Heart Failure Network

Protocol for the CARdiorenal REScue Study in Acute Decompensated Heart Failure

CARRESS HF

Compiled by:

The Heart Failure Network Research Group

March 10, 2011

Amendment 5

Distributed by the Data Coordinating Center:

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1. EXECUTIVE SUMMARY

Patient population	Patients hospitalized with acute decompensated heart failure will be eligible for enrollment if they develop cardiorenal syndrome (defined as an increase in serum creatinine of $\geq$ 0.3 mg per deciliter from baseline) while demonstrating signs and symptoms of persistent congestion.
Study design	Randomized, controlled, multi-center clinical trial
Intervention	1:1 randomization to stepped pharmacologic care versus ultra filtration
Primary endpoint	Change in serum creatinine AND weight together as a "bivariate" endpoint assessed 96 hours after enrollment.
Sample size	200 (100 per treatment arm)
Secondary endpoints	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

2. SPECIFIC AIMS AND OBJECTIVES / HYPOTHESES

The purpose of this study is to test the hypothesis that ultrafiltration compared to a stepped pharmacologic care approach will result in improved renal function and relief of congestion in patients hospitalized with acute decompensated heart failure (ADHF) and cardiorenal syndrome.

Primary hypothesis:

The primary hypothesis is that ultrafiltration in hospitalized ADHF patients with cardiorenal syndrome will result in improved renal function and relief of congestion compared to stepped pharmacologic care. Changes in renal function and congestion will be assessed by serum creatinine concentration and weight loss, respectively, together considered as a "bivariate" end point 96 hours after randomization.

The secondary aims and objectives of this protocol will be to examine the effect of the above treatment assignments on:

a. Primary endpoint (change in serum creatinine AND weight together as a "bivariate" endpoint) assessed 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 follow-up, unscheduled emergency department and office visits.

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

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

3. BACKGROUND AND SIGNIFICANCE

Acute decompensated heart failure (ADHF) is the most common cause for hospitalization among Medicare beneficiaries and is associated with substantial morbidity and mortality – 4% of patients will die during their hospitalization and 44% will be readmitted within 6 months [1, 2]. Given the poor

clinical outcomes of patients with ADHF, there is an urgent need to develop new treatment strategies that will favorably alter the course of this increasingly common and deadly condition [1, 3 - 5.]

Cardiorenal syndrome (renal dysfunction at the time of admission or worsening renal function during therapy) is a powerful predictor of mortality in patients with ADHF [6]. The deleterious physiologic effects associated with the acute administration of loop diuretics may be the proximate cause of worsening renal function in 20% to 75% of patients hospitalized for ADHF [7, 8]. While hospital mortality is 4% among all patients admitted with ADHF, patients with preserved renal function and normal blood pressure have an inpatient mortality rate of 2.3% compared to 19.5% in patients with evidence of advanced renal dysfunction [1, 6]. Length of stay, readmission and early death are much more common when cardiorenal syndrome develops compared to when it does not [8 - 11]. There are no proven treatments or guidelines for cardiorenal syndrome [5].

Ultrafiltration is an attractive alternative to loop diuretics for the management of fluid overloaded patients with ADHF and cardiorenal syndrome. It is a more effective means of restoring sodium balance (isotonic saline is removed during ultrafiltration compared to hypotonic urine that is produced when loop diuretics are used)[12], has no effect on serum electrolytes, and results in rapid and predictable fluid removal [13 - 18]. Ultrafiltration does not stimulate the neurohormonal system and appears to restore responsiveness to loop diuretics in patients with diuretic resistance [13, 14, 19]. Successful volume reduction therapy by ultrafiltration in patients with cardiorenal syndrome and persistent congestion is likely to improve renal perfusion and glomerular filtration rate (GFR). In an animal study controlling for varying degrees of renal vein pressure, substantial decreases in GFR and increases in fluid and sodium retention occurred when renal vein pressures exceeded 18 mmHg. GFR and sodium retention return to normal rapidly after normalizing renal vein pressures indicating that "congestion" of the kidney may significantly impact renal function in patients with ADHF especially those who go on to develop cardiorenal syndrome [20].

The purpose of this study is to evaluate the efficacy and safety of ultrafiltration for the treatment of patients with persistent congestion and cardiorenal syndrome.

4. PRELIMINARY STUDIES

4.1 Recent Published Experience with Ultrafiltration for Heart Failure

Slow continuous ultrafiltration results in effective fluid removal and may be associated with restoration of diuresis and natriuresis. Recent experience with peripheral veno-venous ultrafiltration has yielded promising results in patients with heart failure. In two randomized controlled trials, minimally invasive ultrafiltration was performed using the Aquadex System 100 (CHF Solutions, Inc)[21, 22]. This device has been described previously [17] and details about its operation can be found in the appendix. Briefly, the system 100 is a portable, minimally invasive ultrafiltration device that is FDA approved for the treatment of fluid overloaded states. The ultrafiltration procedure can be performed by nurses without any special dialysis training and can be performed outside the setting of the intensive care unit. While it can be performed effectively through the use of centrally placed intravenous lines, this is not necessary; ultrafiltration can be performed through the use of two peripheral IVs, the combination of an extended length catheter placed in the antecubital fossa and a standard peripheral IV, or in some circumstances, a single dual-lumen peripheral IV.

Several small, uncontrolled case series of ADHF patients treated with slow continuous ultrafiltration demonstrate effective fluid removal that is well tolerated and associated with few complications [23, 24]. One small case series demonstrated that ultrafiltration therapy performed late in the course of advanced heart failure and renal disease was associated with poorer outcomes [25]. More recently, two randomized controlled

studies evaluated the safety and efficacy of ultrafiltration in patients with ADHF [21, 22].

The RAPID-CHF trial was a multi-center randomized controlled trial designed to assess the feasibility, safety and efficacy of early ultrafiltration versus usual care in the management of patients admitted with ADHF [21]. Forty patients with ADHF were randomized to receive usual care (the use of high dose loop diuretics for restoration of fluid and sodium homeostasis) or early ultrafiltration using the Aquadex System 100. The results of the RAPID-CHF trial showed that early ultrafiltration in patients hospitalized with ADHF and fluid overload resulted in a trend toward greater weight loss at 24 hours and greater fluid removal compared to usual care. Ultrafiltration was well tolerated and the median volume of ultrafiltrate removed during a single eight-hour course of ultrafiltration was 3213 mL. Dyspnea and CHF symptoms were significantly improved in the ultrafiltration group compared to usual care at 48 hours.

Results of the RAPID-CHF trial played a critical role in designing the larger, multi-center UNLOAD trial [22]. This clinical trial, compared the safety and efficacy of loop diuretics to ultrafiltration in patients with ADHF. The effectiveness of these two volume management strategies were judged based on weight loss assessed at 48 hours and quality-of-life, functional status and the total number of days of hospitalization and mortality at 90 days. Ultrafiltration resulted in 5.0 kg of weight loss at 48 hours compared to 3.3 kg in the usual care group (p=0.001). Weight loss in the control group exceeded that expected in community practice based on data from the ADHERE registry and is similar to that achieved at the time of discharge in the EVEREST study (late breaking trials, ACC 2007). There was no significant difference in the incidence of cardiorenal syndrome despite a substantial difference in volume reduction experienced by patients in the ultrafiltration treatment arm.

4.2 Early Experience with Ultrafiltration for Cardiorenal Syndrome

We have performed ultrafiltration in a small number of patients with cardiorenal syndrome. A retrospective review of 6 patients meeting CARRESS inclusion criteria (as described below) suggests that ultrafiltration is well tolerated and produces significant fluid removal and *improved* renal function in this carefully selected patient population (see appendix A).

5. BASIC STUDY DESIGN

This is a multi-center, prospective, randomized, controlled trial comparing slow continuous veno-venous ultrafiltration to stepped pharmacologic care in patients admitted to the hospital with the primary diagnosis of ADHF who develop cardiorenal syndrome (defined as an increase in serum creatinine concentration of greater than or equal to 0.3 mg per deciliter) in the setting of persistent congestion.

After meeting all the inclusion and exclusion criteria and signing informed consent, hospitalized ADHF patients with persistent congestion and cardiorenal syndrome will be randomized in a one-to-one fashion to stepped pharmacologic care or ultrafiltration. Patients in the stepped pharmacologic care group will be managed according to a recommended treatment algorithm developed by the Heart Failure Network. This stepped care algorithm provides treating physicians with guidelines for the intensification of diuretic therapy and the possible use of vasodilators and inotropes. Patients in the ultrafiltration group will have all loop diuretics discontinued and will undergo slow continuous ultrafiltration until an optimal volume status has been achieved.

It is anticipated that ultrafiltration will prove to be safe and effective for the management of these patients and that this intervention will effectively address both the worsening renal function and persistent congestion present at the time of enrollment. Patients will be assessed at the time of enrollment and daily until discharge or day 7, whichever occurs first. In addition, patients will be assessed at 30 and 60 days after the time of enrollment.

The primary endpoint of the study is a "bivariate" endpoint of change in creatinine and change in weight assessed 96 hours after the time of enrollment. Other important secondary endpoints include changes in renal function and weight over a 60 day interval, the ability to achieve clinical decongestion, changes in biomarkers and neurohormonal activation, changes in symptoms, treatment failures, length of hospital stay, heart failure rehospitalizations and unscheduled clinic and emergency department visits during a 60 day follow-up interval.

6. STUDY POPULATION AND ELIGIBILITY CRITERIA

6.1 Study Population and Source of Participants

Patients admitted to the hospital with a primary diagnosis of ADHF will be screened for participation in this study. Patients will be eligible for enrollment if they develop cardiorenal syndrome (defined as an increase in serum creatinine of $\geq$ 0.3 mg per deciliter from baseline) while demonstrating signs and symptoms of persistent congestion. The cut-point for identifying patients with cardiorenal syndrome of $\geq$ 0.3 mg/dl was selected because this degree of worsening renal function occurs with a relatively high frequency (approximately 25%) and represents a balance of sensitivity and specificity for the prediction of adverse clinical outcomes [5, 7-10]. Less restrictive definitions of worsening renal function would be more sensitive but less specific for the detection of adverse outcomes and more restrictive definitions would reduce the number of patients experiencing worsening renal failure, enhance specificity, but reduce sensitivity [8].

6.2 Inclusion and Exclusion Criteria

Inclusion criteria:
• 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
    o after hospitalization – onset of cardiorenal syndrome after hospitalization must occur within 10 days from the time of admission after receiving IV diuretics
    o 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
    o 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
    o 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:
• 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 including 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

7. TREATMENT INTERVENTIONS

7.1 All Patients

All patients will be started on a 2 liter per day fluid restriction and a 2gm per day sodium restriction. Decisions regarding the use of standard heart failure medications such as ACE inhibitors, beta-blockers, and digoxin will be left to the discretion of the treating physicians. However, investigators will be encouraged to decrease the doses of these drugs if cardiorenal syndrome develops in temporal association with dose escalations.

7.2 Ultrafiltration

Patients randomized to receive ultrafiltration will have all loop diuretics discontinued for the duration of the ultrafiltration intervention. Fluid status will be managed exclusively by ultrafiltration using the Aquadex System 100 (CHF Solutions, Inc.) according to the manufacturer's specifications. The use of vasodilators or inotropic agents will be prohibited unless deemed necessary for rescue therapy. Ultrafiltration therapy will be initiated after the placement of appropriate intravenous access and will continue until the patient's signs and symptoms of congestion have been optimized.

Vascular access

Ultrafiltration can be performed through the use of two peripheral IV's, the combination of an extended length catheter placed in the antecubital fossa and a standard peripheral IV, or in some circumstances, a single dual lumen peripheral IV. While central venous access is not necessary, it is commonly acquired in patients hospitalized with acute decompensated heart failure - especially those who develop cardiorenal syndrome. During the screening process, the use of pulmonary artery venous catheters to resolve uncertainty regarding patient's hemodynamic and volume status is encouraged. In these instances, ultrafiltration can be performed utilizing the introducer sheath or a triple lumen catheter according to the manufacturer's specifications.

Anticoagulation

In order to prevent clotting of the ultrafiltration circuit, patients should receive heparin to achieve a PTT 2.0 - 2.5 times normal. Therapeutic doses of enoxaparin may be used as an alternative. Standard acute coronary syndrome heparin protocols are appropriate and can be used during the ultrafiltration treatment. Patients anticoagulated on coumadin with INRs <2.5 should still receive treatment with heparin to avoid clotting of the ultrafiltration circuit.

Fluid removal rates and target to therapy

Ultrafiltration will be used to address signs and symptoms of congestion. The ultrafiltration '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 ultrafiltration or intravenous diuretics (see appendix).

Ultrafiltration will be initiated at a fluid removal rate of 200 cc per hour and continued until the patient's signs and symptoms of congestion have been optimized. A fluid removal rate of 200 cc per hour will result in 4.8 L of fluid removal in 24 hours and a net negative fluid balance of approximately 2.8 L assuming the patient adheres to the 2 L fluid restriction mandated per protocol. The inclusion criteria have been carefully considered to maximize the likelihood that this degree of fluid removal is well tolerated. In UNLOAD, the average duration of a single ultrafiltration session was 12 hours and patients averaged two treatments during their hospitalization. The average ultrafiltration rate was 273 cc per hour resulting in 6 to 7 L of fluid removal. This rate of fluid removal was well tolerated with no significant adverse hemodynamic effects and no significant difference in the percentage of patients who ultimately developed worsening renal function (25% in the ultrafiltration group and 20% in the usual care group at 48 hours, not statistically significant). In another study, Marenzi et al. measured the plasma refill rate in patients undergoing ultrafiltration at a rate of 530 cc per hour for an average of nine hours[15]. The plasma refill rate began to drop after 4 L of fluid removal but was still in excess of 400 cc per hour. Therefore, patients with significant persistent congestion as defined above in the inclusion criteria should tolerate these rates of fluid removal. However, as is the case for all heart failure patients, 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 are commonly used to determine optimal volume status. Ultrafiltration rates can be slowed 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, ultrafiltration should be re-initiated until the patient's fluid status has been optimized.

Treatment in the ultrafiltration group will continue until the signs and symptoms of congestion have been optimized and there is no ongoing need for ultrafiltration or intravenous diuretics. Patients receiving IV diuretics to address persistent congestion will be considered crossovers to stepped pharmacologic care. Crossover to stepped pharmacologic care will be discouraged before the 96 hour primary endpoint assessment. The transition from ultrafiltration to oral diuretics prior to discharge will be left to the discretion of the treating physician and will be continued in the outpatient setting as needed for optimal fluid homeostasis. The dose of oral diuretics prior to discharge will be left to the discretion of the treating physician. Typical dosing regimens reflect .75 to 1.0 times the patient's usual outpatient dose of diuretics.

7.3 Stepped Pharmacologic Care Group

There are no widely agreed-upon or proven treatments for cardiorenal syndrome[5]. 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. In order to prevent heterogeneity in the treatment approach used for these patients and to ensure the use of appropriate diuretic doses, a stepped care algorithm developed by the Heart Failure Network will be provided to investigators (see appendix). The first 2 days of this stepped care algorithm will address appropriate intensification of loop diuretics depending on urine output and clinical response. After this point, recommendations regarding the use of vasodilators and inotropes will be made. Investigators will have the ability to opt out of the stepped care treatment algorithm. As is the case for all heart failure patients, 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 are commonly 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 re-initiated until the patient's fluid status has been optimized.

Treatment in the stepped pharmacologic care group will continue until the signs and symptoms of congestion have been optimized and there is no ongoing need for intravenous diuretics. Crossover to ultrafiltration will be discouraged before the 96 hour primary endpoint assessment. The transition from IV to oral diuretics prior to discharge will be left to the discretion of the treating physician and will be continued in the outpatient setting as needed for optimal fluid homeostasis.

8. RECRUITMENT PROCEDURES

8.1 Enrollment Period

Multiple sites within US and Canada will participate in CARRESS HF. Based on site training and initiation, heart failure admission rates and the occurrence of cardiorenal syndrome, enrollment of 200 patients should be complete within 20 - 24 months from the start of the study.

8.2 Common Recruitment Procedures

Patient recruitment will be performed at participating centers on the inpatient hospital service, as well as outpatient clinic settings. Research personnel will identify patients admitted with a primary diagnosis of ADHF and will review the inclusion and exclusion criteria as outlined in the protocol. Patients qualifying for enrollment will be approached by research personnel to further assess eligibility and interest in participating in the study. These activities will occur in cooperation with the primary treating team on the inpatient hospital service.

8.3 Informed Consent Procedures

Eligible patients at participating centers will be approached by research personnel to obtain informed consent. These activities will be performed according to the institutional ethics committee accepted procedures for each participating center. Informed consent will be obtained by the investigator or his/her designee prior to any study related procedures. The subject will be allowed to read the consent and ask questions prior to signing the consent.

8.3.1 Informed Consent

The IRB approved consent will be signed and dated by the subject and the person obtaining consent. The investigator will retain the original signed consent. A copy of the signed consent will be provided to the subject. The consent process will be documented in the source documents. Subjects will be notified that participation is voluntary; subjects may terminate their participation at any time. The research staff's contact information will be provided should the participant have any questions. In the case of consent revisions, all subjects active at the time of the consent form revision will be re-consented. Any new significant safety data findings will be provided to all subjects. All sites will follow their specific IRB requirements.

8.3.2 Confidentiality and HIPAA Requirements

Subjects are assured data obtained is for research purposes only. To ensure confidentiality, each subject is assigned an identification number for data management and case report form data will be identified only by a subject number. A master list identifying the subject's name, identification number and contact information will be kept in a master file retained at the site. All data for this trial will be maintained in a locked area accessed only by the research staff.

8.3.3 Summary of the Risks and Benefits

There are no agreed upon or proven therapies for patients with cardiorenal syndrome. Stepped pharmacologic care may involve, but is not limited to, intensification or de-escalation of a patient's diuretic regimen, the addition of inotropic agents or intravenous vasodilators, and discontinuation of ACE inhibitors and/or beta blockers. Ultrafiltration is recognized as a reasonable approach by the 2005 heart failure treatment guidelines published by the American Heart Association and the American College of Cardiology [26]. While not widely performed in the community setting, many centers do use ultrafiltration as standard of care when treating patients with cardiorenal syndrome.

Identifying a safe and effective treatment for patients developing cardiorenal syndrome could result in improved survival, shorter lengths of hospital stay, fewer

rehospitalizations and unscheduled clinic visits and could influence the practice of cardiology. If safe and effective, this treatment could be applied to the 25% of ADHF patients who develop cardiorenal syndrome.

The risks of the interventions described above vary depending on the intervention and all represent community standard of care. Decreasing or discontinuation of diuretics, ACE inhibitors and beta blockers expose patients to the risk of persistent congestion and deprive patients of therapies known to positively impact clinical outcomes. Inotropic agents are associated with arrhythmias and adverse clinical outcomes. Overaggressive volume reduction therapy with ultrafiltration or stepped pharmacologic care can lead to intravascular volume depletion, hypotension and aggravated renal dysfunction. In addition, ultrafiltration requires therapeutic anticoagulation with heparin exposing patients to a risk of bleeding. In UNLOAD, there was no excess bleeding or decrease in hemoglobin in the ultrafiltration group versus usual care.

9. SCREENING PROCEDURES

9.1 Prescreen

All patients admitted to the hospital with a primary diagnosis of ADHF should be prescreened by research personnel and followed during the first week of their hospital course to see if they develop cardiorenal syndrome and qualify for participation in the study.

9.2 Screening

Patients undergoing the prescreening procedure described above who develop cardiorenal syndrome in the 12 weeks prior to hospitalization in the setting of escalating doses of oral diuretics or who develop cardiorenal syndrome within 10 days following hospital admission after initiation of IV diuretics should be screened for eligibility.

As is often the case, volume status is measured for those who develop cardiorenal syndrome, thus the use of pulmonary artery venous catheters to resolve uncertainty regarding patients' hemodynamic and volume status may be clinically necessary.

10. EVALUATIONS AND RANDOMIZATION

	Day 0 Enrollment	Day 1	D2 - 3	D4	D5 - 6	D7/ DC*	D30	D60
Obtain Informed Consent	X							
Examination, Vital signs (A)	X			X		X	X	X
Weight (B)	X	X	X	X	X	X	X	X
Fluid intake and output (C)	X	X	X	X	X	X		
Medications (D)	X	X	X	X	X	X	X	X
Basic laboratory (E)	X	X	X	X		X	X	X
Neurohormones/biomarkers (F)	X			X		X		X
Major Adverse cardiac events (G)	X	X	X	X	X	X	X	X
Global and Dyspnea VAS (H)	X			X		X		
Urinary Biomarkers	X	X		X				

It is important that daily assessments of I & O and weights are obtained at the same time daily in the morning before breakfast after voiding.

It is anticipated that most patients will be hospitalized for the day 4 evaluation.

Assessments on days 5 - 7 will be obtained only in patients who are still hospitalized

*D7/DC assessments will be performed on day 7 or the day of discharge, whichever occurs first Window of visits for Day 30 and Day 60 will be $\pm$ 7 days

10.1 Evaluations

The table above summarizes the evaluations performed at each time point. The baseline evaluations are included in the column entitled enrollment.

A) A physical examination focusing on cardiac and pulmonary findings will be performed including supine blood pressure and heart rate.

B) Body weight (and height at baseline assessment for BMI calculations) will be obtained by research personnel at enrollment and daily during the first 7 days and again on days 30 and 60. The same scale should be used for all of the inpatient assessments and, whenever possible, for the outpatient follow-up assessments. After the baseline weight, all other weights will be assessed in the morning, before breakfast with patients wearing hospital gowns without shoes. Digital scales should be "zeroed" prior to each use.

C) Daily total fluid intake and output will be recorded from the time of enrollment to day 7. Intake will include oral as well as intravenous fluids/medications. Daily total fluid output will be recorded from the time of enrollment to the time of discharge. These measurements will include urine output as well as total ultrafiltration fluid removal for patients randomized to the ultrafiltration treatment arm.

D) Medication doses and routes of administration will be recorded with special attention to the use of loop diuretics and cardiovascular drugs.

E) Basic laboratory assessments will include CBC, electrolytes, BUN and creatinine. In addition, PT, PTT, and INR will be collected for patients randomized to the ultrafiltration arm (these patients will receive heparin during ultrafiltration sessions). These laboratory assessments will be included as part of the standard care provided to patients with heart failure; there will be no central laboratory.

F) Neurohormones and biomarkers will be sent to a core lab for analysis and the results will be blinded to the treating physician during the course of the study. These tests will include those agreed upon by the Heart Failure Network Biomarker Working Group: BNP, endothelin-1, high sensitivity C-reactive protein, pro-collagen type 111 N-terminal propepide (P111NP), carboxy-terminal telopeptide of collagen type I (CITP) , cardiac troponin T (cTNT), Cystatin C, serum creatinine and uric acid. Plasma renin activity will also be measured.
Urinary biomarkers will be collected at study entry, 24 hours, and 96 hours after study entry, from clean voided urine or Foley catheter. Samples will be obtained and sent to the Biomarker Core Facility. The urinary samples will be ultimately sent to Dr. Joseph Bonventre (Brigham and Women's Hospital, Nephrology Unit) for assay of urinary biomarkers.

G) Major adverse cardiac events will be elicited from the patient or designated contact. The number of days alive outside the hospital over the 60 Day follow-up period will be recorded. If patients are unable to be contacted, hospital records and national death indices and pre-specified patient contacts will be used. Hospital days will include overnight admissions to the hospital as well as emergency department visits.

H) Symptoms will be assessed using a visual analogue scale (VAS) and a global symptom well being assessment (termed patient global assessment) PGA; these tools will be administered by study personnel. Patients will be asked to self-assess both their general well being and their level of dyspnea using a visual analog scale (VAS) method. For PGA, patients will mark their global well being on a 10 cm vertical line, with the top labeled "best you have ever felt" and the bottom labeled "worst you have ever felt". For dyspnea, the labels will be "I am not breathless at all" and "I am as breathless as I have ever been". The VAS is scored from 0 to 100 but the patient is unaware of the numerical value of their response. Patients will self-assess both PGA and dyspnea at randomization, Day 4, and Day 7 or discharge.

10.2 Off-Schedule Evaluations

 It is expected that patients will be seen in the clinic following discharge at time points other than the 30 and 60 Day follow-up intervals. There are no specific study related evaluations planned for these office visits. Serious adverse events will be recorded at the 30 and 60 Day assessments and will include hospitalizations, unscheduled office and emergency department visits.

10.3 Evaluations for Drop-Outs and Withdrawals

The primary outcome in this study will be assessed 96 hours after enrollment during the acute hospital phase of their illness. It is anticipated that most patients will be evaluable at this assessment. Patients discharged prior to the 96 hour endpoint will have the discharge assessments performed at that time and these measurements will be used in the intention to treat analysis.

At discharge, patients will be encouraged to complete their 30 and 60 Day appointments. If they are unable or unwilling to do so, research personnel will attempt to acquire information by telephone contact. Patients formally requesting to withdraw consent will be asked to submit to a final clinical assessment prior to discontinuing from the project and will be included in the intention to treat analysis.

10.4 Randomization Procedures

Patients who meet all the inclusion and exclusion criteria and sign informed consent will be randomized in a one-to-one fashion by research personnel through an automated web based system coordinated by the Data Coordinating Center (DCC) and ALMAC Clinical Services. A permuted block randomization scheme will be used, and the randomization will be stratified by clinical site.
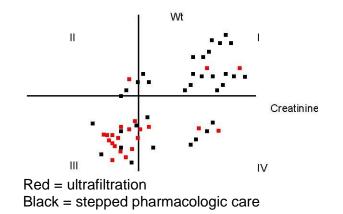
10.5 Blinding of Study Personnel

There is no feasible way to maintain blinding in this study. Patients and investigators will be aware of who is randomized to receive ultrafiltration and who will be receiving stepped pharmacologic care. Fortunately, the primary endpoints of the study (change in creatinine and change in weight) are objective measures not influenced by clinical bias. Researchers and clinicians will be expected and encouraged to treat patients according to the stepped care algorithm with the goal of achieving clinical decongestion and optimized renal function. Use of the treatment algorithm will help prevent conscious or unconscious under treatment of patients assigned to the stepped pharmacologic care group and ensure that potentially harmful therapies such as the use of inotropes are not introduced prematurely. In the UNLOAD study, there was no indication that treating physicians "under treated" patients assigned to usual care; these patients achieved over 3 kg of weight loss in 48 hours exceeding community standards published by the ADHERE investigators[27].

11. OUTCOME DETERMINATIONS

11.1 Primary Outcome

The primary endpoint of this study is a bivariate response that will characterize changes in both creatinine and weight 96 hours after the time of enrollment. This multidimensional endpoint is better suited to measure clinical response than changes in either creatinine or congestion alone.

Changes in creatinine and weight from the time of enrollment to 96 hours will be graphically depicted on a two-dimensional coordinate grid such as shown in the figure below. In this depiction, values in quadrant I of the plot represent patients with *increases* in both weight and creatinine, whereas values in quadrant III represent patients with *decreases* in both variables. It is anticipated that substantially more patients in the ultrafiltration arm will have values in quadrant III compared to the stepped pharmacologic care group. A "confidence region" for the average difference between treatment arms in this bivariate response can be described as an ellipse, and the two treatment arms will be compared statistically using Hotelling's T^2, which is the multivariate analogue of the two sample t-test used with a single continuous variable.

Red = ultrafiltration
Black = stepped pharmacologic care

This novel endpoint incorporates two distinct and critical assessments for patients suffering from cardiorenal syndrome and persistent congestion. Interventions that improve renal function but fail to address persistent congestion cannot be considered a clinical success since patients will experience ongoing symptoms and prolonged hospital stays. Conversely, an intervention that successfully addresses congestion but causes a worsening of renal function may be clinically unacceptable as well. Clinical decision-making in patients with cardiorenal syndrome and persistent congestion evolve around optimizing volume status and renal function-issues addressed by the introduction of this novel bivariate clinical endpoint. The clinical utility of this endpoint is unknown, however, the individual components (change in weight and change in creatinine) are clinically relevant. This novel endpoint allows examination of the importance of changes in both weight and creatinine relative to each other and how the interplay of these clinical parameters relates to outcomes.

11.2 Secondary Outcomes

Bivariate response: The bivariate response of change in creatinine and change in weight from enrollment will be assessed daily for the first 3 days after randomization, and day 7 or discharge in addition to 96 hours (the primary endpoint for the study).

Significant weight loss and renal improvement: The percentage of patients achieving weight loss and renal improvement will be assessed. This endpoint is defined as a reduction in serum creatinine greater than or equal to 0.3 mg per deciliter and a decrease in body weight greater than or equal to 3 kg assessed 96 hours and 7 days or discharge after enrollment. A reduction in creatinine of 0.3 milligrams per deciliter was selected because of the symmetry with respect to the enrollment criteria which requires all patients to experience an increase in serum creatinine of greater than or equal to 0.3 mg per deciliter and is felt to represent a clinically significant improvement in renal function. A decrease in body weight greater than or equal to 3 kg was chosen as a surrogate for effective volume reduction therapy because this is the amount of weight loss achieved in the usual care arm of the UNLOAD trial after 48 hours of standard care treatment. This degree of weight loss was achieved in an unselected population of patients admitted to the hospital with ADHF and represents a higher standard than that observed in routine clinical practice as reported by the ADHERE investigators[3, 27].

Treatment failure: Treatment failure will be defined as any one of the following during the first seven days after randomization: death, worsening/persistent heart failure, or the occurrence of a serious adverse event. Worsening or persistent heart failure is defined as the need for dialysis, mechanical circulatory or mechanical respiratory support during the

first seven days after randomization. In addition, patients randomized to the stepped pharmacologic care group who receive ultrafiltration within the first 7 days will be included as treatment failures.

Renal function: The impact that the randomized intervention has on renal function is an important secondary outcome. Clinically, serum creatinine is the most commonly used marker of renal function. In addition to assessing creatinine at enrollment and at 96 hours for the primary endpoint, changes in creatinine and estimates of glomerular filtration rates will also be assessed at 7 days or discharge, 30 days and 60 days. Changes in serum electrolyte concentrations will also be assessed at randomization, 96 hours and one week. Of the creatinine values obtained during the study, the peak creatinine during the first 7 days of the study or discharge (whichever comes first) will be assessed and compared between the two treatment groups.

Weight: Changes in congestion will be addressed in a variety of ways. Most assessments are subjective related to the degree of edema, orthopnea or clinical estimates of jugular venous pressure. Net fluid balance is difficult to reliably measure during the course of clinical care on an inpatient service; insensitive losses cannot be measured accurately, fluid loss in the form of urine and stool is not always accurately charted and patients have unlimited access to food and fluids that are not always charted appropriately. For this reason, changes in weight are felt to be an important surrogate for clinical decongestion and an accurate representation of net fluid balance. Weight loss is also an important clinical variable in the routine management of patients with ADHF[26]. It is commonly used to determine the degree of treatment success and whether or not patients are ready for discharge. Moreover, clinical outcomes 90 days after hospitalization with ADHF were improved in patients undergoing ultrafiltration in the UNLOAD study[22]. The most obvious difference between patients in the ultrafiltration arm and the usual care arm was a greater degree of weight loss. Therefore, in CARRESS, changes in body weight will be assessed daily for the first seven days following randomization in addition to the assessments at baseline and 96 hours (the primary endpoint). It will also be assessed at 30 days and 60 days. All attempts will be made to reduce the variability in measurements inherent to obtaining body weight. Body weight will be obtained by the same research personnel using the same scale whenever possible. Weights will also be obtained at the same time of day and patients will be instructed to wear hospital gowns without shoes.

Clinical decongestion: Clinical decongestion is another important endpoint that is associated with improved clinical outcomes. The ESCAPE investigators reported improved clinical outcomes in patients achieving clinical decongestion defined as a pulmonary capillary wedge pressure less than 18 (if measurements are available), jugular venous pressure or central venous pressure (if available) less than 8, no more than trace peripheral edema and the absence of orthopnea[32]. Clinical decongestion will be assessed at 96 hours, 7 days or discharge, 30 days and 60 days.

Net fluid loss from the time of the randomization to 96 hours and day 7 or discharge will be assessed

Biomarkers and neurohormones: Biomarkers and neurohormones will be evaluated as secondary endpoints since they are well-established indicators of severity of disease and closely associated with clinical outcomes[33 - 40]. Changes in these biomarkers may be helpful in describing the physiology of clinical responders if one treatment proves to be more effective than another. Neurohormones and biomarkers will be sent to a core lab for analysis and the results will be blinded to the treating physician during the course of the study.

These tests will include those agreed upon by the Heart Failure Network Biomarker Working Group: BNP, endothelin-1, high sensitivity C-reactive protein, procollagen type 111 N-terminal propepide (P111NP), carboxyterminal telopeptide of collagen type I (CITP), cardiac troponin T (cTNT), Cystatin C, serum creatinine and uric acid. Plasma renin activity will also be measured. In addition, we will collect urine samples at study entry, 24 hours, and 96 hours for assay of selected urinary biomarkers (including NGAL, neutrophil gelatinase associated lipocalin; KIM-1, kidney injury molecule-1; NAG, N-Acetyl-β-D-glucosaminidase; sodium; albumin, and urine creatinine). Given the relationship between these markers and acute kidney injury in other cohorts[43-47], serial determination of urinary biomarker concentration may be helpful in identifying novel biomarkers of renal injury (aside from serum creatinine) in cardiorenal syndrome.

Symptoms: Symptoms will be assessed using well validated techniques including global assessment and visual analogue scores at randomization, 96 hours and 7 days or discharge.

Length of hospital stay, re-hospitalization rates and days alive outside the hospital: Length of hospital stay will be assessed from the time of randomization to the time of discharge. Heart failure re-hospitalization rates and days alive outside the hospital during the 60 Day follow-up interval will also be assessed. Unscheduled clinic and emergency department visits will also be addressed since they may significantly impact and reflect upon the patient's quality of life and have cost implications.

Diuretics dosing: The daily dose of diuretics prior to hospitalization, day 7 or discharge, 30 and 60 days will be collected to assess the effect ultrafiltration may have on restoring diuretic responsiveness. Other investigators have reported a "resetting" of the kidney and its responsiveness to subsequent diuretic therapy[41, 42]. The majority of patients treated with chronic diuretics develop some degree of resistance. Diuretics are associated with potentially dangerous electrolyte abnormalities and have consistently been associated with increased mortality[13, 14, 19, 42]. Decreasing diuretic requirements following ultrafiltration would be an important clinical benefit and may shed light on the mechanisms involved in resetting the kidney.

Resource utilization: Resource utilization is an important secondary endpoint. This is directly related to overall cost and will be assessed by tracking the length of hospital stay, rehospitalizations, unscheduled clinic and emergency department visits and the number of disposables consumed by the ultrafiltration intervention.

12. METHODS TO PROMOTE PROFICIENCY IN THE USE OF ULTRAFILTRATION

Participating centers will be required to establish proficiency in ultrafiltration prior to enrolling patients. Representatives from the ultrafiltration device company (CHF Solutions, Inc. Minneapolis, Minnesota) will conduct training sessions for research and hospital personnel at each study site. All study centers will be required to document four successful ultrafiltration treatment sessions prior to enrolling patients.

All training with regard to conducting ultrafiltration and executing the protocol will be documented and retained in the regulatory binder.

13. PARTICIPANT SAFETY AND ADVERSE EVENTS

13.1 Institutional Review Boards

A copy of the protocol, proposed informed consent form, other written information and any proposed advertising material must be presented to each site's Institutional Review Board (IRB) for written approval prior to enrollment of subjects. A copy of the written approval of the protocol and informed consent must be retained by the site in a study file. The investigator must submit and obtain approval from the IRB for subsequent protocol amendments and changes to the consent before implementing such changes. The investigator will notify the IRB of deviations from the protocol or serious adverse events occurring at the site. Each site must have IRB approval prior to enrolling any patients in the study. The IRB will define the review period as annually or semiannually, at which time they will monitor the performance of the study and any adverse events.

13.2 Adverse Events

13.2.1 Definition of an Adverse Event

An Adverse Event (AE) is any sign, symptom, syndrome, or illness that occurs or worsens during the use of the test intervention (drug, biologic, or device) regardless of causality. A medical condition that is already present prior to treatment administration is not defined as an adverse event unless this medical condition worsens after the patient has been administered the test intervention. The details of these signs and symptoms will however be captured in the patient's CRF for inclusion in the database as baseline conditions. Clinically significant laboratory abnormalities (for example, abnormal ECHOs, ECGs, out of range blood parameters etc.) that occur or worsen during the use of a test intervention are also adverse events.

A Serious Adverse Event (SAE) is any adverse event that:
- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of hospitalization which is not specifically required by the protocol nor is it elective.
- Results in permanent impairment of a body function or permanent damage to a body structure
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when they jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed above. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. Medical and scientific judgment must be exercised when classifying events as serious.

The relation between an adverse event and the study intervention, either surgical or medical, will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

Possibly Related: There is a reasonable possibility that the adverse event may have been caused by the study intervention. The temporal relationship of the adverse event to study intervention makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the observed event.

Not Possibly Related: It is unlikely that the event was caused by the study intervention. The temporal relationship of the adverse event to the study intervention makes causal relationship unlikely and other drugs, therapeutic interventions or underlying conditions provide a more likely explanation for the event.

An *Unexpected Adverse Event*: is when the nature or severity of the event is not consistent with the applicable study intervention, expected clinical course or current product labeling.

13.2.2 Adverse Events Anticipated in This Study

Patients admitted with ADHF who subsequently develop cardiorenal syndrome and persistent congestion are at high risk for adverse clinical events. The following adverse events are anticipated, disease-related events in patients with acute decompensated heart failure*:*

- Atrial fibrillation
- Ventricular tachycardia
- Myocardial infarction
- Acute coronary syndrome
- Electrolyte disturbance
- Worsening renal function
- Dialysis
- Worsening heart failure
- Cardiogenic shock
- Re-hospitalization for heart failure
- Pulmonary embolism
- Deep vein thrombosis
- Syncope
- Death

13.2.3 Adverse Event Reporting Protocol

The Site Investigator is responsible for monitoring the safety of patients enrolled into the study at the study sites. All SAEs will be documented in the source documents and captured on the SAE page of the CRF. Non-serious AEs should be documented in the source documents and followed according to local standard of care.

All SAEs that result in death **or** are unexpected for and related to study device (ultrafiltration) must be reported on a HFN Expedited Event form and faxed to DCRI Safety Surveillance at 1-866-668-7138.

Additionally, adverse events which meet the criteria of serious, related to

study device (ultrafiltration), and unexpected for that device, qualify for expedited reporting to the regulatory authorities. The Site Investigator will assess all SAEs occurring at his/her site and evaluate for "unexpectedness" and relationship to study device. The Site Investigator is required to complete and submit a voluntary MedWatch Report for the events identified as serious, study device- related and unexpected at *https://www.accessdata.fda.gov/scripts/medwatch/* . A copy of this report should be kept at the site and also forwarded to the Data Coordinating Center.

Investigators are also responsible for promptly reporting adverse events to their reviewing IRB/EC in accordance with local requirements.

A Data and Safety Monitoring Board (DSMB) will review detailed safety data at regular intervals throughout the study.

14. STATISTICAL CONSIDERATIONS

14.1 Overview

Means, standard deviations, medians, 25th and 75th percentiles will be presented for continuous variables; the number and frequency of patients in each category will be presented for nominal variables. Statistical tests with a p value <0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute, Inc., Cary, NC).

14.2 Sample Size and Power Considerations

Due to the novel design and endpoints for this study, there are no reliable estimates of the variability of the primary endpoints in the population of patients to be studied in this trial. Some insights may be gleaned from the changes in weight and creatinine recently reported in the UNLOAD trial of ultrafiltration in acute decompensated heart failure. While UNLOAD enrolled a different patient population than will be studied in CARRESS, and measurements of weight loss and change in serum creatinine were obtained at different time points than 96 hours, the standard deviation of weight loss at 48 hours was 3.1 and 3.5 kg respectively in the two arms of UNLOAD, and the standard deviation of change in creatinine at 72 hours ranged from approximately 0.55 to 0.75 mg/dl in the two arms. The variability of 96 hour measurements in CARRESS is likely to be at least as large as these values. A sample size of 100 patients per treatment arm will provide 90% power for detecting a difference between treatment groups in each of the primary endpoint variables of one-half standard deviation unit. Thus, if the standard deviation of weight loss is 3.5 to 4.0 kg (which seems plausible based on the UNLOAD data), the study will have high power for detecting an average weight loss difference between groups of 2.0 kg. If the standard deviation of change in creatinine is 0.6 – 0.7 mg/dl, the study will have 90% power for detecting a difference between groups of 0.30 – 0.35 mg/dl. The pooled sample standard deviation of each of the primary clinical endpoints will be assessed after data are available on 100 patients to re-evaluate the appropriateness of the sample size. There is no plan for interim statistical monitoring for efficacy.

14.3 Analysis Populations

The primary endpoint measured at 96 hours will be analyzed on an intention to treat basis. It is anticipated that there may be some "crossover" from stepped pharmacologic

care to ultrafiltration or from ultrafiltration to stepped pharmacologic care before the 96 hour endpoint. The number of crossovers will be documented to provide context for interpreting the primary results; however, treatment crossovers before the 96 hour assessment will be analyzed according to the intention to treat principle and thus will be included in the arm to which they were randomized. In addition, however, a supplementary analysis will be performed censoring patients at the time of "crossover" to ultrafiltration or stepped pharmacologic care and carrying forward change in weight and change in creatinine at the time of "crossover" to the 96 hour primary endpoint.

As described in Section 11.1, changes in creatinine and weight will be graphically depicted on a two dimensional coordinate grid. A "confidence region" for the average difference between treatment arms in this bivariate response can be described as an ellipse, and the two treatment arms will be compared statistically using Hotelling's T^2, which is the multivariate analogue of the two sample t-test used with a single continuous variable. The null hypothesis is that there is no difference between the treatment groups in this two-dimensional endpoint. If the hypothesis of no treatment difference is rejected on the basis of the multivariate test, the difference between treatment arms in each component of this bivariate primary endpoint will be carefully examined to determine whether the group difference is attributable to one or both of the endpoints. This evaluation will be accomplished by generating *simultaneous* 95% confidence intervals for (a) the effect of ultrafiltration on creatinine and (b) the effect of ultrafiltration on weight. In this way, the overall Type I error probability for the two components of the primary endpoint will preserved at $\alpha = 0.05$.

We anticipate that some patients may die before the 96 hour assessment for the primary endpoint. Therefore, for the primary analysis, the highest post baseline creatinine and weight measurements for those patients will be used. Sensitivity analysis, including analysis of only complete cases, and analysis where the post baseline change in weight and creatinine for patients who die prior to 96 hours will be imputed using the largest increase in weight and the largest increase in creatinine across all patients will be employed to assess the degree to which these missing variables impact the results.

14.4 Analysis of Secondary Endpoints

For the evaluation of the bivariate endpoint (change in creatinine and change in weight) at other time points, the approach will be similar to that outlined for the analysis of the primary endpoint. For the secondary endpoint consisting of the binary assessment of whether each patient experienced a reduction in serum creatinine greater than or equal to 0.3 mg/dl and whether each patient experienced a reduction in body weight greater than or equal to 3 kg assessed 96 hours and 7 days or discharge after enrollment, logistic multiple regression will be used, adjusting respectively for the baseline creatinine and the baseline weight. For the "treatment failure" secondary endpoint, as well as other binary outcomes such as clinical decongestion, logistic multiple regression will also be employed for comparing the two treatment groups. For continuous secondary endpoints such as cystatin C and other biomarkers or neurohormones, symptom scores, and days alive outside of the hospital, general linear models and nonparametric approaches will be used to analyze the effects of the ultrafiltration intervention. Analysis of safety and efficacy endpoints will emphasize comparisons among the treatment groups as defined by the randomization.

14.5 Subgroup Analysis

Further analyses will be conducted to determine whether the effect of ultrafiltration vs. stepped pharmacologic care is modified by the presence of diabetes and preserved left ventricular systolic function (ejection fraction ≤40 vs. >40). To provide a conservative framework for the interaction testing, we will consider the interaction terms to be statistically significant if $p<0.001$.

15. DATA MANAGEMENT PROCEDURES

The CARRESS HF trial is a prospective, randomized, controlled study where data will be collected, analyzed, and interpreted by the Duke Clinical Research Institute which functions as the DCC for the NHLBI Heart Failure Clinical Research Network. Data collected in this trial cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the DSMB or Heart Failure Network. This restriction is necessary since dissemination of preliminary information may inappropriately affect the objectivity of this study. For this reason study investigators or other parties will not be allowed to perform subset analyses at any point before the conclusion of the study.

15.1 Hardware and Software Configuration

15.1.1 Hardware and Database Software

Data will be stored in an Oracle database system. Oracle has advantages of processing efficiency and smooth linkage with other software systems. The application and database will be hosted on Solaris UNIX servers at the DCC. Clintrial will be used for data entry.

15.1.2 Statistical Software

SAS will be used as the principal application for the management of analysis data files and statistical computations. S-Plus will be used to provide supplementary functions as needed.

15.1.3 Access Control and Confidentiality Procedures

Access to databases will be controlled centrally by the DCC through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage.

15.1.4 Security

Database and Web servers will be secured by a firewall and through controlled physical access. Oracle has many security features to ensure that any staff member accessing the database has the proper authority to perform the functions he or she requests of the system. Within the secondary SAS databases, UNIX group-access control maintains similar security. The Sun workstation login is secured by extensive user-password facilities under UNIX.

15.1.5 Backup Procedures

Database backup will be performed automatically every day, and standard DCC policies and procedures will be applied to dictate tape rotation and retention practices.

15.1.6 Virus Protection

All disk drives that provide network services, and all user computers, will be protected using virus scanning software. Standard DCC policies will be applied to update these protection systems periodically through the study.

15.2 Sources of Data

Basic clinical information, e.g., demographic information, will be recorded on paper case report forms (CRFs) and forwarded via parcel delivery service or via fax to the DCC for data entry.

15.3 Data Management Activities

In general, the following data management procedures will be applied:

- Paper CRFs will be designed specifically for the needs of this study. The CRF will be partitioned into "booklets" according to the type of data captured (e.g., screening, clinical data, etc.). Identification information will identify key fields, e.g., the participant's ID number, initials, and date of birth as well as the date of the evaluation.

- The CRF will be printed on 3-part NCR paper. At regular intervals, the different parts of the CRF will be separated. One part will remain at the clinical site while the others will be forwarded to the DCC using a parcel delivery system.

- Personnel at clinical sites will record the data mandated by the protocol on the CRFs. They will be abstracted from the participant's medical charts and other source documents. All CRFs will be completed according to the current Good Clinical Practice (GCP) guidelines. Training on completing the CRFs will be included in the training session described in the HF Network Manual of Operating Procedures.

- A database will be created on the DCRI computer network specifically for this study. As described above, the database will be managed with Oracle using Clintrial.

- For every record type, the data dictionary will identify key fields (e.g., the participant's ID number and the type and date of evaluation); the field type (e.g., numeric, character, checklist, or date), and ranges for impossible and improbable values.

- All CRFs will be entered into the study database. Double data entry by 2 different operators will be performed to ensure a high level of confidence in the data entered.

A series of computerized validation checks will be performed at the DCC. "Queries" will be generated, and data clarification forms (DCFs) for problems and exceptions uncovered will be forwarded to the clinical sites for investigation and resolution. Corrections will be made on the data clarification form (DCF) using current GCP standards and forwarded to the DCC. If corrections are needed to the CRF form prior to the initial submission to the DCC, a single line will be drawn through the original entry such that it is still visible. The correct value will be written close to the field and the correction initialed and dated by the HFN staff member making the change.

15.4 Data Management and Quality Control Procedures

Four levels of database quality control will be performed. The first level is the double data entry process as described above. The second level consists of programmatic consistency checks and/or range checks. The third level of database quality is a record or panel level of control. Programs will be written to identify suspected duplicate and blank or missing records and records not double-entered within and across database tables. An independent auditing group will perform the fourth level of database quality control. These internal data quality and process compliance audits are routinely conducted on internal ongoing studies to document the frequency of random errors and identify systematic deviations so that they can be corrected. Other periodic quality control checks will document the frequency of random entry errors and identify systematic and process errors.

In general, the following issues will be addressed:

- Data completeness: Completion by the clinical centers of all evaluations mandated by the protocol are checked.

- Procedural errors: Errors in performing study procedures, e.g., taking the blood samples.

Remedial action will be taken as appropriate; otherwise, the protocol and Manual of Procedures may be revised as appropriate. Training and recertification will be made available to address deficiencies and misunderstandings.

15.5 Reports and Summaries

A variety of standard progress reports will be prepared during the course of a trial and include:

- Data Status/Exception Reports: lag in entering CRFs into the database, missing visits, missing pages, listing of outstanding queries, and summary of totals of outstanding queries

- Quality Control Reports: duplicates, missing from table, blanks Data Surveillance Reports: query frequencies, perfect data

- Protocol Deviation Reports: numbers of ineligible participants enrolled in the study

Reports will be prepared for the periodic meetings of the Steering Group. Some reports, such as the Data Exception report, may be generated more frequently as required.

All prospective publications or presentations must be reviewed and approved by the Heart Failure Network Steering Committee and DCC representatives.

16. STUDY ADMINISTRATION

16.1 Steering Committee

The Steering Committee is the main governing body of the project. The committee is composed of the principal investigators of the nine clinical centers, the principal investigator of the DCC, the NHLBI Project Officer and the Heart Failure Network Chair. The clinical centers, the Data Coordinating Center, the NHLBI and the Chair each have one vote on the Steering Committee. All decisions are determined by majority vote.

All major scientific decisions are determined by the Steering Committee. This committee will assume overall responsibility for the design and conduct of the trial. It will appoint other committees and subcommittees as the need arises; design, approve, and implement the study protocols; oversee the development of the Manual of Procedures; monitor patient recruitment and treatment delivery; evaluate data collection and management; oversee quality assurance procedures; and implement changes and enhancements to the study as required. The Steering Committee also has primary responsibility for facilitating the conduct of the trial and reporting the project's results.

16.2 DSMB

A Data and Safety Monitoring Board (DSMB) will be appointed by the NHLBI. This board will consist of a group of individuals with pertinent expertise in heart failure and in the design and conduct of clinical trials. The DSMB will advise the NHLBI regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.

16.3 Data Coordinating Center (DCC)

The Duke Clinical Research Institute will function as the DCC for this trial as specified by the sponsor (NHLBI Heart Failure Clinical Research Network grant).

16.4 Core Laboratories

This study will utilize a biomarkers core laboratory designated by the NHLBI and the DCC. Plasma and urine specimens will be collected and processed according to the procedures provided by the core laboratory and sent to the core laboratory on dry ice.

16.5 Role of Industry Partnership with CHF Solutions

CHF Solutions, Inc. is the manufacturer of the ultrafiltration device to be used in this protocol. CHF Solutions is providing onsite training in the use of the Aquadex System 100 ultrafiltration device, logistical support in the startup of sites in Canada and the United States as it relates to the approval process, grant support to the Heart Failure Network to support extra costs associated with the use of ultrafiltration.. CHF Solutions has no role in protocol development, data collection or interpretation of the results or publication.

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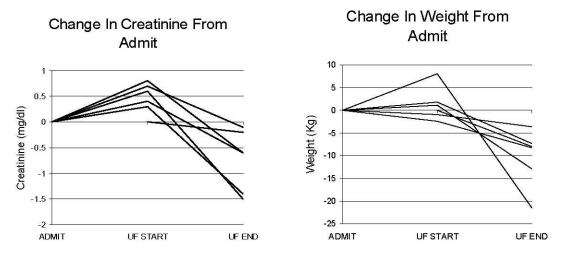
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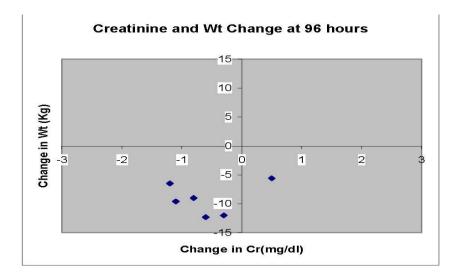
APPENDICES

Appendix A: Early Experience with Ultrafiltration for Cardiorenal Syndrome

We identified 6 patients hospitalized for heart failure and volume overload who developed worsening renal function (increase in creatinine $\geq$0.3 mg/dl from baseline) in the setting of persistent volume overload and escalating doses of intravenous (IV) diuretics who were treated with ultrafiltration. Patients were retrospectively identified based on meeting inclusion and exclusion criteria developed for the CARRESS protocol. Diuretics were held during ultrafiltration and treatment with ultrafiltration continued for each patient until clinically optivolemic.

The mean age was 60.7 years, 5/6 were men, 2/6 had preserved systolic function. The mean peak daily dose of diuretics in IV furosemide equivalents prior to ultrafiltration was 210 +/ 62 mg. The mean weights at admission, ultrafiltration start and ultrafiltration finish were 127.2 +/ 47.1 kg, 128.4 +/ 44.4 kg and 118.2 +/ 47.1 kg, respectively (p=0.01 for change in weight from ultrafiltration start to ultrafiltration finish). The mean creatinines were 2.18 +/ .81 mg/dl, 2.65 +/ .63 mg/dl and 1.92 +/ .9 mg/dl, respectively (p=0.03 for change in creatinine from ultrafiltration start to ultrafiltration finish. Weight and creatinine at these time intervals for each patient are shown in Figures 1 and 2.

Changes in weight and creatinine at 96 hours are plotted on a coordinate grid below to demonstrate the primary endpoint developed for CARRESS. In this figure, changes in weight are depicted on the vertical axis and changes in creatinine are depicted on the horizontal axis. The change in weight and creatinine at 96 hours is shown for each individual patient as a diamond.

Creatinine and Wt Change at 96 hours

(Y-axis: Change in Wt (Kg); X-axis: Change in Cr(mg/dl))

Appendix B: Device Description

Figure 1: The Aquadex System consists of the S-100 Console and the UF 500 blood circuit. The UF blood circuit includes the tubing, filter, pressure sensors and the UF bag. The Aquadex console controls the rate at which blood is removed from the patient and extracts ultrafiltrate at a user set rate. The maximum amount of fluid removed is 40 ml/minute and the maximum filtration rate is 500 ml/hr. The Aquadex is designed to monitor the extracorporeal blood circuit and to alert the user to abnormal conditions. Blood is passed through a filter that removes water (user set rate). The slightly concentrated blood is returned to the patient and the water (ultrafiltrate) is shunted into an ultrafiltrate bag. When the bag is full, the UF pump stops and alerts the user to empty the bag. The blood pump continues to circulate the blood through the circuit until the ultrafiltrate bag is emptied. Once the bag is emptied and the alert is cleared, the UF pump will restart and continue the ultrafiltration. Information to assist the user in priming, setup and operation is shown on the Aquadex display. Most vascular access catheters can be used with the Aquadex circuit.
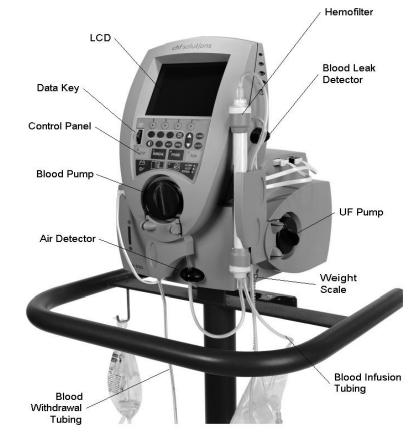

Figure 1 Aquadex Fluid Removal System

Figure 2, shows a schematic of blood and ultrafiltrate flow through the Aquadex blood circuit. Blood is withdrawn from a vein through the withdrawal catheter. Tubing connects the withdrawal catheter to the blood pump. Blood passes through the withdrawal pressure sensor just before it enters the blood pump tubing loop. Both the withdrawal pressure sensor and the pump loop are mounted on a clip-on cartridge. During operation, the pump loop is compressed by rotating rollers that propel the blood through the tubing.

After exiting the blood pump, blood passes through the air detector and enters the hemofilter. The hemofilter is bonded to a clip-on cartridge that mounts onto the ultrafiltrate pump raceway on the side of the console. Blood enters the filter through a port on the bottom, exits through the port at the top of the filter, and passes through the infusion pressure sensor before returning to the patient. Inside the hemofilter, there is a bundle of hollow fibers.

The ultrafiltrate passes through the fiber walls, fills the space between the fibers inside the filter case and exits the filter through a port near the top of the filter case. After exiting the filter, ultrafiltrate passes through a blood leak detector.

Ultrafiltrate then passes through the ultrafiltrate pressure sensor and then to the ultrafiltrate pump. After the pump, the effluent collects in the ultrafiltrate bag that is suspended from the weight scale.
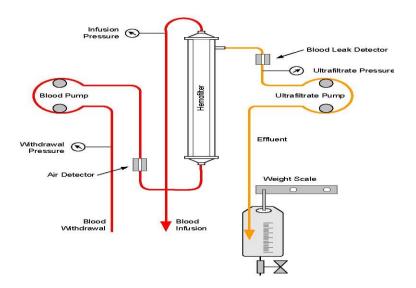

Figure 2 Aquadex Fluid Path

The Aquadex is very simple to use and requires minimal supervision and programming. Setup of the Aquadex System takes less than 10 minutes. Treatment with the Aquadex is prescribed by a physician and can be performed by any nurse trained in the use of the Aquadex. Treatment can be performed in the setting of an ICU/CCU or monitored hospital floor. Its size and weight is comparable to a standard IV pump. Operation requires the same nursing skill level and amount of monitoring as blood transfusion or standard IV pump.

Appendix C: 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

Appendix D: Ultrafiltration Intervention

- Ultrafiltration will be used to address signs and symptoms of congestion

- The ultrafiltration '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 ultrafiltration or intravenous diuretics (patients may require the ultrafiltration 'intervention' beyond the 96 hour primary endpoint assessment)

- A prescription for ultrafiltration developed by the Heart Failure Network is provided below

- 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

- Ultrafiltration rates 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, ultrafiltration should be reinitiated until the patient's fluid status has been optimized

- Crossover to stepped pharmacologic care is discouraged before the 96 hour primary endpoint assessment

- The transition from ultrafiltration 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 (typical dosing regimens after ultrafiltration reflect .75 to 1.0 times the patient's usual outpatient dose of diuretics)

AT RANDOMIZATION – ULTRAFILTRATION ARM

- Stop all loop diuretics
- Obtain appropriate intravenous access
- Start ultrafiltration at a fluid removal rate of 200cc/hour

DAILY ASSESSMENT DURING ULTRAFILTRATION INTERVENTION

Persistent Volume Overload

- If blood pressure stable and no evidence of significant intravascular volume depletion → Continue ultrafiltration at same rate of fluid removal – 200cc/hour

- If blood pressure drops significantly or there is evidence of significant intravascular volume depletion → decrease rate of ultrafiltration to 100cc/hour or discontinue – resume ultrafiltration when the clinical picture has stabilized

- Replace ultrafiltration circuit and filter if clotting of the filter occurs and continue ultrafiltration

Optimal volume

Stop ultrafiltration and Initiate oral diuretics as needed (often 0.75 to 1.0 times usual outpatient dose)

Appendix E: VAS and PGA Assessments

Site Number: ___ ___ ___   **Patient Number:** ___ ___ ___ – ___ ___ ___

Assessment Date: ___ ___ /___ ___ /___ ___ ___ ___   **Time:** ___ ___ : ___ ___
　　　　　　　　　　　Day　　　Month　　　Year

VAS — Dyspnea

Please draw a line on the scale to show how you're breathing feels right now.

The number "0" equals the worst your breathing has ever felt and the number "100" equals the best your breathing has ever felt.

100 = I am not breathless at all

0 = I am as breathless as I have ever been

Appendix E: VAS and PGA Assessments

Site Number: ___ ___ ___   Patient Number: ___ ___ ___ **–** ___ ___ ___

Assessment Date: ___ ___ /___ ___ /___ ___ ___ ___   Time: ___ ___ : ___ ___
  Day   Month   Year

VAS — Global Well Being (PGA)

Please draw a line on the scale to show how you feel right now.
The number "0" equals the worst your have ever felt and the number "100" equals the best you have ever felt.

100 = Best you have ever felt

0 = Worst you have ever felt