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Published in:
Journal of the American College of Cardiology

DOI:
10.1016/j.jacc.2017.03.528

Publication date:
2017

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 69, NO. 19, 2017
ISSN 0735-1097
http://dx.doi.org/10.1016/j.jacc.2017.03.528

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Extracorporeal Ultrafiltration for Fluid Overload in Heart Failure

Current Status and Prospects for Further Research

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ABSTRACT

More than 1 million heart failure hospitalizations occur annually, and congestion is the predominant cause. Rehospitalizations for recurrent congestion portend poor outcomes independently of age and renal function. Persistent congestion trumps serum creatinine increases in predicting adverse heart failure outcomes. No decongestive pharmacological therapy has reduced these harmful consequences. Simplified ultrafiltration devices permit fluid removal in lower-acuity hospital settings, but with conflicting results regarding safety and efficacy. Ultrafiltration performed at fixed rates after onset of therapy-induced increased serum creatinine was not superior to standard care and resulted in more complications. In contrast, compared with diuretic agents, some data suggest that adjustment of ultrafiltration rates to patients' vital signs and renal function may be associated with more effective decongestion and fewer heart failure events. Essential aspects of ultrafiltration remain poorly defined. Further research is urgently needed, given the burden of congestion and data suggesting sustained benefits of early and adjustable ultrafiltration. (J Am Coll Cardiol 2017;69:2428–45) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Annual hospitalizations for heart failure exceed 1 million in both the United States and Europe, and more than 90% are due to symptoms and signs of fluid overload. In addition, up to 1 in 4 patients (24%) are readmitted within 30 days, and 1 in 2 patients (50%) are readmitted within 6 months (1,2). Recurrent fluid overload in heart failure has uniformly been associated with worse outcomes independently of age and renal function (3).

PATHOPHYSIOLOGICAL CONSEQUENCES OF FLUID OVERLOAD

Compared with normal subjects, asymptomatic patients with heart failure have decreased sodium excretion in response to volume expansion (4). Abnormal fluid handling leads to physiological abnormalities in multiple organ systems. Increased myocardial water can lead to ischemia and decreased contractility in animals and humans (5–8). Deranged hemodynamics, neurohormonal activation, excessive tubular sodium reabsorption, inflammation, oxidative stress, and nephrotoxic medications are important drivers of harmful cardiorenal interactions in patients with heart failure (8–10).

Elevation of central venous pressure is rapidly transmitted to the renal veins, causing increased interstitial and tubular hydrostatic pressure, which decreases net glomerular filtration (9,11,12). An increased central venous pressure is independently associated with renal dysfunction and unfavorable outcomes in both acute and chronic heart failure (13,14). Venous congestion itself can produce endothelial activation, up-regulation of inflammatory cytokines, hepatic dysfunction, and intestinal villi ischemia (15). Bacterial endotoxins can then enter the circulation, magnifying the inflammatory milieu created by venous congestion and neurohormonal activity (8).

Three recent studies suggest that failure to adequately reduce fluid excess in patients with acutely decompensated heart failure trumps increases in serum creatinine in predicting poor outcomes (16). Thus, the foremost goal in managing acutely decompensated heart failure is to effectively resolve fluid overload (16). Therefore, if a decrease in intravascular volume by fluid removal causes small transient increases in serum creatinine, effective decongestion may still be essential to protect the kidney in the long term (16,17). Withdrawal of diuretic agents in 30 euvolemic patients with heart failure resulted in increases in urinary levels of kidney injury molecule-1, which returned to baseline with resumption of diuretic agents. Thus, in heart failure, even subclinical fluid overload can be associated with biological evidence of tubular dysfunction (18). An unresolved challenge is the ability to discern whether increase in serum creatinine during fluid removal is driven primarily by hemodynamic decreases in glomerular filtration rate or by development of acute tubular damage, which can progress to chronic kidney disease (19).

ABBREVIATIONS AND ACRONYMS

NGAL = neutrophil gelatinase-associated lipocalin

UF = ultrafiltration

UNRESPONSIVENESS TO DIURETIC AGENTS IN HEART FAILURE

Diuretic agents remain the cornerstone of therapy for fluid overload. Although effective early in heart failure, diuretic agents become increasingly ineffective with disease progression due to the development of unresponsiveness in a significant subset of patients (20). Excellent reviews describe the mechanisms leading to decreased diuretic agent responsiveness (21). In patients with heart failure, impaired absorption, decreased renal blood flow, azotemia, and proteinuria all result in reduced levels of active diuretic agents in the tubular lumen (21). Recently proposed definitions of diuretic resistance include persistent congestion, despite adequate and escalating doses of diuretic agents equivalent to ≥80 mg/day furosemide; the amount of sodium excretion as a percentage of filtered load below 0.2%; and failure to excrete at least 90 mmol of sodium within 72 h of a 160-mg twice-daily dose of furosemide. Metrics for diuretic agent response have also been proposed, including weight loss per 40 mg of furosemide or equivalent; net fluid loss per milligram of loop diuretic agent; and natriuretic response to furosemide as urinary sodium-to-urinary furosemide ratio (21).

The clinical hallmarks of diuretic agent resistance are insufficient symptom relief, higher risk of in-hospital worsening of heart failure, increased mortality after discharge, and a 3-fold increase in rehospitalization rates (21,22). Among more than 50,000 patients enrolled in the ADHERE (Acute

research grants and consultancy fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Cardio3Biosciences, GlaxoSmithKline, Merck/MSD, Novartis, Servier, Sphingotec, Stealth Peptides, Trevena, and Vifor. Dr. Stough was funded by Coridea, LLC. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 3, 2017; accepted March 7, 2017.

Decompensated Heart Failure National Registry) study, only 33% lost ≥2.27 kg (5 lbs), and 16% gained weight during hospitalization. Nearly one-half of hospitalized patients with heart failure are discharged with residual fluid excess after receiving conventional diuretic therapies (23). Regardless of diuretic strategy, 42% of acutely decompensated heart failure subjects in the DOSE (Diuretic Optimization Strategies Evaluation) trial reached the composite endpoint of death, rehospitalization, or emergency department visit at 60 days (24). Vasopressin and adenosine-A1 receptor antagonists, exogenous natriuretic peptides, and low-dose dopamine, studied as either a complement or a replacement for conventional diuretic therapies, can decrease fluid overload in the short term but have failed to improve long-term outcomes (25–27).

Therefore, there is a clear, unmet clinical need for alternative methods of fluid removal with superior efficacy in patients with heart failure. One therapy that might prove successful is extracorporeal ultrafiltration (UF) (28,29). Greater access to UF has been facilitated by the development of simplified devices that do not require specialized technicians or acute care settings (Online Table 1) (30).

Over the past 20 years, several small studies have attempted to define the physiological rationale for the clinical benefits of mechanical fluid removal by UF in heart failure (31–35). However, concerns arose from reports of treatment-related adverse events (32). Thus, the principal aims of this paper were to review the available data for the use of UF in patients with heart failure, describe the knowledge gaps in this area, and outline potential future studies to answer unresolved questions.

PROCESS OF FLUID REMOVAL BY UF, HEMOFILTERS, PUMPS, AND VASCULAR ACCESS

Ultrafiltration consists of the production of plasma water from whole blood across a semipermeable membrane (hemofilter) in response to a transmembrane pressure gradient (29). The newer, simplified UF devices afford the advantages of small size, portability, low blood flow rates, and an extracorporeal blood volume below 50 ml. These devices provide a wide range of UF rates (0 to 500 ml/h) and do not mandate admission to intensive care units or cannulation of a central vein. The characteristics of 2 of these devices are shown in **Figure 1**. Additional details for hemofilters, pumps, and vascular access for UF can be found in Online Appendix in Section 1.0.

DIFFERENTIAL CHARACTERISTICS OF DIURETIC AGENT AND UF-BASED FLUID REMOVAL

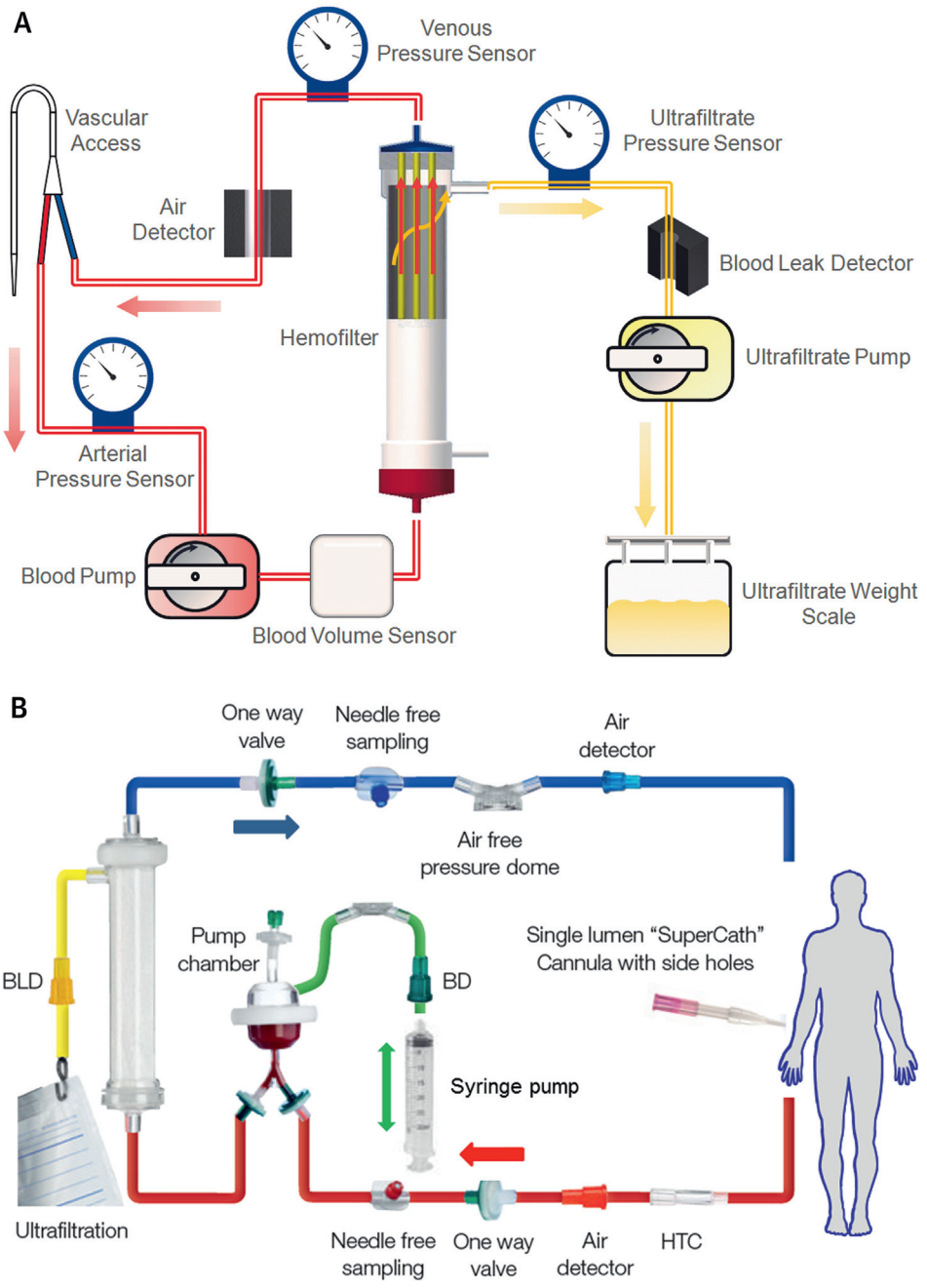
Loop diuretic agents selectively block the $Na^+/K^+/2Cl^-$ cotransporter in the luminal membrane of the medullary thick ascending loop of Henle. Edema in patients with heart failure is isotonic, and therefore normonatremic edematous patients have significantly increased total body sodium. Because loop diuretic agents inhibit sodium reabsorption at a site in the kidney also critical for water reabsorption, they generally result in greater loss of water than sodium and therefore generate hypotonic urine (29).

In contrast, because the ultrafiltrate is almost iso-osmotic and isonatremic compared to plasma, approximately 134 to 138 mmol of sodium are removed with each liter of ultrafiltrate (29). Thus, for any amount of fluid withdrawn, more sodium is likely to be removed with UF than with diuretic agents (29). Conversely, with these drugs, changes in intravascular volume are unpredictable. Furthermore, loop diuretic agents inhibit sodium chloride uptake in the macula densa, an event that, coupled with augmented release of prostacyclin, enhances renal secretion of renin (9,29). These effects augment neurohormonal activation, which ultimately reduces diuretic agents' effectiveness (9). As opposed to the direct effect of loop diuretic agents on the macula densa, with UF, neurohormonal activation should occur only if the fluid removal rate causes intravascular volume depletion by exceeding the plasma refilling rate (**Table 1**) (35). This measure of plasma water transport from the interstitium into the vasculature during fluid removal varies between patients depending upon serum albumin concentration (i.e., serum oncotic pressure) and capillary permeability.

CLINICAL RESEARCH PRECEDING CONTROLLED TRIALS OF UF IN HEART FAILURE

Studies of extracorporeal fluid removal conducted before the introduction of contemporary UF devices are summarized in Online Table 2. The key lessons from these early investigations are that UF can restore diuretic agent responsiveness, but overly aggressive fluid removal can convert nonoliguric renal dysfunction into oliguric failure and dialysis dependence (34,35). A more detailed description of the early studies that specifically evaluated the mechanisms of action of extracorporeal fluid removal can be found in Online Appendix in Section 2.0.

FIGURE 1 **UF Circuit**



(A) The console controls blood removal rates and extracts ultrafiltrate at a maximum rate set by the clinician. Blood is withdrawn from a vein through the withdrawal catheter **(red)** connected by tubing to the blood pump. Blood passes through the withdrawal pressure sensor before entering the blood pump tubing loop. After exiting the blood pump, blood passes through the air detector and enters the hemofilter (made of a bundle of hollow fibers) 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 **(blue)**. The ultrafiltrate passes sequentially through the ultrafiltrate's pressure sensor, the pump, and the collecting bag suspended from the weight scale. A hematocrit sensor is located on the withdrawal line. **(B)** This UF system requires only a single-lumen, multihole, small (18-gauge) cannula inserted in a peripheral vein of the arm. A syringe pump drives the blood inside the extracorporeal circuit, which includes 2 check valves that allow the blood to move from the vein to the filter, and then returns it to the same vein through alternate flows that can be independent. The priming volume of 50 ml and the reduced contact surface between blood and tubing set ensure minimal blood loss if circuit clots and for reduced heparin requirements. BD = blood detector; BLD = blood leak detector; HTC = hematocrit sensor; UF = ultrafiltration.

TABLE 1 Comparative Characteristics of Loop Diuretic Agents and Isolated UF

Loop Diuretic Agents	Isolated UF
Direct neurohormonal activation	No direct neurohormonal activation
Elimination of hypotonic urine	Removal of isotonic plasma water
Unpredictable elimination of sodium and water	Precise control of rate and amount of fluid removal
Development of diuretic agent resistance with prolonged administration	Restoration of diuretic agent responsiveness
Risk of hypokalemia and hypomagnesemia	No effect on plasma concentration of potassium and magnesium
Peripheral venous access	Peripheral or central venous catheter
No need for anticoagulation	Need for anticoagulation
No extracorporeal circuit	Need for extracorporeal circuit

UF = ultrafiltration.

PILOT STUDIES WITH CONTEMPORARY UF SYSTEMS

The SAFE (Simple Access Fluid Extraction) trial showed that, in 21 congested patients with heart failure, removal of an average of 2,600 ml of ultrafiltrate during one 8-h treatment session reduced weight by an average of 3 kg without changes in heart rate, blood pressure, serum creatinine concentration, and electrolytes or the occurrence of major adverse events (30). Results of 2 additional pilot studies with this system are summarized in Online Table 3.

The findings of both studies provided valuable information. First, the clinical benefits of UF can persist beyond the index heart failure hospitalization up to 90 days. Second, UF is unlikely to improve outcomes of patients with end-stage heart failure and should be used very cautiously in this setting. Third, although potentially effective in reducing central venous pressure, aggressive fluid removal in preload-dependent patients with heart failure, who have low forward flow as the predominant mechanism for a reduction in glomerular filtration rate, can rapidly decrease renal perfusion pressure and cause oliguric failure, leading to dialysis dependence (36–38). High pre-treatment intravenous loop diuretic agent doses may increase the risk of tubular injury when additional fluid is removed by UF (39).

RANDOMIZED CONTROLLED TRIALS

The randomized controlled trials of UF are summarized in **Table 2 and** Online Table 4. The RAPID-CHF (Relief of Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure) trial was the first randomized study of UF to use the Aquadex System 100 device (Sunshine Heart, Minneapolis, Minnesota) (40). Although this small study did not evaluate patients' outcomes beyond 48 h, it confirmed that effective fluid removal and clinical improvement may occur with UF (41).

The physiological fact that refill of the intravascular space from the edematous interstitium decreases as fluid is removed led to the hypothesis that initiation of UF before the plasma refilling rate is decreased by previous diuretic agent-based therapies might produce greater benefit than intravenous loop diuretic agents in unequivocally congested patients with heart failure. Hence, in the UNLOAD (Ultrafiltration Versus Intravenous Diuretics Decompensated Heart Failure) trial, randomization had to occur within 24 h of hospitalization, and a maximum of 2 intravenous loop diuretic agent doses were permitted before enrollment (33). Compared with standard care results, the UF group had greater weight loss and similar improvement in dyspnea score (the coprimary endpoints) at 48 h. The percentage of patients with increases in serum creatinine levels ≥0.3 mg/dl was slightly but insignificantly higher in the UF group than in the control group at 24 and 48 h (33). Among UNLOAD patients from a single center, use of iothalamate and *para*-aminohippurate to measure glomerular filtration rate and renal plasma flow showed that UF and furosemide produce similar changes in these variables (41). There were no between-group differences in duration of the index hospitalization, a variable that can be influenced by adjustment of oral heart failure therapy before discharge, performance of additional diagnostic and therapeutic procedures, treatment of comorbidities, issues of patients' placement, and lack of defined discharge criteria (33,42). In UNLOAD, the 90-day heart failure events were a pre-specified secondary endpoint, and the investigators determined whether these were related to worsening heart failure or not. It cannot be said with certainty whether the fewer heart failure events in 90 days in the UF group compared with the standard care group were due to differences in fluid loss, the nature of the fluid removed, or other factors (33). Because UNLOAD did not have an independent clinical events committee (CEC) to adjudicate whether an event was heart failure-related or not, the possibility of patient or investigator bias cannot be excluded. A post hoc analysis of UNLOAD compared the 100 UF patients with 100 usual-care patients subdivided according to intravenous diuretic agent strategy (continuous [n = 32] or bolus [n = 68] administration) (43). Despite removal of the same amount of fluid by UF and diuretic agent infusion, 90-day heart failure events were fewer in the UF group ($p = 0.016$) (43). The simultaneous reduction of

total body sodium and excess fluid by UF may be more effective than removal of hypotonic fluid by diuretic agents or free water by arginine vasopressin V2 receptor antagonists (25,43,44). It is also possible that pre-hospitalization diuretic agent use itself impairs the natriuretic response to subsequent intravenous administration of these drugs (21). In UNLOAD, complications related to UF included clotting of 5 filters, 1 catheter infection, and the requirement for hemodialysis in 1 patient deemed unresponsive to UF (**Table 2**) (33).

The UNLOAD trial lacked treatment targets, blood volume assessments, cost analysis, and adjudication of events by an independent CEC. Nevertheless, compared with standard care, UF initiated before the administration of high-dose intravenous diuretic agents led to greater fluid loss at 48 h and reduced 90-day heart failure events. In the ULTRADISCO (Effects of ULTRAfiltration vs. DIureticS on clinical, biohumoral and hemodynamic variables in patients with deCOmpensated heart failure) study, at 36 h, compared with the diuretic agent group, the UF patients had greater reduction in body weight, signs and symptoms of heart failure, aldosterone and N-terminal pro-B-type natriuretic peptide levels, and systemic vascular resistance, as well as greater improvements in objective measures of cardiac performance (45). Albeit very small, this study suggests that effective fluid removal may be associated with improved cardiac function (35,45–47).

The CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial compared the effects of UF delivered at a fixed rate of 200 ml/h with those of stepped pharmacological therapy inclusive of adjustable doses of intravenous loop diuretic agents, thiazide diuretic agents, vasodilators, and inotropes in acutely decompensated patients with heart failure who had experienced a pre-randomization increase in serum creatinine (19,32,48). The primary endpoint of CARRESS-HF was the bivariate change in serum creatinine and body weight from baseline to 96 h after randomization (32). According to the CARRESS-HF design (48), this primary endpoint assumes that weight loss is a measurement of effective fluid removal and that an increase in serum creatinine represents acute tubular injury. In CARRESS-HF, both groups lost an equivalent amount of weight, but greater increases in serum creatinine occurred with UF (32). In addition, a higher percentage of patients in the UF group experienced serious adverse events (**Table 2**) (32). However, the fact that 37 patients (39%) in the UF group received only diuretic agents or were given these drugs before the assessment of the primary endpoint at 96 h impairs adjudication of adverse events to one or the other therapy.

Although in heart failure increases in serum creatinine (≥0.3 mg/dl) have been equated to actual renal tubular damage, which portends adverse long-term prognosis, transient increases in serum creatinine may simply reflect a hemodynamically driven reduction in glomerular filtration rate akin to that occurring with angiotensin-converting enzyme inhibitors. Furthermore, recent studies suggest that transient increases in serum creatinine may reflect more complete decongestion and, instead, forecast improved post-discharge outcomes (17). Crossover rates in CARRESS-HF also impaired interpretation of the findings of a recent substudy where plasma renin activity and aldosterone levels were higher in the UF group than in the stepped pharmacological therapy group at 96 h. Because neurohormonal levels were not measured beyond this time point, it remains unknown whether the observed neurohormonal changes were transient or sustained (49).

In CARRESS-HF, the rate of fluid removal was mandated to be 200 ml/h in all UF patients, and adjustments were left to the discretion of the investigators, “to address technical problems or clinical care requirements” (32). A UF rate of 200 ml/h may be excessive for patients with a lower blood pressure and greater dependence on preload for hemodynamic stability (50,51). Clinical experience shows that, regardless of the method used, removal of fluid must be tailored to individual patients’ blood pressure, renal function, urine output, and body mass. The stepped pharmacological therapy patients could receive care tailored to their characteristics, including use of vasoactive drugs, which occurred in 12% of patients in this arm before 96 h (32). Vasoactive agents were prohibited in the UF group, except as rescue therapy. Interpretation of the results of the CARRESS-HF trial is also hampered by the fact that overall outcomes were poor, regardless of fluid removal strategy: only 10% of the patients had adequate improvement of signs of fluid overload at 96 h, and more than 30% died or were readmitted for decompensated heart failure within 60 days (32,52).

In the CUORE (Continuous Ultrafiltration for Congestive Heart Failure) trial, UF-treated patients had a lower incidence of heart failure rehospitalizations through 1 year (53) than those undergoing standard care, despite similar weight loss at discharge. In CUORE, diuretic agent therapy was continued during UF in the belief that this approach might help restore diuretic agent responsiveness by enhancing urinary sodium excretion (53). In previous studies, diuretic agent therapy was stopped during

TABLE 2 UF Clinical Trials: Overview of Study Designs and Key Findings

Study Name, Publication Year (Ref. #)	Study Group	UF Arm	Comparison Arm	Primary Efficacy Endpoint
RAPID-HF, 2005 (40)	N = 40 Hospitalized with HF, 2+ edema and ≥1 additional sign of congestion	Single, 8-h course, median duration 8 h, median volume removed 3,213 ml	Standard HF therapies determined by treating physician	Weight loss 24 h post-consent
UNLOAD, 2007 (33)	N = 200 Hospitalized with HF, ≥2 signs of fluid overload	Aquadex System 100† Mean fluid removal rate 241 ml/h for 12.3 ± 12 h	Standard care: IV diuretic agents. For each 24-h period, at least twice the pre-hospitalization daily oral dose	Weight loss and dyspnea assessment at 48 h after randomization
CARRESS-HF, 2012 (32)	N = 188 Hospitalized with HF, ≥2 signs of congestion, and recent ≥0.3 mg/dl sCr increase	Aquadex System 100† at a fixed rate of 200 ml/h Median duration 40 h	SPT with intravenous diuretic agents dosed to maintain urine output 3–5 l/day	Bivariate response of change in sCr and change in weight 96 h after randomization
CUORE, 2014 (53)	N = 56 NYHA III or IV, LVEF ≤40%, ≥4 kg weight gain from peripheral fluid overload, over 2 months	Dedyca device‡ Mean treatment duration 19 ± 90 h; volume removed 4,254 ± 4,842 ml	Intravenous diuretic agents according to guideline recommendations (standard care)	HF rehospitalization at 1 yr
AVOID-HF, 2016 (56)	N = 224 Hospitalized with HF; ≥2 criteria for fluid overload; receiving daily oral loop diuretic agents	AUF with Aquadex FlexFlow System§; adjustments per protocol guidelines on the basis of vital signs and renal function‖ Mean fluid removal rate 138 ± 47 ml/h for 80 ± 53 h	ALD with adjustments per protocol-guidelines on the basis of vital signs and renal function¶ Mean furosemide-equivalent dose 271.26 ± 263.06 mg for 100 ± 78 h	Time to first HF event (HF rehospitalization or unscheduled outpatient or emergency treatment with intravenous loop diuretic agents or UF) within 90 days of hospital discharge
ULTRADISCO, 2011 (45)	N = 30 Hospitalized for HF, ≥2+ peripheral edema, ≥1 other criteria for volume overload	PRISMA# Median treatment duration 46 h; cumulative fluid loss 9.7 ± 2.9 l	Furosemide continuous infusion, initial dose 250 mg/24 h	Change in hemodynamics measured by PRAM

*Other than primary endpoint. †CHD solutions, Minneapolis, Minnesota. ‡Dellco, Mirandola, Italy. §Baxter International, Deerfield, Illinois. ‖See flow chart in Figure 2. ¶See flow chart in Figure 3. #Hospal Gambro Dasco, Medolla, Italy.

ALD = adjustable loop diuretic agent; AUF = adjustable ultrafiltration; CI = confidence interval; CPO = cardiac power output; dP/dt_{max} = maximal rate of rise in left ventricular pressure; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PRAM = pressure recording analytical method; SAE = serious adverse event; sCr = serum creatinine; SPT = stepped pharmacological therapy; UF = ultrafiltration.

Continued on the next page

extracorporeal fluid removal on the basis of the hypothesis that UF may give patients a "diuretic holiday," during which loop diuretic agent-induced neurohormonal activation does not occur (33,54,55). The AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure) trial tested the hypothesis that patients hospitalized for heart failure who were treated with adjustable UF would have a longer time to first heart failure event within 90 days than those receiving adjustable intravenous loop diuretic agents (56). The AVOID-HF trial, designed as a multicenter, 1:1 randomized study of 810 hospitalized patients with heart failure, was terminated unilaterally and prematurely by the sponsor (Baxter Healthcare, Deerfield, Illinois) after enrollment of 224 patients (27.5%). Detailed guidelines were provided to the investigators as to how to adjust both of the therapies in response to patients' vital signs, renal function, and urine output (**Figures 2 and 3**) (57). Patients in the adjustable UF group had a nonstatistically significant trend to longer time to first heart failure event than patients in the adjustable diuretic agents group (62 vs. 34 days, respectively; p = 0.106). Although the primary outcome did

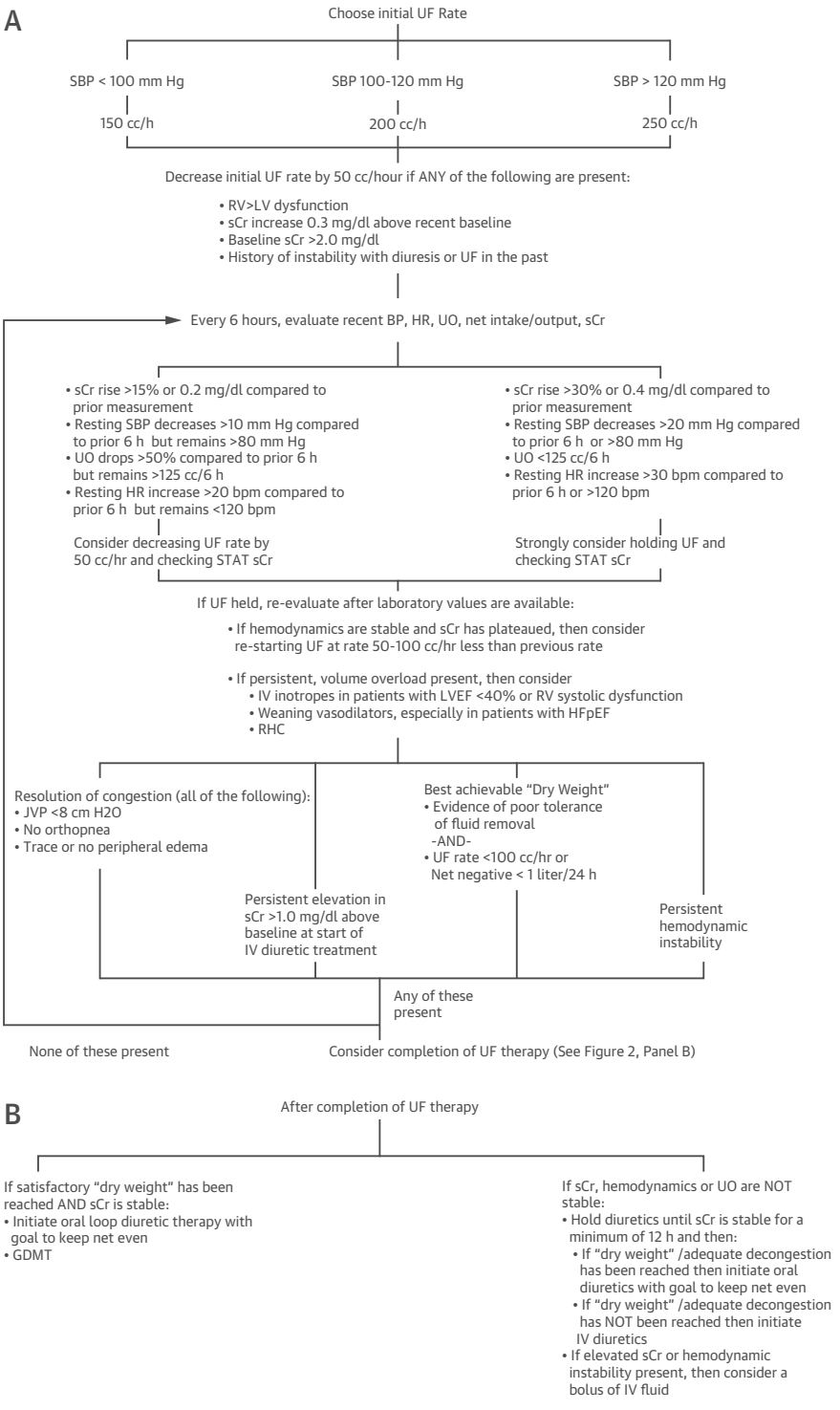
TABLE 2 Continued

Primary Endpoint Result	Reported Clinical Outcomes*	Mortality	Adverse Events
Weight loss approximately −6.25 kg (UF) vs. −7 kg (standard care), p = 0.24	Index length of stay: 6 days (UF) vs. 5 days (standard care); p = NS Volume removal 24 h after consent: 4,650 ml (UF) vs. 1,838 ml (standard care), p = 0.001	30 days: 1 (UF)	1 catheter site infection (UF)
Weight loss: 5.0 ± 3.1 (UF) vs. 3.1 ± 3.5 kg (standard care); p = 0.001 Dyspnea score: 5.4 ± 1.1 (UF) vs. 5.2 ± 1.2 (standard care); p = 0.588	90 days: HF rehospitalization: 18% (UF) vs. 32% (standard care), p = 0.022; HR 0.56; 95% CI: 0.28-0.51; p = 0.04 Unscheduled clinic/emergency visits: 21% (UF) vs. 44%, p = 0.009	90 days: 9 (9.6%) UF vs. 11 (11.6) standard care	No significant between-group differences, except bleeding (1 UF vs. 7 standard care, p = 0.032). UF group: 1 catheter infection, 5 filter clotting events, 1 patient transitioned to hemodialysis due to insufficient response to UF
Mean sCr change: +0.23 ± 0.70 mg/dl (UF) vs. −0.04 ± 0.53 mg/dl (SPT) Mean weight loss: 5.7 ± 3.9 (UF) vs. 5.5 ± 5.1 kg (SPT); p = 0.58	Crossover: STP: 6 patients STP: (6%) also received UF (2 before 96 h) UF: 8 patients (9%) received diuretic agents instead of UF; 28 patients (30%) also received diuretic agents before 96 h. 7 days: no difference in death, worsening or persistent HF, hemodialysis, SAE, or crossover (23% UF vs. 18% SPT, p = 0.45) 60 days HF hospitalization 26% (UF) vs. 26% (SPT) p = 0.97	60 day: 17% UF vs. 13% SPT; p = 0.47	60-day SAE: 72% UF vs. 57% SPT; p = 0.03, attributed to renal failure, bleeding, or catheter complications
3 (11%) UF vs. 14 (48%) standard care; HR: 0.14; 95% CI: 0.04–0.48; p = 0.002	Length of index hospitalization: 7.4 ± 4.6 (UF) vs. 9.1 ± 1.9 days (standard care), p = 0.23 Combined death or HF rehospitalization HR for UF vs. standard care 0.35, 95% CI: 0.15-0.69; p = 0.0035	1 yr: 7 (26%) UF vs. 11 (38%) standard care; p = 0.33	Premature clotting of filter in 6 patients
25% AUF vs. 35% ALD (p = 0.11); HR: 0.66; 95% CI: 0.4–1.1	Length of index hospitalization: median 6 (AUF) vs. 5 (ALD) days, p = 0.106 30-day HF rehospitalizations/days at risk: 11 of 2,876 (AUF) vs. 24 of 2,882 (ALD), p = 0.06 30-day CV rehospitalizations/days at risk: 17 of 2,882 (AUF) vs. 33 of 2,891 (ALD); p = 0.037 For both HF and CV events: fewer patients rehospitalized; fewer number of days rehospitalized/days at risk	90 days 15% AUF vs. 13% ALD, p = 0.83	At least 1 SAE: 66% (AUF) vs. 60% (ALD), p = 0.4 SAEs of special interest: 23% (AUF) vs. 14% (ALD); p = 0.122 Related SAEs: 14.6% (UF) vs. 5.4% (ALD), p = 0.026
Significant between group difference in % change from baseline in cardiac index, CPO, dP/dt_{max}; no significant change in sCr within or between groups	Signs/symptom score decreased significantly in both groups; no difference between groups	Not reported	Not reported

not achieve statistical significance, several prespecified secondary endpoints did. In particular, patients in the adjustable UF group had significantly fewer heart failure and cardiovascular events at 30 days (56). Importantly, these events were adjudicated by an independent committee blinded to randomized therapy (56). The finding of similar renal function changes in the 2 groups is consistent with that of UNLOAD (33,56). In AVOID-HF, 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 (70 vs. 41 h, respectively) (32,56). Adjustments of UF rates to individual patients' hemodynamics and renal function may explain the lack of differences in serum creatinine between groups, despite a larger net fluid loss with UF (**Figures 2 and 3**) (56). Although they are detailed, the therapy guidelines were adopted by the AVOID-HF investigators, most of whom continued to use them in their clinical practice. Individualization of fluid removal rates may explain why the reduction in heart failure events occurred earlier in AVOID-HF than in UNLOAD (33,56). Removal of isotonic fluid and avoidance of renin release by the macula densa may contribute to the benefit of UF (32,54,55). Restoration of diuretic agent responsiveness may be a key mechanism by which UF delays recurrence of heart failure events (56).

Significantly more patients in the UF group than in the diuretic agents group experienced adverse events

FIGURE 2 Adjustable UF Guidelines Used by the AVOID-HF Investigators



(A) Guidelines for the adjustment of UF therapy. **(B)** Guidelines for the completion of ultrafiltration therapy: 40 mg of furosemide = 1 mg bumetanide or 10 mg of torsemide (52,53). b.i.d. = twice daily; GDMT = guideline-directed medical therapy; IV = intravenous; JVP = jugular venous pressure; LV = left ventricular; QD = once daily; RV = right ventricular; SBP = systolic blood pressure; sCr = serum creatinine; UO = urine output; other abbreviations as in Figure 1.

of special interest (infection requiring intravenous antibiotics, bleeding requiring transfusion, symptomatic hypotension requiring vasopressor agents or rapid fluid replacement, a drop in hemoglobin >3 g/dl, and acute coronary syndrome requiring intervention [31% vs. 17%, respectively; $p = 0.018$]). Serious therapy-related adverse events occurred at higher rates in the UF group than in the diuretic agents group (14.6% vs. 5.4%, respectively; $p = 0.026$) (56). Although in AVOID-HF, UF-related adverse events were fewer than in CARRESS-HF, the excess of therapy-related complications with UF is a serious concern (32,56). More study of the specifics of providing UF are needed to identify strategies aimed at minimizing access-related and other potentially preventable complications (32,56). Taken together, the facts outlined in the preceding text indicate that the AVOID-HF trial was unable to demonstrate that adjustable UF is superior to adjustable diuretic agent therapy. The statistically significant secondary outcomes of fewer 30-day heart failure and cardiovascular events are hypothesis-generating and do not diminish the critical need for adequately powered randomized controlled trials comparing the effects of UF versus diuretic agent-based strategies on both heart failure morbidity and mortality.

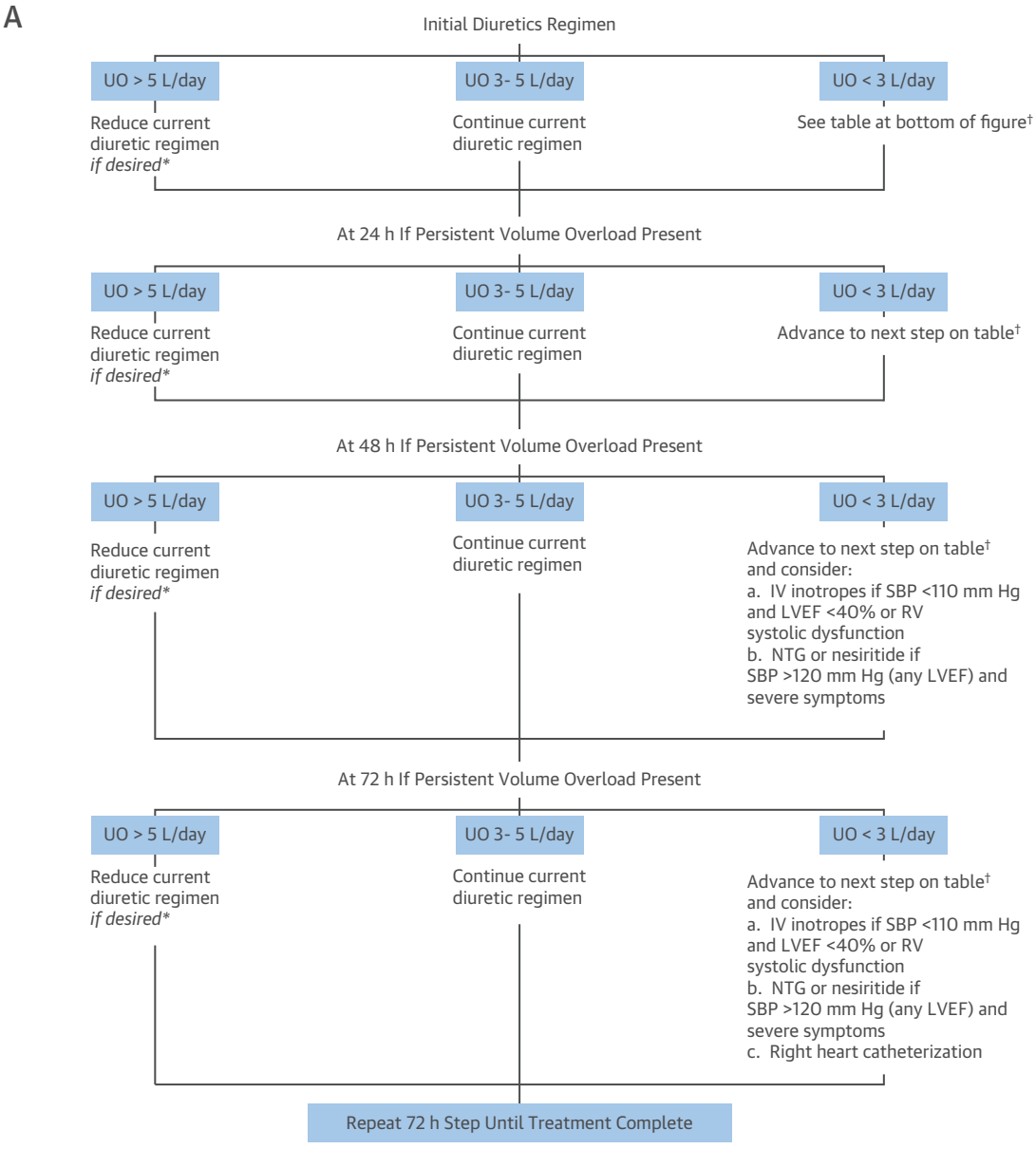
KNOWLEDGE GAPS IN THE USE OF EXTRACORPOREAL UF IN HEART FAILURE

SELECTION OF POTENTIAL CANDIDATES. The conflicting results from UF studies highlight the fact that patient selection and fluid removal targets are incompletely understood (32,56). Practice guidelines suggest that an inadequate response to an initial dose of an intravenous loop diuretic agent be treated with an increased dose of the same drug (54,55). If this intervention is ineffective, invasive hemodynamic assessment is recommended. Evidence of persistent fluid excess can then be treated with the addition of thiazide diuretic agents, aldosterone antagonists, or continuous intravenous infusion of a loop diuretic agent. Only if all these measures fail can UF be considered (58,59). A similar degree of diuretic agent resistance characterized eligibility for enrollment in CARRESS-HF (32,33,53,56). In this trial, the poor outcomes of UF in patients with the acute cardiorenal syndrome may be partially related to the lack of therapy adjustment according to individual patients' characteristics. In AVOID-HF, fine-tuning of UF rates in response to vital signs, renal function, or urine output resulted in greater net fluid loss and was associated with fewer 30-day heart failure events without a greater increase in serum creatinine levels than in the adjustable diuretic agent group (56). These observations underscore the critical need for additional investigation of UF as both first-line and rescue therapies, provided that UF rates are adjusted in each patient in response to changes in vital signs and renal function (32,56).

Due to the potential complications and cost of UF, it should not be used indiscriminately in decompensated heart failure. For example, in patients with de novo heart failure or those not receiving daily diuretic agents, fluid overload can be rapidly eliminated with intravenous diuretic agents, which should be used in such cases instead of UF. The unanswered question is which patients who develop heart failure decompensation despite daily oral diuretic agents should be considered for UF instead of intravenous diuretic agents? To date, all studies of UF in patients with heart failure have relied solely on clinical signs and symptoms of fluid excess, both as inclusion criteria and fluid removal targets. This is problematic due to the poor correlation between clinical assessment and objective measures of increased filling pressures (60). A European consensus statement that graded congestion according to a combination of clinical and laboratory parameters suggested that a score of ≥12, together with urine output of <1,000 ml/24 h, should trigger the use of UF because these values are indicative of diuretic agent resistance (61). This recommendation has not been prospectively validated and relies on the unproven assumption that the magnitude of fluid excess influences diuretic agent responsiveness.

Data from 15 patients with acutely decompensated heart failure show that urinary sodium concentration in response to intravenous loop diuretic agents is highly variable and lower than that in the ultrafiltrate (44). The difficulty in predicting the natriuretic response of individual patients to a given dose of intravenous diuretic agent is underscored by the absence of a correlation between baseline renal function and urinary sodium concentration after furosemide administration (44). The hypothesis that UF may be especially effective in patients with urinary sodium concentrations of <100 mEq after a specified dose of intravenous diuretic agents should be tested in randomized trials. A single nonrandomized prospective cohort study showed similar effects of UF in heart failure with reduced versus preserved left ventricular ejection fraction (62). However, because the 2 types of heart failure possess distinct pathophysiological and clinical characteristics, response to UF should be assessed in controlled trials.

FIGURE 3 Adjustable Loop Diuretic Agent Guidelines Used by the AVOID-HF Investigators

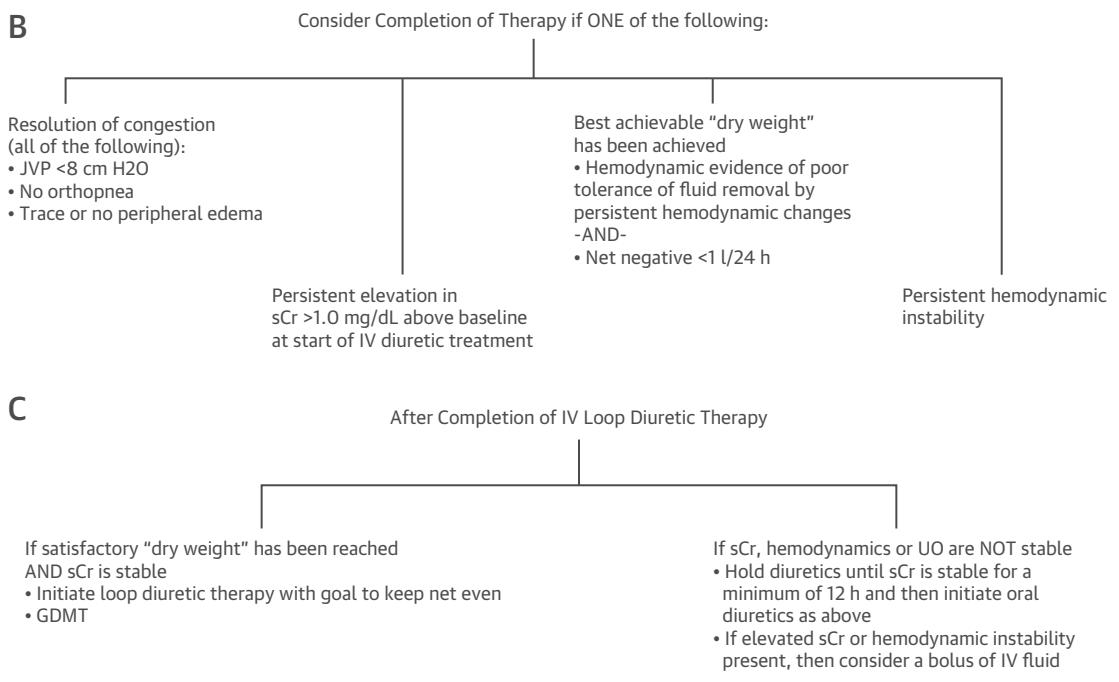


†Current dose		Suggested dose	
Loop (mg/day)	Thiazide	Loop	Thiazide
≤80	+ or –	40 mg IV bolus + 5 mg/h	0
81-160	+ or –	80 mg IV bolus + 10 mg/h	5 mg metolazone QD
161-240	+ or –	80 mg IV bolus + 20 mg/h	5 mg metolazone BID
>240	+ or –	80 mg bolus + 30 mg/h	5 mg metolazone BID

(A) Initiation of loop diuretic agents. *Evaluation of blood pressure, heart rate, urine output, and net intake/output was performed every 6 h; evaluation of serum chemistries was performed every 12 h. Decreasing or holding the diuretic agent dose may be considered if: 1) serum creatinine rises by 30% or ≥0.4 mg/dl (whichever is less) versus previous measurement; 2) resting systolic blood pressure decreases >20 mm Hg compared to previous 6 h or drops <80 mm Hg; or 3) resting heart rate is >30 beats/min compared to previous 6 h or >120 beats/min. LVEF = left ventricular ejection fraction; NTG = nitroglycerin; other abbreviations as in Figure 2.

Continued on the next page

FIGURE 3 Continued



(B) Guidelines for the completion of adjustable loop diuretic agents. **(C)** Guidelines for management after completion of adjustable loop diuretic agents (see also references 52 and 53).

FLUID REMOVAL TARGETS AND MONITORING OF UF THERAPY. One important general recommendation is that, once an initial UF rate has been chosen, it should be either maintained or reduced because capillary refill from the interstitium decreases as fluid is removed (34). Although the optimal rate and duration of UF must be individualized, UF rates of >250 ml/h are not typically recommended (56,57). Patients with predominantly right-sided heart failure or patients with heart failure with preserved ejection fraction are exquisitely susceptible to intravascular volume depletion and may only tolerate low UF rates (50 to 100 ml/h) (63). In addition, clinical experience teaches that extracorporeal fluid removal is better tolerated when conducted with low UF rates over prolonged periods of time (32).

A frequently used approach is to compare patients' current weight with that preceding the signs and symptoms of congestion and to use this "dry weight" as the target for fluid removal. No consensus exists on whether removal of only 60% to 80% of excess fluid by UF and continuation of loop diuretic agents during therapy results in less hemodynamic instability and greater urinary sodium excretion (53). Considering the harmful renal effects of an increased central venous pressure (9,13–15,34,35,64), controlled clinical trials should determine if fluid removal by UF should be adjusted to achieve specific central venous pressure targets. In lieu of invasive measurements, ultrasonography can help estimate central venous pressure with the assessment of the respiratory excursions of the diameter of the inferior vena cava (65). Although ultrasonography is noninvasive and inexpensive, its reliability depends strictly depends on the operator's skill and the patient's respiratory effort (65).

Studies of implantable hemodynamic monitors have consistently shown that baseline pulmonary artery diastolic pressure predicts heart failure events. Interventions aimed at reducing pulmonary artery pressures to pre-specified target ranges have effectively reduced heart failure events without significant renal function changes (66,67). The CardioMEMS sensor (St. Jude Medical, St. Paul, Minnesota) permits measurement of pulmonary artery pressures as frequently as clinically indicated. Therefore, it is conceivable that, in patients in whom the CardioMEMS device has been implanted, fluid can be removed by UF until the target range of pulmonary artery pressures that effectively reduced heart failure events has been achieved (66,67).

BLOOD VOLUME AND FLUID EXCESS ESTIMATION. The hematocrit is the ratio of the volume occupied by red blood cells to that of whole blood. Because red blood cell mass does not change in the short term unless bleeding occurs, fluctuations in hematocrit reflect changes in intravascular volume (68).

Online hematocrit sensors permit continuous estimation of blood volume changes during UF and can be programmed to stop fluid removal if the hematocrit exceeds a threshold set by the clinician (e.g., 5% to 7%) and resume therapy when the hematocrit value falls below the pre-specified limit, indicating an adequate refilling of the intravascular volume from the interstitial space (Online Figure 1) (68).

However, because numerous factors (e.g., change in body position) can alter hematocrit values, physical, laboratory, and hemodynamic variables should be concomitantly assessed to determine the appropriate UF rates and the amount of fluid that should be removed (68). Bioimpedance vector analysis relies on the principle that whole-body impedance to an alternating current reflects total body water ($r = 0.996$) (69). Measurements of bioimpedance vector require 2 pairs of electrodes be placed on the wrist and ankles and the application of a 50-kHz alternating microcurrent (CardioEFG, EFG Diagnostics, Belfast, Northern Ireland) (69). It is therefore attractive to envision the use of bioimpedance vector analysis to determine baseline fluid status and then use of serial measurements to guide the amount and rate of fluid removal by UF or diuretic agents. Accuracy of bioimpedance vector analysis can be reduced by diaphoresis, hirsutism, incorrect electrode placement, cutaneous alterations, or improper electrical grounding. Bioimpedance spectroscopy is also being investigated in patients with heart failure (70). Unfortunately, no existing bioimpedance-based method can differentiate intravascular from interstitial extracellular fluid volume, a distinction that is critical for safe and effective fluid removal (69,70).

Intrathoracic fluid can also be measured noninvasively with electromagnetic technology inserted in a removable vest (Sensible Medical Innovations, Netanya, Israel). This device, shown in preclinical and pilot human studies to measure intrathoracic water as accurately as computed tomography, is being tested in a prospective, randomized clinical trial (NCT02448342) (71). The measurement of blood volume using iodine-131-labeled albumin is accurate, but the 6 to 9 blood draws needed to create the dilution curve make it impractical for the serial assessments needed during fluid removal (72). The lack of optimal methods for the estimation of blood volume and fluid excess underscores the critical need for research in this area.

BIOMARKERS. The use of natriuretic peptides to assess volume status and guide decongestive therapies cannot be recommended because fluid overload is not the sole cause of increases in the levels of these biomarkers (73). The removal of fluid to achieve pre-specified natriuretic peptide levels is untested in acute heart failure. Serum creatinine is the sole biomarker used to guide fluid removal because of the belief that its level reflects both renal filtration function and tubular status. However, serum creatinine was established and validated as a measurement of renal function only at the point of steady-state (constant production from the metabolism of muscle creatine phosphate and unchanging glomerular filtration and urinary flow to excrete creatinine at a constant rate). Therefore, it is unfortunate that serum creatinine is the only widely available measurement of renal function in patients with acute illnesses, such as acutely decompensated heart failure, where the rates of creatinine production and excretion may be altered. Gene expression analysis has shown differences in the genes expressed in acute kidney injury due to different processes, even if the magnitude of rise in creatinine is the same. Conversely, serum creatinine concentration can be normal with documented tubular injury due to the delayed achievement of detectable changes of this analyte (74). Generally, hemodynamically driven increases in serum creatinine resolve with treatment in 24 to 72 h, whereas the cellular derangements due to acute tubular damage, or even necrosis, may last for weeks (75). Therefore, the duration of the elevation in serum creatinine has a greater predictive effect on morbidity and mortality than the extent of this biomarker's elevation (76,77). Indeed, the use of increases in serum creatinine as an endpoint for acutely decompensated heart failure trials has been challenged. Evaluation of the relationship between changes in serum creatinine and 60-day outcomes in DOSE subjects revealed that increases in serum creatinine from baseline to 72 h (DOSE's coprimary endpoint) was associated with lower risk for the composite outcome of death or heart failure events. Conversely, there was a strong relationship between improved renal function and unfavorable 60-day outcomes (78). Thus, serum creatinine changes are an unreliable surrogate endpoint in trials of fluid removal therapies. After the discovery by Mishra et al. (79) of neutrophil gelatinase-associated lipocalin (NGAL), which is secreted in the urine and the plasma by a damaged kidney, it was shown that the expression/secretion of urine NGAL (neutrophil gelatinase-

associated lipocalin) occurred within 3 h of the event (sepsis, nephrotoxins, obstruction, ischemia); and that the amount of secreted protein (from 20 ng/ml to 5 μg/ml) was proportional to the severity and time of resolution of the stimulus. A growing body of evidence suggests NGAL is not expressed when serum creatinine increases due to volume stressors. A systematic study of thousands of genes encoding for several biomarkers including NGAL, kidney injury molecule-1, tissue inhibitor of metalloproteinase-1, and clusterin, found that these molecules were detectable after a brief dose of ischemia, yet none of these genes were expressed after near-fatal volume depletion, despite the rise in serum creatinine in both models (80). Although this method is not yet widely available, in the setting of any method of fluid removal, the levels of urine NGAL and other biomarkers of tubular injury could potentially help distinguish a rise in serum creatinine due to a hemodynamically mediated decrease in glomerular filtration rate or actual tubular injury (74). Numerous genes are differentially expressed depending upon the presence and type of acute kidney injury. The levels of NGAL rise faster than those of other indicators of renal injury, making this biomarker better suited to distinguish between hemodynamically, versus tubular injury-driven increases in serum creatinine that may occur during fluid removal therapies (74,80).

ECONOMIC CONSIDERATIONS. To date, there has been no prospective evaluation of the cost effectiveness of UF therapy. The only published retrospective estimate of UF costs is presented in the Online Appendix in Section 3.0. Therefore, it is imperative that future prospective controlled trials include rigorous cost-benefit analyses.

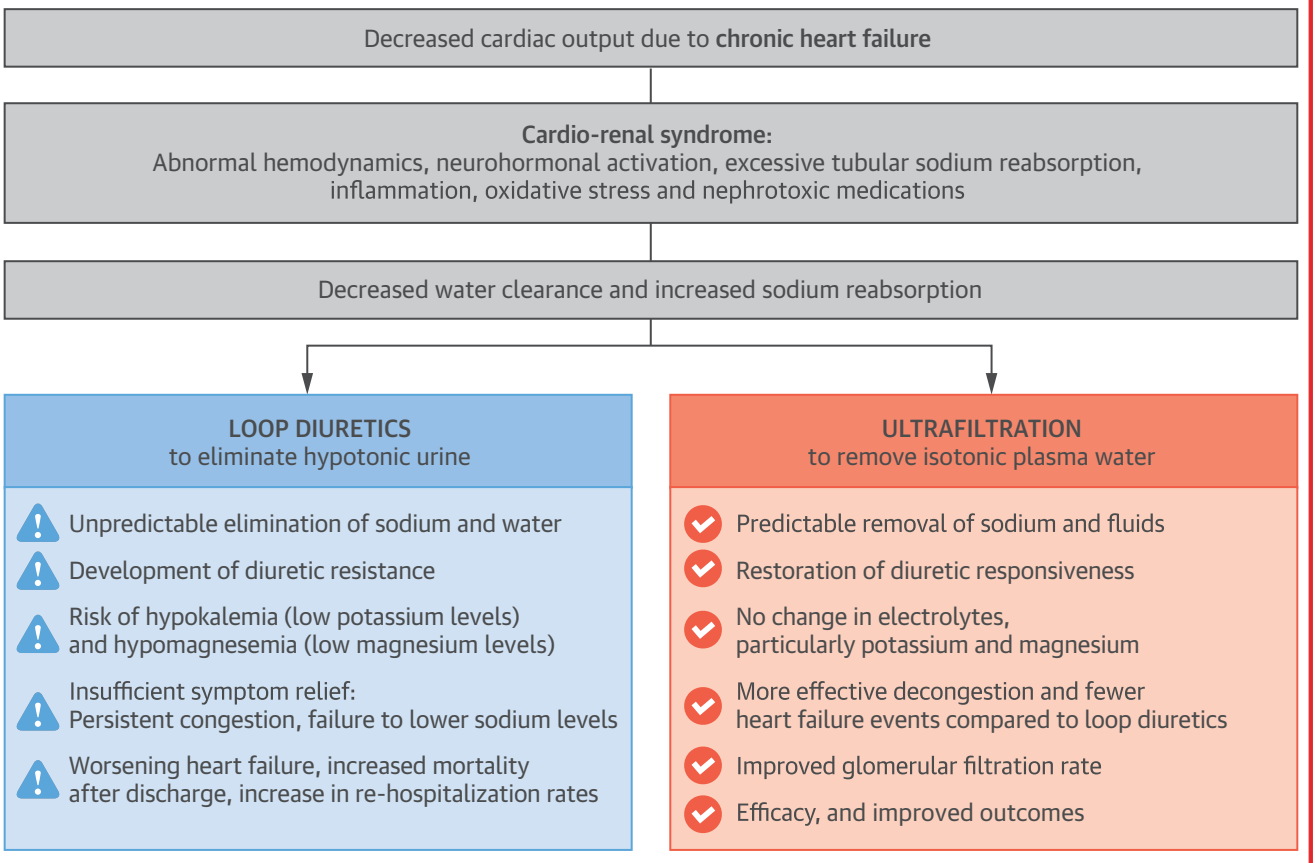
PROPOSAL FOR FUTURE STUDIES. No studies performed to date have conclusively demonstrated the superiority of one fluid removal method over another. It is vital to continue searching for the most effective and safest method to treat congestion, which worsens the outcomes of patients with heart failure and causes unacceptably high hospitalization rates worldwide. Concerning UF, priority should be given to mechanistic studies including evaluation of diuretic agent responsiveness at baseline during and after fluid removal by using the measurements described in this review (21). Hemodynamic measurements that reflect fluid status (e.g., central venous pressure and pulmonary artery diastolic pressure) should also be performed at baseline and throughout therapy. Specific hemodynamic targets indicative of optimal fluid status should be established in individual patients, similar to the strategies used to guide medication adjustment in studies of pulmonary artery pressure sensors (63). Different UF rates should be tested in terms of their ability to reach these hemodynamic targets without causing renal tubular damage, as detectable by increase in urine levels of biomarkers, such as NGAL (70,73,76). This will require simultaneous measurement of the selected hemodynamic values and biomarker levels capable of differentiating rises in serum creatinine due to decreases in glomerular filtration rate produced by intravascular fluid removal from those reflective of renal injury. Serial measurements of urine and ultrafiltrate sodium content (rather than randomly performed single-spot measurements) may also help to better characterize and compare the amount and pattern of sodium extraction during UF therapy and conventional diuretic agent-based regimens. This noninvasive, inexpensive, and readily available test can easily be incorporated into future investigations. The results of mechanistic studies are essential to determine how fluid removal rates and amounts should be adjusted in individual subjects of future controlled trials ("precision" fluid removal).

Equally important is the development of vascular accesses and UF device components that increase the efficiency and safety of the therapy. The device- and therapy-related adverse events observed in previous trials should undergo careful re-evaluation to determine which were preventable or related to operator experience versus those that were inherent to how therapy was delivered or was unpredictable (32,46,47,52).

Only after these issues have been satisfactorily addressed should a carefully designed, adequately powered study be considered to prospectively compare UF with pharmacological fluid removal therapies. All treatments should be tailored to individual patients' hemodynamic and renal status. In addition, the study's follow-up period should be sufficiently long to permit the evaluation of morbidity (rehospitalizations) and mortality. Future trials should also evaluate whether the greater cost of mechanical fluid removal during the index hospitalization is offset by the savings resulting from potentially fewer heart failure events in patients treated with UF.

As the cost of inpatient care is very high, serious consideration should be given to studies in the outpatient setting to determine the relative safety and effectiveness of intermittent pharmacological and mechanical fluid removal therapies for the prevention rather than the treatment of heart failure hospitalizations. Intermittent outpatient UF to restore responsiveness to oral diuretic agents is also a strategy that deserves investigation. Finally,

CENTRAL ILLUSTRATION **Ultrafiltration for Fluid Overload in Heart Failure**



Costanzo, M.R. et al. J Am Coll Cardiol. 2017;69(19):2428–45.

Of the >1 million heart failure hospitalizations in the United States and Europe, 90% are due to signs and symptoms of fluid overload. This enormous worldwide health care burden is aggravated by the fact that recurrent congestion worsens patients' outcomes, regardless of age and renal function. Abnormal hemodynamics, neurohormonal activation, excessive tubular sodium reabsorption, inflammation, oxidative stress, and nephrotoxic medications drive the complex interactions between heart and kidney (cardiorenal syndrome). Loop diuretic agents are used in most congested patients. Due to their mechanism and site of action, loop diuretic agents lead to the production of hypotonic urine and may contribute to diuretic agent resistance ("braking phenomenon," distal tubular adaptation, and increased renin secretion in the macula densa). Increased uremic anions and proteinuria also impair achievement of therapeutic concentrations at their tubular site of action. Ultrafiltration is the production of plasma water from whole blood across a hemofilter in response to a transmembrane pressure. Therefore, ultrafiltration removes isotonic fluid without direct activation of the renin-angiotensin-aldosterone system, provided that fluid removal rates do not exceed capillary refill. Any method of fluid removal may cause an increase in serum creatinine. However, in the absence of evidence of renal tubular injury (e.g., augmented urinary concentration of neutrophil gelatinase-associated lipocalin), this increase represents a physiological decrease in glomerular filtration rate due to decreased intravascular volume from fluid removal. AVP = arginine vasopressin; GFR = glomerular filtration rate; K = potassium; KIM = kidney injury molecule; Mg = magnesium; NGAL = neutrophil gelatinase-associated lipocalin; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system.

technological advances may permit the development of "wearable" UF devices capable of delivering individualized UF therapy.

CONCLUSIONS

Fluid excess drives most heart failure hospitalizations. Recurrent hospitalizations are common and predict unfavorable outcomes. As heart failure progresses, a significant proportion of patients develop an inadequate response to diuretic agent therapy. Additional approaches, such as sequential nephronal blockade with thiazide diuretic agents or high-dose aldosterone antagonists, have not been appropriately validated. Other pharmacological therapies have not improved the outcomes of patients with heart failure who have fluid overload. Ultrafiltration is an attractive alternative therapy because it predictably removes total body sodium. In future studies, UF should be adjusted according to the

patient's hemodynamic and renal profiles; and patient selection, fluid removal amount, duration, and rate should be guided by objective, complementary, and informative measurements of fluid overload and kidney function (**Central Illustration**). The urgency of these investigations is underscored by the alarming prognostic and economic implications of recurrent heart failure hospitalizations, which remain unacceptably high with conventional pharmacological therapies.

ACKNOWLEDGMENT The authors thank Wendy Gattis Stough, PharmD, who worked under the direction and supervision of Dr. Costanzo, for editing assistance.

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KEY WORDS biomarkers, creatinine, diuretics, glomerular filtration rate, venous congestion

APPENDIX For an expanded Methods section as well as supplemental tables and a figure, please see the online version of this article.