

Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

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- Objectives** This study was designed to compare the safety and efficacy of veno-venous ultrafiltration and standard intravenous diuretic therapy for hypervolemic heart failure (HF) patients.
- Background** Early ultrafiltration may be an alternative to intravenous diuretics in patients with decompensated HF and volume overload.
- Methods** Patients hospitalized for HF with ≥ 2 signs of hypervolemia were randomized to ultrafiltration or intravenous diuretics. Primary end points were weight loss and dyspnea assessment at 48 h after randomization. Secondary end points included net fluid loss at 48 h, functional capacity, HF rehospitalizations, and unscheduled visits in 90 days. Safety end points included changes in renal function, electrolytes, and blood pressure.
- Results** Two hundred patients (63 ± 15 years, 69% men, 71% ejection fraction $\leq 40\%$) were randomized to ultrafiltration or intravenous diuretics. At 48 h, weight (5.0 ± 3.1 kg vs. 3.1 ± 3.5 kg; $p = 0.001$) and net fluid loss (4.6 vs. 3.3 l; $p = 0.001$) were greater in the ultrafiltration group. Dyspnea scores were similar. At 90 days, the ultrafiltration group had fewer patients rehospitalized for HF (16 of 89 [18%] vs. 28 of 87 [32%]; $p = 0.037$), HF rehospitalizations (0.22 ± 0.54 vs. 0.46 ± 0.76 ; $p = 0.022$), rehospitalization days (1.4 ± 4.2 vs. 3.8 ± 8.5 ; $p = 0.022$) per patient, and unscheduled visits (14 of 65 [21%] vs. 29 of 66 [44%]; $p = 0.009$). No serum creatinine differences occurred between groups. Nine deaths occurred in the ultrafiltration group and 11 in the diuretics group.
- Conclusions** In decompensated HF, ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics, reduces 90-day resource utilization for HF, and is an effective alternative therapy. (The UNLOAD trial; <http://clinicaltrials.gov/ct/show/NCT00124137?order=1>; NCT00124137). (J Am Coll Cardiol 2007;49:675–83)
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In the U.S., 90% of the one million annual hospitalizations for heart failure (HF) are due to symptoms of volume overload (1,2). Hypervolemia contributes to HF progression and mortality (3–5). Treatment guidelines recom-

mend that therapy of patients with HF be aimed at achieving euvolemia (6).

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Illinois; and §§CHF Solutions, Brooklyn Park, Minnesota. This study was supported by CHF Solutions Inc., Brooklyn Park, Minnesota. Dr. Costanzo is a member of the Medical Advisory Board of CHF Solutions, has CHF Solutions stock options as compensation for Medical Advisory Board membership, and receives speaker's honoraria from CHF Solutions. Dr. Saltzberg is a consultant for CHF Solutions and receives speaker's honoraria from CHF Solutions. Dr. Sobotka is Chief Medical Officer for CHF Solutions Inc. Dr. Schollmeyer is Director of Clinical Affairs for CHF Solutions Inc. Partially presented as a Late Breaking Clinical Trial at the 55th Scientific Sessions of the American College of Cardiology, March 11–14, 2006, Atlanta, Georgia.

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Abbreviations
and Acronyms

HF = heart failure

Intravenous loop diuretics induce a rapid diuresis that reduces lung congestion and dyspnea (7). However, loop diuretics' effectiveness declines with repeated exposure (8). Unresolved congestion may contribute to high rehospitalization rates (3). Furthermore, loop diuretics may be associated with increased morbidity and mortality attributable to deleterious effects on neurohormonal activation, electrolyte balance, and cardiac and renal function (7-10).

Ultrafiltration is an alternative method of sodium and water removal that safely improves hemodynamics in patients with HF (11-14). Application of this technology has been limited by the need for high flow rates, large extracor-

poreal blood volumes, and large-bore central venous catheters. A modified ultrafiltration device has overcome these limitations (14-16). We tested the hypothesis that ultrafiltration may be a safe and effective alternative to intravenous diuretics in the treatment of decompensated HF.

Methods

The UNLOAD (Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) trial was a prospective, randomized, multicenter trial of early ultrafiltration versus intravenous diuretics in patients hospitalized with HF and hypervolemia. Patients were enrolled from June 2004 until July

Table 1 Baseline Characteristics

Characteristic	Ultrafiltration (n = 100)	Standard Care (n = 100)	p Value
Age (yrs)			
Mean \pm SD	62 \pm 15	63 \pm 14	0.823
Range	27-86	23-88	
Male gender (%)	70 (70)	68 (68)	0.879
Race			
Caucasian (%)	55 (55.0)	52 (52.0)	
African American (%)	41 (41.0)	40 (40.0)	0.489
Comorbidities			
History of hypertension (%)	74 (74.0)	74 (74.0)	1.000
Coronary artery disease (%)	56 (56.0)	48 (48.0)	0.474
Chronic obstructive pulmonary disease (%)	27 (27.0)	30 (30.0)	0.755
Diabetes (%)	50 (50.0)	50 (49.0)	0.887
Heart failure characteristics			
Prior heart failure (%)	95 (95.0)	95 (95.0)	1.000
Hospitalizations for heart failure in \leq 12 months	n = 89	n = 90	
Mean \pm SD	1.6 \pm 1.9	1.5 \pm 1.7	0.981
Range	0-10	0-10	
Left ventricular ejection fraction \leq 40% (%)	71 (71.0)	70 (70.0)	0.736
Third heart sound (%)	44 (44.0)	32 (32.0)	0.109
Jugular venous distension $>$ 10 cm (%)	68 (68.0)	62 (62.0)	0.363
Pulmonary rales (%)	59 (59.8)	51 (51.3)	0.343
Peripheral edema (%)	81 (81.0)	79 (79.0)	0.860
New York Heart Association functional class			
Mean \pm SD	3.4 \pm 0.6	3.4 \pm 0.6	0.861
Range	2-4	2-4	
III (%)	52 (52)	48 (48)	
IV (%)	45 (45)	45 (45)	
Minnesota Living with Heart Failure score	n = 81	n = 72	
Mean \pm SD	70 \pm 23	74 \pm 18	0.707
Range	4-105	36-105	
Vital signs			
Weight (kg)	n = 100	n = 99	
Mean \pm SD	101 \pm 27	96 \pm 29	0.194
Range	51-198	51-210	
Systolic blood pressure (mm Hg)	n = 100	n = 100	
Mean \pm SD	126 \pm 26	129 \pm 24	0.233
Range	80-221	90-214	
Heart rate (beats/min)	n = 100	n = 100	
Mean \pm SD	81 \pm 17	83 \pm 16	0.381
Range	50-134	44-131	

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Table 1 Continued

Characteristic	Ultrafiltration (n = 100)	Standard Care (n = 100)	p Value
Laboratory measurements			
Blood urea nitrogen (mg/dl)	n = 99	n = 100	
Mean ± SD	32 ± 16	33 ± 20	0.920
Range	7–85	8–102	
Serum creatinine (mg/dl)	n = 99	n = 100	
Mean ± SD	1.5 ± 0.5	1.5 ± 0.5	0.834
Range	0.7–2.8	0.5–2.7	
Serum sodium (mg/dl)	n = 100	n = 100	
Mean ± SD	139 ± 5	139 ± 5	0.751
Range	125–147	121–151	
Serum potassium (mg/dl)	n = 99	n = 100	
Mean ± SD	4.0 ± 0.6	4.2 ± 0.6	0.028
Range	2.0–5.9	3.0–6.3	
B-type natriuretic peptide level (pg/ml)	n = 71	n = 81	
Mean ± SD	1,256 ± 1,203	1,309 ± 1,494	0.840
Range	8–5,000	5–9,791	
Hematocrit (%)	n = 99	n = 100	
Mean ± SD	36 ± 5	36 ± 6	0.643
Range	25–47	12–51	
Medications			
Angiotensin-converting enzyme inhibitors (%)	49 (49.0)	49 (49.0)	1.000
Angiotensin receptor blockers (%)	14 (14.0)	19 (19.0)	0.446
Beta-blockers (%)	65 (65.0)	66 (66.0)	1.000
Calcium channel blockers (%)	8 (8.0)	8 (8.0)	1.000
Aldosterone antagonists (%)	21 (21.0)	22 (22.0)	0.864
Loop diuretics (%)	72 (72.0)	77 (77.0)	0.517
Furosemide-equivalent diuretic dose* (mg)	n = 72	n = 77	
Mean ± SD	129 ± 122	119 ± 116	0.559
Range	20–800	20–800	

*1 mg bumetanide = 10 mg torsemide = 20 mg furosemide.

2005 at 28 U.S. centers experienced in the use of the Aquadex System 100 (CHF Solutions, Minneapolis, Minnesota) after approval by the institutions' ethics committees and patients' written informed consent were obtained. Treatment was not blinded. Prespecified follow-up was 90 days.

Patients. Eligible patients were at least 18 years of age, hospitalized for HF, randomized within 24 h of hospitalization, and hypervolemic by at least 2 of the following: 1) peripheral edema $\geq 2+$; 2) jugular venous distension ≥ 7 cm; 3) radiographic pulmonary edema or pleural effusion; 4) enlarged liver or ascites; or 5) pulmonary rales, paroxysmal nocturnal dyspnea, or orthopnea. By study design, there was no ejection fraction inclusion criterion. Patients were excluded for: 1) acute coronary syndrome, 2) serum creatinine >3.0 mg/dl, 3) systolic blood pressure ≤ 90 mm Hg, 4) hematocrit $>45\%$, 5) unattainable venous access, 6) requirement for intravenous pressors, 7) vasoactive drug use during the index hospitalization before trial entry, 8) use of iodinated radiocontrast material, 9) comorbidities expected to prolong hospitalization, 10) contraindications to anticoagulation, 11) systemic infection, or 12) heart transplant.

Study procedures. All patients received daily 2 g sodium and 2,000 ml fluid intake restriction. Angiotensin-

converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers were continued throughout the study, as tolerated, in all patients. Patients requiring intravenous vasoactive drugs (nitroglycerin, nesiritide, dobutamine, dopamine, or milrinone) in the first 48 h after randomization for worsening HF or urine output ≤ 30 ml/h were considered to have treatment failure but were followed for 90 days. Patients were randomized through a secure website.

Patients randomized to ultrafiltration were treated with heparin according to standard protocols to maintain the activated clotting time between 180 and 220 s or the partial thromboplastin time between 65 and 85 s. Intravenous access for blood withdrawal and return was obtained using any combination of peripheral, midline, and central venous catheters. The ultrafiltration procedure has been previously described (14). During the first 48 h after enrollment, hypervolemia was treated exclusively with ultrafiltration and intravenous diuretics were prohibited. The duration and rate (up to 500 ml/h) of fluid removal were decided by treating physicians. The ultrafiltration device consists of a 0.12-m² polysulphone filter with a blood flow adjustable between 10 and 40 ml/min and total extracorporeal blood volume of 33 ml (14).

Patients randomized to standard care were treated with intravenous diuretics. By protocol, minimum intravenous diuretics doses for each 24-h period beginning with the time of randomization and ending at 48 h after randomization had to be at least twice the before-hospitalization daily oral dose. Loop diuretic doses are referenced to their furosemide-equivalent dose (1 mg bumetamide = 10 mg torsemide = 20 mg furosemide) (17).

Assessments and follow-up. Weight was measured in kilograms using appropriately calibrated scales at randomization; daily during hospitalization; at discharge; and days 10, 30, and 90. Weight loss was the difference between randomization weight and the weight recorded at subsequent evaluations. Total fluid intake and output (ultrafiltrate and urine) measured during the first 48 h after randomization were used to calculate net fluid losses.

Assessments during the study included patients' perception of dyspnea (Likert scale from 1 = markedly worse to 7 = markedly better) at 48 h after randomization; vital signs, complete blood count, chemistries, and physical examinations daily during hospitalization, at discharge, and days 10, 30, and 90 after randomization; B-type natriuretic peptide levels measured at each center using the Triage BNP Test (Biosite Inc., San Diego, California) at trial entry, 48 h after randomization, and at 30 and 90 days (18); New York Heart Association functional class; 6-min walk distance (in meters) (19); quality of life (Minnesota Living with Heart Failure Questionnaire scores [20]); and Global Assessment (from 1 = markedly worse to 7 = markedly better) at discharge and at 30 and 90 days.

Investigators reported all rehospitalizations for HF and their duration, unscheduled office and emergency department visits, and all adverse events during the 90-day follow-up period.

End points. The primary efficacy end points in the UNLOAD trial were weight loss and patients' dyspnea assessment 48 h after randomization. The primary safety end points were: 1) changes in serum blood urea nitrogen, creatinine, and electrolytes at 8, 24, 48, and 72 h after randomization, discharge, 10, 30, and 90 days; and 2) episodes of hypotension (a decrease in systolic blood pressure requiring therapeutic intervention) at 48 h after randomization. The secondary efficacy end points were: 1) net fluid loss 48 h after randomization; 2) length of index hospitalization; 3) change in B-type natriuretic peptide levels at 48 h after randomization, 30, and 90 days; 4) changes in New York Heart Association functional class, Minnesota Living with Heart Failure Questionnaire scores, Global Assessment scores, 6-min walk distance and loop diuretic doses at discharge, 30, and 90 days; and 5) rehospitalizations for HF, percentage of patients rehospitalized for HF, days of rehospitalization, and unscheduled office and emergency department visits within 90 days. Cause of death was adjudicated by 2 independent observers.

CHF Solutions funded the trial and provided a study manager. All data were entered by the investigators, sent to a data-management group, and verified with source documents. Investigators had complete access to the database and directed all statistical analyses, which were performed by an independent statistician.

Statistical analysis. Differences between treatment groups were evaluated using the Fisher exact test for categorical variables and Wilcoxon's rank-sum test for continuous and ordinal variables. The effects of covariates on weight loss at 48 h were tested using analysis of variance. Change over time within treatment groups was tested using Wilcoxon's matched-pairs signed-ranks test. Correlations were calculated using Spearman's rho. A *p* value (2-tailed) ≤ 0.05 was considered statistically significant. Kaplan-Meier analysis was used to analyze time until rehospitalization, and Cox's regression was used to estimate univariate hazard ratios and their confidence intervals.

Results

One hundred patients were randomized to each treatment arm and followed for 90 days or until death. Twenty patients (10%) died by 90 days. Baseline characteristics were similar (Table 1). In the ultrafiltration group, fluid was removed at an average rate of 241 ml/h for 12.3 ± 12 h. In the standard-care group, average intravenous furosemide-equivalent daily diuretic dose during the 48 h after randomization was 181 ± 121 mg. Of the patients randomized to standard care, 68 received intravenous diuretics as bolus injections and 32 as continuous infusion.

Primary efficacy end points. At 48 h, weight loss was greater in the ultrafiltration than in the standard-care group (5.0 ± 3.1 kg [range 14.1 loss to 1.3 gain] vs. 3.1 ± 3.5 kg [range 11.3 loss to 2.5 gain]; $p = 0.001$) (Fig. 1A). Dyspnea score at 48 h improved to a similar degree in the 2 groups (Fig. 1B). Dyspnea scores were similarly improved in the ultrafiltration and standard-care group also at 8 h after randomization (5.4 ± 1.1 [range 3 to 7] vs. 5.2 ± 1.2 [range 1 to 7]; $p = 0.588$). Subgroup analyses revealed no heterogeneity in the effect of ultrafiltration on 48-h weight loss. Fewer patients in the ultrafiltration group required vasoactive drugs at 48 h (3 of 8 [3.1%] vs. 12 of 99 [12%]; $p = 0.015$). In both groups, a significant correlation existed between the 48-h weight and fluid loss ($r = -0.60$ and -0.40 , respectively, $p = 0.001$). There was no correlation, however, between the 48-h dyspnea score and either 48-h weight or fluid loss.

Primary safety end points. Changes in serum creatinine were similar in the 2 groups throughout the study (Fig. 1C). The percentage of patients with rises in serum creatinine levels >0.3 mg/dl was similar in the ultrafiltration and standard-care group at 24 h (13 of 90 [14.4%] vs. 7 of 91 [7.7%]; $p = 0.528$); at 48 h (18 of 68 [26.5%] vs. 15 of 74 [20.3%]; $p = 0.430$); and at discharge (19 of 84 [22.6%] vs. 17 of 86 [19.8%]; $p = 0.709$). There was no correlation

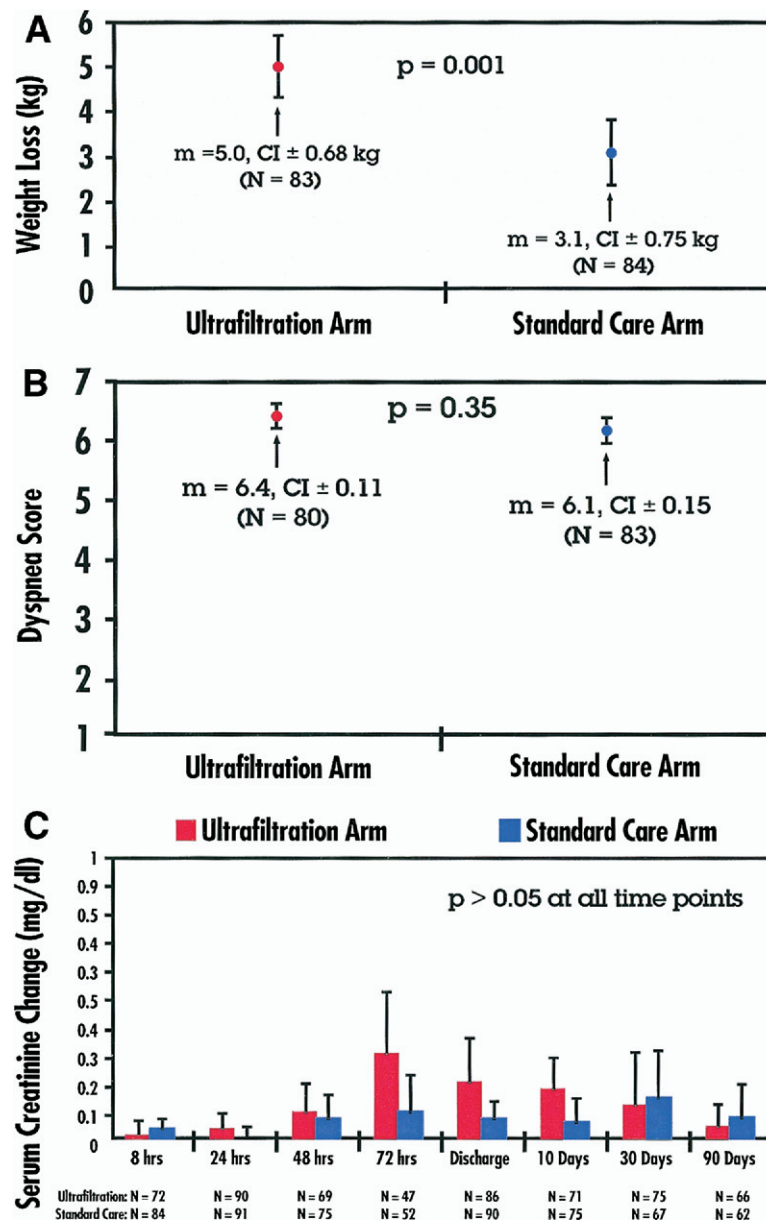


Figure 1 Primary Efficacy and Safety End Points

(A) Mean weight loss in kilograms; (B) mean dyspnea score (from 1 = markedly worse to 7 = markedly better) at 48 h after randomization in the ultrafiltration (blue circles) and standard-care (red circles) groups; p values are for the comparison between ultrafiltration and standard care. Error bars indicate 95% confidence intervals (CIs). (C) Mean changes from baseline serum creatinine levels at 8, 24, 48, and 72 h after randomization; at discharge; and 10, 30, and 90 days in the ultrafiltration (red bars) and standard-care (blue bars) groups. Error bars indicate 95% CIs. Differences between groups at each time point were evaluated with the Wilcoxon's rank-sum test; $p > 0.05$ at all time points for the comparison of mean change in serum creatinine levels between groups.

between net fluid removed and changes in serum creatinine in the ultrafiltration ($r = -0.050$; $p = 0.695$) or in the intravenous diuretics group ($r = 0.028$; $p = 0.820$). No clinically significant changes in serum blood urea nitrogen, sodium, chloride, and bicarbonate occurred in either group. Serum potassium <3.5 mEq/l occurred in 1 of 77 patients (1%) in the ultrafiltration group and in 9 of 75 patients (12%) in the diuretics group ($p = 0.018$). Episodes of

hypotension during 48 h after randomization were similar (4 of 100 [4%] vs. 3 of 100 [3%]).

Secondary end points. Net fluid loss 48 h after randomization was greater in the ultrafiltration than in the standard-care group (4.6 ± 2.6 l vs. 3.3 ± 2.6 l; $p = 0.001$). Lengths of index hospitalization were comparable (6.3 ± 4.9 days vs. 5.8 ± 3.8 days; $p = 0.979$). At each assessment, New York Heart Association functional class, Minnesota

Living with Heart Failure scores, 6-min walk distance, Global Assessment scores, and B-type natriuretic peptide levels were similarly improved in the 2 groups. Although 90% of patients in each group were discharged with oral loop diuretics, compared with baseline, oral furosemide-equivalent doses tended to decrease more in the ultrafiltration than in the standard-care group at discharge (14 ± 68 mg decrease vs. 11 ± 61 mg increase; $p = 0.058$), at 10 days (11 ± 79 mg decrease vs. 12 ± 53 mg increase; $p = 0.049$), and this trend continued at 30 and 90 days.

At 90 days, the ultrafiltration group had fewer patients rehospitalized for HF (16 of 89 [18%] vs. 28 of 87 [32%]; $p = 0.037$), HF rehospitalizations (0.22 ± 0.54 vs. 0.46 ± 0.76 ; $p = 0.022$), and rehospitalization days (1.4 ± 4.2 vs. 3.8 ± 8.5 ; $p = 0.022$) per patient and fewer unscheduled office and emergency department visits (14 of 65 [21%] vs. 29 of 66 [44%]; $p = 0.009$). Kaplan-Meier analysis demonstrated a greater freedom from rehospitalization in 90 days for the ultrafiltration group ($p = 0.037$) (Fig. 2). Use of ultrafiltration during the index hospitalization was associated with a 53% reduction in the risk of rehospitalization for HF (hazard ratio 0.5625, 95% confidence interval 0.2848 to 0.5086; $p = 0.0367$). Furthermore, compared to intravenous diuretics, ultrafiltration resulted in hazard ratios consistently below 1.0 for HF rehospitalization according to selected baseline characteristics (Fig. 3).

There were 9 deaths (9.6%) in the ultrafiltration group due to HF ($n = 3$), renal failure ($n = 1$), and causes unrelated to HF or treatment ($n = 5$). Eleven patients (11.6%) died in the standard-care group because of HF ($n = 5$), myocardial infarction ($n = 1$), other causes ($n = 3$), and unknown causes ($n = 2$).

Adverse events. Adverse events are shown in Table 2. Five ultrafiltration filters clotted in 2 patients, but treatment was completed after filter replacement. Transient discomfort at the venous access site occurred in 3 ultrafiltration patients. One central venous catheter infection occurred in the ultrafiltration group. One patient received hemodialysis because volume overload was refractory to ultrafiltration. Fewer bleeding events ($p = 0.032$) occurred in the ultrafiltration group (1 gastrointestinal bleeding 7 days after randomization) than in the standard-care group (gastrointestinal bleeding [$n = 5$], hematuria [$n = 1$], and ocular hemorrhage [$n = 1$] 1 to 60 days after randomization).

Discussion

The UNLOAD trial is the first randomized comparison of intravenous diuretic therapy alone against an alternative therapy, ultrafiltration, in hypervolemic HF patients. The principal findings of this trial are: 1) in hypervolemic HF patients ultrafiltration produces greater weight and fluid loss than intravenous diuretics at the doses used in this trial; 2) volume removal with ultrafiltration at the index hospitalization was associated with significant reductions in the rate and length of rehospitalization and unscheduled medical visits for HF; and 3) the benefit of short-term ultrafiltration over 90 days was achieved without significant adverse effects.

The results of the UNLOAD trial expand those of a pilot study in which patients randomized to a single 8-h course of ultrafiltration plus usual care had greater weight and fluid loss at 24 h than usual-care patients (15).

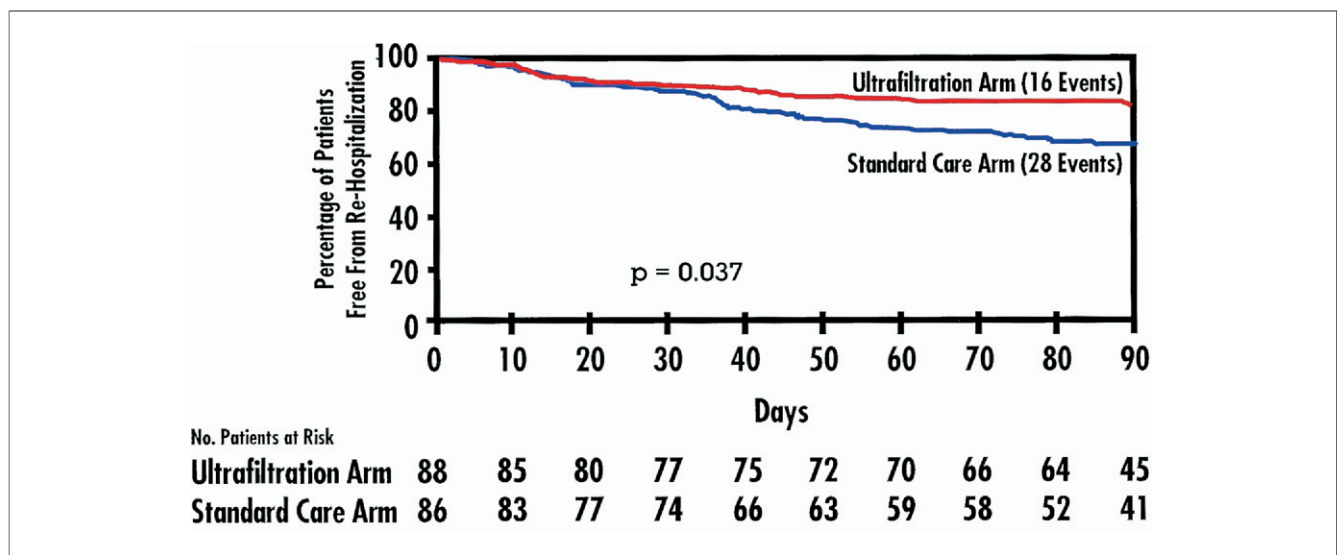


Figure 2 Freedom From Heart Failure Rehospitalization

Kaplan-Meier estimate of freedom from rehospitalization for heart failure within 90 days after discharge in the ultrafiltration (red line) and standard care (blue line) groups.

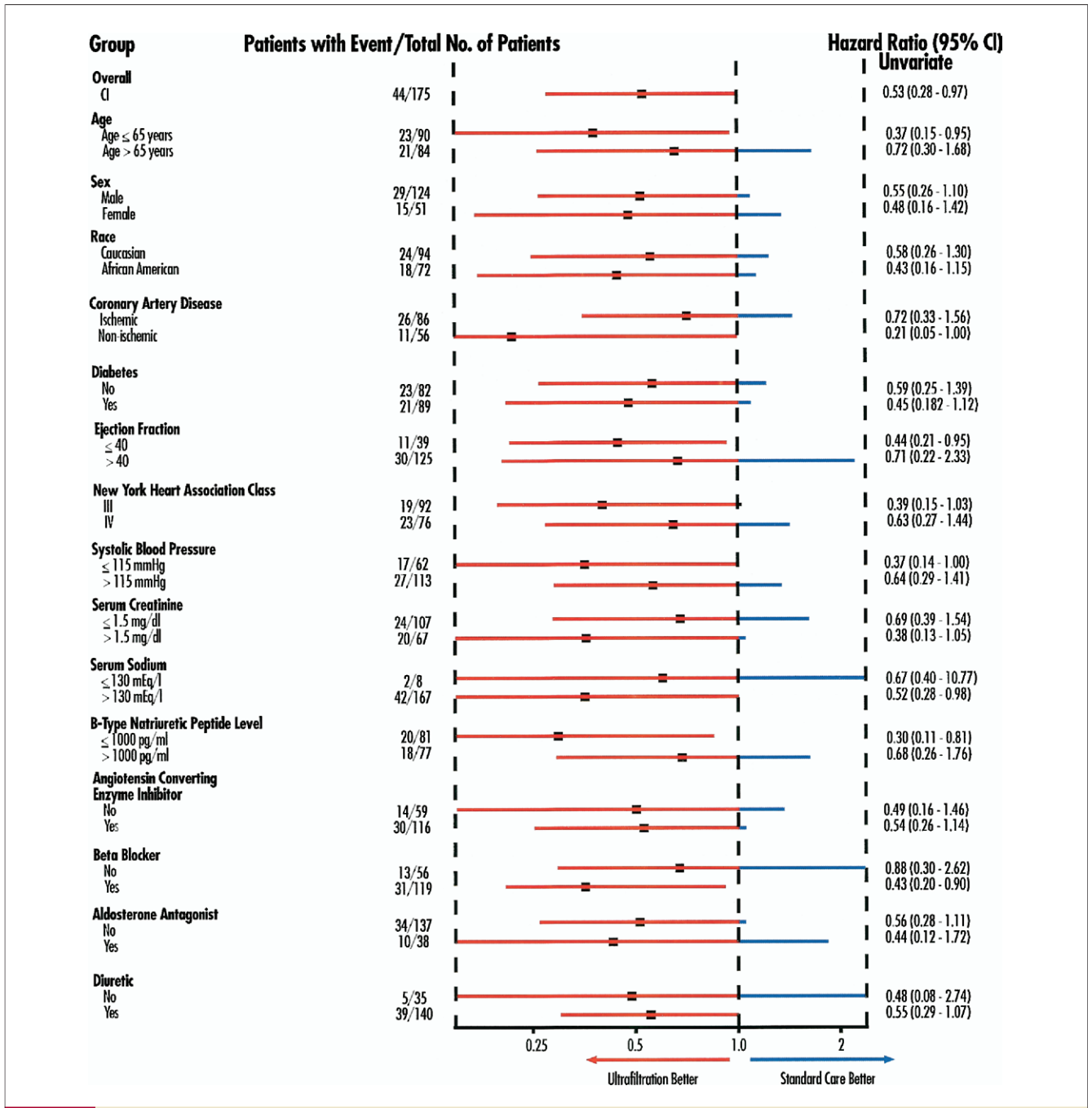


Figure 3 Hazard Ratios for Heart Failure Rehospitalization According to Selected Baseline Characteristics

Cox proportional hazards analysis estimate of hazard ratios and their 95% confidence intervals (CIs) for rehospitalization owing to heart failure according to selected baseline characteristics of the study patients.

Weight changes were highly variable in both the ultrafiltration and intravenous diuretics groups. This finding is consistent with the data from the Acute Decompensated Heart Failure National Registry showing that, during hospitalizations for decompensated HF, changes in weight range from a loss of 20 lbs to a gain of more than 10 lbs (2). In the UNLOAD trial, fewer patients gained weight in the ultrafiltration group than in the standard-care group at 48 h

(3 of 83 [3.6%] vs. 16 of 84 [19%]; $p = 0.003$), and this trend persisted at discharge (4 of 89 [4.5%] vs. 10 of 87 [11.5%]; $p = 0.101$).

The similar improvement in dyspnea, quality of life, functional status, and biomarkers in the 2 treatment groups, despite greater weight and fluid loss with ultrafiltration, suggest that such measures are unable to quantify significant differences in volume changes and lack the sensitivity to

Table 2 Adverse Events

	Ultrafiltration	Standard Care	p Value
Catheter/needle site	3	0	0.156
Filter	5	NA	NA
Infection			
Catheter-related	1	0	0.315
Other	4	9	0.202
Bleeding	1	7	0.032
Hypotension	22	10	0.113
Anemia	3	0	0.080
Dialysis	1	0	0.315
Worsening heart failure	39	63	0.094
Myocardial infarction	3	2	0.988
Arrhythmias	10	7	0.968
Cardiac arrest	4	6	0.987
Neurologic	5	15	0.070

NA = not applicable.

predict long-term outcomes. Indeed, compared to intravenous diuretics, ultrafiltration was associated with a 44% reduction in the percentage of patients rehospitalized for HF, more than 50% reduction in the number and length of HF rehospitalizations, and in the occurrence of unscheduled medical visits for HF. The inability to demonstrate a shorter index hospitalization with ultrafiltration may be related to the lack of specific criteria for discharge in the study protocol or to the open-label design of the study. Patients undergoing ultrafiltration may have been observed for a longer period of time owing to physicians' lesser familiarity with this therapy. Alternatively, fluid removal may not be the sole determinant for discharge of hypervolemic HF patients.

Improved 90-day event rates in the ultrafiltration group suggest a link between volume reduction during hospitalization and subsequent clinical events. A possible explanation is that for similar volumes of fluid removed, ultrafiltration removes more total body sodium (7). Because sodium and its anion are the major determinants of extracellular fluid volume, total body fluid volume can be reduced more by ultrafiltration than by diuretics (7). Indeed, urine produced by loop diuretics is hypotonic compared to plasma, whereas ultrafiltrate is iso-osmotic and isonatremic. Furthermore, unlike diuretics, ultrafiltration does not decrease sodium presentation to the macula densa and thus avoids neurohormonally mediated sodium and water reabsorption (21). In 16 HF patients treated with either ultrafiltration or diuretics to achieve equivalent fluid removal, sustained hemodynamic and neurohormonal benefits occurred only in the ultrafiltration group because isotonic fluid was removed without protracted intravascular volume depletion (22,23).

Improved outcomes following ultrafiltration could also be due to reduced exposure to diuretics (22). Indeed, discharge oral diuretic doses were reduced in the ultrafiltration group and increased in the standard-care group. These observations suggest that a strategy of early ultrafiltration

and "diuretic holiday" may improve responsiveness to diuretics (23).

The safety of ultrafiltration in the UNLOAD trial confirms previous observations (14–16). Renal function changes were modest and similar in the 2 groups throughout the study. In addition, the lack of correlation between weight removed and serum creatinine changes suggests that intravenous diuretics may independently contribute to renal dysfunction, which, in turn, may accelerate HF progression (24,25). In a porcine HF model, furosemide shortened time to left ventricular dysfunction independent of cardiac preload (26). Ultrafiltration was also associated with fewer episodes of hypokalemia, an electrolyte disturbance that increases morbidity and mortality in HF patients (10).

Study limitations. The treatment targets for both diuretics and ultrafiltration were not prespecified. Although treatment was not blinded, it is unlikely that a placebo effect influenced either weight loss or the improved 90-day outcomes associated with ultrafiltration. The possibility that standard-care patients were inadequately treated is diminished by the observation that improvements in symptoms of HF, biomarkers, and quality of life were similar in the 2 treatment groups throughout the study. Furthermore, 43% of patients in the standard-care group lost at least 4.5 kg during hospitalization, a weight loss greater than that observed in 75% of patients enrolled in the Acute Decompensated Heart Failure National Registry (2).

Although the study did not include measurements of blood volume, plasma refill rate, interstitial salt and water, cardiac performance, or hemodynamics, ultrafiltration was not associated with excessive hypotension or renal or electrolyte abnormalities.

The economic impact of ultrafiltration as an initial strategy for decompensated HF was also not addressed in this trial. Although the costs associated with ultrafiltration during the index hospitalization may exceed those of intravenous diuretics, total cost over time may be lower because of decreased resource utilization for HF.

Conclusions. In summary, the UNLOAD trial conclusively shows that early ultrafiltration safely produces greater weight and fluid loss than intravenous loop diuretics in hypervolemic HF patients. Ultrafiltration significantly decreased rehospitalizations for HF and unscheduled medical visits. The cost-effectiveness of ultrafiltration is not established; however, this treatment may have favorable economic implications for patients and payers owing to reduced resource utilization after the index hospitalization. Mechanisms linking different methods of fluid removal to clinical benefit deserve further study.

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APPENDIX

For a list of investigators and institutions that participated in the UNLOAD trial, please see the online version of this article.