JACC: HEART FAILURE
VOL. 4, NO. 2, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2015.08.005

FOCUS ISSUE: CLINICAL TRIALS AND REGISTRIES

Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure

Maria Rosa Costanzo, MD,[a] Daniel Negoianu, MD,[b] Brian E. Jaski, MD,[c] Bradley A. Bart, MD,[d] James T. Heywood, MD,[e] Inder S. Anand, MD, DPHIL (OXON),[f] James M. Smelser, MD,[g] Alan M. Kaneshige, MD,[h] Don B. Chomsky, MD,[i] Eric D. Adler, MD,[j] Garrie J. Haas, MD,[k] James A. Watts, MD,[l] Jose L. Nabut, MS,[m] Michael P. Schollmeyer, DVM,[m] Gregg C. Fonarow, MD[n]

ABSTRACT

OBJECTIVES The AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure) trial tested the hypothesis that patients hospitalized for HF treated with adjustable ultrafiltration (AUF) would have a longer time to first HF event within 90 days after hospital discharge than those receiving adjustable intravenous loop diuretics (ALD).

BACKGROUND Congestion in hospitalized heart failure (HF) patients portends unfavorable outcomes.

METHODS The AVOID-HF trial, designed as a multicenter, 1-to-1 randomized study of 810 hospitalized HF patients, was terminated unilaterally and prematurely by the sponsor (Baxter Healthcare, Deerfield, Illinois) after enrollment of 224 patients (27.5%). Aquadex FlexFlow System (Baxter Healthcare) was used for AUF. A Clinical Events Committee, blinded to the randomized treatment, adjudicated whether 90-day events were due to HF.

RESULTS A total of 110 patients were randomized to AUF and 114 to ALD. Baseline characteristics were similar. Estimated days to first HF event for the AUF and ALD group were, respectively, 62 and 34 ($p = 0.106$). At 30 days, compared with the ALD group, the AUF group had fewer HF and cardiovascular events. Renal function changes were similar. More AUF patients experienced an adverse effect of special interest ($p = 0.018$) and a serious study product-related adverse event ($p = 0.026$). The 90-day mortality was similar.

CONCLUSIONS Compared with the ALD group, the AUF group trended toward a longer time to first HF event within 90 days and fewer HF and cardiovascular events. More patients in the AUF group experienced special interest or serious product-related adverse event. Due to the trial's untimely termination, additional AUF investigation is warranted.
(J Am Coll Cardiol HF 2016;4:95–105) © 2016 by the American College of Cardiology Foundation.

From the [a]Advocate Heart Institute, Edward Heart Hospital, Naperville, Illinois; [b]Division of Nephrology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; [c]San Diego Cardiac Center, Sharp Memorial Hospital, San Diego, California; [d]Division of Cardiology, Department of Medicine, Hennepin County Medical Center, Minneapolis, Minnesota; [e]Heart Failure Recovery & Research Program, Scripps Clinic, San Diego, California; [f]University of Minnesota VA Medical Center, Minneapolis, Minnesota; [g]Huntsville Renal Clinic, Huntsville, Alabama; [h]Oklahoma Heart Institute, Tulsa, Oklahoma; [i]Saint Thomas Heart Hospital, Nashville, Tennessee; [j]Division of Cardiology, University of California, San Diego, California; [k]Division of Cardiology, Ohio State University, Columbus, Ohio; [l]Brooke Army Medical Center, San Antonio, Texas; [m]Baxter Healthcare Corporation, Deerfield, Illinois; and the [n]Division of Cardiology, University of California, Los Angeles, California. Drs. Costanzo, Negoianu, Jaski, Heywood, and Fonarow have received compensation for their work for the AVOID-HF Trial Steering Committee. Dr. Costanzo was the principal investigator of the AVOID-HF trial sponsored by Baxter Healthcare; and has received research grant support from Baxter Healthcare to the Advocate Heart Institute. Dr. Negoianu has served on the Speakers Bureau of Fresenius, DaVita, and Gambro. Dr. Nabut previously was employed by Baxter Healthcare. Dr. Fonarow has served as a consultant for Baxter Healthcare, Gambro, Novartis, Medtronic, Amgen, Bayer, and Janssen. Mr. Nabut is a former employee of Baxter Healthcare. Dr. Schollmeyer is a former consultant for Baxter Healthcare. The institutions of all authors have received a research grant initially from Gambro and subsequently from Baxter for the conduct of the AVOID-HF trial. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 3, 2015; revised manuscript received August 25, 2015, accepted August 25, 2015.

ABBREVIATIONS AND ACRONYMS

ALD = adjustable loop diuretics

AUF = adjustable ultrafiltration

BNP = B-type natriuretic peptide

CV = cardiovascular

HF = heart failure

IV = intravenous

LD = loop diuretics

SEC = Study Endpoint Committee

UF = ultrafiltration

Persistent congestion in patients hospitalized with heart failure (HF) is associated with worse prognosis regardless of age and underlying renal function (1,2). Most pharmacologic approaches to treat congestion have not reduced HF events, renal dysfunction, or mortality (3–6). These unmet therapeutic needs underlie the interest in the role of fluid removal with isolated venovenous ultrafiltration (UF) in acutely decompensated HF patients (7). The UNLOAD (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure) trial showed that, compared with patients receiving intravenous (IV) loop diuretics (LD), those randomized to the UF arm had greater weight and net fluid loss at 48 h and a 53% reduction in the 90-day risk of rehospitalization for HF ($p = 0.037$) (8). In contrast to the results of the UNLOAD trial, which tested the effects of *early* decongestive strategies, the CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial showed that a stepped pharmacologic therapy algorithm was both superior and safer than a fixed 200 ml/h UF rate for the preservation of renal function at 96 h (9). The discouraging results of CARRESS-HF do not disprove the potential physiological benefits of UF (10,11). Recently, in the CUORE (Continuous Ultrafiltration for Congestive Heart Failure) trial, HF patients meeting the inclusion criteria of a >4 kg weight gain had a greater freedom from HF events at 1 year when treated with UF compared to IV LD (12).

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The primary objective of the AVOID-HF (Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure) study (NCT01474200) was to determine whether UF prolonged the time to first HF event within 90 days of hospital discharge when fluid removal therapy is adjusted in *both* arms according to the patients' vital signs and renal function. Thus the AVOID-HF study's design went beyond the assessment of fluid removed and symptoms by exploring whether titrated UF impacts HF events.

METHODS

STUDY DESIGN, PATIENT POPULATION, AND INCLUSION/EXCLUSION CRITERIA. This was a multicenter, prospective, unblinded, 1-to-1 randomized study. A total of 810 patients hospitalized with the primary diagnosis of HF were to be enrolled in the trial. The AVOID-HF trial was initially supported by Gambro (Lund, Sweden) and subsequently by Baxter Healthcare (Deerfield, Illinois), which acquired Gambro in September 2013. The determination that acutely decompensated HF was the primary cause of hospitalization was made by the site's principal investigator, based on the assessment of the clinical signs and symptoms that triggered the admission. Patients meeting all of the inclusion criteria and none of the exclusion criteria for this study (Online Table 1) and considered treatable with either adjustable ultrafiltration (AUF) or IV adjustable loop diuretics (ALD) were eligible for enrollment. All participants provided written informed consent. Patients had to be randomized within 24 h of hospital admission. Up to 2 doses of IV LD were allowed before randomization to reflect events typical of clinical practice. Using a central web-based system, study subjects were randomized to one or the other fluid removal therapies during their index hospitalization. Subjects' monitoring schedule has been previously described (13). Resolution of congestion was defined as a jugular venous pressure <8 mm Hg, absence of dyspnea, and trace or no peripheral edema. Treatment failure was defined as death, worsening or persistent HF as indicated by requirement for vasoactive drugs or renal replacement therapy, or technical failures in the AUF arm. Following discharge patients were evaluated at 30, 60, and 90 days.

All adverse events were evaluated according to severity, causality, expectedness, and relationship to study product and treatment. Adverse events of special interest (central line-associated bloodstream infections, bleeding requiring transfusion, symptomatic hypotension necessitating intervention, drop in hemoglobin >3 g/dl, acute coronary syndrome) were documented and followed throughout the study (13). Requirements for site selection have also been specified earlier and study sites are listed in the Online Appendix (13).

PRIMARY ENDPOINT. The primary hypothesis of AVOID-HF was that patients hospitalized with a primary diagnosis of decompensated HF who are treated with AUF will have a longer time to first HF event within 90 days after discharge from index hospitalization compared with patients treated with ALD. HF events were defined as either a HF rehospitalization or as an unscheduled outpatient or emergency room treatment with IV LD or UF.

SECONDARY OBJECTIVES. Secondary endpoints were classified as efficacy, clinical, and safety variables. The pre-specified clinical and safety endpoints were assessed at 30 and 90 days (Online Table 2) (13).

TREATMENT DETAILS. In both the AUF and ALD arms, patients had a daily fluid and sodium restriction of 1,500 cc and 1.5 g, respectively. Guidelines-Directed Medical Therapy for HF was adjusted during fluid removal as deemed appropriate by treating physicians. Vasoactive drugs were prohibited in both arms unless necessary as rescue therapy. In the AUF arm diuretics were withheld for the duration of treatment, and AUF was performed with the Aquadex FlexFlow System (Baxter International, Deerfield, Illinois) (13). AUF patients received heparin to achieve an activated partial thromboplastin time 2.0 to 2.5 times normal to prevent clotting of the UF circuit and filter.

Guidelines were devised for both the AUF and ALD groups to permit adjustment of therapy according to patients' vital signs and renal function. The diuretic protocol adopted by the AVOID-HF Steering Committee is similar to that of the CARRESS-HF trial (9) (Online Tables 3 and 4). Online Figure 1 shows the study flow chart (13).

For the primary endpoint, patients were evaluated every 30 days after discharge from index hospitalization for a maximum of 90 days or until rehospitalization for HF, unscheduled outpatient or emergency room treatment for HF with IV diuretics or UF, or death occurred. Secondary objectives were assessed from randomization to 90 days after discharge or patient's death.

Subjects who developed complications that, in the judgment of the treating physician, precluded continuation of the trial were withdrawn from the study. The study was interrupted if the investigators and/or the sponsor judged that therapy resulted in inadequate treatment. The decision to resume the study was made jointly by the investigator and the sponsor.

STUDY MONITORING. An independent Study Endpoint Committee (SEC) of 3 HF specialists adjudicated whether the primary reason for HF events within 90 days of discharge from the index hospitalization were due to exacerbation of HF (Online Appendix). The SEC members were blinded to the randomized therapy. An independent group of experts (3 cardiologists and 1 independent statistician) formed the Data Safety and Monitoring Board. The primary responsibilities of the Data Safety and Monitoring Board were to: 1) periodically evaluate study data for patient safety, study conduct, and progress; and 2) make recommendations to the sponsor and the Study Endpoint Committee concerning continuation, modification, or termination of the study.

The rules provided by the AVOID-HF trial Steering Committee to the Data Safety and Monitoring Board for stopping the study were based on all-cause mortality differences between the 2 treatment arms at 30 $\pm$ 5 days) and at 90 $\pm$ 10 days) after index hospitalization: all-cause mortality related to the study product >1.5 times higher in one than in the other treatment arm (50% higher). For this point the significance level was set at 0.01. The relationship of any death to study treatment was determined by the investigator.

OUTCOMES DETERMINATION AND STATISTICAL PLAN. All analyses were carried out using SAS software (SAS Institute, Cary, North Carolina) release 9.2 or later. After randomization, study subjects were analyzed as part of their assigned treatment, regardless of any unexpected event (intention to treat). Crossover was strongly discouraged. Patients designated as "treatment failures" remained in the study, and all endpoints were analyzed. Patients who died before initiation of treatment were excluded from the analysis, and their death was assigned as an event to the appropriate secondary endpoint (13).

Baseline characteristics were compared between the 2 groups using mean, standard deviation, median, first and third quartiles, minimum and maximum for continuous variables, and frequency and percent for nominal and ordinal variables. The comparison was performed with appropriate *t* test if its assumptions held or with appropriate nonparametric test otherwise.

Survival analysis using the log-rank test was applied to model the time to first HF, as adjudicated by the SEC, by treatment group. The significance level was set to $p < 0.05$, and the 2-tailed test was applied. Every patient discharged alive from the index hospitalization was included in all rehospitalizations, HF events, and cardiovascular (CV) events after discharge, as planned. For the primary endpoint analysis, patients who died or were lost to follow-up without having suffered an HF event were included in the analysis of the primary endpoint as "censored" at the date of last available information. All patients who suffered an HF event were included with their event date, regardless of whether they later died or were lost to follow-up. For HF events rates, HF rehospitalization days, CV events, and CV rehospitalization days, patients who died and were lost to follow-up after discharge were also included in the analyses of event rates and days at risk up to the date of last available information.

Mean comparison was used for total and net fluid removed, weight loss at 72 h after initiation of treatment and throughout admission, and changes in B-type natriuretic peptide (BNP) levels over time.

Time to freedom from congestion was evaluated with the log-rank test for survival analysis. Freedom from congestion was evaluated using binomial proportion. Length of stay during the index hospitalization was assessed with the log-rank test for survival analysis.

Generalized linear model with appropriated link was used to calculate the total number of HF and CV events and quality-of-life measures at 30 and 90 days after randomization. Mortality rates up to 90 days after randomization were analyzed using binomial proportion, whereas days alive and out of hospital at 30 and 90 days after discharge and renal function values were assessed by means comparison up to 90 days after randomization.

Sample size calculation was done using SAS software (SAS Institute) release 9.2, and Power Analysis and Sample Size software (NCSS, LLC, East Kaysville, Utah) (version 08.0.15) by NCSS. For the primary endpoint probability for type I error (alpha) was set at 0.05, and type II error (beta) was set to 0.10. The original sample size of 810 patients was based on the assumption that combined event rate in 90 days after discharge would be 25% for the ALD group and that the treatment effect of AUF would be a 35% to 37.5% reduction in 90-day HF events, or a hazard ratio of 0.616 to 0.590. A sample size of 810 patients was needed to achieve power of 90% with the log-rank test to demonstrate a reduction in 90-day HF events by 37.5% in the AUF group (13). No interim analyses were done.

In April 2014 the sponsor stopped the study prematurely because of slower-than-projected study enrollment without advance review of the data or prior consultation with the study's Steering Committee or Data Safety and Monitoring Board. The Steering Committee disagreed with the Sponsor's decision. The termination of the trial was in no way related to signals of futility or safety concerns. A total of 224 patients (27.5 %) had been enrolled in the AVOID-HF trial at study termination by the sponsor and these are the subjects analyzed here until the end of study period as planned in the protocol.

Due to the untimely termination of the study, trends emerging from the available data were interpreted as follows: 1) statistically significant reductions in the primary or secondary endpoints were interpreted as indicative of a benefit with AUF compared to ALD; 2) nonsignificant trends for reductions in the primary or secondary endpoints with a relative risk reduction similar to that initially hypothesized was interpreted as insufficient evidence but suggestive of a potential benefit with AUF compared with ALD; 3) nonsignificant trends for reduction in the primary or secondary endpoints smaller than the relative risk reduction initially hypothesized was interpreted as not providing evidence of potential benefit with AUF compared with control; and 4) nonsignificant trend for increases in primary or secondary endpoints was interpreted as suggesting potential harm with AUF compared with ALD.

The database was locked on November 24, 2014, after the last enrolled subject had completed the 90-day follow-up, and analysis of the AVOID-HF trial data began on November 25, 2014.

No extramural funding was used to support the preparation of the manuscript. We were solely responsible for the design and conduct of the study, all study analyses, and the drafting and editing of this manuscript.

RESULTS

PATIENT POPULATION AND TREATMENT. Of the 224 patients enrolled in the AVOID-HF trial, 110 were randomized to AUF and 114 to ALD. Three patients randomized to ALD were withdrawn from the study for medical reasons before treatment initiation and were excluded from analysis. Baseline characteristics were similar between groups (Table 1). During the index hospitalization, the patients in the AUF group received UF at an average rate of 138 ± 47 ml/h (range 50 to 300 ml/h) for an average of 80 ± 53 h (median 70 h; range 12 to 283 h). The average number of UF filters/patient was 1.67 ± 0.93. The ALD patients received an average daily dose of furosemide-equivalent IV LD of 271.26 ± 263.06 mg (range 36.00 to 1,446.67 mg) for an average of 100 ± 78 h (median 70 h; range 70 to 472 h). Treatment failure occurred in 14 of 110 (14.5%) AUF subjects (7 [6.4%] requirement for vasoactive drugs, 1 [0.9%] need for renal replacement therapy, 8 [7.3%] device-related technical problems) and in 9 of 111 (11.3%) ALD patients (8 [7.2%] requirement for vasoactive drugs, 1 [0.9%] need for renal replacement therapy; $p = 0.139$). Crossover to the other treatment arm occurred in 14 of 110 (13%) patients randomized to AUF and 4 of 111 (0.03%) assigned to ALD.

By 90 days, of the 221 patients, 165 (75%) completed the study, 31 (14%) died, 9 (4%) were lost to follow-up, 3 (1.4%) withdrew consent, 7 (3%) were removed from the trial by their physician for medical reasons, and 6 (2.7%) did not finish the study due to other causes (Figure 1).

PRIMARY ENDPOINT. Analysis of the primary endpoint, time to first HF event within 90 days of discharge from the index hospitalization, was

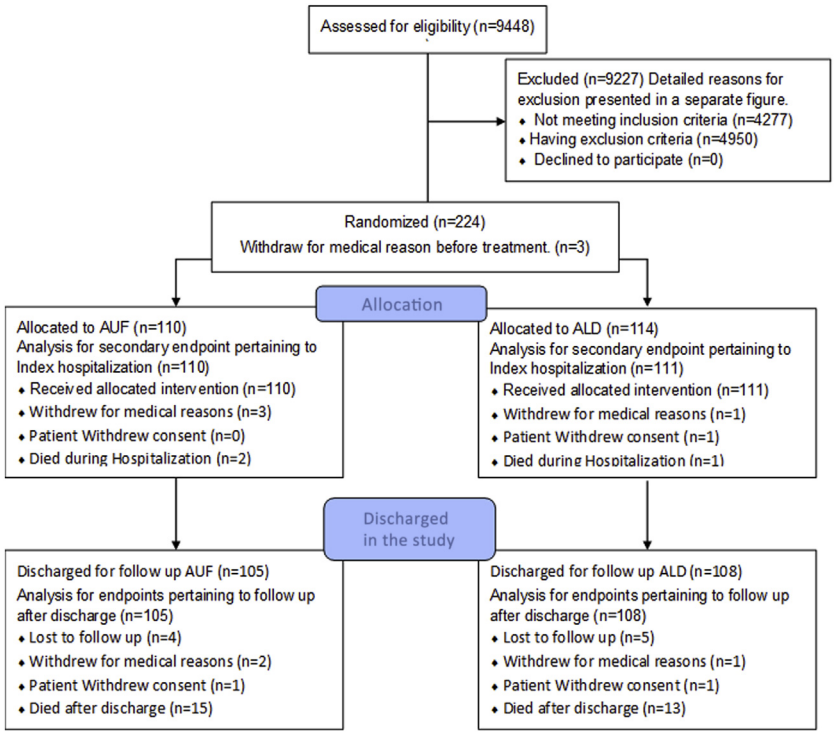
TABLE 1 Baseline Characteristics

Characteristic	AUF (n = 110)	ALD (n = 111)	Total (n = 221)	p Value
Age, yrs	67 ± 13	67 ± 13		0.806
Male, %	69.1	73.0	71.0	0.555
Race				>0.999
Caucasian, %	68.2	64.0	66.1	
African American, %	28.2	27.0	28.0	
Comorbidities				
History of hypertension	97 (88.2)	92 (83.0)	189 (85.5)	0.339
Coronary artery disease	70 (63.6)	68 (61.3)	138 (62.4)	0.782
Chronic obstructive pulmonary disease	38 (34.5)	35 (31.5)	73 (33.03)	0.669
Diabetes	68 (61.8)	71 (64.0)	139 (63.0)	0.782
Heart failure characteristics				
Etiology				
Ischemic	44 (40.0)	41 (34.0)	85 (38.5)	0.679
Nonischemic	59 (53.6)	58 (52.2)	117 (52.9)	0.893
Prior heart failure	110 (100.0)	110 (99.1)	220 (99.5)	>0.999
Hospitalization for heart failure in ≤12 months	1.4 ± 1.9	1.3 ± 2.0	1.3 ± 2.0	0.499
Left ventricular ejection fraction, %	36.3 ± 16.3	36.6 ± 16.8	36.5 ± 16.5	0.862
Third heart sound, %	17.3	13.5	15.4	0.459
Jugular venous pressure, cm	12.15 ± 5.09	12.92 ± 5.33	12.54 ± 5.21	0.449
Pulmonary rales, %	30.9	40.5	35.7	0.138
Peripheral edema, %	87.27	87.30	87.29	0.788
Kansas City Cardiomyopathy Questionnaire	25.4 ± 19.4	28.6 ± 22.6	27.0 ± 21.1	0.350
Vital signs				
Weight, kg	110.2	110.6	110.4	0.971
Systolic blood pressure, mm Hg	124.3	120.4	122.3	0.120
Heart rate, beats/min	78.0	77.8	78.0	0.995
Laboratory measurements				
Blood urea nitrogen, mg/dl	32.6 ± 15.8	36.1 ± 17.4	34.4 ± 16.6	0.161
Serum creatinine, mg/dl	1.5 ± 0.5	1.6 ± 0.51	1.5 ± 0.5	0.096
Serum sodium, mg/dl	137.6 ± 4.4	138.3 ± 3.6	138.0 ± 4.0	0.336
Serum potassium, mEq/ml	4.0 ± 0.5	4.0 ± 0.5	4.0 ± 0.5	0.089
B-type natriuretic peptide, pg/ml	814.0 ± 827.7	904.1 ± 843.4	860.1 ± 835.0	0.310
Hematocrit, %	36.3 ± 6.3	35.3 ± 8.0	35.8 ± 7.2	0.571
Medications				
Angiotensin converting enzyme inhibitors, %	29.1	28.8	29.0	>0.999
Angiotensin receptor blockers, %	9.1	14.4	11.8	0.297
Beta-blockers, %	52.7	57.7	52.2	0.500
Calcium channel blockers, %	12.7	10.8	11.8	0.682
Digoxin, %	11.8	15.3	13.6	0.556
Vasoactive agents, %	21.8	21.6	21.7	>0.999
Diuretics, %	55.4	55.9	55.7	>0.999

Values are mean ± SD or n (%).
ALD = adjustable loop diuretics; AUF = adjustable ultrafiltration.

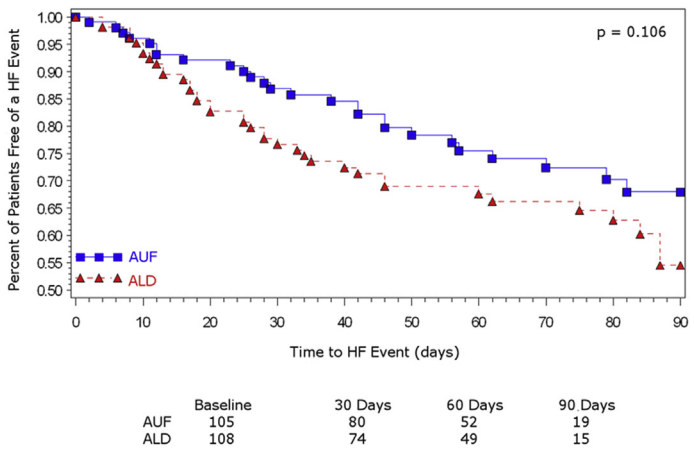
performed in 105 AUF and 108 ALD subjects as 5 AUF subjects and 3 ALD patients died or withdrew before discharge from the index hospitalization (Figure 1). The smaller than projected sample size (221 of 810 [27.5%]) did not provide enough evidence for the log-rank test to identify a significant difference between survival curves (log-rank p = 0.106) (Figure 2). An HF event within 90 days occurred in 25% of AUF patients and 35% of ALD patients. Estimated days to first event for the 25th percentile of patients in the AUF and ALD groups were, respectively, 62 and 34, but this difference was not statistically significant (log-rank p = 0.106) (Figure 2). The hazard ratio of 0.663 (95% confidence interval: 0.402 to 1.092), which suggests a 37% reduction in the risk of a HF event with AUF versus ALD therapy, was also not statistically significant. In a post-hoc sensitivity analysis, time to first event or death from any cause

FIGURE 1 CONSORT Flow Diagram of the Progress Through the Phases of the AVOID-HF Trial



ALD = adjustable loop diuretics; AUF = adjustable hospitalization; AVOID-HF = Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure trial; IV = intravenous.

FIGURE 2 Primary Endpoint: Time to Heart Failure Event after Discharge



Log-rank analysis of the time to first heart failure (HF) event after discharge from index hospitalization up to 90 days in the adjustable ultrafiltration (AUF) **(squares)** and adjustable loop diuretics (ALD) **(triangles)** groups. The difference in time to first heart failure event within 90 days after discharge from the index hospitalization was not statistically significant at the 0.05 alpha level (p = 0.106) due to the smaller than originally planned sample size. AQ = aquapheresis; LD = loop diuretics.

was analyzed. The log-rank test did not find enough evidence of difference between time to first event or death from any cause between the 2 groups (log-rank p = 0.297). Estimated days to first HF event or death for the 25th percentile of patients in the AUF and ALD groups were, respectively, 46 and 30, but this difference was not statistically significant (log-rank p = 0.297) (Online Figure 2).

SECONDARY ENDPOINTS. Efficacy. During the index hospitalization, compared with the ALD group, the AUF group had greater total amount of fluid removed (18.7 l vs. 14.0 l; p = 0.015) and net fluid loss (12.9 l vs. 8.9 l; p = 0.006). There was no statistically significant difference between the AUF and ALD groups in terms of weight loss at 72 h after randomization (10.7 ± 7.2 kg vs. 10.3 ± 9.2 kg; p = 0.343), total weight loss during index hospitalization (7.9 ± 5.8 kg vs. 7.5 ± 6.5 kg; p = 0.321), time to freedom from congestion (5.3 ± 4.1 days vs. 3.4 ± 3.2 days; p = 0.076), and percentage of patients free of congestion at discharge (40 [36.4%] vs. 46 [41.4%]; p = 0.492). The BNP levels declined significantly from baseline to

discharge (p = 0.005 for AUF, p = 0.041 for ALD) and to a similar extent in both groups (-250 ± 527 pg/ml for AUF vs. -219 ± 539 pg/ml for ALD; p = 0.888). The changes in BNP levels were similar between groups up to 90 days of follow-up.

Clinical. The length of stay during the index hospitalization was not significantly different for the AUF and ALD groups (median 6 days confidence interval (range: 6 to 7) vs. 5 days confidence interval (range: 5 to 6); p = 0.106). Despite the fact that the study was stopped after the enrollment of only 27.5% of the originally planned sample size, there is sufficient evidence to show that within 30 days after discharge, compared with the ALD group, patients in the AUF group had, per days at risk: fewer patients rehospitalized for HF (p = 0.034), fewer days in the hospital due to HF readmissions (p = 0.029), lower rehospitalization rates due to a CV event (p = 0.037), fewer rehospitalization days due to a CV event (p = 0.018), and fewer patients rehospitalized for a CV event (p = 0.042) (Table 2).

Following discharge, quality of life measured with the Kansas City Cardiomyopathy Questionnaire and Global Clinical Score improved significantly within each treatment group, and the changes were similar between groups (Online Tables 5 and 6).

Safety. Evaluation of secondary safety endpoints showed that there was no difference between the AUF and ALD groups in terms of blood urea nitrogen, serum creatinine, blood urea nitrogen/serum creatinine, and estimated glomerular filtration rate during treatment and up to 90 days (Table 3).

Adverse events. Adverse events were reported and analyzed according to the Medical Dictionary for Regulatory Activities. The proportion of patients who had at least 1 adverse event (89 [81%] vs. 88 [79%]; p = 0.866) and at least 1 serious adverse event (3 [66%] vs. 67 [60%]; p = 0.403) was similar in the AUF and ALD groups. Although there were significantly more patients in the AUF than in ALD group experiencing an adverse event of special interest (34 [31%] vs. 19 [17%]; p = 0.018), the number of patients experiencing a serious adverse event of special interest was similar in the AUF and ALD groups (25 [23%] vs. 15 [14%]; p = 0.122). Serious adverse events deemed to be related to study therapy occurred in a higher number of patients in the AUF than in the ALD group (16 [14.6%] vs. 6 [5.4%]; p = 0.026) (Table 4, Online Table 7).

Mortality. By 90 days death occurred in 17 (15%) AUF patients and in 14 (13%) ALD patients (p = 0.827). In the AUF group 12 deaths (71%) were due to CV causes, 4 (24%) to renal function deterioration and 1 (6%) to a respiratory disorder. In the ALD patients, 9 deaths (64%) were due to CV causes, 1 (7%) to infection, 1 to hypoxemia (7%), and 3 (21%) to causes that could not be verified. No death was attributed to study therapy in either the AUF or the ALD group.

TABLE 2 Secondary Clinical Endpoints

Endpoint	Days After Discharge	AUF (n = 105)	ALD (n = 108)	p Value
Total number of HF rehospitalizations/ days at risk	30	11/2,876	24/2,882	0.060*
	90	36/6,546	52/6,681	0.182*
Total number of ED or unscheduled office visits with unplanned IV diuretics, vasoactive drugs or, UF/days at risk	30	4/2,869	5/2,863	0.737*
	90	7/6,517	8/6,637	0.840*
Total number of patients with HF rehospitalization	30	10 (9.5)	22 (20.4)	0.034†
	90	27 (25.7)	39 (36.1)	0.106†
Total number of days rehospitalized for HF/days at risk	30	68/2,933	172/3,030	0.029*
	90	338/6,848	460/7,089	0.321*
Total number of CV rehospitalizations/ days at risk	30	17/2,882	33/2,891	0.037‡
	90	46/6,556	66/6,695	0.0969*
Total number of patients with CV rehospitalization	30	15 (14.3)	27 (25.0)	0.042†
Total number of days for CV rehospitalization/days at risk	30	88/2,953	207/3,065	0.018*
	90	377/6,887	554/7,183	0.154*
All-cause rehospitalization rates/ days at risk	30	26/2,891	37/2,895	0.237*
	90	73/6,583	83/6,712	0.571*
Days alive and out of hospital	30	27.3 (5.8)	26.5 (6.3)	0.333§
	90	62.0 (24.6)	61.4 (25.0)	0.803§

Values are n/N or n (%). The p values from proportions (%) are from Fisher exact test; the other p values are from the Wilcoxon rank sum test. *Based on fitted Poisson distribution with dispersion parameter estimated by Pearson. †From Fisher exact test. ‡From generalized linear model with negative binomial distribution. §From Wilcoxon rank sum test.

CV = cardiovascular; ED = emergency department; HF = heart failure; IV = intravenous; UF = ultrafiltration.

TABLE 3 Changes in Serum Creatinine up to 90 Days After Randomization

Time Point	AUF (n = 110)	ALD (n = 111)	p Value
24 h	0.02 ± 0.24 (n = 109) (-0.60 to 0.86)	0.03 ± 0.24 (n = 109) (-0.50 to 1.40)	0.692
48 h	0.13 ± 0.88 (n = 107) (-2.13 to 7.98)	0.05 ± 0.30 (n = 107) (-0.60 to 1.10)	0.565
72 h	0.09 ± 0.38 (n = 83) (-0.60 to 1.58)	0.05 ± 0.35 (n = 91) (-0.80 to 1.50)	0.875
96 h	0.02 ± 0.30 (n = 56) (-0.51 to 0.91)	0.07 ± 0.45 (n = 51) (-0.90 to 1.70)	0.579
120 h	-0.05 ± 0.23 (n = 37) (-0.60 to 0.60)	0.06 ± 0.49 (n = 37) (-0.90 to 1.27)	0.289
Discharge	0.12 ± 0.42 (n = 105) (-0.82 to 2.10)	0.12 ± 0.50 (n = 108) (-0.90 to 3.90)	0.527
30 days	0.37 ± 3.41 (n = 93) (-1.01 to 3.21)	0.17 ± 0.63 (n = 95) (-1.00 to 3.40)	0.450
60 days	0.09 ± 0.52 (n = 85) (-0.83 to 2.70)	-0.01 ± 0.44 (n = 84) (-1.07 to 2.29)	0.115
90 days	-0.30 ± 0.42 (n = 4) (-0.60 to 0.00)	-0.26 ± 0.30 (n = 6) (-0.70 to 0.10)	0.829

Values are mean ± SD (n) (range). All p values are based on 2 randomized arms and from Wilcoxon rank sum test.

Abbreviations as in Table 1.

TABLE 4 Number of Subjects With at Least 1 Serious Adverse Event of Special Interest by MedDRA System Organ Class and Preferred Term

MedDRA System Organ Class	MedDRA Preferred Term	AUF (n = 110)	ALD (n = 111)	p Value
Serious adverse events of special interest		25 (22.73)	16 (14.41)	0.122
Cardiac disorders	Acute coronary syndrome/chest pain	2 (0.9)	0 (0.0)	0.2466
	Supraventricular arrhythmias	2 (1.8)	3 (2.7)	1.000
	Ventricular tachycardia	2 (1.8)	0 (0.0)	0.247
	Cardiac arrest	3 (2.7)	0 (0.0)	0.121
	Cardiac failure	4 (3.6)	3 (2.7)	0.721
	Cardiogenic shock	1 (0.9)	0 (0.0)	0.498
	Cardiorenal syndrome	0 (0.0)	1 (0.9)	>0.999
	Ventricular tachycardia	2 (1.82)	0 (0.0)	0.247
	Cardiac death	0 (0.0)	2 (1.8)	0.497
Gastrointestinal disorders	Gastrointestinal hemorrhage	2 (1.82)	2 (1.8)	0.622
Infections	Access site infections	2 (1.8)	1 (0.9)	0.621
	Other infections	4 (3.6)	1 (0.9)	0.212
Injury, poisoning, and procedural complications	Procedural hemorrhage	1 (0.9)	0 (0.0)	0.498
	Renal hematoma	1 (0.9)	0 (0.0)	0.498
Metabolism and nutrition disorders	Dehydration	1 (0.9)	0 (0.0)	0.498
Nervous system disorders	Syncope	1 (0.9)	1 (0.9)	1.000
Renal and urinary disorders	Renal failure	1 (0.9)	1 (0.9)	0.498
Surgical and medical procedures	Cardiac ablation/cardioversion	1 (0.9)	2 (1.8)	1.000
Vascular disorders	Hypotension/orthostatic hypotension	1 (0.9)	1 (0.9)	1.000

Values are n (%). Sample n value includes all randomized and treated subjects. All p values are based on 2 randomized arms and are from Fisher exact test.
ALD = adjustable loop diuretics; AUF = adjustable ultrafiltration; MedDRA = Medical Dictionary for Regulatory Activities.

DISCUSSION

The distinctive features of the AVOID-HF trial are the evaluation of the hypothesis that hospitalized HF patients treated with AUF would have a longer time to first HF event within 90 days than those receiving ALD and the adjustment of fluid removal in both treatment arms according to patients' vital signs and renal function. Only 30% of the study subjects experienced an HF event. In this population, the time to first HF event at 90 days after a hospitalization for decompensated HF was twice as long in the AUF compared with the ALD group (62 vs. 34 days). However, the smaller than planned sample size does not provide enough evidence to conclude that this difference is statistically significant ($p = 0.106$). Despite enrollment of only 27.5% of the originally planned sample size of 810 subjects, there was evidence to show significant differences between groups in several pre-specified secondary endpoints, including fewer patients rehospitalized for HF or CV causes as well as shorter rehospitalizations for HF or CV causes at 30 days. The validity of these results is bolstered by the fact that HF and CV events were adjudicated by an independent SEC whose members were blinded to the type of randomized fluid removal therapy. Hospital length of stay showed a trend favoring the ALD group.

No differences in changes in renal function occurred between groups from 24 h after initiation of treatment to 90 days after randomization. These findings are consistent with those of the UNLOAD trial and confirm the hypothesis that early initiation of UF, before worsening of renal function from prior decongestive therapies, is a key element for delaying recurrent HF decompensation without producing greater kidney dysfunction (12,13). In contrast, in the CARRESS-HF trial, UF was a rescue treatment for patients who already had an acute rise in serum creatinine levels in response to standard-of-care therapy. In the AVOID-HF trial, the average UF rate of 138 ml/h was lower than the fixed 200 ml/h rate of the CARRESS-HF trial, and therapy was delivered over a longer period of time (70 h vs. 41 h). These facts, in addition to adjustments in UF rates according to individual patients' hemodynamics and renal function, may explain why in the AVOID-HF trial no differences occurred between groups in renal function changes, despite a larger net fluid loss in the AUF than in the ALD group. The adjustable ALD protocol in the AVOID-HF trial is very similar to that used in the CARRESS-HF trial. The AUF guidelines were aimed at removing plasma fluid without exceeding the capillary refill rate to prevent hypovolemia-related worsening of renal function. Although detailed, both AUF and ALD guidelines were

easily adopted by the AVOID-HF investigators, who continue to use these protocols as part of routine clinical care of decompensated HF patients at their Institutions. Indeed the availability of guidelines on how to adjust fluid removal rates according to specific clinical and laboratory measurements may be an important reason for the earlier reduction in HF events in the AVOID-HF trial compared with the UNLOAD trial, in which the greater freedom from HF events in the UF compared to the LD group became apparent later than 30 days after discharge from index hospitalization (8,14). Alternatively, the earlier reduction in HF rehospitalizations in the AVOID-HF trial may be due to the more recent implementation across the United States of programs aimed at avoidance of 30-day readmissions (15). Early HF rehospitalizations are associated with a higher number of subsequent HF events, poorer outcomes, and higher health care costs (1,2,15).

It is important to question why in both the UNLOAD and AVOIF-HF trials, decongestion with UF is associated with fewer HF rehospitalization than treatment with IV LD. In the UNLOAD trial, the fact that the UF group experienced significantly greater weight and net fluid loss compared to the diuretic group, suggests that the decrease in HF rehospitalizations in the UF group may have resulted from more effective decongestion. In the AVOID-HF trial, with the exception of a greater net fluid loss in the AUF than in ALD group, all other measures of decongestion were similar between treatment arms. It is plausible that the simultaneous reduction of total body sodium and excess isotonic fluid by UF may be more effective than removal of hypotonic fluid by diuretics (10,11). Furthermore, UF may avoid the direct stimulation of renin release caused by the blockade of the Na-K-2Cl cotransporter by LD in the macula densa (10,16). It is also possible that pre-hospitalization diuretic use itself reduces the natriuresis achievable with the subsequent administration of IV LD (17,18). In contrast, fluid removal by UF has been shown to restore diuretic responsiveness in patients with diuretic resistance (17). Increased diuretic sensitivity may explain why AUF-treated patients have a longer time to first HF event even if the weight loss during index hospitalization was not greater than that achieved with ALD.

Serious adverse events judged by the investigators to be related to study product occurred in a greater number of patients in the AUF than in the ALD group ($p = 0.026$). Although in the AVOID-HF trial the rate of adverse events occurring in the AUF group was lower than that occurring in the CARRESS-HF trial population, the fact that there was an excess of study product-related adverse events in the AUF group is a serious concern. Given the distribution of adverse effects across organ systems and the smaller than planned sample size, it is difficult to determine the precise causality of these events. Both the frequency and the nature of adverse events would likely have been better described if the study had enrolled the originally planned number of patients. Taken together, the findings of the AVOID-HF trial suggest that the choice of using UF as a decongestive therapy requires physicians to carefully assess the benefit of reducing HF rehospitalizations and the risk of UF-related adverse events during treatment.

STUDY LIMITATIONS. The principal limitation of the AVOID-HF trial is its untimely termination by the sponsor. The sponsor indicated that the decision to stop the trial was made on the basis of slower than projected enrollment. The AVOID-HF enrollment rates were 0.4 patients/site/month, twice the enrollment rate of the CARRESS-HF trial (13). A recent systematic assessment of the temporal trends for 154 phase II to IV HF clinical trials involving 162,725 patients published between 2001 and 2012 showed that median enrollment rates were 0.49 patients/site/month and did not change significantly over time (19). Therefore, the AVOID-HF trial's enrollment rate is not inferior to that of a large number of contemporary trials. Given these facts, the Steering Committee strongly disagreed with the sponsor that the trial's enrollment rate was a valid reason for stopping the study.

Only 40% of patients in both groups were deemed to be adequately decongested at discharge from the index hospitalization. Although this decongestion rate is much higher than in the CARRESS-HF trial in which only 10% of the patients were judged to be euvolemic upon completion of treatment, the reasons why 60% of the patients were discharged with residual congestion were not assessed (20). Adjustment for multiple comparisons for some groups of correlated secondary endpoints was not done. The use of these significance level adjustment methods may have eliminated the statistical significance of several secondary endpoints. Measurements of blood volume, plasma refill rate, and cardiac performance were not done. A further limitation of the AVOID-HF trial is that investigators could not be blinded to treatment assignment. Thus deliberate or nonintentional bias could influence patients' management after discharge, which, in turn, could affect hospital admissions. A cost analysis was not done. Although the costs associated with UF during the index hospitalization may exceed those of IV LD, it is important to determine if these higher initial costs are offset by

the savings resulting from reduced 30- and 90-day HF rehospitalizations.

CONCLUSIONS

Data from the AVOID-HF trial shows that, compared with the ALD group, the AUF group had a non-statistically significant trend toward a longer time to first HF event after index hospitalization, significantly fewer patients rehospitalized for HF or CV causes at 30 days, as well as shorter rehospitalizations for HF or CV causes at 30 days. Whereas 90-day mortality did not differ between groups, the number of patients experiencing an adverse event of special interest or a serious product-related side effect was greater in the AUF than in the ALD group. The AVOID-HF trial's results should be interpreted with caution as the study was unilaterally and prematurely terminated by the sponsor. Nevertheless, the results of the AVOID-HF trial suggest that decongestion with UF requires careful evaluation of the benefit of reducing HF rehospitalizations with the risk of UF-related adverse events. These findings underscore the need for additional investigation of this fluid removal approach.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Maria Rosa Costanzo, Advocate Heart Institute, Edward Heart Hospital, 4th Floor, 801 South Washington Street, Naperville, Illinois 60566. E-mail: mariarosa.costanzo@advocatehealth.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Persistent congestion in hospitalized HF patients portends unfavorable outcomes regardless of age and underlying renal function. Most pharmacologic approaches to treat congestion have not reduced HF events, renal impairment, or mortality. Isolated venovenous UF may reduce HF events because it removes isotonic plasma fluid without the direct stimulation of renin secretion by the macula densa, which occurs with LD. In addition UF restores diuretic responsiveness and therefore prolongs euvolemia. The choice of using UF to decongest HF patients requires careful assessment of the benefit of reducing HF rehospitalizations and the risk of therapy-related adverse events.

TRANSLATIONAL OUTLOOK: The results of the AVOID-HF trial underscore the need for further investigation of UF as a decongestive therapy for fluid overloaded HF patients. Future research should focus on refining patients' selection, reducing therapy-related adverse events, and furthering the knowledge of the mechanisms responsible for improved outcomes. The premature and unilateral termination of the AVOID-HF trial belies lack of interest by the sponsor in further developing the therapy. It is hoped that the intriguing results of the study will rekindle interest in supporting UF.

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KEY WORDS aquapheresis, congestion, fluid overload, heart failure, hospitalizations, loop diuretics, worsening renal function

APPENDIX For a list of the Study Sites and Principal Investigators and Clinical Events Committee, as well as supplemental tables and figures, please see the online version of this article.