment groups (9% with pharmacologic therapy and 10% with ultrafiltration, P=0.83) (Table 2). Within the first 7 days, there was no significant difference between the groups in the percentage of participants whose condition worsened (with worsening condition defined as death, worsening or persistent heart failure, need for dialysis, or the occurrence of a serious adverse event) or who crossed over to alternate therapy (18% with pharmacologic therapy and 23% with ultrafiltration, P=0.45) or the change in the furosemide-equivalent dose of diuretics (an increase of 2.2 mg per day in the pharmacologic-therapy group and a decrease of 20.6 mg per day in the ultrafiltration group, P=0.18). At 96 hours and at day 7 or hospital discharge, there were no significant between-group differences in scores on the dyspnea and global well-being visual-analogue scales (Table 2). The total fluid output differed significantly between the two groups on the second day after randomization but not on days 1, 3, or 4 (Fig. S3 in the Supplementary Appendix).

Table 2. Secondary End Points.*

End Point	Pharmacologic Therapy (N=94)	Ultrafiltration (N=94)	P Value
Significant body weight loss and renal improvement — no. (%)†			
At 96 hr	20 (21)	16 (17)	0.62
At 7 days	20 (21)	15 (16)	0.52
Worsening condition or crossover during the first 7 days — no./total no. (%)‡	17/94 (18)	21/93 (23)	0.45
Clinical decongestion at 96 hr — no./total no. (%)§	7/80 (9)	8/82 (10)	0.83
Change in sodium from baseline to 96 hr — mmol/liter	0.0±3.6	−2.3±3.5	<0.001
Change in hemoglobin from baseline to 96 hr — g/dl	0.38±0.76	−0.01±0.92	0.002
Change in NT-proBNP from baseline to 96 hr — pg/ml	−979±2902	−814±9239	0.30
Change in cystatin C from baseline to 96 hr — mg/liter	0.14±0.52	0.22±0.52	0.37
Change in blood urea nitrogen from baseline to 96 hr — mg/dl	5.68±18.29	12.54±24.81	0.02
Change in glomerular filtration rate from baseline to 96 hr — ml/min/1.73 m^2	1.67±10.94	0.93±14.60	0.66
Change in score on global well-being scale from baseline to 96 hr¶	22.8±25.8	13.7±27.9	0.33
Change in score on dyspnea assessment scale from baseline to 96 hr¶	20.5±27.8	16.5±29.2	0.57
Total net fluid loss from randomization to 96 hr — ml	7082±4183	7443±4329	0.59
Change in furosemide-equivalent dose from preadmission to discharge — mg/day	2.2±166.5	−20.6±116.0	0.18
Death — no. (%)	13 (14)	16 (17)	0.55
Hospitalization — no./total no. (%)			
For heart failure	24/93 (26)	23/90 (26)	0.97
For any cause	37/93 (40)	46/90 (51)	0.12
Unscheduled emergency department or clinic visit — no./total no. (%)	13/93 (14)	19/90 (21)	0.21

* Plus–minus values are means ±SD.
† Significant weight loss was defined as a loss of 3 kg (6.6 lb) or more; significant renal improvement was defined as a decrease in the creatinine level of 0.3 g per deciliter (27 μmol per liter) or more.
‡ Worsening condition was defined as death, worsening or persistent heart failure, need for dialysis, or the occurrence of a serious adverse event.
§ Clinical decongestion was defined as jugular venous pressure of less than 8 cm of water, no more than trace peripheral edema, and the absence of orthopnea.
¶ Global well-being and dyspnea were assessed with the use of a visual-analogue scale that ranged from 0 to 100, with higher scores indicating greater well-being and lesser severity of dyspnea, respectively.[9]

SERIOUS ADVERSE EVENTS AND CLINICAL OUTCOMES

A higher percentage of patients in the ultrafiltration group than in the pharmacologic-therapy group had a serious adverse event over the 60-day period of follow-up (72% vs. 57%, P=0.03). The higher percentage in the ultrafiltration group was attributable mainly to higher incidences of kidney failure, bleeding complications, and intravenous catheter-related complications (Table 3).

The 60-day estimated mortality was 17% in the ultrafiltration group, as compared with 13% in the pharmacologic-therapy group (P=0.47) (Fig. S4 in the Supplementary Appendix). There was no significant difference in the composite rate of death or rehospitalization for heart failure (38% and 35%, respectively; P=0.96) (Fig. S5 in the Supplementary Appendix) or in the composite rate of death or rehospitalization for any reason (61% and 48%, respectively; P=0.12) (Fig. S6 in the Supplementary Appendix).

DISCUSSION

In CARRESS-HF, we compared ultrafiltration with diuretic-based therapy in patients with acute de-

Table 3. Serious Adverse Events.

Event	Pharmacologic Therapy (N = 94)	Ultrafiltration (N = 94)
	no. of patients (%)	
Any	54 (57)	68 (72)
Heart failure	28 (30)	31 (33)
Other cardiovascular disorder	5 (5)	6 (6)
Renal failure	14 (15)	17 (18)
Anemia or thrombocytopenia	5 (5)	8 (9)
Catheter-site hemorrhage	0	2 (2)
Electrolyte disorder*	3 (3)	0
Gastrointestinal hemorrhage	3 (3)	7 (7)
Pneumonia or other respiratory disorder	6 (6)	10 (11)
Sepsis, bacteremia, or cellulitis	4 (4)	8 (9)
Other	19 (20)	17 (18)

* Included in this category are hyperkalemia, hypokalemia, hypernatremia, hyponatremia, and hyperuricemia.

compensated heart failure and worsened renal function. The serum creatinine level 96 hours after enrollment was significantly increased in the ultrafiltration group as compared with the pharmacologic-therapy group but the weight loss was not significantly greater. There were also no significant between-group differences in weight loss, mortality, or the rate of hospitalization for heart failure during the 60-day follow-up period. Given the high cost and complexity of ultrafiltration, the use of this technique as performed in the current study does not seem justified for patients hospitalized for acute decompensated heart failure, worsened renal function, and persistent congestion.

The reason for the early rise in the creatinine level in the patients who underwent ultrafiltration is unclear. It is possible that these patients had transient intravascular volume depletion during ultrafiltration. Previous studies examining plasma refill rates in patients with heart failure have shown that rates of volume removal greater than 200 ml per hour, which was the rate used in our trial, are not associated with adverse effects.[14] The duration of ultrafiltration was longer in the present study than it was in other trials,[10,14,15] a fact that may have contributed to the increase in the creatinine level at 96 hours in the patients who received this treatment. At 30 days and at 60 days, the mean creatinine level was below the baseline level in both treatment groups. The lesser reduction in the creatinine level in the ultrafiltration group may be real, but it may also represent a chance finding or an imbalance in baseline features between the two treatment groups, or it may be the result of other events influencing kidney function that may have occurred after the patients' discharge from the hospital.

On the basis of prior studies of the use of ultrafiltration in patients with acute decompensated heart failure,[10,15,16] we anticipated that the patients in the ultrafiltration group would lose more weight than would those in the pharmacologic-therapy group. Ultrafiltration was discontinued early owing to multiple reasons other than attainment of a satisfactory fluid volume, a finding that shows the complexity of the use of ultrafiltration in patients with acute decompensated heart failure and the cardiorenal syndrome. Patients in the pharmacologic-therapy group had substantial diuresis as a result of the aggressive use of diuretics and adjuvant therapies.

The rates of death and rehospitalization did not differ significantly between the two treatment strategies, despite the increase in the creatinine level at 96 hours in the ultrafiltration group. Several retrospective studies have shown an association between worsening renal function and poor outcomes.[17-19] Other trials, however, indicate that the relationships among the degree of clearing of congestion, changes in renal function, and outcomes are less clear.[10,20-23] In the Diuretic Optimization Strategies Evaluation (DOSE) trial, worsening renal function in the high-dose furosemide group was not associated with worse outcomes.[20] In the UNLOAD trial, a trend toward worsening renal function and greater weight loss in the ultrafiltration group was associated with a reduction in the rate of hospitalization for heart failure.[10] The relationships among changes in renal function, degree of clearing of congestion, and outcomes in patients with acute decompensated heart failure are complex and require more study. In our trial, the rates of death or rehospitalization at 60 days were very high, showing the need for better therapies for this patient population.

Our study has several limitations. First, although the trial was randomized, the treatment assignments were not blinded, and biases on the part of study investigators may have affected the

duration or relative intensity of ultrafiltration and pharmacologic therapy. Second, the safest and most effective rates of fluid removal, the duration of therapy, and the conditions for termination of ultrafiltration are unknown. A different intensity of ultrafiltration might have resulted in more fluid loss in the ultrafiltration group; however, the effect of a different intensity on renal function and outcomes is unknown. Finally, the results of the strategies tested here may not apply to other patient populations with acute decompensated heart failure, such as patients with less severe cardiorenal syndrome.

In summary, we conducted a randomized trial involving patients hospitalized for acute decompensated heart failure, worsened renal function, and persistent congestion. We found that the use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function, with the amount of weight loss at 96 hours similar with the two approaches. Ultrafiltration was associated with higher rates of adverse events.

The authors are solely responsible for the content of this article, which does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

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Disclosure forms provided by the authors are provided with the full text of this article at NEJM.org.

We thank the patients who participated in this study, the Heart Failure Network site investigators and coordinators, the members of the Heart Failure Network data and safety monitoring board and protocol review committee, and the National Heart, Lung, and Blood Institute representatives — all of whom are listed in the Supplementary Appendix.

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Supplementary Appendix

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

Supplement to: Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296-304. DOI: 10.1056/NEJMoa1210357

Contents

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria from final protocol:

- age 18 or older
- admitted to the hospital with a primary diagnosis of decompensated heart failure
- onset of cardiorenal syndrome after hospitalization or pre-hospitalization
    - after hospitalization—onset of cardiorenal syndrome after hospitalization must occur within 10 days from the time of admission after receiving IV diuretics
    - pre-hospitalization—onset of cardiorenal syndrome pre-hospitalization must occur within 12 weeks of the index hospitalization in the setting of escalating doses of outpatient diuretics
- persistent volume overload
    - for patients with a pulmonary artery catheter, persistent volume overload will include:
        - pulmonary capillary wedge pressure greater than 22mmHg and one of the following clinical signs:
            - at least 2+ peripheral edema and/or
            - pulmonary edema or pleural effusions on chest x-ray
    - for patients without a pulmonary artery catheter, persistent volume overload will include at least two of the following:
        - at least 2+ peripheral edema
        - jugular venous pressure greater than 10 cm on physical examination (or central venous pressure greater than 10 mmHg when measured)
        - pulmonary edema or pleural effusions on chest x-ray

Exclusion criteria from final protocol:

- intravascular volume depletion based on investigator's clinical assessment
- acute coronary syndrome within 4 weeks
- indication for hemodialysis
- creatinine > 3.5 mg per deciliter at admission to the hospital
- systolic blood pressure < 90 mmHg at the time of enrollment
- alternative explanation for worsening renal function such as obstructive nephropathy,
- contrast induced nephropathy, acute tubular necrosis
- Hematocrit > 45%
    - poor venous access
    - clinical instability likely to require the addition of intravenous vasoactive drugs, vasodilators and/or inotropic agents
    - allergy or contraindications to the use of heparin
    - the use of iodinated radio contrast material in the last 72 hours or anticipated use of IV
    - contrast during the current hospitalization
    - known bilateral renal artery stenosis
    - active myocarditis
    - hypertrophic obstructive cardiomyopathy
    - severe valvular stenosis
    - complex congenital heart disease
- sepsis or ongoing systemic infection
- enrollment in another clinical trial involving medical or device based interventions

STEPPED PHARMACOLOGIC CARE ALGORITHM

- Intravenous diuretics will be used to address signs and symptoms of congestion

- The stepped pharmacologic care 'intervention' will be finished when the patient's volume status has, in the opinion of the investigator, been optimized and there is no ongoing need for intravenous diuretics (patients may require the stepped pharmacologic care 'intervention' beyond the 96 hour primary endpoint assessment)

- A stepped care algorithm developed by the Heart Failure Network is provided below

- Investigators may opt-out of the stepped care treatment algorithm if they feel it is in the best interests of patient care

- Careful clinical monitoring is necessary so that volume reduction therapy can be reduced as patients approach an optimized volume state. Blood pressure, physical exam findings, hemodynamics, BUN and creatinine should be used to determine optimal volume status

- Intravenous diuretics can be decreased or temporarily discontinued if there is a decrease in blood pressure or an increase in creatinine that is felt to be due to a transient episode of intravascular volume depletion. After the patient has stabilized, if congestion persists, intravenous diuretics should be reinitiated until the patient's fluid status has been optimized.

- Crossover to ultrafiltration is discouraged before the 96 hour primary endpoint assessment

- The transition from IV to oral diuretics prior to discharge is left to the discretion of the treating physician and will be continued in the outpatient setting as needed for optimal fluid homeostasis

AT RANDOMIZATION – STEPPED PHARMACOLOGIC CARE ARM

UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → See table

	Current Dose		Suggested Dose	
	loop (/day)	thiazide	loop (/day)	thiazide
A	≤ 80	+ or -	40 mg iv bolus+ 5 mg/hr	0
B	81-160	+ or -	80 mg iv bolus+ 10 mg/hr	5 mg metazolone QD
C	161-240	+ or -	80 mg iv bolus+ 20 mg/hr	5 mg metazolone BID
D	> 240	+ or -	80 mg iv bolus+ 30 mg/hr	5 mg metazolone BID

AT 24 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table

AT 48 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 (any EF) and Severe Symptoms

AT 72 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 (Any EF) and Severe Symptoms
Advanced Cardiorenal Therapy Hemodynamic guided iv therapy, LVAD, Dialysis or UF Cross over

AT 96 Hrs - STEPPED PHARMACOLOGIC CARE ARM
Persistent Volume Overload Present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3-5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 (Any EF) and Severe Symptoms
Advanced Cardiorenal Therapy Hemodynamic guided iv therapy, LVAD, Dialysis or UF Cross over

CARRESS-HF END POINTS

Primary End Point

Change in serum creatinine AND weight together as a "bivariate" endpoint assessed 96 hours after enrollment.

Secondary End Points

a) Primary endpoint (change in serum creatinine AND weight together as a "bivariate" endpoint) assessed after randomization on hospital days 1 - 3 and at one week.

b) Significant weight loss and renal improvement assessed at 96 hours and one week.

c) Treatment failure during the first seven days after randomization.

d) Changes in renal function from randomization to days 7, 30 and 60. Peak creatinine during hospitalization.

e) Changes in electrolytes from randomization to 96 hours and one week.

f) Changes in weight measured daily from randomization to one week, 30 and 60 days.

g) Percent of patients achieving clinical decongestion at 96 hours, one week, 30 and 60 days.

h) Total net fluid loss from randomization to 96 hours and 1 week.

i) Changes in biomarkers from randomization to 96 hours, at one week and at 60 days.

j) Changes in global assessment and visual analogue scores from enrollment to 96 hours and one week.

k) Length of hospital stay from time of enrollment to discharge, days alive outside the hospital at 60 days, and heart failure rehospitalizations during the 60 day followup, unscheduled emergency department and office visits.

l) Changes in daily oral diuretic doses from prior to hospitalization to discharge, at 30 and at 60 days.

m) Resource utilization as described in item K above plus the number of disposables consumed by the ultrafiltration intervention

FIGURE S1: CONSORT FLOW DIAGRAM

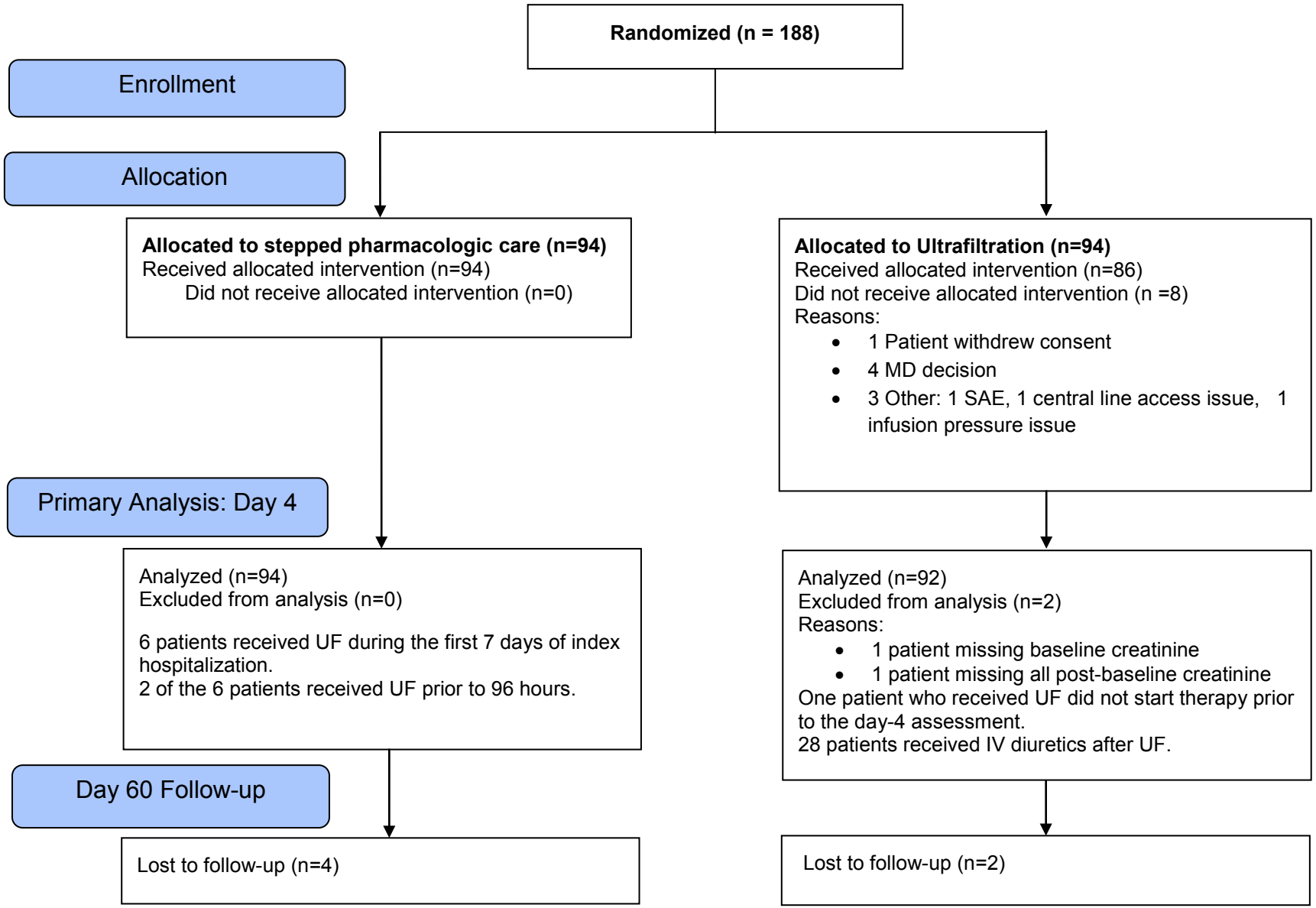


FIGURE S2: 95% CONFIDENCE REGION (ELLIPSE) FOR THE MEAN TREATMENT DIFFERENCES AT 96 HOURS

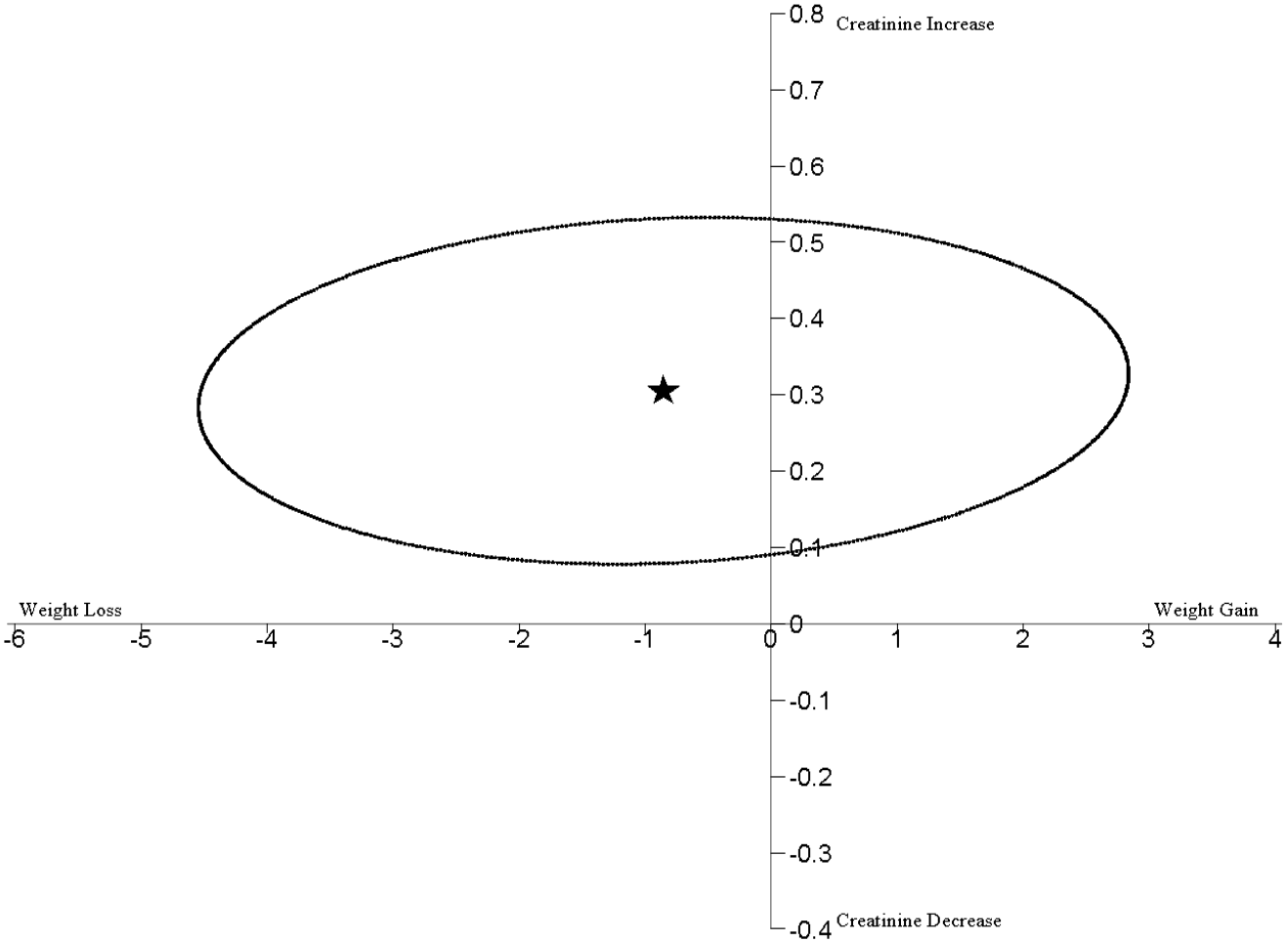
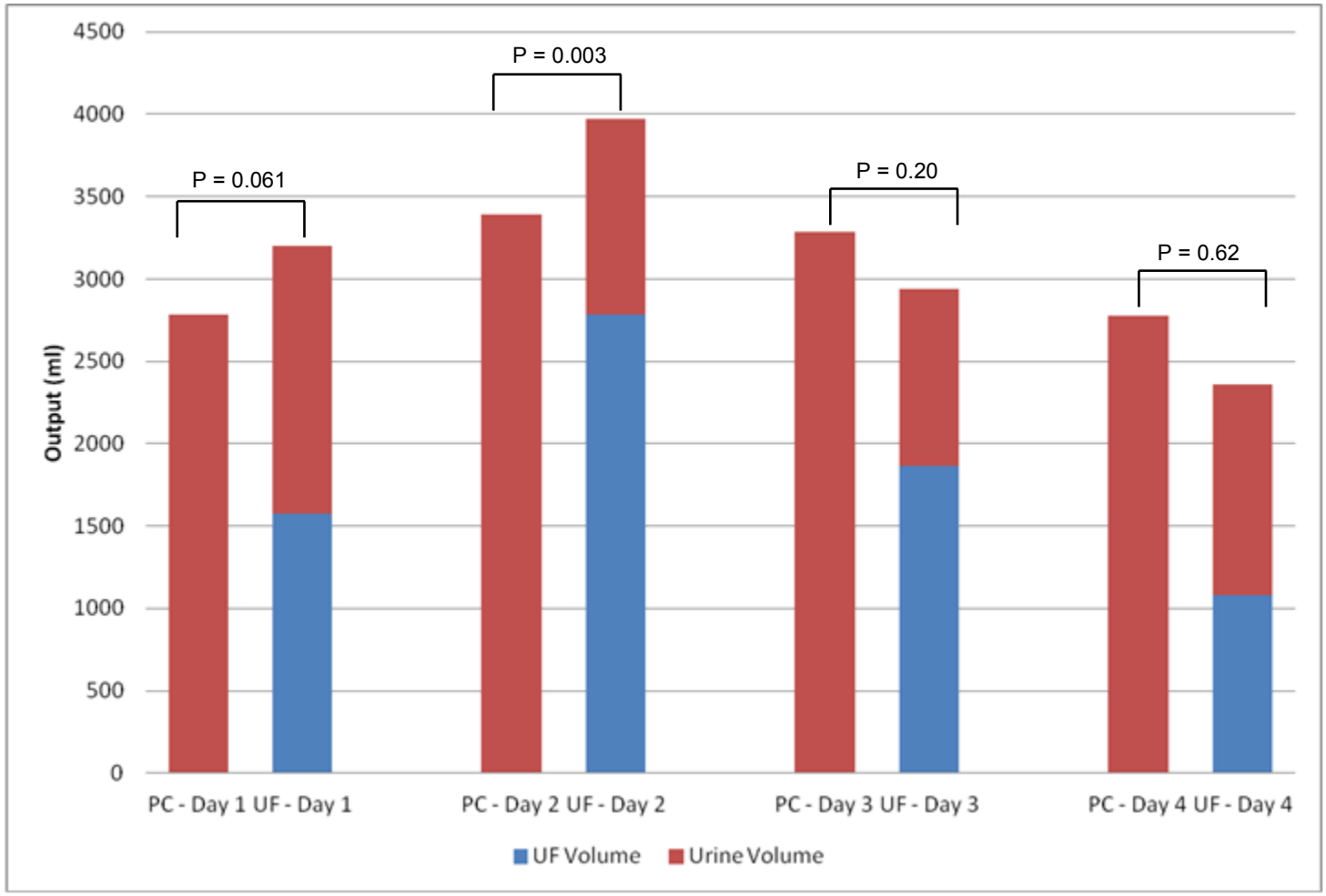
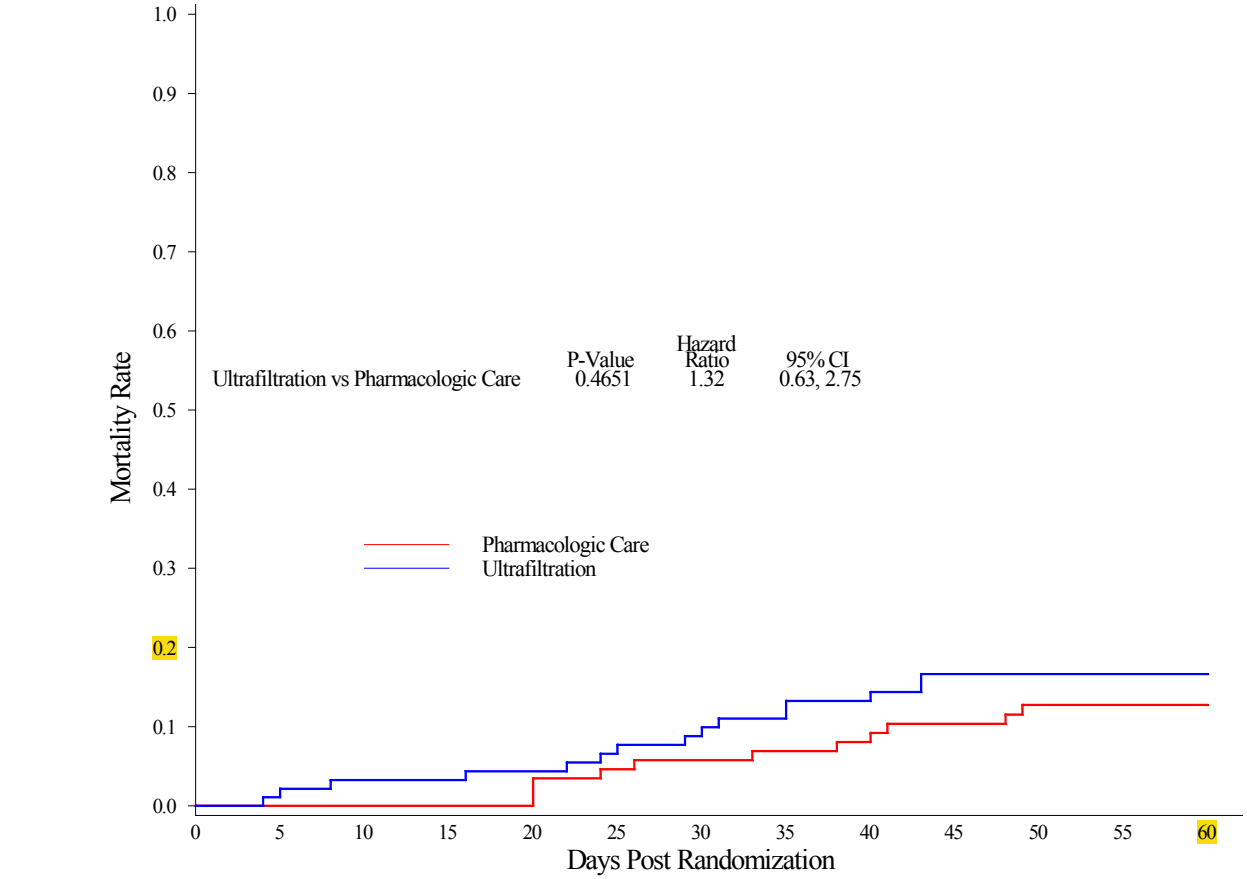


FIGURE S3: TOTAL FLUID OUTPUT BY DAY



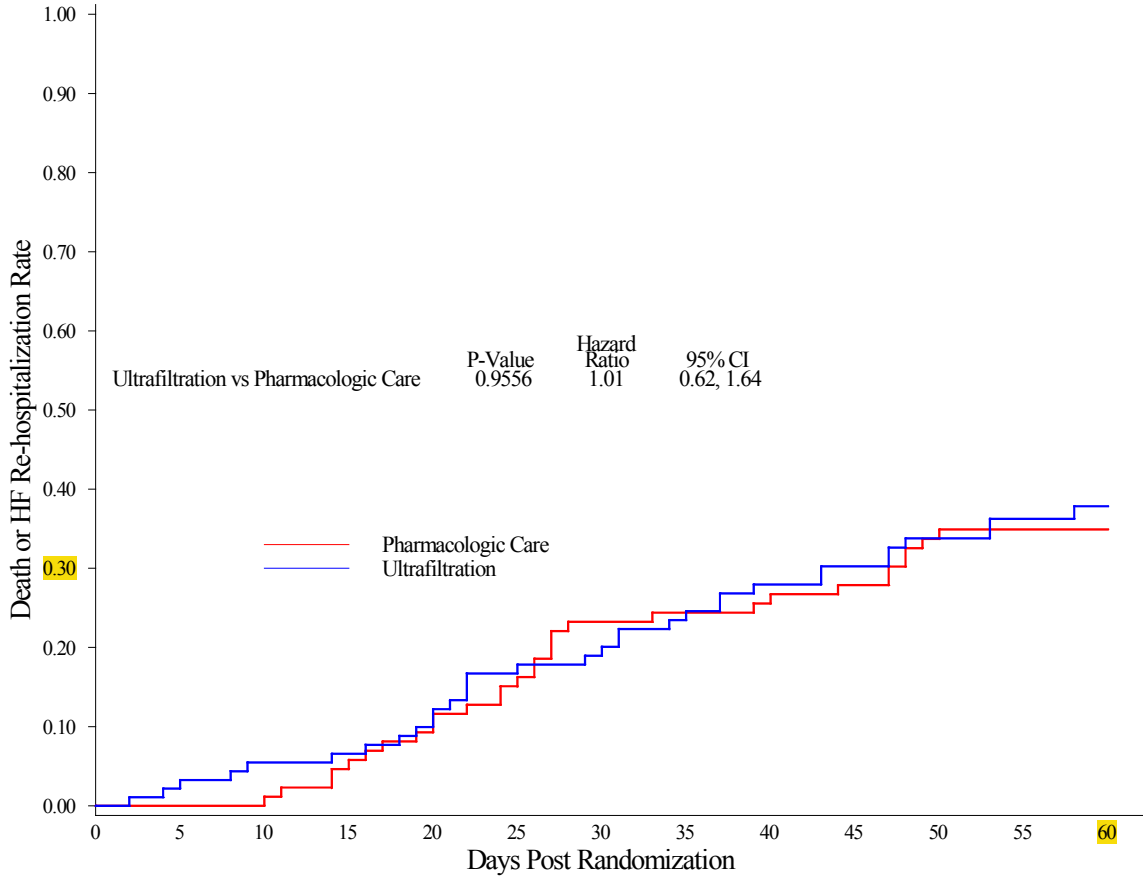
PC=Pharmacologic care; UF=Ultrafiltration

FIGURES S4: KAPLAN-MEIER TIME TO DEATH



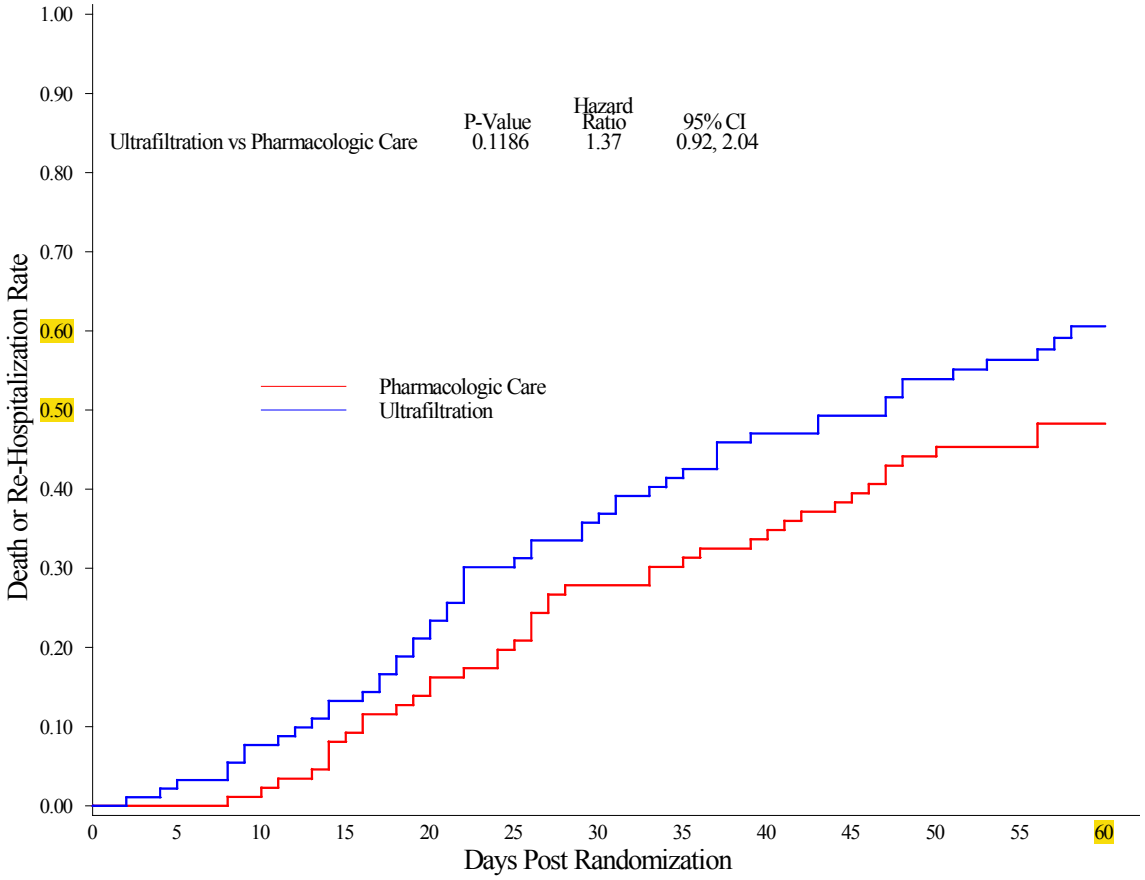
Number at Risk:	Baseline	Day 5	Day 10	Day 15	Day 20	Day 25	Day 30	Day 35	Day 40	Day 45	Day 50	Day 55	Day 60
Pharmacologic Care	94	92	88	87	87	83	82	81	80	77	72	61	40
Ultrafiltration	94	92	88	88	86	84	82	80	78	73	70	64	44

FIGURE S5: KAPLAN-MEIER TIME TO DEATH OR HEART FAILURE REHOSPITALIZATION



Number at Risk:	Baseline	Day 5	Day 10	Day 15	Day 20	Day 25	Day 30	Day 35	Day 40	Day 45	Day 50	Day 55	Day 60
Pharmacologic Care	93	91	87	82	78	73	66	65	64	62	56	47	32
Ultrafiltration	93	90	85	84	80	74	72	68	64	61	55	51	36

FIGURE S6: KAPLAN-MEIER TIME TO DEATH OR ANY REHOSPITALIZATION



Number at Risk:	Baseline	Day 5	Day 10	Day 15	Day 20	Day 25	Day 30	Day 35	Day 40	Day 45	Day 50	Day 55	Day 60
Pharmacologic Care	93	91	86	79	74	69	62	60	57	53	47	40	25
Ultrafiltration	93	90	83	78	70	62	57	52	47	45	39	36	24

CORRESPONDENCE

Ultrafiltration in Heart Failure with Cardiorenal Syndrome

TO THE EDITOR: Bart et al. (Dec. 13 issue)[1] report the results of the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF). They state that ultrafiltration was inferior to a strategy of stepped pharmacologic therapy with respect to the bivariate primary end point of the change in the serum creatinine level and body weight in patients with acute decompensated heart failure. In clinical practice, at least in Europe, the use of ultrafiltration would not be considered in patients with average urine outputs of 2.8 liters (on day 1), 3.4 liters (on day 2), 3.3 liters (on day 3), and 2.8 liters (on day 4) during medical therapy (see Fig. S3 in the Supplementary Appendix, available with the full text of their article at NEJM.org) and a baseline serum creatinine concentration of approximately 2 mg per deciliter. Ultrafiltration presumably should be restricted to patients with impairment of renal function, cardiac function, or both that is more severe than the impairment in patients involved in the current trial. Furthermore, it is unclear at first sight why renal function should be different at 96 hours only when serum creatinine concentrations are used as a marker of renal function, but not when the level of cystatin C or the glomerular filtration rate are used. How can this discrepancy be explained?

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No potential conflict of interest relevant to this letter was reported.

1. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296-304.

DOI: 10.1056/NEJMc1300456

TO THE EDITOR: Given the bivariate primary end point that entailed the serum creatinine level for the comparison of ultrafiltration with pharmacologic therapy in patients with heart failure and worsening renal function, this trial could not have had different results.

In the ultrafiltration group, most of the fluid removal was achieved with ultrafiltration, which implied that less fluid was eliminated by the kidney through glomerular filtration (Fig. 1, and Fig. S3 in the Supplementary Appendix of the article by Bart et al.). By contrast, in the pharmacologic-therapy group, the excess fluid was eliminated exclusively through the kidney. Since, according to the manufacturer, creatinine is not removed with the Aquadex System 100 ultrafiltration procedure used in the study, it could be anticipated that a smaller amount of creatinine was excreted through glomerular filtration and tubular secretion. Hence, besides being

THIS WEEK'S LETTERS

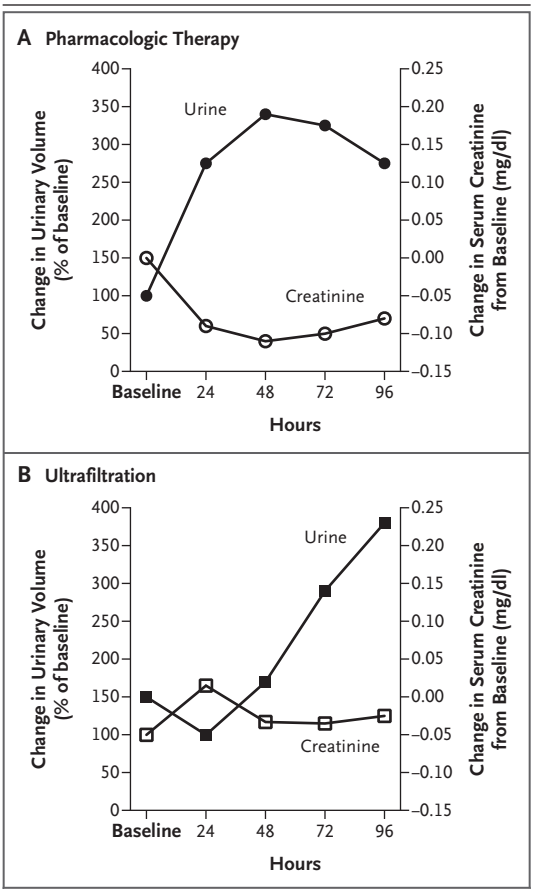

Figure 1. Changes from Baseline in Urine Output and Serum Creatinine at Various Time Points, According to Treatment Group.

The relationship between the percent changes in urine output from baseline (100%) and absolute changes in levels of serum creatinine from baseline throughout 96 hours in the patients with heart failure who were randomly assigned to pharmacologic therapy (Panel A) and to ultrafiltration (Panel B) is shown. A significant inverse correlation (calculated with the use of Spearman's rank-correlation coefficients) was seen in the pharmacologic-therapy group but not in the ultrafiltration group. The data on serum creatinine levels and urine output in both groups were derived from Figure 2A of the article by Bart et al. and Figure S3 in the Supplementary Appendix of the article, with approximation.

clinically irrelevant, the small increase in the serum creatinine level (0.23±0.70 mg per deciliter [20.3±61.9 μmol per liter]) in the ultrafiltration group, as compared with the changes observed in the pharmacologic-therapy group, was nothing other than the expected result given the choice of this primary end point.

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Dr. Rossi reports receiving consulting fees from Gambro UF Solutions. No other potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc1300456

TO THE EDITOR: Publication of the results of the CARRESS-HF trial is an important step in establishing the value of ultrafiltration therapy in specific patient populations. As manufacturers of the Aquadex FlexFlow ultrafiltration system, we would like to highlight some points. First, the study population in this trial had more advanced disease than that which is indicated for this therapy. Second, ultrafiltration was performed at a fluid-removal rate of 200 ml per hour, which may have been inappropriate for this patient population. Third, rates of intravascular volume refill were not monitored.[1]

Gambro UF Solutions welcomes the critical evaluation and vigorous study of ultrafiltration therapy for fluid removal in patients with volume overload and resistance to diuretic therapy.

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Dr. Bosch reports being an employee of Gambro, and Dr. Rios-Nogales Garces reports being an employee of Gambro UF Solutions. No other potential conflict of interest relevant to this letter was reported.

1. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007;49:675-83. [Erratum, J Am Coll Cardiol 2007;49:1136.]

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TO THE EDITOR: In this trial, ultrafiltration, as compared with pharmacologic therapy, was associated with similar weight loss, but greater increases in the creatinine level and a higher rate of adverse events. In acute decompensated heart failure, transient increases in the creatinine level may not portend a poor prognosis.[1] Whereas doses of diuretics were adjusted in the pharmacologic-therapy group, the ultrafiltration rate was

uniformly 200 ml per hour, which may be excessive because of venous blood sequestration in patients with low blood pressure or right ventricular dysfunction.[2] In contemporary ultrafiltration devices, hematocrit sensors estimate blood volume so that the capillary refill time is not exceeded and hypovolemia is prevented. A total of 12% of patients in the pharmacologic-therapy group received inotropic agents, which are prohibited in ultrafiltration; this may have attenuated hypotension-related worsening renal function. A total of 23% of patients in the ultrafiltration group crossed over to alternative therapy, and 39% received intravenous diuretics before the 96-hour assessment, which may have contributed to worsening renal function. The duration of increases in the creatinine level of 0.3 mg per deciliter or more before randomization was not reported.[3]

The results of this phase 2 trial indicate that data are lacking about ultrafiltration. The Aquapheresis versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF) trial (ClinicalTrials.gov number, NCT01474200), which involves 810 patients in 40 sites in the United States, is testing whether ultrafiltration, as compared with intravenous diuretics before worsening renal function, reduces hospitalizations for acute decompensated heart failure.

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Dr. Costanzo reports being a principal investigator in the AVOID-HF Trial; receiving grant support, consulting fees, and lecture fees from Gambro; and receiving consulting fees from Sorbent Therapeutics. Dr. Fonarow reports serving as a member of the steering committee of the AVOID-HF Trial and receiving consulting fees from Gambro. Dr. Filippatos reports receiving grant support and consulting fees from Bayer and Novartis. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: The diversity of responses to the results of our trial highlights the uncertainty in clinical practice for patients with acute decompensated heart failure and kidney disease. Haas et al. recommend that ultrafiltration be reserved for patients with more advanced kidney disease or cardiac dysfunction, whereas Bosch and Rios-Nogales Garces suggest that the patients in our trial had disease that was more advanced than the disease stage for which ultrafiltration is recommended. Thus, the criticism comes from both sides. Data are lacking from trials to inform clinical decisions in patients with resistance to diuretics. Data are also lacking on the role of ultrafiltration, especially ultrafiltration techniques and the understanding of how to best implement them to overcome the complexities of administration.

Both Haas et al. and Rossi et al. question the use of the serum creatinine level to assess renal function. We selected change in the creatinine level as a key component of the primary end point in our trial because it is one of the few measures routinely used for clinical decision making in patients with acute heart failure and it is associated with outcomes. With a sieving coefficient of 1, the concentration of creatinine in the ultrafiltrate is the same as that in the plasma. Thus, creatinine is removed from the plasma during ultrafiltration without directly influencing the serum creatinine concentration.[1] The early increase in the creatinine level in patients in the ultrafiltration group might indicate a real decrement in kidney function. However, the clinical significance of this change cannot be fully assessed in our trial because of the relatively small sample size. Why the level of cystatin C, which is thought to be a more accurate indicator of renal function, did not increase in the ultrafiltration group is unknown.

Bosch and Rios-Nogales Garces, and Costanzo et al., raise important issues related to the application of ultrafiltration in our trial. We acknowledge that the ideal rate of fluid removal, supportive medical therapy, monitoring measures, and the conditions used to determine the best time for discontinuing acute decongestive therapies for ultrafiltration are unknown. Changes in hematocrit may be a useful surrogate for measuring the plasma refill rate during ultrafiltration therapy. However, this approach has not been shown to be superior to any other method

of monitoring during ultrafiltration. Conditions for discontinuation need to be prospectively defined and validated. Data are lacking to answer these and many other questions that directly affect the outcomes of patients with volume overload and renal dysfunction.

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Since publication of their article, the authors report no further potential conflict of interest.

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Continuous Renal-Replacement Therapy for Acute Kidney Injury

TO THE EDITOR: Tolwani (Dec. 27 issue)[1] recommends continuous renal-replacement therapy over intermittent hemodialysis (for 4 hours per day) for a patient with postoperative acute kidney injury. We believe that there is an even better option: prolonged intermittent renal-replacement therapy (i.e., 8 to 12 hours per day or every other day); this is commonly called sustained low-efficiency dialysis.

Sustained low-efficiency dialysis is a hybrid form of renal-replacement therapy that is well suited for critically ill patients with acute kidney injury. In fact, it shares the advantages of both the classic intermittent forms of renal-replacement therapy (e.g., the simple procedure, flexible scheduling during the day or night, and low cost due to the use of a standard dialysis machine and production of the dialysate by a dialysis machine) and continuous renal-replacement therapy (e.g., hemodynamic stability with fluid removal without adverse effects, narrow osmotic fluctuation, and good metabolic control).[2,3] Also, sustained low-efficiency dialysis, like continuous renal-replacement therapy, can be performed with citrate in patients who are at high risk for hemorrhage.[4] In fact, sustained low-efficiency dialysis has now become the standard treatment of choice in many different centers throughout the world for patients such as the one described in the vignette.[5]

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHOR REPLIES: No specific form of renal-replacement therapy has been shown to increase survival among critically ill patients with acute kidney injury.[1] Therefore, the choice of the form of renal-replacement therapy should be guided by the patient's clinical status and the expertise and resources of the institution.

More than one type of renal-replacement therapy can be used for treating patients with acute kidney injury. Transitions in therapy are common and reflect the changing needs of patients during hospitalization.

Prolonged intermittent renal-replacement therapy, also known as sustained low-efficiency dialysis, is a viable option. However, the focus of my review was the use of continuous renal-replacement therapy in acute kidney injury. Data are lacking from studies of prolonged intermittent renal-replacement therapy in patients with cardiogenic shock, fulminant liver failure, and increased intracranial pressure, and pharmacokinetic data for effectively dosing antibiotics are also lack-